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## Moving?

Our subscribers' records and publication labels are computergenerated. Please send your new address, and your latest label, or an exact copy of it, to: USPC, PF Customer Service Dept., 12601 Twinbrook Parkway, Rockville, MD 20852. Fax: (301) 816-8148.

## STANDARDS DEVELOPMENT

This section presents an overview of the public review and comment process, conducted through Pharmacopeial Forum $(P F)$, for the development of official pharmaceutical standards.

USP publishes Pharmacopeial Forum ( $P F$ ) bimonthly as the working vehicle of the USP Council of Experts. PF provides interested parties an opportunity to review and comment as the Council of Experts develops or revises standards for the United States Pharmacopeia and the National Formulary ( $U S P-N F$ ).
$P F$ includes the following:

1. Potential revisions-entirely new standards, revision ideas, and drafts not yet targeted for official adoption (Pharmacopeial Previews)
2. Proposed revisions - new or revised standards targeted for official adoption (In-Process Revision)
3. Adopted revisions-new or revised standards that become official and binding before the publication of the next $U S P$ NF or Supplement (Interim Revision Announcement)
USP welcomes comments and data on potential, proposed, or official standards. ${ }^{*}$ Comments, along with USP's responses, will be published either in PF Briefings, the Commentary section of $P F$, the Commentary section of Supplements to $U S P-N F$, or the Commentary section of $U S P-N F$.
[^1]The chart below shows the public review and comment process and its relationship to standards development.

# Public Review and Comment Process for Standards Development 



Questions on the process should be addressed to John W. Gasper, M.A., J.D., Director, Office of the Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: jg@usp.org).

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## HOW TO USE PF

This section provides descriptions of the various parts of $P F$. It also includes Committee Designations and the Staff Directory.

The contents of the different sections of $P F$ are briefly described below. Readers will get an idea of how each section is relevant to their job functions. They may contact USP scientific staff liaisons or staff members of the Executive Secretariat (listed in the Staff Directory) if they have any questions. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a Request for Revision is available on the USP website (www.usp.org/standards/revisionguideline/).

# Proposed and Adopted Revisions 

| Section | Content | How Readers Can Respond |
| :---: | :---: | :---: |
| Pharmacopeial <br> Previews <br> Early ideas for revisions | -Briefing: Scientific rationale for potential inclusion or change. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -Potential revisions not yet targeted for official adoption that require a longer public review and comment process because of issues such as: <br> - the controversial nature of an item; <br> - the application of new technologies that require further study; and <br> - articles produced by multiple sources. | Review drafts and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview. |
| In-Process Revision Revisions targeted for adoption | -BriEfing: Scientific rationale for proposed changes. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -New and revised standards that have been approved for publication by the appropriate USP Committee when it is considering whether to advance standards to official status (see Standards Development). New or revised text is marked with symbols ( ${ }^{\square}$ or ) to specify the tentative earliest date on which the revision would be officially adopted. | Review material and send comments promptly to USP staff liaison (see the Staff Directory). Guidelines on how to comment are found at the end of the Po licies and Announcements section. |
| Harmonization <br> Items the Pharmacopeial Discussion Group (PDG) is trying to harmonize internationally | -Briefing: Scientific rationale for the potential inclusion or change or for the proposed change. The designated stage of harmonization. The stage determines whether an item appears under Pharmacopeial Previews or under In-Process Revision, both separate sections of Harmonization. <br> -For In-Process Revision, new or revised text is marked with symbols (■) to specify the tentative, earliest date on which the revision would be officially adopted. | Review material and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview or In-Process Revision. |
| Interim Revision Announcement Adopted standards | Standards that have been adopted and will become officially binding on the specified date. Effective date is specified in the section's introductory page or within parentheses following a particular item. New or revised text is set off by the symbols | Review to see if affected by any of the changes. Note effective date when standards become official and ensure compliance. |

## Other Sections

## Committee Designations

Names of the committees (composed of volunteer scientific experts) that USP staff work with on the development of standards.

## Staff Directory

Names of all USP scientific staff liaisons with contact information.

## Policies and Announcements

- General scientific and policy issues affecting $U S P-N F$ standards and processes
- Update on standards-related issues being considered by USP
- Summaries of meetings of the Council of Experts
- Guidelines on how to comment
- Publication and comment schedules


## Stimuli to the Revision Process

- Articles on standards development issues authored by the USP Council of Experts, USP staff, or other interested parties
- Discussions of issues on which USP desires public input prior to further development


## Nomenclature

- Latest adopted United States Adopted Names (USAN) and International Nonproprietary Names (INN) for drugs
- Revisions to existing names as a supplement to the USP Dictionary of USAN and International Drug Names
- Suggested, proposed, and recommended USAN and INN
- Information on how nonproprietary drug names are devised
- Articles relevant to compendial nomenclature issues


## Index

Cumulative directory for the content of all issues of $P F$ beginning with $P F$ 30(1).

## Reference Standards Catalog

List of official USP Reference Standards specified in $U S P-N F$, along with availability and ordering information.

## Chromatographic Reagents Used in USP-NF and Pharmacopeial Forum

Update of chromatographic reagents based on the proposals published in this issue of $P F$.

## EXPERT COMMITTEE DESIGNATIONS*

The names of the Committees and their abbreviations are as follows:

| AER | Aerosols |
| :--- | :--- |
| AMB | Analytical Microbiology |
| BBP | Blood and Blood Products |
| BNA | Bioavailability and Nutrient Absorption |
| BNT | Biotechnology and Natural Therapeutics and Diagnostics |
| BPC | Biopharmaceutics |
| BST | Biostatistics |
| CRX | Compounding Pharmacy |
| DSB | Dietary Supplements-Botanicals |
| DSI | Dietary Supplements-Information |
| DSN | Dietary Supplements-Non-Botanicals |
| EMC | Excipient Monograph Content ${ }^{\dagger}$ |
| ESC | Excipients-Substances and Characterization ${ }^{\dagger}$ |
| ETM | Excipients-Test Methods |
| GCT | Gene Therapy, Cell Therapy, and Tissue Engineering |
| GTB | General Toxicity and Biocompatibility |
| NL | Nomenclature and Labeling |
| PA1 | Pharmaceutical Analysis 1 |
| PA2 | Pharmaceutical Analysis 2 |
| PA3 | Pharmaceutical Analysis 3 |
| PA4 | Pharmaceutical Analysis 4 |
| PA5 | Pharmaceutical Analysis 5 |
| PA6 | Pharmaceutical Analysis 6 |
| PA7 | Pharmaceutical Analysis 7-Antibiotics |
| PDF | Pharmaceutical Dosage Forms |
| PPC | Parenteral Products-Compounding and Preparation |
| PPI | Parenteral Products-Industrial |
| PSD | Packaging, Storage, and Distribution |
| PW | Pharmaceutical Waters |
| RMI | Radiopharmaceuticals and Medical Imaging |
| SMU | Safe Medication Use |
| VET | Veterinary Drugs |
| VVI | Vaccines, Virology, and Immunology |
|  |  |

[^2]
## STAFF DIRECTORY

This is an updated directory that reflects assignment changes based on the reorganization of USP. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Committee is not identified. The Fax number is (301) 816-8373.

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## POLICIES AND ANNOUNCEMENTS

In this section, readers may find statements about general scientific and policy issues that may have an impact on $U S P-N F$ standards and processes, announcements about issues being considered by USP, and summaries of Council of Experts meetings. This section also includes publication and comment schedules.

USP GUIDELINE FOR SUBMITTING REQUESTS FOR REVISION TO THE USP-NF. We are pleased to announce the availability of the USP Guideline for Submitting Requests for Revision to the USP-NF. This document was developed in conjunction with the USP Council of Experts and its Expert Committees, USP Staff, and the Drug Substance, Complex Actives, and Excipients Project Teams of the Prescription/Nonprescription Stakeholders Forum. This document includes information to aid submission of new monographs and revisions to existing monographs for Non-Complex Active Substances and Products, Biological and Biotech Substances and Products, Excipients, and Vaccines. It incorporates many of the concepts and suggestions included in the ICH Q3A, Q3B, Q3C, Q6A, and Q6B guidelines. These include the definition of a specification and incorporate much of the terminology of Q3A for the control of impurities. The guideline clearly defines the information needed for the

USP's Council of Experts and its Expert Committees to evaluate a request for revision. The document is approximately 75 pages in length with about 25 pages of addenda and is available in PDF format from the USP website at www.usp.org. Hard copies will be provided upon request.

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education series has been developed to enhance the knowledge, skills, and expertise of pharmaceutical industry personnel.
The following list indicates tentatively scheduled course dates. For further information, contact Barbara B. Hubert, Director, Pharmacopeial Education, BBH@usp.org, 301-816-8333, or Diana Lenahan, Program Associate, DPL@ usp.org, 301-816-8530. Call 301-816-8530 to get information on customized courses offered at USP or at your site.

Calendar of Pharmacopeial Education Courses, 2004

| Date | Name of course | Location |
| :---: | :---: | :---: |
| January 12 and 13 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| January 14 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| February 4 and 5 | Fundamentals of Titrations | USP Headquarters, Rockville, MD |
| February 9 | Standards 100: Fundamentals of the Use of $U S P$ $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| February 10 | Standards 101: Advanced Use of $U S P-N F$, General Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| March 22 and 23 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| March 24 | Fundamentals of Microbiological Testing | USP Headquarters, Rockville, MD |
| April 1 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| April 21 and 22 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| May 19 | Standards 100: Fundamentals of the Use of USP$N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| May 20 | Standards 101: Advanced Use of $U S P-N F$, General Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| June 10 | Fundamentals of Microbiological Testing | USP Headquarters, Rockville, MD |
| July 19 and 20 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| August 10 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| August 11 | Standards 100: Fundamentals of the Use of USP$N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| August 12 | Standards 101: Advanced Use of $U S P-N F$, General Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| October 14 | Fundamentals of Microbiological Testing | USP Headquarters, Rockville, MD |
| October 18 and 19 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| November 11 | Analytical Method Validation | USP Headquarters, Rockville, MD |

Calendar of Pharmacopeial Education Courses, 2004 (continued)

| Date | Name of course | Location |
| :--- | :--- | :--- |
| November 11 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| November 12 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| November 12 | Fundamentals of Dissolution (Lecture) | USP Headquarters, Rockville, MD |
| December 2 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| December 8 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| December 9 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |

VISIT THE USP WEB SITE AT 〈http://www.usp.org〉. Various resources related to Pharmacopeial standards are presented, including highlights from $P F$.

## USP-NF AVAILABLE IN THREE ELECTRONIC

 FORMATS. The trusted reference for official pharmaceutical standards is available in three convenient electronic formats-CD, intranet, and online. The CD is ideal for single users who prefer to have $U S P-N F$ on their hard drives. The intranet format allows Web browser-based access to multiple users within a company, through their own intranet server. The online format can be accessed by individual registered users through the World Wide Web. All three electronic formats provide fast and easy access to official $U S P-N F$ content. More information can be obtained by visiting www.usp.org/products or by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.CHROMATOGRAPHIC REAGENTS NOW AVAILABLE. Chromatographic Reagents lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic test methods that has been published in Pharmacopeial Forum (PF) since 1980. Chromatographic Reagents also helps to track which column reagents were used to validate methods that have become official and are included in $U S P-N F$. The branded column reagents list is updated bimonthly through Pharmacopeial Forum. Chromatographic Reagents can be ordered by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

INTERNATIONAL CORRESPONDENCE. Individuals who wish to correspond with the European and Japanese Pharmacopoeias concerning monographs in the Official

Inquiry and Consensus stages of international harmonization should address their comments to the coordinating pharmacopeia for a given article. The addresses for the European and Japanese Pharmacopoeias are as follows:

Technical Secretariat of the
European Pharmacopoeia Commission
B.P. 907

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HOW TO SUBMIT COMMENTS. The USP welcomes and encourages interested parties to submit comments and data regarding potential, proposed, or adopted (official) standards. Submissions concerning a particular item that has appeared in a $P F$ should be submitted to the appropriate USP scientific staff liaison identified at the end of the Briefing accompanying each item. To submit comments and data to a liaison, use the e-mail address and telephone numbers listed in the Staff Directory included in every $P F$.

Please note that $U S P-N F$ is being published in an annual edition with one main book and two Supplements a year. In addition, the following schedule will repeat every year so that users will know what to expect and become familiar with the deadlines.

The publication and comment schedule for USP 27-NF 22 is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2003 | November 2003 | January 2004 |
| Supplement One | October 15, 2003 | February 2004 | April 2004 |
| Supplement Two | February 17, 2004 | June 2004 | August 2004 |

The publication and comment schedule for USP $28-N F 23$ is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2004 | November 2004 | January 2005 |
| Supplement One | October 15, 2004 | February 2005 | April 2005 |
| Supplement Two | February 17, 2005 | June 2005 | August 2005 |

In the future, USP anticipates including the comment submission deadline in each briefing of every revision proposal when it is published for public review and comment.

For general inquiries or in cases where a particular liaison is not identified, use the general USP telephone number 301-881-0666 or FAX number 301-816-8373.

All official revisions are published in Supplements to $U S P-N F$ (twice yearly). Between Supplements, official revisions are published in PF in the Interim Revision Announcement; these revisions are also incorporated in the upcoming Supplement. The electronic version of $U S P-N F$ is updated as each Supplement becomes available and, therefore, contains all official text up to and including the contents of the latest Supplement.

## Publication Schedules

| Publication | Publication Date | Official Date |
| :---: | :---: | :---: |
| $1{ }^{\text {st }}$ Supplement | Feb. 2004 ${ }^{*}$ | Apr. 1, 2004 ${ }^{*}$ |
| PF 30(2) [Mar.-Apr. 2004] | Mar. 2004* | Not Applicable |
| $2{ }^{\text {nd }}$ IRA [published in $P F$ 30(2)] | Mar. 2004* | Apr. 1, 2004* |
| PF 30(3) [May-June 2004] | May 2004* | Not Applicable |
| $3{ }^{\text {rd }}$ IRA [published in PF 30(3)] | May 2004* | June 1, 2004* |
| $2^{\text {nd }}$ Supplement | June 2004* | Aug. 1, 2004* |
| PF 30(4) [July-Aug. 2004] | July 2004* | Not Applicable |
| $4^{\text {th }}$ IRA [published in PF 30(4)] | July 2004* | Aug. 1, 2004* |
| PF 30(5) [Sept.-Oct. 2004] | Sept. 2004* | Not Applicable |
| $5{ }^{\text {th }}$ IRA [published in PF 30(5)] | Sept. 2004* | Oct. 1, 2004* |
| PF 30(6) [Nov.-Dec. 2004] | Nov. 2004 ${ }^{*}$ | Not Applicable |
| $6^{\text {th }}$ IRA [published in PF 30(6)] | Nov. 2004 ${ }^{*}$ | Dec. 1, 2004* |

[^3]
## INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

- The list of new USP Reference Standards that have become available
- The list of assays or tests that are adopted but held in abeyance pending availability of required USP Reference Standards
- New adopted (official) revisions to the $U S P-N F$ that become effective before the effective date of the next Supplement or that were not ready for adoption by the closing date for the upcoming Supplement. (The effective date for these revisions is stated on the next page.)

Readers should review this section to determine if they are affected by any of the changes.
Symbols-Interim revisions are shown with new text (if any) enclosed in circles, ${ }^{\bullet}$ new text. Text enclosed in squares, $\mathbf{■ n e w}^{\mathbf{n}}$ text $\mathbf{n}$, has already been adopted in a Supplement. Where the symbols appear together with no enclosed text, such as $\bullet \bullet$ or $■$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the IRA or Supplement in which the revision first appeared. For example, ${ }_{\bullet 2}$ indicates that the revision was officially adopted in the Second Interim Revision Announcement, and $\mathbf{m}_{2 \mathrm{~S} \text { (USP27) }}$ indicates that the revision was officially adopted in the Second Supplement to USP 27.

Errata-At the end of the Interim Revision Announcement section is a list of errata and corrections to USP 27-NF 22. The page number indicates where the item is found in $U S P-N F$. If necessary, this list will be updated with every issue of $P F$. This information will also be cumulative in the next available Supplement, and will appear in its corrected form in the next annual edition of $U S P-N F$. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.
FIRST INTERIM REVISION ANNOUNCEMENT ..... 25
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# FIRST INTERIM REVISION ANNOUNCEMENT 

By authority of the United States Pharmacopeial Convention, Inc. Prepared by the Council of Experts and published by the Board of Trustees

Larry L. Braden, Chair USP Board of Trustees Roger L. Williams, Executive Vice President and Chairman, USP Council of Experts

John W. Gasper, Director, Executive Secretariat

Official February 2, 2004.
Released January 1, 2004.

[^4]
## New USP Reference Standards

The following USP Reference Standards, which were indicated in past Supplements to $U S P-N F$ as being not yet available, have since become available. Thus, the official date of each USP 27 or NF 22 standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list.

USP Acesulfame Potassium RS (January 1, 2004)
USP Allantoin RS (March 1, 2004)
USP Amifostine Disulfide RS (March 1, 2004)
USP Ammonium Chloride RS (March 1, 2004)
USP Aspartame Acesulfame RS (March 1, 2004)
USP Benazepril Hydrochloride RS (July 1, 2004)
USP Benazepril Related Compound A RS (May 1, 2004)
USP Benazepril Related Compound B RS (May 1, 2004)
USP Betahistine Hydrochloride RS (January 1, 2004)
USP Bupropion Hydrochloride RS (March 1, 2004)
USP Cefipime Hydrochloride RS (January 1, 2004)
USP Cefipime Hydrochloride System Suitability RS (January 1, 2004)

USP Chlorhexidine RS (July 1, 2004)
USP Chlorhexidine Acetate RS (July 1, 2004)
USP Choline Bitartrate RS (January 1, 2004)
USP Choline Chloride RS (March 1, 2004)
USP Clonazepam Related Compound C RS (July 1, 2004)
USP Copovidone RS (March 1, 2004)
USP Desflurane RS (May 1, 2004)
USP Desflurane Related Compound A RS (March 1, 2004)
USP Dextran 40 RS (May 1, 2004)
USP Dextran 70 RS (May 1, 2004)
USP Dolasetron Mesylate RS (July 1, 2004)
USP Dolasetron Mesylate Related Compound A RS (July 1, 2004)
USP Dorzolamide Hydrochloride Related Compound A RS (January 1,2004$)$
USP Doxazosin Mesylate RS (March 1, 2004)
USP Powdered Eleuthero Extract RS (July 1, 2004)
USP Fenoldopam Mesylate RS (March 1, 2004)
USP Fenoldopam Related Compound A RS (January 1, 2004)
USP Fenoldopam Related Compound B RS (January 1, 2004)
USP Flumazenil RS (May 1, 2004)
USP Fluoxetine Related Compound C RS (July 1, 2004)
USP Formononetin RS (March 1, 2004)
USP Fosphenytoin Sodium RS (March 1, 2004)
USP Gadoversetamide RS (March 1, 2004)
USP Gadoversetamide Related Compound A RS (March 1, 2004)
USP Ganciclovir RS (May 1, 2004)
USP Ganciclovir Related Compound A RS (July 1, 2004)
USP Gemfibrozil Related Compound A RS (January 1, 2004)
USP Glucosamine Hydrochloride RS (July 1, 2004)
USP Hydrocodone Bitartrate Related Compound A CII RS (March 1, 2004)
USP Isoflupredone Acetate RS (January 1, 2004)
USP Powdered Kava Extract RS (March 1, 2004)
USP Kawain RS (March 1, 2004)
USP Ketamine Related Compound A RS (January 1, 2004)
USP Lamivudine RS (July 1, 2004)
USP Meropenem RS (March 1, 2004)
USP Metformin Hydrochloride RS (March 1, 2004)
USP Metformin Related Compound A RS (March 1, 2004)
USP Metoprolol Related Compound A RS (July 1, 2004)
USP Nabumetone RS (January 1, 2004)
USP Norgestimate RS (January 1, 2004)
USP Ondansetron Hydrochloride RS (March 1, 2004)
USP Ondansetron Related Compound A RS (March 1, 2004)
USP Ondansetron Related Compound C RS (March 1, 2004)
USP Ondansetron Related Compound D RS (March 1, 2004)

USP Oxaprozin RS (January 1, 2004)
USP Oxfendazole RS (March 1, 2004)
USP Paclitaxel RS (March 1, 2004)
USP Paclitaxel Related Compound A RS (March 1, 2004)
USP Paclitaxel Related Compound B RS (March 1, 2004)
USP Paroxetine Related Compound D RS (May 1, 2004)
USP Phenytoin Related Compound A RS (March 1, 2004)
USP Phenytoin Related Compound B RS (July 1, 2004)
USP Quinapril Related Compound A RS (January 1, 2004)
USP Quinapril Related Compound B RS (January 1, 2004)
USP Quinine Hydrochloride Dihydrate RS (March 1, 2004)
USP Ramipril RS (January 1, 2004)
USP Ramipril Related Compound A RS (January 1, 2004)
USP Powdered Red Clover Extract RS (May 1, 2004)
USP Rimantidine Hydrochloride RS (July 1, 2004)
USP Scopoletin RS (July 1, 2004)
USP Sevoflurane RS (May 1, 2004)
USP Sevoflurane Related Compound A RS (May 1, 2004)
USP Sodium Starch Glycolate RS (January 1, 2004)
USP Sotalol Hydrochlride RS (July 1, 2004)
USP Sotalol Related Compound A RS (May 1, 2004)
USP Sotalol Related Compound B RS (May 1, 2004)
USP Sotalol Related Compound C RS (May 1, 2004)
USP Stearoyl Polyoxyglycerides RS (May 1, 2004)
USP Sumatriptan RS (March 1, 2004)
USP Sumatriptan Succinate RS (March 1, 2004)
USP Sumatriptan Succinate Related Compound A RS (March 1, 2004)

USP Sumatriptan Succinate Related Compound C RS (March 1, 2004)

USP Tacrine Hydrochloride RS (January 1, 2004)
USP Taurine RS (January 1, 2004)
USP Terazosin Hydrochloride RS (March 1, 2004)
USP Terazosin Related Compound A RS (March 1, 2004)
USP Terazosin Related Compound B RS (March 1, 2004)
USP Terazosin Related Compound C RS (March 1, 2004)
USP Tiamulin Fumarate RS (July 1, 2004)
USP Tiamulin Related Compound A RS (July 1, 2004)
USP Tinidazole RS (January 1, 2004)
USP Tinidazole Related Compound A RS (January 1, 2004)
USP Thalidomide RS (January 1, 2004)
USP Urea C13 RS (January 1, 2004)
USP Valsartan Related Compound A RS (March 1, 2004)
USP Valsartan Related Compound C RS (March 1, 2004)
USP Verteporfin RS (March 1, 2004)
USP Verteporfin Related Compound A RS (March 1, 2004)
USP Vinorelbin Related Compound A RS (March 1, 2004)
USP Vinorelbine Tartrate RS (May 1, 2004)
USP Vitexin RS (March 1, 2004)
USP Zileuton RS (January 1, 2004)

The official dates of any USP 27 or NF 22 standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards.

## USP Alteplase RS

USP Amiloxate RS
USP Positive Bioreaction RS
USP Cefpiramide RS
USP Cinoxate RS
USP Decoquinate RS
USP Diethylstilbestrol Diphosphate RS
USP Enalapril Related Compound B RS
USP Enzacamene RS
USP Fludeoxyglucose RS
USP Ginseng Extract RS
USP Gonadorelin Hydrochloride RS
USP Hypericin RS

USP Lactase RS
USP Medroxyprogesterone Acetate Related Compound A RS
USP Menotropins RS
USP Methyldopa-Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Ondansetron Related Compound B RS
USP Potassium Perchlorate RS
USP Pyrethrum Extract RS
USP Sargramostim RS
USP Sulisobenzone RS

USP $\Delta^{8}$-tetrahydrocannabinol RS
USP $\Delta^{9}$-tetrahydrocannabinol RS
USP Thiacetarsamide RS
USP Tilmicosin RS
USP Tinidazole Related Compound B RS
USP Trenbolone RS
USP Trenbolone Acetate RS
USP Powdered Valerian RS
USP Vasopressin RS

## USP 27 MONOGRAPHS

## Gemfibrozil

## Change to read:

Related compounds-
Mobile phase - Add 10 mL of glacial acetic acid to 750 mL of methanol in a $1000-\mathrm{mL}$ volumetric flask, dilute with water to volume, mix, and pass through a membrane filter.
System suitability solution-Dissolve accurately weighed quantities of USP Gemfibrozil RS, USP Gemfibrozil Related Compound A RS, and 2,5-dimethylphenol in Mobile phase to obtain a solution having known concentrations of about 0.2 mg per mL , 0.05 mg per mL , and 0.05 mg per mL , respectively.

Standard solution-Transfer 10 mg each of USP Gemfibrozil RS and USP Gemfibrozil Related Compound A RS, both accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with methanol to volume, and mix. Transfer 5.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.
Test solution-Transfer about 100 mg of Gemfibrozil, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $276-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L 1 . The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.35 for 2,5-dimethylphenol, 1.0 for gemfibrozil, and 2.1 for gemfibrozil related compound A; and the relative standard deviation for replicate injection is not more than $3.0 \%$.
Procedure-Separately inject equal volumes (about $100 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms for at least three times the retention time of gemfibrozil, and measure the areas for the major peaks. Calculate the percentage of gemfibrozil related compound A in the portion of Gemfibrozil taken by the formula:

$$
\bullet 1000(C / W)\left(r_{U} / r_{S}\right), \bullet 1
$$

in which $C$ is the concentration, in mg per mL , of USP Gemfibrozil Related Compound A RS in the Standard solution; ${ }^{\bullet} W$ is the weight, in mg , of Gemfibrozil taken to prepare the Test solution; 1 and $r_{U}$ and $r_{S}$ are the peak areas for gemfibrozil related compound A obtained from the Test solution and the Standard solution, respectively: not more than $0.1 \%$ of gemfibrozil related compound A is found. Calculate the percentage of any other impurity in the portion of Gemfibrozil taken by the formula:

$$
\bullet 1000\left(C_{G} / W\right)\left(r_{i} / r_{G}\right), \bullet \bullet
$$

in which ${ }^{\bullet} C_{G}$ is the concentration, in mg per mL , of USP Gemfibrozil RS in the Standard solution; $r_{i}$ is the peak area of each individual impurity obtained from the Test solution; $r_{G}$ is the gemfibrozil peak area obtained from the Standard solution; and $W$ is as defined above: 1 not more than $0.1 \%$ of any other impurity is found; and not more than $0.5 \%$ of total impurities is found.

## Loperamide Hydrochloride Oral Solution

## Change to read:

$\mathbf{p H}\langle 791\rangle$ : between 2.7 and ${ }^{\mathbf{6}} 6.5 . \bullet 1$

## Lovastatin

## Change to read:

## Limit of lovastatin related compound A-

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and 0.01 M phosphoric acid (13:7). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
System suitability solution-Dissolve accurately weighed quantities of USP Lovastatin RS and USP Lovastatin Related Compound A RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, to obtain a solution containing $2.0 \mu \mathrm{~g}$ of each per mL.

Standard solution-Dissolve an accurately weighed quantity of USP Lovastatin RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about $2.0 \mu \mathrm{~g}$ per mL .
Test solution-Transfer about 25 mg of Lovastatin, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with acetonitrile to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $200-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The column temperature is maintained at $40^{\circ}$. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.0 for lovastatin and 1.3 for lovastatin related compound A ; and the resolution, $R$, between lovastatin and lovastatin related compound A is not less than 6.0. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $5.0 \%$.
Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of lovastatin related compound A in the portion of Lovastatin taken by the formula:

$$
2.5 F(C / W)\left(r_{U} / r_{S}\right)
$$

in which $F$ is the response factor for lovastatin related compound A and is equal to $1.6 ; C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Lovastatin RS in the Standard solution; $W$ is the weight, in mg , of Lovastatin in the Test solution; $r_{U}$ is the peak response for lovastatin related compound A obtained from the Test solution; and $r_{S}$ is the peak response for lovastatin obtained from the Standard solution: not more than ${ }^{\bullet} 0.5 \%_{\bullet}$ of lovastatin related compound A is found.

## Quinidine Gluconate Extended-Release Tablets

## Change to read:

Drug release $\langle 724\rangle$ -
TEST 1-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 1.

Medium: $\mathrm{pH} 5.4,0.1 \mathrm{M}$ acetate buffer prepared as follows. Add 6.9 g of anhydrous sodium acetate and 0.525 mL of glacial acetic acid to 1 L of water, and mix. Adjust with 0.1 N hydrochloric acid or 0.1 N sodium hydroxide to a pH of $5.4 ; 900 \mathrm{~mL}$.

Apparatus 2: 75 rpm .
Times: 1, 2, 4, and 8 hours.
Procedure-Determine the amount of $\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{O}_{2} \cdot \mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{7}$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 235 nm , using filtered aliquots of the solution under test, diluted with Medium if necessary, in comparison with a Standard solution having a known concentration of USP Quinidine Gluconate RS in the same Medium.

Tolerances-The percentages of the labeled amount of quinidine gluconate dissolved at the times specified conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $30 \%$ and $50 \%$ |
| 2 | between $45 \%$ and $65 \%$ |
| 4 | between $60 \%$ and $85 \%$ |
| 8 | not less than $85 \%$ |

TEST 4-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 4.

Medium: 0.1 N hydrochloric acid; 600 mL .
Apparatus 2: 75 rpm .
Times and Procedure - Proceed as directed for Test 1.
Tolerances-The percentages of the labeled amount of quinidine gluconate dissolved at the times specified conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $30 \%$ and $45 \%$ |
| 2 | between $45 \%$ and $60 \%$ |
| 4 | between $60 \%$ and $80 \%$ |
| 8 | not less than $85 \%$ |

${ }^{-}$TEST 5-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 5.

Medium, Apparatus, and Procedure-Proceed as directed for Test 1, using 8-mesh sinker baskets. ${ }^{*}$

Times: 1, 2, and 4 hours.
Tolerances-The percentages of the labeled amount of quinidine gluconate dissolved at the times specified conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $20 \%$ and $50 \%$ |
| 2 | between $40 \%$ and $70 \%$ |
| 4 | not less than $75 \%$ |

USP Homatropine
Hydrobromide RS- Do not dry. $\bullet 1$ Keep container tightly closed. Protect from light.

## Change to read:

USP Lamivudine RS-Do not dry. ${ }^{\bullet}$ Keep container tightly closed. Protect from light. Store in a freezer. $\bullet 1$

# General Tests and Assays 

## General Requirements for Tests and Assays

## 〈11〉 USP REFERENCE STANDARDS

## Change to read:

USP Chlorhexidine RS_-Keep container tightly closed. Protect from light. Store in a refrigerator. $\bullet 1$

## Change to read:

USP Chlorhexidine Acetate RS-- ${ }^{\bullet}$ Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. Store in a refrigerator. $\bullet 1$

## Change to read:

USP Clonazepam Related Compound C RS [2-bromo-2'-(2-chlorobenzoyl)-4'-nitroacetanilide]-Do not dry © Keep container tightly closed. Protect from light. Store in a refrigerator. $\bullet 1$

## Change to read:

USP Crospovidone RS-Dry portion in vacuum at $105^{\circ}$ for 1 hour before using. Keep container tightly closed. Store in a desiccator once removed from hermetic bag. ${ }^{\bullet}$ This material is hygroscopic.. 1

## Change to read:

USP Ganciclovir Related Compound A RS [(RS)-2-Amino-9-(2,3-dihydroxy-propoxymethyl)-1,9-dihydro-purin-6-one]- ${ }^{\circ}$ Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator. $\bullet 1$

## Change to read:

USP Glucosamine Hydrochloride RS-- Do not dry.•॰1 Keep container tightly closed. Protect from light.

## Change to read:

USP Haloperidol Related Compound A RS [4,4'-bis[4-p-chlor-ophenyl)-4-hydroxypiperidino]butyrophenone] $\left(\mathrm{C}_{32} \mathrm{H}_{36} \mathrm{Cl}_{2} \mathrm{~N}_{2} \mathrm{O}_{3} \diamond\right.$ 567.56 )- Do not dry. Keep container tightly closed. Protect from light. 1

## Change to read:

[^5]
## Add the following:

${ }^{\bullet}$ USP Levodopa Related Compound B RS [3-methoxythyrosine] $\left(\mathrm{C}_{10} \mathrm{H}_{13} \mathrm{NO}_{4} \triangleleft 211.22\right)$-Do not dry. Keep container tightly closed. Protect from light. Store in a cool, dry place. $\bullet 1$

## Change to read:

USP 3-Methoxytyrosine RS- © (NAME ChANGE) See USP Levodopa Related Compound B RS. $\bullet 1$

## Change to read:

USP Metoprolol Related Compound A RS [( $\pm$ )1-ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol] $\left(\mathrm{C}_{14} \mathrm{H}_{23} \mathrm{NO}_{3} \diamond\right.$ 253.34)-Do not dry. Keep container tightly closed. Protect from light. ${ }^{\circ}$ Store in a freezer. $\bullet 1$

## Change to read:

USP Niacin RS- - Do not dry.e1 Keep container tightly closed.

## Change to read:

USP Oxprenolol Hydrochloride RS-- Do not dry. Keep container tightly closed. Protect from light. $\bullet 1$

## Change to read:

USP Penicillin G Procaine RS- ${ }^{\circ}$ Do not dry. $\bullet$ This is the monohydrate form of Penicillin G Procaine. Keep container tightly clos${ }^{\mathrm{e}} \mathrm{C}$. ${ }^{\circ}$ Store in a refrigerator. $\bullet$

## Change to read:

USP Phenylephrine Hydrochloride RS-- Do not dry. $\bullet 1$ Keep container tightly closed. Protect from light.

## Change to read:

USP Propafenone Hydrochloride RS- ${ }^{\bullet}$ Do not dry. Keep container tightly closed. Protect from light. $\bullet 1$

Change to read:
USP Ribavirin RS- ${ }^{\bullet}$ Do not dry.•1 Keep container tightly closed.

## Change to read:

USP Scopoletin RS-Do not dry. ${ }^{\bullet}$ Keep container tightly closed. Store in a refrigerator. Protect from light.e

## Add the following:

${ }^{\circ}$ USP Tiamulin Related Compound A RS [tosyl pleuromuti-lin]-Do not dry. Keep container tightly closed. Protect from light. 1

Change to read:
USP Tosyl Pleuromutilin RS-- (NAME CHANGE) See USP Tiamulin Related Compound A RS. $\bullet 1$

## ERRATA

Following is a list of errata and corrections to $U S P 27-N F 22$. The page number indicates where the item is found in USP 27-NF 22. If necessary, this list will be updated with every issue of $P F$. This information will also be available as a cumulative table in the next available Supplement and will appear in its corrected form in the next annual edition of $U S P-N F$. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff are available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

| Page | Title | Section | Description |
| :---: | :---: | :---: | :---: |
| 454 | Ciprofloxacin | Sulfate | Lines 4 and 5: Change "a concentration of 18.1 mg per mL, , to: a concentration of $18.1 \mu \mathrm{~g}$ per mL |
| 1286 | Narasin Granular | Assay | Lines 24-27 under Procedure: Change " $(1.402 D+$ $0.0111 I)(D+I)$, in which $D$ and $I$ are the specified percentages of narasin $D$ and narasin $D+I$ in USP Narasin RS," to: $(1.402 D+0.0111 I) /(D+I)$, in which $D$ and $I$ are the specified percentages of narasin D and narasin I in USP Narasin RS, |
| 1516 | Potassium Chloride Extended-Release Tablets | Assay | Line 5 of Assay preparation 2: following "using a magnetic bar" reinsert official text as follows: , for 90 minutes. Dilute with a mixture of acetonitrile and water (1:1) to volume. Allow to stand for 90 minutes. Pass through a filter having a $0.2-\mu \mathrm{m}$ porosity. Transfer an accurately measured volume of the filtrate, quantitatively dilute with water to obtain a solution having a concentration of about 0.06 mg per mL , and mix. [NOTE-Retain a portion of the filtrate for use in the test for Identification.] Transfer 5.0 mL of the resulting solution to a $100-\mathrm{mL}$ volumetric flask, add 2.0 mL of sodium chloride solution (1 in 5) and 1.0 mL of hydrochloric acid, dilute with water to volume, and mix. |
| 1716 | Sotalol Hydrochloride | Limit of methanol, isopropyl alcohol, and acetone | Line 3 under Chromatographic system: Change " 1.8 $\mathrm{mm} \times 1.8-\mathrm{m}$ glass column" to: $2.0-\mathrm{mm} \times 1.8-\mathrm{m}$ glass column |
| 1842 | Tiamulin Fumarate | Chromatographic purity | Line 8 under Procedure: Change "bisdimethylderivative" to: bisdimethylthioderivative |
| 2111 | 〈11〉 USP Reference Standards | USP Isradipine Related Compound A RS | Change "isopropyl methyl 4-(4-benzofurazanyl)-2,6-di-methyl-3,5-pyridinecarboxylate" to: isopropyl methyl 4-(4-benzofurazanyl)-2,6-dimethyl-3,5-pyridinedicarboxylate |
| 2662 | Reagent Specifications | Methyl Carbamate | Reagent mistakenly omitted. Reinstate as: <br> Methyl Carbamate, $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{NO}_{2}-75.07$-White crystals. Freely soluble in water. <br> Melting range $\langle 741\rangle$ : between $54^{\circ}$ and $56^{\circ}$. |
| 2747 | Reference Tables | Description and Solubility | Line 2 under Cephapirin Benzathine: Change "freely soluble in alcohol;" to: insoluble in alcohol; |
| 2799 | Alcoholmetric Table | Column 8, line for 26\% | Change the Specific gravity in air " 0.9653 " to: 0.9635 |

## IN-PROCESS REVISION

This section contains proposals for adoption as official $U S P$ or $N F$ standards (either proposed new standards or proposed revisions of current $U S P$ or $N F$ standards). These may be any of the following: (1) items that previously appeared under Pharmacopeial Previews and are now formally proposed as revisions; (2) proposed revisions placed directly under In-Process Revision; or (3) modifications of revisions previously proposed under In-Process Revision. Readers should review material in this section and provide comments to the staff liaison (use the Staff Directory to find the contact information). Information on how to comment is found in the Policies and Announcements section. It is important to send comments promptly so that the Committee members can consider readers' input as they are deciding whether to advance standards to official status.

Briefings Each Proposal is preceded by a Briefing in the following format:

## BRIEFING

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being proposed, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see How to Use $P F$ ), the name of the scientific staff liaison who handled the particular issue, and the USP tracking correspondence number, as shown in the example below:
(PA5: K. Russo) RTS-55678-1

Symbols Proposed revisions are shown with language proposed for deletion or replacement crossed off. New text (if any) follows, and is enclosed in symbols and set off from the current official text by a paragraph break and by larger type, thus:

- new text.
if slated for an Interim Revision Announcement to USP 27-NF 22 (IRA), thus:
$\Delta_{\text {new text }}{ }_{\text {USP28 }}$
if slated for $U S P 28-N F 23$, and thus:
-new text.
if slated for a Supplement to $U S P-N F$. The same symbols not set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as ${ }^{\bullet}$ 。 or $\boldsymbol{\bullet}^{\boldsymbol{n}}$ or ${ }^{\boldsymbol{\Delta}}$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular IRA or Supplement or indicates the USP or NF as the publication where the revision will appear if approved. For example, $\bullet 2$ indicates that the revision is proposed for the Second Interim Revision Announcement, and $\mathbf{■}^{2 S}$ (USP 27) indicates that the proposed revision is slated for the Second Supplement to USP 27, and $\Delta_{\triangle S P 28}$ and ${ }_{\triangle N F 23}$ indicate that the revisions are proposed for $U S P 28$ and $N F 23$, respectively.

Official Title Changes Where the specification "Monograph title change" is found, it indicates that the official title stated after that specification will be substituted for the former title in the appropriate places throughout that monograph once this revision becomes official.
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# MONOGRAPHS (USP) 

## Briefing

Acetaminophen Oral Solution, USP 27 page 17 and page 2494 of $P F 27$ (3) [May-June 2001]; Acetaminophen Oral Suspension, USP 27 page 18 and page 2494 of $P F$ 27(3) [May-June 2001]; Oral Powder Containing at Least Three of the FollowingAcetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine, USP 27 page 28 and page 2496 of $P F$ 27(3) [May-June 2001]; Oral Solution Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine, USP 27 page 30 and page 2496 of $P F$ 27(3) [May-June 2001]; Acetaminophen and Codeine Phosphate Oral Solution, USP 27 page 34 and page 2497 of $P F$ 27(3) [May-June 2001]; Acetaminophen and Codeine Phosphate Oral Suspension, USP 27 page 35 and page 2497 of $P F 27$ (3) [May-June 2001]; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution, USP 27 page 36 and page 2499 of PF 27(3) [May-June 2001]; Brompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution, USP 27 page 272; Brompheniramine Maleate and Pseudoephedrine Sulfate Syrup, USP 27 page 273; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Oral Solution, USP 27 page 432; Dexamethasone Oral Solution, USP 27 page 560; Dexbrompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution, USP 27 page 567; Dexbromethorphan Hydrobromide Oral Solution, USP 27 page 581; Dextromethorphan Hydrobromide Syrup, USP 27 page 581; Guaifenesin Oral Solution, $U S P 27$ page 888; Guaifenesin Syrup, $U S P 27$ page 888; Guaifenesin and Codeine Phosphate Oral Solution, USP 27page 889; Guaifenesin and Codeine Phosphate Syrup, USP 27 page 890; Ibuprofen Oral Suspension, USP 27 page 954; Indomethacin Oral Suspension, USP 27 page 978; Meperidine Hydrochloride Oral Solution, USP 27 page 1161; Meperidine Hydrochloride Syrup, USP 27 page 1161; Methadone Hydrochloride Oral Solution, USP 27 page 1186; Naproxen Oral Suspension, USP 27 page 1283; Oxycodone Hydrochloride Oral Solution, USP 27 page 1376; Phenylpropanolamine Hydrochloride Oral Solution, USP 27 page 1477; Prednisone Oral Solution, USP 27 page 1545; Propoxyphene Napsylate Oral Suspension, $U S P 27$ page 1583; Pseudoephedrine Hydrochloride Oral Solution, USP 27 page 1599; Pseudoephedrine Hydrochloride Syrup, USP 27 page 1599; Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution, USP 27 page 1601 . It is proposed to improve the standards in monographs for a number of Oral Solutions, Syrups, and Oral Suspensions, as well as powders for Oral Solution and for Oral Suspension. It is proposed to add requirements for Uniformity of dosage units $<905>$ to apply to single-unit containers, and Deliverable volume $<698>$ to apply to multiple-unit containers.
(PA2: C. Anthony) RTS-40618-1

## Change to read:

Packaging and storage-Preserve in tight containers,
$\square$ and store at controlled room temperature. $\boldsymbol{m}_{1 S}$ (USP27)

## Add the following:

${ }^{\boldsymbol{\Delta}}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. _USP 28

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\quad$ USP 28

## Briefing

Acetaminophen Oral Suspension, USP 27 page 18 and page 2494 of $P F$ 27(3) [May-June 2003]-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40618-2

## Change to read:

Packaging and storage-Preserve in tight containers,
■and store at controlled room temperature.■1S (USP27)

## Add the following:

${ }^{\boldsymbol{\Delta}}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\Delta U S P 28$

## Add the following:

${ }^{\text {s }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements._USP28

## BRIEFING

Acetaminophen and Aspirin Tablets, USP 27 page 19 and page 2495 of $P F$ 27(3) [May-June 2001]. USP Expert Committee on Biopharmaceutics has decided not to accept any new proposal for the test for Dissolution test employing pooled sampling. The Committee felt that the use of pooled sampling techniques prevents interpretation of intertablet variability. As a result of this decision, the instructions for pooled samples will be removed from the USP general chapter Dissolution $\langle 711\rangle$, and the instructions for the use of previously approved pooled sampling will be incorporated into each of the current USP monographs that uses the pooled sampling technique.

The monographs affected by this decision are the following: Acetaminophen and Aspirin Tablets
Acetaminophen and Codeine Phosphate Capsules
Acetaminophen and Diphenhydramine Citrate Tablets
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets
Acetaminophen and Pseudoephedrine Hydrochloride Tablets
Tablets containing at least three of the following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine
Capsules containing at least three of the following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine
Tablets containing at least three of the following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine
Acetohydroxamic Acid Tablets
Albuterol Tablets
Alprazolam Tablets
Amantadine Hydrochloride Capsules
Aminosalicylate Sodium Tablets
Amphetamine Sulfate Tablets
Ampicillin Capsules
Ampicillin Tablets
Ascorbic Acid Tablets
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules
Baclofen Tablets
Betamethasone Tablets
Butalbital, Acetominophen, and Caffeine Tablets
Calcium Lactate Tablets
Calcium Pantothenate Tablets
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules
Colchicine Tablets
Cyclizine Hydrochloride Tablets
Dextroamphetamine Sulfate Capsules
Dextroamphetamine Sulfate Tablets
Diethylcarbamazine Citrate Tablets
Diphenhydramine Hydrochloride Capsules
Diphenhydramine and Pseudoephedrine Capsules
Dyphylline and Guaifenesin Tablets
Ethosuximide Capsules
Glycopyrrolate Tablets
Guaifenesin Capsules
Guaifenesin Tablets
Hydrocodone Bitartrate and Acetaminophen Tablets
Isosorbide Dinitrate Sublingual Tablets
Kanamycin Sulfate Capsules
Lisinopril Tablets
Loperamide Hydrochloride Tablets
Meclizine Hydrochloride Tablets
Meprobamate Tablets
Methenamine Tablets
Methocarbamol Tablets
Methylphenidate Hydrochloride Tablets
Nadolol and Bendroflumethiazide Tablets
Neostigmine Bromide Tablets

Niacinamide Tablets
Oxycodone and Acetaminophen Capsules
Oxycodone and Acetaminophen Tablets
Oxycodone and Aspirin Tablets
Penicillamine Capsules
Phentermine Hydrochloride Capsules
Phentermine Hydrochloride Tablets
Phenylpropanolamine Hydrochloride Capsules
Phenylpropanolamine Hydrochloride Tablets
Pimozide Tablets
Pindolol Tablets
Piperazine Citrate Tablets
Procyclidine Hydrochloride Tablets
Propantheline Bromide Tablets
Propoxyphene Hydrochloride and Acetaminophen Tablets
Pseudoephedrine Hydrochloride Tablets
Pyridoxine Hydrochloride Tablets
Pyrilamine Maleate Tablets
Terbutaline Sulfate Tablets
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets
Thiamine Hydrochloride Tablets
Timolol Maleate Tablets
Triprolodine and Pseudoephedrine Hydrochlorides Tablets
(BPC: M. Marques) RTS-40306-1

## Change to read:

Packaging and storage-Preserve in tight containers,
■and store at controlled room temperature.■1S (USP27)
Change to read:
Dissolution Proedure for a Pooled sample
$\Delta$
〈711 ${ }^{\text {USP28 }}$
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Mobile phase-Prepare as directed in the Assay.
Solvent mixture-Prepare as directed in the Assay.
Internal standard solution-Prepare a solution of benzoic acid in methanol having a concentration of about 1 mg per mL .

Standard preparation I-Dissolve an accurately weighed quantity of USP Salicylic Acid RS in the Solvent mixture to obtain a solution having a known concentration of about $70 \mu \mathrm{~g}$ per mL . Combine 4.0 mL of this solution and 1.0 mL of the Internal standard solution, and mix.

Standard preparation II-Dissolve accurately weighed quantities of USP Acetaminophen RS and USP Aspirin RS in the Solvent mixture to obtain a solution having known concentrations of about $360 \mu \mathrm{~g}$ of acetaminophen and about $360 \mu \mathrm{~g}$ of aspirin per mL . Combine 4.0 mL of this solution and 1.0 mL of the Internal standard solution, and mix.

Test preparation-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled
sample as the test solution. $\mathbf{\triangle U S P 2 8}$
Combine 4.0 mL of a-filtered pertion of the selution under test
$\boldsymbol{\Delta}_{\text {the pooled sample }}^{\mathbf{\Delta} U S P 28}{ }^{\text {a }}$
and 1.0 mL of the Internal standard solution, and mix.
Chromatographic system-Proceed as directed in the Assay.
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the two Standard preparations and the Test preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.3 for acetaminophen, 0.4 for salicylic acid, 0.6 for aspirin, and 1.0 for benzoic acid. Determine the amount of acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$ dissolved by the formula:

$$
90(C / W)\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Acetaminophen RS in Standard preparation II; $R_{U}$ and $R_{S}$ are the relative peak response ratios obtained from the Test preparation and Standard preparation II, respectively; and $W$ is the labeled amount, in mg , of acetaminophen. Determine the amount of aspirin $\left(\mathrm{C}_{9} \mathrm{H}_{8} \mathrm{O}_{4}\right)$ dissolved by the formula:

$$
\left[\left[90 C_{1}\left(R_{U 1} / R_{S I}\right)\right]+\left[90 C_{2}\left(R_{U 2} / R_{S 2}\right)(1.3044)\right]\right] / W
$$

in which $C_{1}$ and $C_{2}$ are the concentrations, in $\mu \mathrm{g}$ per mL, of USP Aspirin RS in Standard preparation II and USP Salicylic Acid RS in Standard preparation $I$, respectively; $R_{U I}$ and $R_{S I}$ are the relative peak response ratios for the aspirin peak and the internal standard peak obtained from the Test preparation and Standard preparation $I I$, respectively; $R_{U 2}$ and $R_{S 2}$ are the relative peak response ratios for the salicylic acid peak and the internal standard peak obtained from the Test preparation and Standard preparation I, respectively; and $W$ is the labeled amount, in mg , of aspirin.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ and not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{9} \mathrm{H}_{8} \mathrm{O}_{4}$ are dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

## BRIEFING

Tablets Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine, USP 27 page 25-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40306-3

## Change to read:

Dissolution Proedure for a Poded Sample-
$\langle\mathbf{A} U S P 28$
$\langle 711\rangle-$
Medium: 0.1 M hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Test solution-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled
sample. $\triangle$ USP28
Mix 9.0 mL of a filtered portion of the solution under test
$\Delta^{\circ}$ of the pooled sample ${ }_{\mathbf{\Delta U S P 2 8}}$
with 1.0 mL of $1 \%$ phosphoric acid solution.
Procedure-Determine the amounts of phenylpropanolamine hydrochloride, acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide dissolved, employing the procedures set forth in the Assay for phenylpropanolamine hydrochloride, Assay for acetaminophen, Assay for chlorpheniramine maleate, and Assay for dextromethorphan hydrobromide, respectively, making any necessary volumetric adjustments.

Tolerances-Not less than $75 \%(Q)$ of the labeled amounts of phenylpropanolamine hydrochloride $\left(\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO} \cdot \mathrm{HCl}\right)$, acetaminophen ( $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ ), chlorpheniramine maleate $\left(\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{ClN}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right)$, and dextromethorphan hydrobromide $\left(\mathrm{C}_{18} \mathrm{H}_{25} \mathrm{NO} \cdot \mathrm{HBr} \cdot \mathrm{H}_{2} \mathrm{O}\right)$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results
conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number |
| :---: | :---: | :--- |
| Stage | Tested |$\quad$| Acceptance Criteria |
| :---: |

## Briefing

Capsules Containing at Least Three of the FollowingAcetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine, USP 27 page 26 and page 2496 of $P F$ 27(3) [May-June 2001]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40315-7

## Change to read:

Packaging and storage-Preserve in tight containers,
-and store at controlled room temperature. $\quad$ IS (USP27)
Change to read:
Dissolution Procedure for a Pooled Sample
$\triangle$
$\langle 711\rangle-$
Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
${ }^{\text {4 }}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample. $\triangle$ USP28
Test preparation-Mix 9.0 mL of a filtered portion of the solu tion under test
${ }^{\boldsymbol{\Delta}}$ the pooled sample ${ }_{\Delta S P 28}$
with 1.0 mL of $1 \%$ phosphoric acid solution.
Procedure-Determine the amounts of pseudoephedrine hydrochloride or pseudoephedrine sulfate (as appropriate), acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide dissolved, employing the procedures set forth in the Assay for pseudoephedrine hydrochloride or Assay for pseudoephedrine sulfate, Assay for acetaminophen, Assay for chlorpheniramine maleate, and Assay for dextromethorphan hydrobromide, respectively, making any necessary volumetric adjustments.

Tolerances-Not less than $75 \%(Q)$ of the labeled amounts of pseudoephedrine hydrochloride $\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}\right)$ or pseudoephedrine sulfate $\left[\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}\right]$, acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$, chlorpheniramine maleate $\left(\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{ClN}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right)$, and dextromethorphan hydrobromide $\left(\mathrm{C}_{18} \mathrm{H}_{25} \mathrm{NO} \cdot \mathrm{HBr} \cdot \mathrm{H}_{2} \mathrm{O}\right)$ are dissolved in 45 minutes.
${ }^{\Delta}$ The requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

|  | Number |  |
| :---: | :---: | :--- |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less |
| than $Q+10 \%$. |  |  |

## Briefing

Oral Powder Containing at Least Three of the FollowingAcetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine, USP 27 page 28 and page 2496 of $P F$ 27(3) [May-June 2003]-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40618-3

## Change to read:

Packaging and storage-Preserve in tight containers,
■and store at controlled room temperature.■1S (USP27)

## Change to read:

Uniformity of dosage units $\langle 905\rangle$ - meets the requirements.
© FOR ORAL POWDER PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP28

## Briefing

Oral Solution Containing at Least Three of the FollowingAcetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine, USP 27 page 30 and page 2496 of PF 27(3) [May-June 2001]-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40618-4

Change to read:
Packaging and storage-Preserve in tight containers,
$\square_{\text {and }}$ store at controlled room temperature.■1S (USP27)

## Add the following:

${ }^{\boldsymbol{4}}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\quad$ USSP28

## Add the following:

${ }^{\text {s }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\triangle U S P 28$

## BRIEFING

Tablets Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine, USP 27 page 31 and page 1065 of $P F$ 28(4) [July-Aug. 2002]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40306-5

## Change to read:

Dissolution-Proedure for a Pooled Sample

- $\Delta U S P 28$

Medium: water;
-pH 5.8 phophate buffer (see Buffer Solutions in the section
Reagents, Indicators, and Solutions); (USP27)
900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Test solution-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.

Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled
sample as the Test solution._(USP28
Mix 9.0 mL of a fllered pertion Of the solution under test
$\Delta_{\text {the pooled sample }}^{\Delta U S P 28}$
with 1.0 mL of $1 \%$ phosphoric acid solution.
Procedure-Determine the amounts of pseudoephedrine hydrochloride or pseudoephedrine sulfate (as appropriate), acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide dissolved, employing the procedures set forth in the Assay for pseudoephedrine hydrochloride or Assay for pseudoephedrine sulfate, Assay for acetaminophen, Assay for chlorpheniramine maleate, and Assay for dextromethorphan hydrobromide, respectively, making any necessary volumetric adjustments.
Tolerances-Not less than $75 \%(Q)$ of the labeled amounts of pseudoephedrine hydrochloride $\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}\right)$ or pseudoephedrine sulfate $\left[\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}\right]$, acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$, chlorpheniramine maleate $\left(\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{ClN}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right)$, and dextromethorphan hydrobromide $\left(\mathrm{C}_{18} \mathrm{H}_{25} \mathrm{NO} \cdot \mathrm{HBr} \cdot \mathrm{H}_{2} \mathrm{O}\right)$ are dissolved in 45 minutes:
the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number <br> Tested |  |
| :---: | :---: | :--- |

## BRIEFING

Acetaminophen and Codeine Phosphate Capsules, USP 27 page 33 and page 601 of $P F 29(3)$ [May-June 2003]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) $\quad$ RTS-40306-6

## Delete the following:

DPharmacy Equivalent Name: Co codAPAP Capsules 1 1S (USP27)

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers,

■and store at controlled room temperature.■1S (USP27)

## Change to read:

Dissolution, Procedure for a Pooled Sample
${ }_{\langle }^{4}$ U USP28
Medium: 0.01 N hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle U S P 28$
Determine the amounts of acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$ and codeine phosphate hemihydrate $\left(\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{3} \cdot \mathrm{H}_{3} \mathrm{PO}_{4} \cdot 1 / 2 \mathrm{H}_{2} \mathrm{O}\right)$ dissolved by employing the procedure set forth in the Assay, except to use 0.01 N hydrochloric acid to prepare the Codeine phosphate standard stock solution and to make any other necessary volumetric adjustments.
Tolerances-Not less than $75 \%(Q)$ of the labeled amounts of $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ and $\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{3} \cdot \mathrm{H}_{3} \mathrm{PO}_{4} \cdot 1 / 2 \mathrm{H}_{2} \mathrm{O}$ is dissolved in 30 minutes:
the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## Briefing

Acetaminophen and Codeine Phosphate Oral Solution, USP 27 page 34 and page 601 of $P F 29(3)$ [May-June 2003]-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40618-5

## Delete the following:

-Pharmacy Equivalent Name: Co Solution!1S (USP27)

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers,
-and store at controlled room temperature. $\quad$ IS (USP27)

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle-$
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements. $\triangle$ USP28

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. ${ }_{\Delta U S P 28}$

BRIEFING
Acetaminophen and Codeine Phosphate Oral Suspension, USP 27 page 35 and page 601 of $P F$ 29(3) [May-June 2003]See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40618-6

Delete the following:
-Pharmacy Equivalent Name: Co codAPAP Oral SuspenSion!1S (USP27)

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers,
-and store at controlled room temperature. $\quad$ IS (USP27)

## Add the following:

${ }^{\boldsymbol{4}}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\Delta$ USP28

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP28

## BRIEFING

Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution, USP 27 page 36 and page 2499 of PF 27(3) [May-June 2003]-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40618-7

## Change to read:

Packaging and storage-Preserve in tight containers,
■and store at controlled room temperature. $\mathbf{1 S}$ (USP27)
Add the following:
${ }^{4}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements.__USP28

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP 28

## BriEfing

Acetaminophen and Diphenhydramine Citrate Tablets, USP 27 page 37 and page 2499 of $P F 27$ (3) [May-June 2001]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40306-7

## Change to read:

Packaging and storage-Preserve in tight containers,
■and store at controlled room temperature.mis (USP27)

## Change to read:

Dissolution Proedure for a Porled Sample
$\triangle$
$\langle 711\rangle-$
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\mathbf{\Delta}}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle U S P 28$
Determine the amount of acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$ and of diphenhydramine citrate $\left(\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7}\right)$ dissolved, employing the procedures set forth in the Assay for acetaminophen and the Assay for diphenhydramine citrate, respectively, making any necessary volumetric adjustments.

Tolerances-Not less than $75 \%(Q)$ of the labeled amounts of $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ and $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7}$ are dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the ac companying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

| Number <br> Stage |  |  |
| :---: | :---: | :---: |
| $\mathrm{S}_{1}$ | 6 | Tested |$\quad$| Average amount dissolved is not less |
| :---: |
| than $Q+10 \%$. |
| $\mathrm{S}_{2}$ |

## Briefing

Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets, USP 27 page 38 and page 2499 of $P F 27$ (3) [May-June 2001]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40306-08

## Change to read:

Packaging and storage-Preserve in tight containers,
■and store at controlled room temperature. $\quad$ 1S (USP27)

## Change to read:

Dissolution, Proedtre for a Pooled Sample

Medium: pH 5.8 phosphate buffer (see Buffer Solutions in the section Reagents, Indicators, and Solutions); 900 mL .

Apparatus 2: 50 rpm .
Time: 45 minutes.
Determine the amounts of acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$, diphenhydramine hydrochloride $\left(\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{HCl}\right)$, and pseudoephedrine hydrochloride $\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}\right)$ dissolved by employing the following method.

Buffer solution, Diluting solvent, Mobile phase, and Chromatographic system-Proceed as directed in the Assay for acetaminophen.

Standard solution-Prepare as directed for the Standard preparation in the Assay for acetaminophen.

Test solution 1 - Combine equalvolumes of the filtered selutions under test, and use the pooled sample.
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as Test solution 1.

Test solution 2-Transfer 5.0 mL of Test solution 1 to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Procedure-Using Test solution 1 and the Standard solution, and making any necessary volumetric adjustments, proceed as directed in the Assay for diphenhydramine hydrochloride and the $A s$ say for pseudoephedrine hydrochloride, and determine the amounts of diphenhydramine hydrochloride ( $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{HCl}$ ) and pseudoephedrine hydrochloride $\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}\right)$ dissolved. Using Test solution 2 and the Standard solution, and making any necessary volumetric adjustments, proceed as directed in the Assay for acetaminophen, and determine the amount of acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$ dissolved.
Tolerances-Not less than $75 \%(Q)$ of the labeled amounts of $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}, \mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{HCl}$, and $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ is dissolved in 45 minutes;
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Number |  |  |
| :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |
| S1 | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| S2 | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| S3 | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$ |

FOR TABLETS LABELED AS CHEWABLE-
Medium: pH 5.8 phosphate buffer (see Buffer Solutions in the section Reagents, Indicators, and Solutions); 900 mL .

Apparatus 2: 75 rpm .
Time: 45 minutes.
Tolerances-Not less than 75\% (Q) of the labeled amounts of $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}, \mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{HCl}$, and $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ is dissolved in 45 minutes.

## BRIEFING

Acetaminophen and Pseudoephedrine Hydrochloride Tablets, $U S P 27$ page 39 and page 2500 of $P F$ 27(3) [May-June 2001]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40306-9

## Change to read:

Packaging and storage-Preserve in tight containers,
$\boldsymbol{m}^{\text {and }}$ store at controlled room temperature. $\mathbf{m S ~}_{\text {IS }}$ (USP27)

## Change to read:

Dissolution Procdure for a Pooled sample
$\Delta$
〈 711 USP 28
Medium: pH 5.8 phosphate buffer (see Buffer Solutions in the section Reagents, Indicators, and Solutions); 900 mL .

Apparatus 2: 50 rpm .
Time: 45 minutes.
Determine the amount of acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$ and pseudoephedrine hydrochloride $\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}\right)$ dissolved by employing the following method.

Mobile phase-Proceed as directed in the Assay.
Standard solution-Prepare a solution in Dissolution Medium having known concentrations of about $L / 900 \mathrm{mg}$ of USP Pseudoephedrine Hydrochloride RS and $L J / 900 \mathrm{mg}$ of USP Acetaminophen RS per mL , in which $L$ is the labeled quantity, in mg , of pseudoephedrine hydrochloride in each Tablet; and $J$ is the ratio of the labeled quantity, in mg , of acetaminophen to the labeled quantity, in mg, of pseudoephedrine hydrochloride in each Tablet.

Test solution Use a fllered pertion of the solution under test.
${ }^{\text {® }}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled sample. $\Delta U S P 28$

Chromatographic system-Proceed as directed in the Assay, except to inject the Standard solution.
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the acetaminophen and pseudoephedrine peaks. Calculate the quantity, in mg, of acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$ and pseudoephedrine hydrochloride $\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}\right)$ dissolved by the formula:

$$
900 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of the appropriate USP Reference Standard in the Standard solution; and $r_{U}$ and $r_{S}$ are the peak responses of the corresponding analyte obtained from the Test solution and the Standard solution, respectively.
Tolerances-Not less than $75 \%$ (Q) of the labeled amounts of $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ and $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample.

Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

## Number

| Stage | Tested | Acceptance Criteria |
| :---: | :---: | :---: |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $\mathrm{Q}+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved ( $\mathrm{S}_{1}+\mathrm{S}_{2}+$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |
| ETS LABELED AS CHEWABLE- |  |  |
| Medium: pH 5.8 phosphate buffer (see Buffer Solutions in the section Reagents, Indicators, and Solutions); 900 mL . |  |  |
| Apparatus 2: 75 rpm . |  |  |
| Time: 45 minutes. |  |  |
| Standard solution, Test solution, Chromatographic system, and Procedure-Proceed as directed above. |  |  |
| Stuple. |  |  |
| $\Delta_{\triangle U S 28}$ <br> Tolerances-Not less than $75 \%(Q)$ of the labeled amounts of $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ and $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ is dissolved in 45 minutes: |  |  |
|  |  |  |
| ments are met if the quantities |  |  | ents dissolved from the pooled sample conform to the $A c$ ceptance Table for a Pooled Sample above. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified in the individual monograph, expressed as a percentage of the labeled content. $\triangle U S P 28$

## BRIEFING

Acetohydroxamic Acid Tablets, USP 27 page 44 and page 2502 of PF 27(3) [May-June 2001]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) $\quad$ RTS-40306-2

## Change to read:

Packaging and storage-Preserve in tight containers,
■and store at controlled room temperature.■1S (USP27)

## Change to read:

Dissolution Procdure for a Pooled Sample

| 4 |
| :--- |
| 〈 711 USP28 |

Medium: 0.01 N hydrochloric acid; 900 mL .
Apparatus 1: 100 rpm .
Time: 30 minutes.
Procedure-
© Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\quad$ USP28 Determine the
$\Delta_{\text {average }}{ }_{\text {USP } 28}$ amount of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{NO}_{2}$ dissolved
${ }^{\Delta}$ in the pooled sample, employing the procedure set forth in the Assay, using afiled tion of the solution under test
${ }^{\Delta}$ the pooled sample ${ }_{\Delta U S P 28}$
as the Assay preparation in comparison with a Standard solution having a known concentration of USP Acetohydroxamic Acid RS in the same Medium.
Tolerances-Not less than $85 \%(Q)$ of the labeled amount of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{NO}_{2}$ is dissolved in 30 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform
at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved ( $\mathrm{S}_{1}+\mathrm{S}_{2}+$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## BriEfing

Albuterol Tablets, USP 27 page 56-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40306-10

## Change to read:

Dissolution Predure for a Porled Sample

Medium: water; 500 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
Determine the amount of $\mathrm{C}_{13} \mathrm{H}_{21} \mathrm{NO}_{3}$ dissolved using the following method.
Mobile phase, Standard preparation, and Chromatographic sys-tem-Prepare as directed in the Assay.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. USP28 $^{\text {IS }}$
Inject a suitable volume (about $100 \mu \mathrm{~L}$ ) of apertion under test,
the pooled sample, ${ }_{\mathbf{\Delta S S P 2 8}}$
previously filtered through a $0.45-\mu \mathrm{m}$ nylon filter, into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $\mathrm{C}_{13} \mathrm{H}_{21} \mathrm{NO}_{3}$ dissolved by comparing this peak response with the major peak response similarly obtained on chromatographing the Standard preparation previously diluted, if necessary, with a mixture of water and methanol (6:4) to obtain a Standard solution having a known concentration of USP Albuterol Sulfate RS approximately corresponding to the concentration of the solution under test.
Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{21} \mathrm{NO}_{3}$ is dissolved in 30 minutes:
the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :--- |
| Stage | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> $\mathrm{S}_{2}$ |
| $\mathrm{~S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

BRIEFING
Alprazolam Tablets, USP 27 page 65 -See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40311-1

## Change to read:

Dissolution Proedure for a Pooled Sample

Stock buffer solution-Dissolve 160 g of monobasic potassium phosphate and 40 g of dibasic potassium phosphate in water, and dilute with water to obtain 2.0 liters of solution. Add, with mixing, phosphoric acid or potassium hydroxide solution (45 in 100), as necessary to adjust the solution such that, when this Stock buffer solution is diluted 1 in 10 with water, the resulting solution has a pH of $6.0 \pm 0.1$.

Buffer solution-Prepare a 1 in 10 dilution of Stock buffer solution in water to obtain a Working buffer solution having a pH of 6.0 $\pm 0.1$.

Medium: Buffer solution; 500 mL .
Apparatus 1: 100 rpm .
Time: 30 minutes.
Procedure-
Stock standard solution-Prepare a solution in methanol of USP Alprazolam RS having a known concentration of about 0.05 mg per mL.

Standard solution-Add 50 mL of Stock buffer solution and 250 mL of water to a $500-\mathrm{mL}$ volumetric flask. Add to the flask 5.0 mL of Stock standard solution for every 0.25 mg of alprazolam contained in the Tablet being assayed. Dilute with water to volume, and mix.

Mobile phase-Prepare a degassed and filtered solution of Buffer solution, acetonitrile, and tetrahydrofuran (60:35:5). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ analytical column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed under Procedure: the column efficiency is not less than 500 theoretical plates, and the relative standard deviation for replicate injections is not more than $3.0 \%$.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled
sample as the test solution. $\triangle$ USP28
Separately inject equal volumes of a fltered portion of the solution under test
$\Delta^{\Delta}$ of the pooled sample $\mathbf{\Delta U S P 2 8}$
and the Standard solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity of $\mathrm{C}_{17} \mathrm{H}_{13} \mathrm{ClN}_{4}$ dissolved based on the peak responses obtained from the solution under test and the Standard solution.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{13} \mathrm{ClN}_{4}$ is dissolved in 30 minutes:
$\Delta_{\text {the }}$ the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient of interest expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

|  | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :--- |

## Briefing

Amantadine Hydrochloride Capsules, USP 27 page 107—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40311-9

## Change to read:

Dissolution, Predtre for a Pooled sample
$\Delta$
〈711) ${ }^{\text {USP28 }}$
Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Internal standard solution-Dissolve an accurately weighed quantity of naphthalene in hexane to obtain a solution having a known concentration of about 0.054 mg per mL .

Standard solution-Dissolve an accurately weighed quantity of USP Amantadine Hydrochloride RS in water to obtain a solution having a known concentration of about 0.1 mg per mL . Pipet 15.0 mL of this solution into a $50-\mathrm{mL}$ screw-capped test tube, add 5.0 mL of 5 N sodium hydroxide and 10.0 mL of Internal standard solution, and shake for 60 minutes. Collect the hexane layer.

Test solution-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the Test solution. $\triangle$ USP28
Filter
${ }^{\Delta}$ Transfer ${ }_{\text {ASSP28 }}$
15.0 mL of the selution under test
${ }^{\Delta}$ pooled sample, ${ }_{\mathbf{\Delta U S P 2 8}}$
and place into a $50-\mathrm{mL}$ screw-capped test tube. Pipet 5.0 mL of 5 N sodium hydroxide and 10.0 mL of the Internal standard solution into the test tube, and shake for 60 minutes. Collect the hexane layer (Test solution).

Chromatographic system-Proceed as directed under the Assay. Procedure-Separately inject equal volumes (about $2.5 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution. Record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $\mathrm{C}_{10} \mathrm{H}_{17} \mathrm{~N} \cdot \mathrm{HCl}$ dissolved.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{10} \mathrm{H}_{17} \mathrm{~N} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
$\Delta_{\text {the }}$ requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample


## BRIEFING

Amifostine, USP 27 page 109 and page 1413 of $P F$ 29(5) [Sept.-Oct. 2003]. It is proposed to revise the HPLC method in the test for Related compounds and in the Assay to avoid peak distortion caused by interaction with some column packings. The methods were validated using Luna C8 (phenomenex) brand of L7 column. Typical retention times are about 4 minutes for amifostine and about 20 minutes for amifostine thiol.
(PA5: A. Wilk) RTS-40669-1

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■2s (USP27)

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Amifostine RS. USP Amifostine Thiol RS.

- USP Endotoxin RS. ■ 2 (USP27) $^{\text {- }}$


## Add the following:

-Other requirements-Where the label states that Amifostine is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Amifostine for Injection. Where the label states that Amifostine must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Amifostine for Injection. ${ }^{\text {2S }}$ (USP27)

## Change to read:

Assay-
Mobile phase-Dissolve $0.54 \frac{\mathrm{~g}}{\mathrm{~F}}$
${ }^{\Delta} 0.94 \mathrm{~g}_{\text {USSP28 }}$
of sodium + -etanesulfenate in 500 mL
${ }^{\text {© }}$ 1-hexanesulfonate in $1000 \mathrm{~mL}_{\mathbf{\Delta} U S P 28}$
of water. Adjust with phosphoric acid to a pH of 2.5 .
$\Delta 3.0$. ASPP 28
Prepare a filtered and degassed mixture of this solution and methanol (1:1).
©(72:28). $\mathbf{\Delta U S P 2 8}$
Make adjustments if necessary (seeSystem Suitability under Chromatography (621〉).

Standard preparation-Transfer about 30 mg of USP Amifostine RS, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask. Dissolve in 5 mL of water, dilute with methanol to volume, and mix. [NOTE-Inject immediately after preparation, or refrigerate until use.]

Assay preparation-Transfer about 30 mg of Amifostine, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask. Dissolve in 5 mL of water, dilute with methanol to volume, and mix. [NOTE-Inject immediately after preparation, or refrigerate until use.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing E . ${ }^{\Delta}$ L7.
The flow rate is about 1 mL per minute. Chromatograph the Standard preparation and the Assay preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more than 2 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{5} \mathrm{H}_{15} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{PS}$ in the portion of Amifostine taken by the formula:

$$
10 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Amifostine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Aminosalicylate Sodium Tablets, USP 27 page 127—See briefing under Acetaminophen and Aspirin Tablets.

$$
\text { (BPC: M. Marques) } \quad \text { RTS-40311-14 }
$$

## Change to read:

Dissolution Proedure for a Pooled sample
$\Delta$
〈711) ${ }^{\text {USP28 }}$
Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the six or twelve individuals specimens withdrawn, and use the pooled sample as the test solution.aUSP28
Determine the amount of $\mathrm{C}_{7} \mathrm{H}_{6} \mathrm{NNaO}_{3} \cdot 2 \mathrm{H}_{2} \mathrm{O}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{7} \mathrm{H}_{6} \mathrm{NNaO}_{3} \cdot 2 \mathrm{H}_{2} \mathrm{O}$ is dissolved in 45 minutes.
${ }^{\Delta}$ The requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

| Number <br> Tested |  |  |
| :---: | :---: | :---: |
| $\mathrm{S}_{1}$ | 6 | Aveceptance Criteria <br> Average amount dissolved <br> is not less than $Q+10 \%$. <br> $\mathrm{S}_{2}$ |
|  | 6 | Average amount dissolved <br> $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or <br> greater than $Q+5 \%$. <br> $\mathrm{S}_{3}$ |
|  | 12 | Average amount dissolved <br> $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\mathrm{S}_{3}\right)$ is equal to <br> or greater than $Q$. |

## Briefing

Amoxicillin and Clavulanate Potassium for Oral Suspension, USP 27 page 142 and page 605 of $P F$ 29(3) [May-June 2003]; Cefprozil for Oral Suspension, $U S P 27$ page 380; Clarithromycin for Oral Suspension, USP 27 page 463. It is proposed to improve the standards in monographs for these powders for Oral Suspension. It is proposed to add requirements for Uniformity of dosage units $\langle 905\rangle$ to apply to single-unit containers, and for Deliverable volume $\langle 698\rangle$ to apply to multiple-unit containers.
(PA7a: W. Wright) RTS-40663-1

## Delete the following:

-Phammacy Equivalent Name: Co amoxiclav for Oral Suspen sien 1 1S (USP27)

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ —FOR POWDER PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements. $\triangle U S P 28$

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$-FOR POWDER PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements._UUSP28

## Delete the following:

-Water, Method $I\langle 921\rangle \div$ not more than $7.5 \%$, where the label in dicates that after constitution as directed, the suspension contains an amount of amoxicillin that is less than 40 mg per mL ; not more than $8.5 \%$ where the label indicates that after constitution as direc ted the suspension contains an amount of amoxicillin that is equal to or mere than 40 mg per mL and is less than or equalto 50 mg per mL ; not more than $11.0 \%$ where the label indieates that after constiftution as directed the suspension contains an amount of amoxieillin that is more than 50 mg per mL and is less than or equal to 80 ms per mL ; and not more than $12.0 \%$ where the label indicates that after constitution as directed the suspension contains an amount of amoxicillin that is more than 80 mg per mL . 1 IS (USP27)

## Add the following:

-Limit of free water-Determine the total percentage, $T$, of water in the powder by the titrimetric procedure specified in Method I under Water Determination $\langle 921\rangle$. Assay a portion of the powder as directed under Assay to determine its content, $A$, in mg of amoxicillin $\left(\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{5} \mathrm{~S}\right)$ per g. Calculate the percentage of free water in the portion of Amoxicillin and Clavulanate for Oral Suspension taken by the formula:

$$
T-0.0148 A
$$

It contains not more than $2.0 \%$ of free water. ${ }^{1 S}$ (USP27)

## Change to read:

Dissolution, Procedure for a Pooled Sample
$\langle 711\rangle \frac{-}{4}$
Medium: water; 500 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Mobile phase-Dissolve 1.1 g of sodium 1-heptanesulfonate in 575 mL of water. Add 25 mL of dilute glacial acetic acid (14 in 100) and 400 mL of methanol. Adjust by the dropwise addition of glacial acetic acid to a pH of $3.3 \pm 0.1$, if necessary, filter, and degas the solution. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph replicate injections of the Standard solution, prepared as directed below, and record the peak responses as directed for Procedure: the relative standard deviation is not more than $2.0 \%$.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. USP28 Inject a volume (about $500 \mu \mathrm{~L}$ ) of the selution under test
${ }^{\Delta}$ pooled sample ${ }_{\Delta U S P 28}$
into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $\left(\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{~N}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ dissolved in comparison with a Standard solution having a known concentration of USP Dextroamphetamine Sulfate RS in the same medium and similarly chromatographed.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\left(\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{~N}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## BRIEFING

Amphetamine Sulfate Tablets, USP 27 page 144-See briefing under Acetaminophen and Aspirin Tablets.

$$
\text { (BPC: M. Marques) } \quad \text { RTS-40313-9 }
$$

## Acceptance Table for a Pooled Sample

Number

| Stage | Tested | Acceptance Criteria |
| :---: | :---: | :---: |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. <br> $\mathrm{S}_{2}$ |
| $\mathrm{~S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## BRIEFING

Ampicillin Capsules, USP 27 page 147—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40315-11

## Change to read:

Dissolution Proedure for a Pooted Sample
$\Delta$
〈711 USP28
Medium: water, 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Standard solution-Dissolve an accurately weighed quantity of USP Ampicillin RS in water to obtain a solution having a known concentration of about $L / 900 \mathrm{mg}$ per $\mathrm{mL}, L$ being the labeled amount, in mg , of ampicillin per Capsule.

## Procedure-

${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample. ${ }^{\text {USPP28 }}$
Proceed as directed for Procedure in the section Antibiotics-Hydroxylamine Assay under Automated Methods of Analysis $\langle 16\rangle$, using a fltered pertion of the solution under test
${ }^{\Delta}$ the pooled sample ${ }_{\mathbf{A} U S P 28}$
as the Assay Preparation. Calculate the quantity, in mg , of $\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{~S}$ dissolved by the formula:

$$
0.9 C P\left(A_{U} / A_{S}\right)
$$

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{~S}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient of interest, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

| Number |  |  |  |
| :---: | :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |  |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |  |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |  |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |  |
| ムUSP28 <br> O. <br> $\stackrel{9}{6}$ <br> $\frac{0}{5}$ <br> 1 |  |  |  |


#### Abstract

Ampicillin Tablets, USP 27 page 149—See briefing under Acetaminophen and Aspirin Tablets.


(BPC: M. Marques) RTS-40313-12

## Change to read:

Dissolution Proedure for a Porled Sample
${ }^{\Delta}$ (711 USP28 -1
Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Standard preparation-Dissolve an accurately weighed quantity of USP Ampicillin RS in water to obtain a solution having a known concentration of about $L / 900 \mathrm{mg}$ per $\mathrm{mL}, L$ being the labeled amount, in mg , of ampicillin per Tablet.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.

Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. ${ }^{\text {USP2 } 8}$
Proceed as directed for Procedure in the section Antibiotics-Hydroxylamine Assay under Automated Methods of Analysis $\langle 16\rangle$, using a filtered pertion of the solution under test
$\Delta_{\text {portion }}$ of the pooled sample ${ }_{\Delta U S P 28}$
as the Assay preparation. Calculate the quantity, in mg, of $\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{~S}$ dissolved by the formula:

$$
0.9 C P\left(A_{U} / A_{S}\right)
$$

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{~S}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample


## Add the following:

## ©Antithrombin III Human

## » Antithrombin III Human is a glycoprotein,

 which is the major inhibitor of thrombin and other activated clotting factors including factors IX, X, XI, and XII, and the cofactor through which heparin exerts its effect. It is obtained from human plasma of healthy donors who must, as far as can be ascertained, be free from detectable agents of infection transmissible by transfusion of blood or blood derivatives. The method of manufacturing includes steps that have been shown to remove or inactivate known agents of infection. If sub-stances are used for inactivation of viruses during production, the subsequent purification procedure must be validated to demonstrate that the concentration of these substances is reduced to an acceptable level and any residues are such as not to compromise the safety of the preparation for patients. The antithrombin III concentrate is passed through a bacteria-retentive filter, filled aseptically into its final, sterile containers, and immediately frozen. It is then freeze-dried, and the containers are closed under vacuum. No antimicrobial preservative is added at any stage of production. Antithrombin III Human complies with the requirements for Biologicals $\langle 1041\rangle$. When reconstituted in the recommended volume of diluent, the potency is not less than 25 USP Antithrombin III Units per mL. [note-One USP Antithrombin III Unit is the amount of antithrombin III that forms a complex with one unit of thrombin at $25^{\circ}$ in the presence of heparin at a pH of 8.4.]

Packaging and storage-Use a Type I glass container with an appropriate stopper and seal. Store protected from light between $2^{\circ}$ and $8^{\circ}$, excursions permitted at room temperature.

Labeling-The labeling should state the content of antithrombin III expressed in USP Antithrombin III Units. The diluent and the volume to be used to reconstitute the preparation are indicated.

USP Reference standards $\langle 11\rangle$ —USP Albumin Human $R S$. USP Antithrombin III Human RS. USP Heparin Sodium RS.

Identification-It meets the requirements of the Assay.
$\mathbf{p H}\langle 791\rangle$ —Reconstitute with the diluent according to the manufacturer's instruction: between 6.0 and 7.5 .

Osmolality $\langle 785\rangle$ —Reconstitute with the diluent according to the manufacturer's instruction: not less than 240 mosmol per kg for the solution.

## Heparin content-

pH 8.4 Buffer—Dissolve tris(hydroxymethyl)aminomethane, edetic acid, and sodium chloride in water containing $0.1 \%$ polyethylene glycol 6000 to obtain a solution having concentrations of $0.050 \mathrm{M}, 0.0075 \mathrm{M}$, and 0.175 M, respectively. Adjust with hydrochloric acid or sodium hydroxide solution to a pH of 8.4.

Chromogenic substrate solution-Prepare a solution of chromogenic substrate for amidolytic test for factor $\mathrm{X}_{\mathrm{a}}$ in water to obtain a solution of concentration of 2.5 mM .

Factor $X_{a}$ solution-Dissolve an accurately weighed quantity of Factor $\mathrm{X}_{\mathrm{a}}$ in $p H$ 8.4 Buffer to obtain a solution containing about 20 nanokatalytic units (nkats).

Stopping solution-Prepare a $20 \%(\mathrm{v} / \mathrm{v})$ solution of acetic acid in water.

Standard solution-Dissolve an accurately weighed quantity of USP Antithrombin III Human RS in pH 8.4 Buffer to obtain a solution containing 1.0 USP Antithrombin III Unit.

Test solution-Dissolve an accurately weighed quantity of Antithrombin III Human in $p H$ 8.4 Buffer to obtain a solution containing 1.0 USP Antithrombin III Unit.

Procedure-Pipet $250 \mu \mathrm{~L}$ each of pH 8.4 Buffer, the Standard solution, and the Test solution to suitable tubes placed in a water bath set at $37^{\circ}$. Add $250 \mu \mathrm{~L}$ of Factor $X_{a}$ solution, pre-warmed at $37^{\circ}$, to each tube, mix, and incubate for 2 minutes. Add $250 \mu \mathrm{~L}$ of Chromogenic substrate solution pre-warmed at $37^{\circ}$ to each tube, mix, and incubate for 120
seconds. Stop the reaction by adding $250 \mu \mathrm{~L}$ Stopping solution. Record the absorbance at 405 nm using pH 8.4 Buffer as the blank.

Calculation-Calculate the USP Heparin Unit per USP Antithrombin III Unit using the formula:

$$
P_{R}\left(A_{F}-A_{T}\right) /\left(A_{F}-A_{R}\right),
$$

in which, $A_{F}, A_{R}$, and $A_{T}$ are the absorbance values from pH 8.4 Buffer, the Standard solution, and the Test solution, respectively; and $P_{R}$ is the heparin content of USP Antithrombin III Human RS in USP Heparin Unit per USP Antithrombin III Unit: not more than 0.1 USP Heparin Unit per USP Antithrombin III Unit.

Sterility $\langle 71\rangle$-It meets the requirements when tested as directed for Direct Inoculation of the Culture Medium under Test for Sterility of the Product to be Examined.

Water, Method I $\langle 921\rangle$ : not more than $3.0 \%$.
Pyrogen $\langle 151\rangle$-Inject per kg of the rabbit's weight 50 USP Antithrombin III Units, calculated from the activity stated on the label. It meets the requirements.

General safety-It meets the requirements for biologics as set forth for Safety Tests-Biologicals under Biological Reactivity Tests, In Vivo $\langle 88\rangle$.

## Molecular weight distribution-

Mobile phase-Prepare a suitable degassed and filtered solution containing 0.1 M sodium phosphate, 0.15 M sodium chloride, and $0.05 \%$ sodium azide, having a pH of 6.5 .
$V_{o}$ - Marker solution-Prepare a solution of thyroglobulin in Mobile phase containing 4 to 5 mg per mL .

Test solution-Prepare a solution of Antithrombin III Human containing 8 to 10 mg per mL .

System suitability solution-Dilute USP Albumin Human RS, if necessary, with water to obtain a solution containing approximately $5 \%$.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $7.5 \times 75-\mathrm{mm}$ guard column, a $7.5 \times 300-\mathrm{mm}$ analytical column, both containing packing L\#\# (see Chromatography $\langle 621\rangle$ ), maintained at ambient temperature, and a $280-\mathrm{nm}$ UV detector. The flow rate is 0.5 mL per minute maintained constant to $\pm 1 \%$; the tailing factor is between 0.5 and 2.5 ; and the column efficiency is greater than 1500 theoretical plates.

Procedure-Inject $10 \mu \mathrm{~L}$ System suitability solution, and record the chromatogram. Inject $10 \mu \mathrm{~L}$ each of $V_{o}$ - Marker solution and the Test solution. Note the retention times of the major peak in the $V_{o}$ - Marker solution chromatogram. The relative peak area of the high molecular weight peak eluting at about the same retention time as the major peak in the $V_{o}$ - Marker solution chromatogram, or earlier, is not more than $13 \%$.

## Total protein content-

Trichloroacetic acid solution-Prepare a solution of trichloroacetic acid in water containing 100 g trichloroacetic acid per 100 mL of the solution.

Test solution-Dissolve an accurately weighed quantity of Antithrombin III Human in 0.15 M sodium chloride solution to obtain a solution containing about 7.5 mg per mL .

Blank: 0.15 M solution of sodium chloride.
Procedure-To each of 2.0 mL of the Test solution and the Blank in suitable centrifuge tubes add 1.5 mL of Trichloroacetic acid solution. Mix, allow to stand for at least 10 min utes, centrifuge for 5 minutes, and decant the supernatant. Resuspend the precipitates in 1.5 mL of Trichloroacetic acid solution, centrifuge for 5 minutes, decant the supernatant, and hold the tubes inverted on a filter paper to drain. Quantitatively transfer the residues with a minimum quantity of water to a micro-Kjeldahl flask, and determine the
nitrogen content using Method II (see Nitrogen Determination $\langle 461\rangle$ ). Multiply the result, corrected for the Blank, by 6.25 to calculate the quantity of protein.

Assay-
pH 8.4 Buffer-Dissolve tris(hydroxymethyl)aminomethane, edetic acid, and sodium chloride in water containing $0.1 \%$ polyethylene glycol 6000 to obtain a solution having concentrations of $0.050 \mathrm{M}, 0.0075 \mathrm{M}$, and 0.175 M, respectively. Adjust with hydrochloric acid or sodium hydroxide solution to a pH of 8.4.

Albumin-pH 8.4 buffer—Prepare a $0.05 \%(\mathrm{w} / \mathrm{v})$ solution of Albumin Human in pH 8.4 Buffer.
Polybrene buffer-Prepare a 10 mg per mL solution of polybrene in Albumin-pH 8.4 buffer.

Heparin buffer-Dissolve an accurately weighed amount of USP Heparin Sodium RS in Albumin-pH 8.4 Buffer to obtain a solution containing 15 USP Heparin Unit per mL.

Thrombin bovine solution-Reconstitute thrombin bovine, and dilute with Albumin-pH 8.4 buffer to obtain a solution having a concentration of 1000 Thrombin Units per mL.

Chromogenic substrate solution for factor $I I_{a}$ - Prepare a solution of chromogenic substrate for amidolytic test (see Reagents Specifications in the section Reagents, Indicators, and Solutions) for factor $\mathrm{II}_{\mathrm{a}}$ in water to obtain a solution having a concentration of about 5.0 mM , and dilute the solution further with Polybrene Buffer to 1.0 mM .

Stopping solution-Prepare a $20 \%(\mathrm{v} / \mathrm{v})$ solution of acetic acid in water.
Standard preparation A-Dissolve an accurately weighed quantity of USP Antithrombin III Human RS in Heparin buffer to obtain a solution containing 1.0 USP Antithrombin III Unit.

Standard preparations B, C, D, and E-Dilute Standard preparation $A$ with Heparin buffer $60-, 120-, 180$-, and 300fold.

Test preparation $A$-Dissolve an accurately weighed quantity of Antithrombin III Human in Heparin buffer to obtain a solution having about the same concentration as Standard preparation $A$.

Test preparations B, C, $D$, and $E$-Dilute Test preparation A 60-, 120-, 180-, and 300-fold with Heparin buffer.

Procedure—Pipet $400 \mu \mathrm{~L}$ each of Standard preparations $B, C, D$, and $E$, and Test preparation $B, C, D$, and $E$ to suitable tubes placed in a water bath set at $37^{\circ}$. Add $200 \mu \mathrm{~L}$ of Thrombin bovine solution, prewarmed at $37^{\circ}$, to each tube, mix, and incubate for 1 minute. Add $200 \mu \mathrm{~L}$ of Chromogenic substrate solution for factor $I I_{a}$ prewarmed at $37^{\circ}$ to each tube, mix, and incubate for 60 seconds. Stop the reaction by adding $200 \mu \mathrm{~L}$ Stopping solution. To prepare a blank, add the reagents in reverse order, starting with 200 $\mu \mathrm{L}$ Stopping solution, followed by the addition of $200 \mu \mathrm{~L}$ of Chromogenic substrate solution for factor $I I_{a}$, then adding $200 \mu \mathrm{~L}$ of Thrombin bovine solution, and ending with $400 \mu \mathrm{~L}$ Heparin buffer. Record the absorbance at 405 nm against the blank.

Calculations-For Standard preparations and Test preparations calculate the regression of the absorbance against log concentrations, and calculate the activity of Antithrombin III Human in USP Antithrombin III Units using a suitable statistical method for parallel-line assays. The four independent relative activity estimates are then combined to obtain the final mean and the confidence limits are calculated. The estimated potency is not less than $80 \%$ and not greater than $120 \%$ of the potency stated on the label. The specific activity is not less than 6.0 USP Antithrombin III

Units per mg of total protein. The confidence interval $(p=0.95)$ is between than $90 \%$ to $110 \%$ of the estimated potency. $\mathbf{U S P 2 8}$

## BRIEFING

Ascorbic Acid Tablets, USP 27 page 170—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-6

Change to read:
Dissolution Predtre for a Pooled Sample
${ }^{\mathbf{A}}\langle 711\rangle-2$ USP28
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled sample as the test solution. $U S P 28$
Determine the amount of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{6}$ dissolved, employing the procedure set forth in the Assay and conducting the procedure without delay, making any necessary modifications.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{6}$ is dissolved in 45 minutes:
$\Delta_{\text {the }}$ requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform
at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |

## Change to read:

Dissolution Preedre for a Poled sample

Medium: 0.05 M acetate buffer, prepared by mixing 2.99 g of sodium acetate trihydrate and 1.66 mL of glacial acetic acid with water to obtain 1000 mL of solution having a pH of $4.50 \pm 0.05$; 500 mL .
Apparatus 1: 50 rpm .
Time: 45 minutes.
Mobile phase and Chromatographic system-Prepare as directed in the Assay and limit of salicylic acid.
Standard preparation-Prepare a solution in Dissolution Medium containing known concentrations of about $0.002 A \mathrm{mg}$ of USP Aspirin RS, $0.002 C \mathrm{mg}$ of USP Caffeine RS, and $0.002 D$ mg of USP Dihydrocodeine Bitartrate RS per $\mathrm{mL}, A, C$, and $D$ being the labeled amounts, in mg , of aspirin, caffeine, and dihydrocodeine bitartrate, respectively, in each Capsule.
Test preparation Filter a portion of the solution under test.
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle U S P 28$
Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Test preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantities, in mg, of aspirin $\left(\mathrm{C}_{9} \mathrm{H}_{8} \mathrm{O}_{4}\right)$, caffeine $\left(\mathrm{C}_{8} \mathrm{H}_{10} \mathrm{~N}_{4} \mathrm{O}_{2}\right)$, and dihydrocodeine bitartrate $\left(\mathrm{C}_{18} \mathrm{H}_{23} \mathrm{NO}_{3} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}\right)$ dissolved by the same formula:

$$
500 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of the appropriate USP Reference Standard in the Standard preparation, and $r_{U}$ and $r_{S}$ are the peak responses of the relevant analyte obtained from the Test preparation and the Standard preparation, respectively.
Tolerances-Not less than $75 \%$ (Q) of the labeled amounts of $\mathrm{C}_{9} \mathrm{H}_{8} \mathrm{O}_{4}, \mathrm{C}_{8} \mathrm{H}_{10} \mathrm{~N}_{4} \mathrm{O}_{2}$, and $\mathrm{C}_{18} \mathrm{H}_{23} \mathrm{NO}_{3} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$ are dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample.
Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :--- |
| Stage | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> $\mathrm{S}_{2}$ |
| $\mathrm{~S}_{3}$ | 12 | equal to or greater than $Q+5 \%$. <br> Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## Briefing

Aztreonam, USP 27 page 200. It is proposed to revise the IR Identification test. In the current procedure the sample under test and the Reference Standard are dissolved in methanol to obtain a solution having a concentration of 3 mg per mL . Then 0.5 mL of this solution is added to 200 mg of potassium bromide, dried, mixed, and compressed into a disc. This procedure was intended to yield "polymorphic equalization" of the $\alpha$ and $\beta$ crystalline forms. However, it was found that the methanol solution was not clear and that the IR spectra were unpredictable. Various drying conditions were tried but no improvement was observed. It was found that consistent spectra were obtained from discs prepared from undried Aztreonam intimately mixed with potassium bromide as directed in general chapter Spectrophotometric Identification Tests $\langle 197\rangle$.
(PA7a: W. Wright) RTS-40377-1

## Change to read:

Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$. Prepare dispersion of 0.5 mL of a methanel solution of it, containing 3 mg per mL , in 200 mg of potascium bromide.
${ }^{\Delta}$ Do not dry the specimen. $\triangle U S P 28$

## BRIEFING

Baclofen Tablets, USP 27 page 207-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-17

## Change to read:

Dissolution Procedure for a Pooled Sample
〈
$\langle 711\rangle$ USP28
Medium: 0.01 N hydrochloric acid; 500 mL for Tablets containing 10 mg or less of drug and 1000 mL for Tablets containing more than 10 mg of drug.

Apparatus 2: 50 rpm .
Time: 30 minutes.
Determine the amount of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{ClNO}_{2}$ dissolved by employing the following method.
Mobile phase and Chromatographic system-Proceed as directed in the Assay.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle U S P 28$
Inject an accurately measured volume (about $190 \mu \mathrm{~L}$ ) of pertion of the solution under test
${ }^{\Delta}$ the pooled sample ${ }_{\text {ASP28 }}$
into the chromatograph by means of a microsyringe or a sampling valve, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{ClNO}_{2}$ dissolved in comparison with a Standard solution having a known concentration of USP Baclofen RS in the same Medium and similarly chromatographed.

Tolerances-Not less than $75 \%$ ( $Q$ ) of the labeled amount of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{ClNO}_{2}$ is dissolved in 30 minutes:
$\Delta_{\text {the }}$ requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

| Number |  |  |
| :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |


| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. <br> $\mathrm{S}_{2}$ |
| :---: | :---: | :--- |
| $\mathrm{~S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## BRIEFING

Betamethasone Tablets, USP 27 page 232 and page 1011 of $P F$ 29(4) [July-Aug. 2003]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-19

## Change to read:

Packaging and storage-Preserve in well closed containers.
${ }^{\square}$ Store between $2^{\circ}$ and $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$, and preserve in a tight container. [NOTE-Protect the 21-tablet pack from excessive moisture.] $]_{\text {1S (USP27) }}$
Delete the following:
IIdentifiention-Evaperate- 50 mL of the Assay preparation, prepared as directed in the Assety, on a steam bath just to dryness, and dissolve the residue in 1 mL of chloreform. Proeed as directed for Itentifican test $B$ under Betane begimning with " $A$ "pply $10 \mu \mathrm{~L}$ of this solution." ${ }^{2 S}$ (USP27)

## Add the following:

-Thin-Layer Chromatographic Identification Test〈201〉—
Test solution-Evaporate 50 mL of the Assay preparation, prepared as directed in the Assay, on a steam bath just to dryness, and dissolve the residue in 1 mL of chloroform.

Developing solvent system: a mixture of chloroform and diethylamine (2:1).
Procedure-Proceed as directed in the chapter. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear.11S (USPP2)

Change to read:
Dissolution Proedure for a Pooled Sample

Medium: water; 900 mL . Add 1.0 mL of Internal standard solution to each vessel.

Apparatus 2: 50 rpm .
Time: 45 minutes.
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle$ USP28

Mobile phase-Prepare a filtered and degassed mixture of methanol and water ( $60: 40$ ), making adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard solution-Prepare a solution in methanol of testosterone having a final concentration of about 0.5 mg per mL .
Standard solution-Prepare a solution of USP Betamethasone RS, in methanol, having an accurately known concentration of about 0.5 mg per mL . Pipet 1 mL of this solution and 1 mL of the Internal standard solution into a container, and dilute quantitatively with water to 900 mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph replicate injections of the Standard solution, and record the peak responses as directed for Procedure: the resolution, $R$, between betamethasone and testosterone is not less than 1.5 , and the relative standard deviation for replicate injections is not more than $3.0 \%$.

Procedure-Separately inject equal volumes (about $200 \mu \mathrm{~L}$ ) of the Standard solution and filtered pertions of the solution under test
${ }^{\boldsymbol{\Delta}}$ the pooled sample ${ }_{\Delta U S P 28}$
into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.5 for betamethasone and 1.0 for testosterone. Calculate the quantity of $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{FO}_{5}$ dissolved in comparison with the Standard solution, similarly chromatographed.

Tolerances-Not less than $75 \%$ (Q) of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{FO}_{5}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

|  | Number |  |
| :---: | :---: | :---: |
| Stage | Tested |  |$\quad$| Acceptance Criteria |
| :---: |

## BRIEFING

Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers; Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions. The development of these proposed new monographs reflects the wide range of forms of biological indicators. The monographs are structured similarly to the official USP monographs pertaining to biological indicators. The proposed monographs refer to sections of the proposed revision to the general chapter Biological Indicators-Resistance Performance Tests $\langle 55\rangle$, published elsewhere in this issue of $P F$.

Comments should be sent to USP Headquarters for consideration by the Expert Committee on Analytical Microbiology no later than March 1, 2004.
(AMB: D. Porter) RTS-40482-1

## Add the following:

## - Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers

» Biological indicators for moist heat, dry heat, and gaseous modes of sterilization may be metal or plastic carriers inoculated with a culture of viable spores derived from one of several steriliza-tion-resistant microorganisms, based on the intended sterilization use. Cultures used for inoculation of metal or plastic carriers may include Clostridium sporogenes, Geobacillus stearothermophilus (formerly B. stearothermophilus), Bacillus atrophaeus (formerly B. subtilus), or Bacillus coagulans. The metal or plastic carriers should be individually packaged for use either within the package or for use upon removal from the package as an unpackaged biological indicator. The packaged biological indicator on the metal or plastic carrier has a particular labeled spore count of not less than $10^{4}$ and not more than $10^{9}$ spores per carrier. It has a survival time and kill time appropriate to the labeled spore count and to the decimal reduction value ( $D$ value, in minutes), specified by:

Survival time (in minutes) $=$ not less than (labeled $D$ value $) \times(\log$ of labeled spore count per carrier -2 ), and

Kill time $($ in minutes $)=$ not more than (labeled $D$ value $) \times(\log$ of labeled spore count per carrier $+4)$.

Packaging and storage-Preserve in the original package under the conditions recommended on the label, and protect the package from light, toxic substances, excessive heat, and high relative humidity or moisture. The packaging or container materials do not adversely affect the performance of the article used as directed in the labeling.

Expiration date-The expiration date is determined on the basis of stability studies and is not less than 18 months from the date of manufacture. The date of manufacture is the date on which the first determination of the total viable count was made.

Labeling-Label the package or package insert to state that it is a biological indicator prepared on a metal carrier for use in label-specified applications for moist heat, dry heat, and/ or gaseous sterilization. State the biological indicator $D$ val$u e$ obtained under defined exposures to stated sterilization conditions using the Survival Curve method, SpearmanKarber method, or Stumbo-Murphy-Cochran method of $D$ value analysis. State the survival time and kill time for the biological indicator carrier under specified conditions on the label. The total count viable spore count per carrier following heat shock treatment must also appear on the label. State in the labeling the size of the carrier, the strain and ATCC number of the spore suspension used to inoculate the carriers, and instructions for spore recovery and for safe disposal of the carriers. Indicate in the labeling that the stated $D$ value is reproducible only under the exact conditions determined by the manufacturer and that the user would not necessarily obtain the same results if different exposure conditions were used. State that the user should determine the suitability of the metal or plastic carrier biological indicator for the user's particular purpose and exposure conditions.

Identification-Identification schemes are listed for four microorganisms that may be used as biological indicators for metal or plastic carriers.

Clostridium sporogenes, ATCC No. 7955. The biological indicator microorganism complies with the morphological, cultural, and biochemical characteristics of the strain derived from Clostridium sporogenes, ATCC No.7955. Under microscopic examination it consists of Gram-positive rods with oval endospores in subterminally swollen cells. When incubated in appropriate media between $30^{\circ}$ to $40^{\circ}$ for 72 hours, growth occurs under anaerobic conditions. Similarly inoculated media incubated aerobically between $30^{\circ}$ to $40^{\circ}$ for 72 hours shows no evidence of growth in the same period. When examined using conventional biochemical tests for the microbial characterization, glucose is fermented while adonitol, dulitol, erythritol, and sorbose are not; hydrogen sulfide and ammonia are produced. Gelatin is hydrolyzed; lipase is produced. The mol $\% \mathrm{G}+\mathrm{C}$ (guanine plus cytosine) content of DNA is $26 .{ }^{1}$

Geobacillus stearothermophilus (formerly Bacillus stearothermophilus), ATCC No. 7953. The mol \% G + C content of DNA is 43.5 to $62.2 .{ }^{1}$ It meets the requirements of the Identification test under Biological Indicator for Steam Sterilization, Paper Carrier.

Bacillus atrophaeus (formerly Bacillus subtilis), ATCC No. 9372 . The mol $\% \mathrm{G}+\mathrm{C}$ content of DNA is 41.5 to $47.5^{1}$. It meets the requirements of the Identification tests under Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier.

Bacillus coagulans, ATCC No. 51232. The biological indicator microorganism complies with the morphological, cultural, and biochemical characteristics of the strain derived from Bacillus coagulans, ATCC No. 51232. Under

[^6]microscopic examination it consists of Gram-positive rods, and considerable morphological variation may occur, with sporangia not appreciably swollen by oval or cylindrical spores, not sporangia swollen by oval spores. Minimal nutritional requirements may be diverse. Various amino acids and vitamins may potentiate its growth. When incubated in appropriate media at $50 \pm 2^{\circ}$ for 72 hours, growth occurs under aerobic conditions. Optimum growth pH is close to 6.0. The $\mathrm{mol} \% \mathrm{G}+\mathrm{C}$ content of DNA is 44.3 to 50.3 . ${ }^{1}$

D value-Proceed as directed in the relevant procedure for D Value Determination under Biological Indicators-Resistance Performance Tests $\langle 55\rangle$. The requirements of the test are met if the determined $D$ value is within $20 \%$ of the labeled $D$ value for the selected sterilizing temperature, and if the confidence limits of the estimate are within $10 \%$ of the determined $D$ value. While calculations for the Limited Spearman-Karber D-value method appears in chapter Biological Indicators-Resistance Performance Tests $\langle 55\rangle$, it is included for compendia or referee testing of biological indicators. It is recognized that other methods, such as the Stumbo-Murphy-Cochran procedure or the Survival Curve method, can be routinely used by manufacturers or users of biological indicators for $D$-value determinations. The $D$-value method used by a manufacturer should be stated in the manufacturer's literature.

Survival time and kill time-Follow the procedure for Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers in the section Survival Time and Kill Time under D-Value Determination in chapter Biological Indicators-Resistance Performance Tests $\langle 55$.$\rangle The requirements of the test are$ met if all of the carriers subjected to sterilization exposure conditions intended to indicate survival show evidence of growth among the exposed carriers, while none of the carriers subjected to conditions designed to induce total kill
show growth. If for either the survival test or the kill time test, not more than one carrier out of both groups fails the survival or kill requirements, continue the corresponding test with four additional groups, each consisting of 10 carriers, according to the procedure described. If all of the additional specimens subjected to the specific sterilization process either meet the survival requirements for the survival test time or meet the kill requirement for the kill test, whichever is applicable, the requirements are met.

Total viable spore count-Proceed as directed for Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers in the section Total Viable Spore Count under Biological IndicatorsResistance Performance Tests $\langle 55\rangle$. The requirements of the test are met if the average number of viable spores per carrier are within $-50 \%$ and $+300 \%$ of the labeled count per carrier or within a lesser range that may be stated by the manufacturer.

Purity-There is no evidence of contamination with other microorganisms following examination of spores recovered from the metal or plastic carriers using a suitable plate culture medium.

Disposal-Prior to destruction or discarding the metal or plastic carriers, sterilize by moist heat sterilization to ensure that the carrier surface is exposed to $121^{\circ}$ for not less than 30 minutes, or by an equivalent method recommended by the manufacturer. $\triangle$ USP28

## BRIEFING

Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions-See briefing under Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers.

Comments should be sent to USP Headquarters for consideration by the Expert Committee on Analytical Microbiology no later than March 1, 2004.
(AMB: D. Porter) RTS-40482-2

## Add the following:

## - Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions

» Liquid spore suspensions may be used to prepare biological indicators for moist heat, dry heat, and gaseous modes of sterilization. On the basis of the intended sterilization use, the suspension is prepared inoculated from a culture of viable spores derived from one of several sterilization resistant microorganisms. Cultures used for liquid spore suspensions may include the following: Clostridium sporogenes, Geobacillus stearothermophilus (formerly B. stearothermophilus), Bacillus atrophaeus (formerly B. subtilus), or Bacillus coagulans. Each tube or container containing the spore suspension is individually packaged for use. The packaged biological indicator spore suspension has a particular labeled spore count of not less than $10^{4}$, and not more than $10^{9}$, spores per mL of suspension. The suspending medium or vehicle is identified according to chemical composition. It has a survival time and kill time appro-
priate to the labeled spore count, and to the decimal reduction value (the $D$ value, in minutes), specified by:

Survival time (in minutes) $=$ not less than (labeled $D$ value $) \times(\log$ of labeled spore count per mL from 1:100 dilution of original suspension -2 ); and

Kill time $($ in minutes $)=$ not more than (labeled $D$ value $) \times(\log$ of labeled spore count per mL $+4)$.

Packaging and storage-Preserve in the original tube or container under the conditions recommended on the label, and protect the contents of the tube or container from light, toxic substances, and excessive heat. The materials of composition of the tube or container must not adversely affect the performance of the spore suspension.

Expiration date-The expiration date is determined on the basis of stability studies. The date of manufacture is the date on which the first determination of the total viable count was made.

Labeling-Label the spore suspension tube or container or package insert to state that it is a biological indicator spore suspension for use in label specified applications for moistheat, dry-heat, and/or gaseous sterilization. State the biological indicator $D$ value obtained under defined exposures to stated sterilization conditions using the Survival Curve Method of $D$-value analysis. State the Survival time and kill time for the biological indicator suspension under specified conditions on the label. The total count viable spore count per mL of the suspension following heat shock treatment must also appear on the label. State in the labeling the strain and ATCC number of the microorganisms used in the spore suspension and instructions for spore recovery and for safe
disposal of the suspension. Indicate in the labeling that the stated $D$ value is reproducible only under the exact conditions determined by the manufacturer and that the user would not necessarily obtain the same results if different exposure conditions were used. State that the user should determine the suitability of the biological indicator spore suspension for the user's particular purpose and exposure conditions.

Identification-Identification information is listed below for four microorganisms that may be supplied as biological indicator spore suspensions:

Clostridium sporogenes, ATCC No. 7955. The biological indicator microorganism complies with the morphological, cultural, and biochemical characteristics of the strain derived from Clostridium sporogenes, ATCC 7955. Under microscopic examination it consists of Gram-positive rods with oval endospores in subterminally swollen cells. When incubated in appropriate media at $30^{\circ}$ to $40^{\circ}$ for 72 hours, growth occurs under anaerobic conditions. Similarly inoculated media incubated aerobically at $30^{\circ}$ to $40^{\circ}$ for 72 hours shows no evidence of growth in the same period. When examined using conventional biochemical tests for the microbial characterization, glucose is fermented while adonitol, dulitol, erythritol, and sorbose are not; $\mathrm{H}_{2} \mathrm{~S}$ and ammonia are produced. Gelatin is hydrolyzed; lipase is produced. The mol \% G + C content of DNA is $26 .{ }^{1}$

Geobacillus stearothermophilus (formerly Bacillus stearothermophilus), ATCC No. 7953. The mol \% G + C content of DNA is 43.5 to $62.2 .{ }^{1}$ It responds to the Identification test under Biological Indicator for Steam Sterilization, Paper Carrier.

[^7]Bacillus atrophaeus (formerly Bacillus subtilis), ATCC No. 9372 . The mol $\% \mathrm{G}+\mathrm{C}$ content of DNA is 41.5 to 47.5. ${ }^{1}$ It meets the requirements of the Identification test under Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier.
Bacillus coagulans, ATCC No. 51232. The biological indicator microorganism complies with the morphological, cultural, and biochemical characteristics of the strain derived from Bacillus coagulans, ATCC no. 51232. Under microscopic examination it consists of Gram-positive rods, and considerable morphological variation may occur, with sporangia not appreciably swollen by oval or cylindrical spores, not sporangia swollen by oval spores. Minimal nutritional requirements may be diverse. Various amino acids and vitamins may potentate its growth. When incubated in appropriate media at $50 \pm 2^{\circ}$ for 72 hours, growth occurs under aerobic conditions. Optimum growth pH is close to 6.0. The $\mathrm{mol} \% \mathrm{G}+\mathrm{C}$ content of DNA is 44.3 to 50.3 . ${ }^{1}$

D value-If the biological indicators are being used in moist-heat or dry-heat sterilization, proceed as directed for the relevant procedure in the section $D$-Value Determination under Biological Indicators-Resistance Performance Tests $\langle 55\rangle$. The requirements of the test are met if the plot of the biological indicator survivor curve on a semi-log scale results in a straight line with an $R$-value of $>95 \%$.

While calculations for the Limited Spearman-Karber $D$ value method appears in Biological Indicators-Resistance Performance Tests $\langle 55\rangle$, it is included for compendia or referee testing of biological indicators. It is recognized that other methods such as the Stumbo-Murphy-Cochran procedure, or the Survival Curve method can be routinely used by manufacturers or users of biological indicators for $D$-value determinations. The Survival Curve method for establish-
ment of $D$ values in liquid suspensions will be used for referee purposes. The $D$-value method used by a manufacturer should be stated in the manufacturer's literature.

Survival time and kill time-Follow the procedure for Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspension under Survival Time and Kill Time in the section D-Value Determination under Biological Indicators-Resistance Performance Tests $\langle 55\rangle$. The test is conducted using 1:100 dilution aliquots of the original suspension to inoculate carrier substrates that are most likely to be used by the purchaser of the spore suspensions for a given mode of sterilization. The following represents examples of substrates that may be used in the survival-time and kill-time test for specific spore suspensions. Metallic, plastic, or paper substrates may be used for C. sporogenes, G. stearothermophilus, B. atrophaeus, and B. coagulans. Following a total viable count analysis, the inoculated substrates are subjected to sterilization exposure conditions intended to indicate survival. The inoculated carriers must show evidence of growth among the exposed carriers. A second study is conducted to demonstrate the conditions necessary to result in total kill of the carriers. None of the carriers subjected to conditions designed to induce total kill should show growth. If for either the survival-time test or the kill-time test, not more than one carrier out of both groups fails the survival or kill requirements, continue the corresponding test with four additional groups, each consisting of 10 carriers, according to the procedure described. For biological indicators for use with moist-heat or dry-heat sterilization, if all of the additional specimens subjected to the specific sterilization process either meet the survival requirements for the survi-val-time test or meet the kill requirement for the kill-time test, whichever is applicable, the requirements are met.

Total viable spore count-Proceed as directed for Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions in the section Total Viable Spore Count under Biological IndicatorsResistance Performance Tests $\langle 55\rangle$. The requirements for this test are met if the total viable spore count within the suspension is within $\pm 1 \log$ of the value stipulated by the manufacturer.

Purity-There is no evidence of contamination with other microorganisms following examination of spores recovered from the metal carriers using suitable plate-culture medium.

Shipment—Spore suspensions must be shipped following EPA requirements for the shipment of biological and/or etiological agents.

Disposal-Spore suspensions that a user or manufacturer wishes to dispose of are first sterilized by moist heat by a process that achieves temperatures of approximately $121^{\circ}$ for not less than 30 minutes. Alternative sterilization methods yielding equivalent or greater levels of lethality may be used. $\triangle$ USP28

Briefing
Red Blood Cells, USP 27 page 262 and page 431 of $P F$ 29(2) [Mar.-Apr. 2003]. It is proposed to revise the existing abbreviated monograph for Red Blood Cells to update the Definition and sections on Packaging and storage, Expiration date, and Labeling and to include test specifications, procedures, and acceptance criteria consistent with current FDA requirements. The revised monograph is intended to apply to Red Blood Cells regardless of the method of preparation, i.e., whole blood derived or derived from apheresis. It describes the requirements for an acceptable unit of allogeneic red blood cells. The procedures for ABO blood group, Rh type, Leukocyte count, and Adequacy of deglycerolization were adapted from the $A A B B$ Technical Manual (50th Anniversary Edition), 2002, 14th Edition, American Association of Blood Banks, Bethesda, MD. The procedure for Hemoglobin content is recommended by the National Institutes of Health and approved by the International Committee on Standardization in Hematology as the standard method for hemoglobin assay. The proposed hemoglobin content of 50 g is the minimum amount of hemoglobin in a unit of red cells collected under minimally acceptable parameters. Specifically, a
$405-\mathrm{mL}$ collection (the lower limit of a $450-\mathrm{mL}$ collection $\pm$ $10 \%$ ) with a minimum donor hematocrit of $38 \%$. In this case, $405 \mathrm{~mL} \times 0.38=154 \mathrm{~mL}$ red cell mass, which equates approximately to 50 g hemoglobin. The volume stated refers to the total fluid volume, including any residual plasma, anticoagulants, or additive solution. Total volumes will vary depending on processing method. A range is given here to accommodate process methods and to give clinicians a reference for calculating transfusion volumes given to a patient. The proposed hemoglobin content and volume of Red Blood Cells, Leukocyte Reduced are calculated numbers based on a minimum of $85 \%$ recovery of starting material of Red Blood Cells during leukoreduction filtration. The $85 \%$ recovery is a CBER/FDA minimum, a minimum defined in the Circular of Information, and also a minimum recovery claim of filter manufacturers. Actual recovery is typically higher. The proposed hemoglobin content in Red Blood Cells, Deglycerolized is a calculated number based on an $80 \%$ recovery from the starting material of Red Blood Cells. The $80 \%$ recovery is an FDA minimum and a minimum defined in the Circular of Information. Actual recovery is typically higher. The volume is not reduced because it is adjusted after deglycerolization. The proposed hemoglobin content of Red Blood Cells, Leukocyte Reduced and Deglycerolized is a calculated number based on an $80 \%$ recovery of starting material of Red Blood Cells, Leukoreduced. The $80 \%$ recovery is an FDA minimum and a minimum defined in the Circular of Information. Actual recovery is typically higher. The volume is not reduced because it is adjusted after deglycerolization.
(BBP: R. Tirumalai) RTS-40461-1

## Change to read:

\# Red Bleod Cells conforms to the regulations of the federal Food and Drug Administration concerning biologies ( 640.10 to 640.18 ) (see Biolegics $\langle 1044\rangle$ ). It is the remaining red blood cells of whole human blood that has been collected from suitable whole blood donors, and from which plasma has been removed. It may be prepared at any time during the dating period of the whole blood from which it is derived, by centrifuging or undisturbed sedimentation for the separation of plasma and cells, not later than 21 days after the blood has been drawn, except that when acid citrate dextrese adenine solution has been used as the anticoagulant, sueh preparation may be made within 35 days therefrom. It contains a portion of the plasma sufficient to ensure optional cell preservation or contains a cryophylactic substance if it is for extended manufacturers' storage at $65^{\circ}$ or colder.
\#Red BloodCells is the pertion of blood that contains hemoglobin and is derived from whole human blood, from which plasma is removed by mantal centrifugation or sedimentation, or by apheresis, in which case the plasma is automatically removed and returned directly to the donor. Red Blood-Cells derived from whole human blood may be prepared at any time dur ing the dating period of the whole human blood from which it is derived.

Red Blood Cells may be further processed by filtation for removal of leukocytes, may be washed to remove proteins, may be frozen and thawed, or may be


#### Abstract

rejurenated using validated and approved procedures. The source blood for Red Blood Cells must be tested for syphilis, hepatitis $B$, and human T-cell virus Type 4 and Type 2 using approved commercially available test kits, the results of which must be below the limits of detection speciffed in the respective test kits by the manufacturers. In addition, the source blood must alse be tested for hepatitis C and for antibodies to HIV using a nucleic acid assay, the results of which must be below the approved limits of detection for the meth ed. A unit (dose) of Red Blood Cells contains a minimum of 50 g of hemoglobin in a total volume of about 180 mL to 325 mL . A unit (dose) of Red Blood Cells, Leukecytes Redured, contains a minimum of 42.5 g of hemeglobin in a total volume of about 150 mL to 275 mL and has a residual leukneytermin of less than 5-* $10^{6} . A$ unit (dose) of Red Blood Cells, Deglyeerolized, eontains a minimum of 40 g of hemoglobin in a total velume of about 180 mL to 325 mL . A unit (dose) of Red Blood-Cells, Leuk eytes-Redueed and Deglyeerelized, contains a minimum of 35 g of hemoglebin in a total volume of about 180 mL to 325 mL and has a residtal leukeyte count of less than $5 \times 10^{6}$ :


${ }^{\wedge}$ Red Blood Cells is the portion of blood that contains hemoglobin and is derived from human whole blood, from which plasma and cellular components are removed by centrifugation, sedimentation, or, by apheresis, in which case the plasma is automatically removed and returned directly to the donor. Red Blood Cells derived from whole blood may be prepared at any time during the dating period of the whole blood from which it is derived.

Red Blood Cells may be further processed by addition of red cell preservatives, irradiation to inactivate lymphocytes, filtration for removal of leukocytes, washing to remove proteins, freezing and thawing, or rejuvenation using validated and approved procedures. The source blood for Red Blood Cells must be tested for syphilis, hepatitis B virus, hepatitis $C$ virus, human T-cell virus (HTLV) type I and type II, human immunodefi-
ciency virus (HIV) type 1 and type 2 , and unexpected antibodies to red cell antigens using FDA-approved and licensed commercially available test kits, the results of which must be below the limits of detection specified in the respective test kits by the manufacturers. In addition, the source blood must also be tested for hepatitis C and HIV using FDA-approved nucleic acid assays, the results of which must be below the approved limits of detection for the method. A unit (dose) of Red Blood Cells contains a minimum of 50 g of hemoglobin in a total volume of approximately 180 to 325 mL . A unit (dose) of Red Blood Cells, Leukocytes Reduced contains a minimum of 42.5 g of hemoglobin in a total volume of approximately 150 to 275 mL , and has a residual leukocyte count of less than $5 \times 10^{6}$. A unit (dose) of Red Blood Cells, Deglycerolized contains a minimum of 40 g of hemoglobin in a total volume of approximately 180 to 325 mL . A unit (dose) of Red Blood Cells, Leukocytes Reduced and Deglycerolized contains a minimum of 34 g of hemoglobin in a total volume of approximately 180 to 325 mL and has a residual leukocyte count of less than $5 \times 10^{6}$. A unit (dose) of Red Blood Cells, Pheresis contains a mean hemoglobin content of 60 g of hemoglobin. A unit (dose) of Red Blood Cells, Pheresis, Leucocytes Reduced contains a mean hemoglobin content of 51 g (or $153-\mathrm{mL}$ packed red cell volume, and has a residual leukocyte count of less than $5 \times 10^{6} \cdot$ aUSP2s $^{\text {us }}$

## Change to read:

Packaging and storage-Preserve in a hermetic container, which is of colorless, transparent, sterile, pyrogen free Type I or Type H glass, or of a suitable plastic material(seeTransfusion and Infusion Assemblies $\langle 164\rangle$ ), in which it was placed by the precessor. Store if unfrozen at a temperature between $1^{\circ}$ and $6^{\circ}$, held enstant within a $2^{\circ}$ rang exeept during shipment when the temperature may be between $1^{\circ}$ and $10^{\circ}$, and store if for extended manufacturers' stor age in frozen form at $65^{\circ}$ or colder. The entainer of Red Blood Gells is aceompanied by a securely attached smaller container holding an original pilot sample of blood taken from the doner at the same time as the whole human bleod, or a pillat sample of Red Blood Cells removed at the time of its preparation.
${ }^{\Delta}$ Collect into an approved container (see Transfusion and Infusion Assemblies $\langle 161\rangle$ ) containing a sterile, pyrogenfree approved anticoagulant (see Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose, or Anticoagulant Citrate Phosphate Dextrose Adenine Solution). An approved additive solution may be added after removal of the plasma. Store Red Blood Cells in the original container, or transfer to an equivalent container using a technique that does not compromise sterility. Liquid Red Blood Cells is stored at a temperature between $1^{\circ}$ and $6^{\circ}$ (see General Notices and Requirements). Frozen Red Blood Cells is stored at $-65^{\circ}$ or colder. $\triangle$ USP28

## Change to read:

Expiration date-The-expiration date-for unfrozen-Red Blood Gells is not later than that of the whole human blood from which it is derived if plasma has not been removed, except that if the her metic seal of the container is broken during preparation, the expira tion date is net later than 24 hours after the seat is broken. The expiration date for frozen Red Blood Cells is not later than 3 years after the date of collection of the souree blood when stored at $65^{\circ}$ er colder and not later than 24 hours after removal from- $65^{\circ}$ stor age provided it is then stored at the temperature for unfrozen Red Blood Cells.
${ }^{\Delta}$ Red Blood Cells in Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution, or in Anticoagulant Citrate Phosphate Dextrose-Dextrose Solution may be stored for up to 21 days at $1^{\circ}$ to $6^{\circ}$ after the blood has been drawn. Red Blood Cells in Anticoagulant Citrate Phosphate Dextrose Adenine Solution may be stored for up to 35 days at $1^{\circ}$ to $6^{\circ}$. Red Blood Cells may be stored in an approved additive solution (AS), ${ }^{*}$ for up to

[^8]42 days at $1^{\circ}$ to $6^{\circ}$. If the hermetic seal of the container is broken during collection, preparation, or further processing, the expiration date is not later than 24 hours after the seal is broken. The expiration far frozen Red Blood Cells is net later than 3 years frem the date feollection when stored at $65^{\circ}$ or colder, except when RedBlood Cells are prepared for freezing with high glycerel content ( $40 \%$ glycerol), in which case they may be stored for not more than 10 years from the The expiration date for frozen Red Blood Cells prepared with low glycerol content ( $20 \%$ glycerol) is not later than 10 years from the date of collection when stored at $-120^{\circ}$ or colder, except when Red Blood Cells is prepared for freezing with high glycerol content ( $40 \%$ glycerol), in which case it may be stored at $-65^{\circ}$ or colder for no later than 10 years from date of collection. If the frozen Red Blood Cells is processed for freezing or for thawing, in an open system, the expiration date for the thawed Red Blood Cells is 24 hours after removal from $-65^{\circ}$ storage, provided it is then stored at the temperature of unfrozen Red Blood Cells. . USP28 $^{\text {S }}$

## Change to read:

Labeling In addition to labeling requirements of Whole Blood applieable to this produet, labelit to indieate the approved variation to which it conforms, such as "Frozen," or "Deglycerolized." Label it also with the instruction to use a filter in the administration equipment.
${ }^{\Delta}$ Label the container to indicate the volume of the whole human blood collected from the donor, the collection date, the donation number or other coding means to uniquely identify the unit and to provide traceability to the donor, and the expiration date. Label it to indicate the type of anticoagulant used to collect whole human blood and any additive solutions added subsequent to collection. Label it also to identify donor status (i.e., volunteer or paid). Label it also with the following statements: "See Circular of Information for indications, contraindications, cautions, and methods of infusion."; "Properly identify recipient."; and "Caution: Rx only." In addition, label it to indicate the product name as
indicated in Table 1. [NOTE-The name is determined by the method of preparation of the Red Blood Cells (derived from whole human blood or from apheresis) and by performing the necessary testing to ensure that the product meets the minimum requirements for the named products, as indicated in Table 1.]

Table 1. Red Blood Cells Preparations

| Product Name | Method of Preparation |
| :---: | :---: |
| Red Blood Cells | Prepared from whole human |
| blood |  |
| Red Blood Cells, Apheresis | Prepared using automated |
| Pheresis | apheresis systems |
| Red Blood Cells, Leukocyte | Prepared from Red Blood |
| Reduced | Cells |
|  | or Red Blood Cells, |
|  | Apheresis |
|  | Pheresis (Total leukocytes |
| Red Blood Cells, Frozen | Prepared from Red Blood |
|  | Cells or Red Blood Cells, |
|  | Apheresis |
|  | Pheresis suspended in |
|  | cryoprotective solution |
|  | (glycerol) and frozen at |
|  | an appropriate |
| Red Blood Cells, | temperature |
| Deglycerolyzed | Prepared from Red Blood |
|  | Cells, |
|  | Frozen, from which |
|  | glycerolis removed by |
|  | washing by an approved |
|  | procedure |

Label it to indicate the ABO blood group and Rh lype, as indieated in Table 2. [note-Every RedBleodCells product must have determination made as to its $A B O$ blood group and Phtype. Label it to indicate, the ABO Group/Rh Type, as indicated in Table 2. [NOTE-Every Red Blood Cell product must have a determination made as to its ABO Group and Rh Type and specificity of unexpected red cell antibodies, if any.]

If an ABO blood group color scheme is used, use the following labeling color: Group A (yellow), Group B (pink), Group O (blue), and Group AB (white).
Label the Red BloodCells with the name of the adventitious agents tested and the results of the tests. If it has been issued prior to determination of the test results, label it also with a warning not to use it until the test results have been received and to specify that a cross mateh must be perLabel the Red Blood Cells with names of the adventitious agents tested and the results of the tests. If it has been issued prior to determination of the test results, label it also with a warning "Donor Untested" and to specify "Uncrossmatched Blood", when appropriate.

Table 2. Blood Group and Rh Type

| ABO Group | Rh Type |
| :---: | :---: |
| A | Positive |
| A | Negative |
| B | Positive |
| B | Negative |
| AB | Positive |
| AB | Negative |
| O | Positive |
| O |  |

## Add the following:

${ }^{4}$ USP Reference standards $\langle 11\rangle — U S P$ Hemoglobin
$R S_{. \Delta U S P 28}$

## Add the following:

${ }^{4}$ Identification-
A: ABO blood group-
Anti-A reagent-Use menoclenal-or polyelenal anti-A
blood grouping reagent, two different lots from the same or different manufacturers. Dilute, if neeessary, following the manufacturer's instructions. Use approved commercially available monoclonal or polyclonal anti-A blood grouping reagent, two different lots from the same or different manufacturers. Use in accordance with manufacturer's instructions.

Anti-B reagent-Use monoclonal-or polyclonal anti B
blood grouping reagent, two different lots from the same or different manufacturers. Dilute, if neeessary, following the manufacturer's instructions. Use approved commercially available monoclonal or polyclonal anti-B blood grouping reagent, two different lots from the same or different manufacturers. Use in accordance with manufacturer's instructions.

Anti-AB reagent-Use anti AB blood grouping reagent.
Bilute, if neeessary, following the manufacturer's instrue-
Use approved commercially available anti-AB blood grouping reagent. Use in accordance with manufacturer's instructions.

Control preparations-On the day of use, dilute Blood Group $\mathrm{A}_{1}$ (Control preparation $A_{1}$ ) and Blood Group B (Control preparation B) red blood cells, obtained from an approved commercial source or prepared by the testing laboratory, with $0.9 \%$ saline to suspensions of approximately the same concentration between $2 \%$ to $5 \%(\mathrm{v} / \mathrm{v})$. [NOTE-If the Blood Group $\mathrm{A}_{1}$ and Blood Group B red blood cells are prepared in the testing laboratory from whole blood of a known blood group, it must be prepared on the day of use following the procedure for the Test preparation under Whole Blood.]

Test preparation-On the day of use, dilute Red Blood Cells with $0.9 \%$ saline to a suspension of about the same concentration as the Control preparations.

Procedure-On a suitable U-bottomed microtiter plate, place 1 drop of $0.9 \%$ saline in each of three different wells in a row (Blank Row). Place 1 drop from one of the lots of Anti-A reagentin each of three different wells in a second row. Place 1 drop from the second lot of Anti-A reagent in each of three different wells in a third row. Repeat the same with two different lots of Anti-B reagent and one lot of Anti$A B$ reagent in separate rows. To each row, add one drop of Control preparation $A_{1}$, Control preparation $B$, and the Test preparation in the first, second, and the third well, respectively, of each row. Mix the contents of the wells by gently tapping the sides of the plate. Centrifuge the plate at the appropriate conditions established for the centrifuge. Resuspend the cell buttons by manually tapping the plate or with the aid of a suitable mechanical shaker. Read the optical densities at different wells using a suitable automated photometric microtiter plate reader. Compare the optical density of each well in the Blank Row with the optical density of the wells to which the corresponding Control preparation $A_{1}$, Control preparation B, or Test preparation were added. [NOTE-A high optical density comparable to those obtained for the wells in the Blank Row indicates negative results (no hemagglutination), which can be corroborated by visual observation of smooth suspensions. A low optical density indicates positive results (hemagglutination), which can be corroborated by visual observation of formation of clumps.] The ble group of Red Bleod Cells is $\Lambda, B$, of O-ceording to whether the Test preparation is hemagglutinated by $A n t i-A$ reagent, Anti-Breagent, or neither, respecThe blood group of Red Blood Cells is A, B, AB, or O accordingly as the Test preparation is hemagglutinated by Anti-A reagent, Anti-B reagent, both reagents, or neither, re-
spectively. The blood group of the Test preparation conforms to the blood group indicated on the label. Thest is not valid if Control preparation $A_{+}$and Contol preparat tion $B$ are not gegolutinated by Anti A reagent and Anti Bre agent, respectively, and both Control preparations are not agglutinated by Anti-AB-rent. The test is not valid if Control preparations for Blood Group A and Blood Group B red blood cells are not agglutinated by Anti-A Reagent and Anti-B Reagent, respectively, or if both Control preparations are not agglutinated by Anti-AB Reagent. The test is also not valid if the Test preparation is not agglutinated by Anti- $A B$ reagent but is agglutinated by either Anti-A reagent or Anti-B reagent, or is agglutinated by Anti-AB reagent but not by either Anti-A reagent or Anti-B reagent.
B: Rh type-
TEST 1-
Anti-D $\left(R h_{o}\right)$ reagent-Use anti-D $\left(\mathrm{Rh}_{0}\right)$ blood grouping reagent approved for use in microtiter plate tests. Dilute, if necessary, following the manufacturer's instructions.

Test preparation-On the day of use, dilute Red Blood Cells with $0.9 \%$ saline to obtain a $2 \%$ to $5 \%(\mathrm{v} / \mathrm{v})$ suspension.

Procedure-On a suitable U-bottom microtiter plate, place 1 drop each of $0.9 \%$ saline and Anti-D $\left(R h_{o}\right)$ reagent in two separate wells. Label them as the B well (Blank) and the T well, respectively. Add 1 drop of Test preparation to each well, and mix by gently tapping the side of the plate. Centrifuge the plate at appropriate conditions established for the centrifuge. Resuspend the cell buttons by manually tapping the plate or with the aid of a suitable mechanical shaker. Read the optical densities of the wells using a suitable automated photometric microtiter plate reader, and determine if the Red Blood Cells in the T well is agglutinated as described under Identification test $A$. If the T well indicates negative results (no hemagglutination), incubate the
plate at $37^{\circ}$ for 15 minutes, centrifuge, resuspend the cells, and read the optical densities of the wells as above. Agglutination of cells after immediate-spin or after $37^{\circ}$ incubation indicates Rh positive typing of Red Blood Cells. The test is valid if cells in the B well are not agglutinated. If the cells are not agglutinated in the T well, proceed as directed in Test 2.

## TEST 2-

Anti-D reagent-Use anti-D blood grouping reagent approved for use for a weak D blood group test.

Antihuman globulin reagent-Use polyspecific or antiIgG antihuman globulin reagent. Dilute, if necessary, following the manufacturer's instructions.

Control preparation-Use IgG-coated red cells approved for use as a control for Rh typing. Dilute with $0.9 \%$ saline to obtain a $2 \%$ solution.

Test preparation-Prepare as directed for Test 1.
Procedure—Place 1 drop of $0.9 \%$ saline into a suitable test tube and 1 drop of Anti-D reagent in another, and mark them as the Blank and Anti-D, respectively. To each tube add 1 drop of Test preparation, mix, and incubate at $37^{\circ}$ for 15 to 30 minutes. Centrifuge the tubes at about 1000 g for 15 to 30 seconds. Gently resuspend the cell buttons, and examine them for hemagglutination (formation of clump) by visual examination. The Rh typing of Red Blood Cells is positive or negative according to whether the cells in Anti-D tube are agglutinated or not. If the cells are not agglutinated, add 1 mL of $0.9 \%$ saline to the Anti-D tube, and resuspend the cells. Centrifuge the tube at about 1000 g for 1 minute and remove the saline completely. Repeat the step two to three times more to wash the Red Blood Cells. Add 1 drop of $0.9 \%$ saline and 1 to 2 drops of Antihuman globulin reagent to the Anti-D tube. Mix gently, and centrifuge the tube at about 1000 g for 15 to 30 seconds. Gently resuspend the cell button, add 1 drop of Control prepara-
tion, mix gently, centrifuge as above, and examine for agglutination. The Rh Type of the Test preparation conforms to the Rh Type indicated on the label. The test is not valid if the cells in the Anti-D tube are not agglutinated after addition of the Control preparation. Also, for the test to be valid, the cells in the Blank tube not-must not beagglutinated. $\triangle U S P 28$

## Add the following:

${ }^{4}$ Visual inspection-Inspect visually during storage and immediately prior to use. If the color or physical appearance is abnormal or there is any indication or suspicion of microbial contamination, the unit is unsuitable for transfusion. $\triangle$ USP28

## Add the following:

${ }^{\wedge}$ Hemoglobin content-
Drabkin's solution-Dissolve Drabkin's reagent in a suitable volume of water, and add a suitable volume of a $30 \%$ (w/v) polyoxyethylene (23) lauryl ether solution such that the final concentrations of potassium cyanide, potassium ferrocyanide, and polyoxyethylene (23) lauryl ether in the solution are approximately $0.75 \mathrm{mM}, 0.6 \mathrm{mM}$, and $0.015 \%$, respectively. Store the solution in the dark between $18^{\circ}$ to $26^{\circ}$. [Caution-Drabkin's reagent and Drabkin's solution contain cyanide and are HIGHLY TOXIC. Do not inhale or swallow or allow contact with skin or with eyes. Wear suitable protective clothing, gloves, and eye and face protection. Do not mix with acids. Contact with acids liberates a very toxic gas. If ingested, perform gastric lavage, and immediately call a physician.]

## Blank solution: water.

Standard solution A-Transfer about 300 mg USP Hemoglobin RS, accurately weighed, to a $2-\mathrm{mL}$ volumetric tube, add 1 mL water, dissolve, dilute with water to volume, and mix.

Standard solution B-Mix $50 \mu \mathrm{~L}$ of Standard solution $A$ with $25 \mu \mathrm{~L}$ of water.

Standard solution C—Mix $50 \mu \mathrm{~L}$ of Standard solution $A$ with $100 \mu \mathrm{~L}$ of water.

Test solution-Mix $50 \mu \mathrm{~L}$ of Red Blood Cells with $50 \mu \mathrm{~L}$ of water.

Procedure-Label suitable tubes as B1, B2, SA1, SA2, SB1, SB2, SC1, SC2, T1, and T2. Add 5.0 mL of Drabkin's solution to each tube. Add $20 \mu \mathrm{~L}$ of water to each of B1 and B2, $20 \mu \mathrm{~L}$ of Standard solution $A$ to each of SA1 and SA2, $20 \mu \mathrm{~L}$ of Standard solution B to each of SB1 and SB2, 20 $\mu \mathrm{L}$ of Standard solution $C$ to each of SC1 and SC2, and 20 $\mu \mathrm{L}$ of Test solution to each of T 1 and T 2 , rinsing the pipet tip three to four times with Drabkin's solution, and mix. Allow to stand for at least 15 minutes at room temperature. [NOTERed Blood cells with appreciable carboxyhemoglobin content, such as those obtained from smokers, may require longer reaction time. If the donor characteristics are not known, the incubation time should be optimized prior to testing.] Read the absorbances of the solutions against the solution in tube B1 at 540 nm . The absorbance of the solution in tube B 2 is recorded at the end. The test is not valid if the absorbance of the solution in tube B2 is not within $\pm 0.005$.

Calculations-Calculate the concentrations, in mg per mL , of hemoglobin in Standard solution A, B, and C. Plot a calibration curve of absorbance values against the hemoglobin concentration by drawing a best-fit straight line using the least-square linear regression analysis. From the absorbance value of the Test solution, obtain the concentration, in mg per mL , of hemoglobin in the Test solution. Multiply the value by 2 to obtain the concentration, in mg per mL , of hemoglobin in Red Blood Cells. Calculate the total hemoglobin content in the Red Blood Cells unit, in g, by the formula:

Conc. of hemoglobin (in $\mathrm{mg} / \mathrm{mL}$ ) $\times$ the volume of the Red Blood Cells unit (in mL) $/ 10^{3}$. $\mathbf{\Delta U S P 2 8}$

## Add the following:

${ }^{4}$ Leukocyte count-[NOTE-Perform at least six repeaf the .f Pipet $40 \mu \mathrm{~L}$ of a suitable red cell-lysing agent into a clean test tube, add $100 \mu \mathrm{~L}$ of Red Blood Cells diluted with $0.9 \%$ saline, if necessary, such that the hematocrit of Red Blood Cells is not greater than $60 \%$. Mix by pipetting up and down several times. Add $360 \mu \mathrm{~L}$ of $0.01 \%$ (w/v) crystal violet in $15 \%(\mathrm{v} / \mathrm{v})$ acetic acid into the mixture, and mix thoroughly. Fit a hemocytometer with a $50-\mu \mathrm{L}$ counting volume and a bright background, with a cover slip, and load the counting chamber with the mixture until the counting area is completely covered, but not overfull. Cover the counting chamber with a suitable moist lid to prevent evaporation, and allow to settle undisturbed for 10 to 15 minutes. Remove the lid, place the chamber on the stage of a light microscope fitted with $10 \times$ ocular lens and $20 \times$ objective. Count the leukocytes in the entire $50-\mu \mathrm{L}$ counting volume. Calculate the leukocyte count in Red Blood Cells, expressed in leukocytes per $\mu \mathrm{L}$, by dividing the observed leukocyte count by 10. Calculate the total number of leukocytes in the Red Blood Cells unit by using the following formula:

Total leukocytes $=$ leukocytes $/ \mu \mathrm{L} \times 10^{3} \times$ the volume of the Red Blood Cells unit in mL. |  |
| :--- | :--- | :--- |
| 28 |

## Add the following:

${ }^{\wedge}$ Adequacy of deglycerolization (for Red Blood Cells, De-glycerolized)-Interrupt the last wash cycle of the deglycerolization process at a point where the wash fluid is visible in the clear tubing segment leading to the waste receptacle. Hold the tubing against a well-lighted, white background. Note the coloration of the fluid in the tubing, and compare
it to a suitable hemolysis color comparator standard. The color of the fluid should be no stronger than the block indicating $3 \%$ hemolysis. [NOTE-If the level of hemolysis is more than $3 \%$, continue the wash process, and repeat the test until the color is within acceptable limits.] $]_{\triangle U S P 28}$

## BRIEFING

Whole Blood, USP 27 page 262 and page 445 of PF 29(2) [Mar.-Apr. 2003]. It is proposed to revise the existing abbreviated monograph for Whole Blood to update the Definition and sections on Packaging and storage, Expiration date, and Labeling and to include test specifications, procedures, and acceptance criteria consistent with the current FDA requirements. The proposed hemoglobin content of 50 g is the minimum amount of hemoglobin in a unit of red cells collected under minimally acceptable parameters, specifically, a $405-\mathrm{mL}$ collection (the lower limit of a $450 \pm 10 \% \mathrm{~mL}$ collection) with a minimum donor hematocrit of $38 \%$. In this case, a $405-\mathrm{mL}$ collection corresponds to $405 \mathrm{~mL} \times 0.38=154 \mathrm{~mL}$ red cell mass, which equates approximately to 50 g of hemoglobin. The volume stated refers to the total fluid volume, including any residual plasma, anticoagulants, or additive solution. Total volumes will vary depending on processing method. A range is given here to accommodate process methods and to give clinicians a reference for calculating transfusion volumes given to a patient.

The procedures for $A B O$ blood group, Rh type, and Leukocyte count were adapted from the $A A B B$ Technical Manual (50th Anniversary Edition), 2002, 14th Edition, American Association of Blood Banks, Bethesda, MD. The procedure for Hemoglobin content is recommended by the National Institutes of Health and approved by the International Committee on Standardization in Hematology as the standard method for hemoglobin assay.
(BBP: R. Tirumalai) RTS-40461-2

## Change to read:

» Whole Blood conforms to the regulations of the federal Food and Drug Administration concerning biologics $(640.1-640.7)$
${ }^{\wedge}$ (21 CFR 640.1 to 640.6) $)_{\triangle U S P 28}$
(see Biologics $\langle 1041\rangle$ ). It is blood that has been collected from suitable whele blood
A 4 USP28
human donors under rigid aseptic precautions, for transfusion to human recipients It contams eitrate ion (acid eitrate dextrose or citrate phesphate dextrese or eitrate phosphate dextrese with adenine) or Heparim Sodium as an antieoagulant. It may consist of blood
from which the antihemophilic factor has been removed, in which ease it is termed "Modified." It meets the requirements of tests made on a pilot sample in nomreacting in a serologic test for syphilis; for $\Lambda B \Theta$ blood group-designation; and for classification in regard to Rh type, ineluding those tests specified for var rants and other related factors. Containers of Whole Blood shall not be entered for sterility testing prior to use of the blood for transfusion. [NOTE-Whole Blood may be issued prior to the results of testing, un der the specified provisions.]
© or for further processing into one or more of its components for transfusion. It contains a citratebased anticoagulant. Whole Blood must be tested for syphilis, hepatitis B, and human T-cell virus Type 1 and Type 2, and unexpected antibodies to red cell antigens using approved commercially awilable test kits, the results of which must be be tow the limits of detection specified in the respective test kits. In addition, Whole Blood must also be tested for hepatitis $C$ and for antibodies to HIV using a nueleic acid assay, the results of which must be below the approved limits of detection for the procedure. A unit (dose) of Whole Bloed eentains a minimum of 50 g (basedon a minimum donor hematerrit $38 \%$ ) fhemeglobin in a total volume of $450 \mathrm{~mL} \pm 10 \%$ or $500 \mathrm{~mL} \pm 10 \%$ as indicated on the label. Whole Blood may be further processed by filtration for removal of let koeytes, in which case the quantity of residual let koeytes in the unit of Whole Blood must be less than $5 \times 10^{6}-$ Whole Blood must be tested for syphilis, hepatitis B virus, human T-cell virus (HTLV) type I and type II, and tested for blood group and Rh factors and unexpected antibodies to red cell antigens using FDA-licensed commercially available test kits, the results of which must
be below the approved upper limit of detection specified in the respective test kits. In addition, Whole Blood must also be tested for hepatitis C and HIV using using FDA-approved nucleic acid assays, the results of which must be below the approved upper limit of detection for the method. A unit (dose) of Whole Blood contains a minimum of 50 g (based on a minimum donor hematocrit of $38 \%$ ) of hemoglobin in a total volume of 450 mL $\pm 10 \%$ or $500 \mathrm{~mL} \pm 10 \%$ as indicated on the label. Whole Blood may be further processed. When filtered for removal of leukocytes, the quantity of residual leukocytes in the unit of Whole Blood must be less than $5 \times 10^{6} \cdot$ AUSP28 $^{\text {U }}$

## Change to read:

Packaging and storage-Preserve in the eontainer inte-which-it was originally drawn. Use pyregen free, sterile containers of coler less, transparent, Type- -or Type- II glass, or of a suitable-plastie material (see Transfusion and Infusion Assemblies $\langle 164\rangle$ ). The enntainer is provided with a hermetic eontamination proef clesureAccessory equipment supplied with the blood is sterile and pyregen free (see Transfusion and Infusion Assemblies $\langle 164\rangle$ ). Store at a temperature between $1^{\circ}$ and $6^{\circ}$ held constant within a $2^{\circ}$ range, exeept during shipment, when the temperature may be bewween $1^{\circ}$ and $10^{\circ}$. The eentainer of Whele-Bleod is aeempanied by at least ene securely attached smaller container holding an original pilet sample of blood, for test purpeses, taken at the same time from the same dener, with the same antieergulant. Both centainers bear the dener's identification symbel or number.
${ }^{\wedge}$ Collect into an approved container (see Transfusion and Infusion Assemblies and Similar Medical Devices 〈161〉) containing a sterile, pyrogen-free approved anticoagulant (see USP monographs Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution, or Anticoagulant Citrate Phosphate Dextrose Adenine Solution). Store Whole Blood in the original container, or transfer to an equivalent one using a technique that does not compromise sterility. Whole Blood is stored at a temperature between $1^{\circ}$ and $6^{\circ}$ unless platelets are to be prepared, in which case the blood is stored for no longer than 6 hewrs
following collection at a temperature between $20^{\circ}$ to $24^{\circ} 8$ hours following collection at room temperature. (see General Notices and Requirements). $\mathbf{\Delta U S P 2 8}$

## Change to read:

Expiration date-Its expiration date is not later than 21 days after the date of bleeding the doner, if it contains anticoagulant cittate dextrose solution or anticeagulant ittrate phosphate dextrose solut tion, as the anticongulant; or not later than 35 days if it contains anticoagulant citrate phesphate dextrese adenine-solution as the antieoagulant; or not later than- 48 hours after date of bleeding the doner, if it contains heparin ion as the antieongulant.
${ }^{\Delta}$ Whole Blood collected in Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution, or in Anticoagulant Citrate Phosphate Dextrose-Dextrose Solution may be stored for up to 21 days at $1^{\circ}$ to $6^{\circ}$ after the blood has been drawn. Whole Blood collected in Anticoagulant Citrate Phosphate Dextrose Adenine Solution may be stored for up to 35 days at $1^{\circ}$ to $6^{\circ}$. If the hermetic seal of the container is broken during collection, preparation, or further processing, the expiration date is not later than 24 hours after the seal is broken (when blood is stored at $1^{\circ}$ to $6^{\circ}$ ), but not to exceed the original expiration date of the unit. $\triangle U S P 28$

Change to read:
Labeling-Label it to indicate the doner classification, quantity and kind of anticoagulant used and the correspending volume of blood, the designation of $A B O$ blood group and Rh factors, and in the case of Group $O$ blood, whether or not isoagglatinin titers or other tests for exclusion of specified Group-O bloods were per formed and to indieate any group classifieation of the blood result ing therefrom. If an $A B O$ blood group color scheme is used, the tabeling color used shall be: Group A (yellow), Group B (pink), Group O (blue), and Group AB (white). Label it also with the type and result of a serolegie test for syphilis, of to indicate that it was nomreactive in such test; and with the type and result of a test for hepatitis $B$ surface antigen, or to indicate that it was non reactive in such test. If it has been issued prior to determination of test results, tabel it also with a waming not to use it until the test results have been received and to specify that a crossmatch be performed. Where applicable, label it as "Modified," and indicate that antihemophilic factor has been removed and that it should not be used for patients requiring that factor.
${ }^{\Delta}$ Label the container to indicate the volume of the Whole Blood collected from the donor, the collection date, the donation number or other coding means to uniquely identify the unit and to provide traceability to the donor, and itsex piration date. Label it to indicate the ype of anticoagulant und it the storage temperature and the expiration
date (see below). Label it to indicate the type of anticoagulant or other preservative solution used to collect it. Label it also to identify donor status (i.e., volunteer or paid). Label it also with the following statements: "See Circular of Information for indications, contraindications, cautions, and methods of infusion."; "Properly identify recipient."; and "Caution: Rx only." Label it to indicate the ABO group and Rh type, as indicated in Table 1. [NOTE-Each Whole Blood product must have a determination made as to its ABO group and Rh type and specificity of unexpected red cell antibodies, if any.] If an ABO blood group color scheme is used, use the following labeling color: Group A (yellow), Group B (pink), Group O (blue), and Group AB (white). Label Whole Blood with the type and results of tests for adventitious agents. If it has been issued prior to determination of the test results, label it also with a warning not to use it until the test results have been received and to further specify that acress match must be performed. If it has been issued prior to determination of the test results, label it also with the warning "Donor Untested" and to further specify "Uncrossmatched Blood," when appropriate. If the unit of Whole Blood was filtered to reduce leukocytes, label it as "Whole Blood, Leukocytes Reduced."

Table 1

| ABO Group | Rh Type |
| :---: | :--- |
| A | Positive |
| A | Negative |
| B | Positive |
| B | Negative |
| AB | Positive |
| AB | Negative |
| O | Positive |
| O |  |
|  |  |

## Add the following:

${ }^{4}$ USP Reference standards $\langle 11\rangle — U S P$ Hemoglobin $R S_{.}{ }_{\triangle U S P 28}$

## Add the following:

${ }^{4}$ Identification-
A: ABO blood group-
Anti-A reagent, Anti-B reagent, Anti-AB reagent, Control preparations, and Procedure-Proceed as directed under Red Blood Cells.

Test preparation-Centrifuge at $4^{\circ}$ a suitable volume of Whole Blood at 5000 g for 5 minutes. Remove the plasma from the top, taking care not to disturb the pellet of red blood cells at the bottom. Add $0.9 \%$ saline to obtain a final volume that is about equal to the volume of Whole Blood. Resuspend the pellet, and centrifuge as above. Repeat the procedure once more. Dilute the red blood cells with $0.9 \%$ saline to a suspension to obtain a concentration of red blood cells that is about the same as those of the Control preparations.

B: Rh type-
TEST 1:
Anti-D $\left(R h_{0}\right)$ reagent and Procedure-Proceed as directed under Red Blood Cells.

Test preparation-Prepare as directed for Identification test $A$ under Red Blood Cells.

TEST 2:
Anti-D reagent, Antihuman globulin reagent, Control preparation, and Procedure-Proceed as directed under Red Blood Cells.

Test preparation-Prepare as directed for Test 1._USP28

## Add the following:

${ }^{\mathbf{4}}$ Visual inspection-Inspect visually during storage and immediately prior to use. If the color or physical appearance is abnormal or there is any indication or suspicion of microbial contamination, the unit is unsuitable for transfusion. $\triangle U S P 28$

## Add the following:

${ }^{\Delta}$ Hemoglobin content—Proceed as directed under Red Blood Cells, except to use $20 \mu \mathrm{~L}$ of Whole Blood (without dilution) as the Test solution. Calculate the hemoglobin concentration in Whole Blood from the calibration curve as directed under Red Blood Cells, except do not multiply by 2. $\mathbf{4}$ USP28

## Add the following:

${ }^{4}$ Leukocyte count (For units labeled as Whole Blood, Leukocytes Reduced)—Proceed as directed under Red Blood Cells, except to use $100 \mu \mathrm{~L}$ of Whole Blood. $\Delta$ USP28

## Briefing

Brompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution, USP 27 page 272-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40618-8

## Brompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution <br> (Monograph under this new title-to become official June 1, 2005) <br> (Current monograph title is Brompheniramine Maleate and Pseudoephedrine Sulfate Syrup)

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\Delta$ USP28

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\quad$ USP ${ }^{\text {. }}$

## BRIEFING

Brompheniramine Maleate and Pseudoephedrine Sulfate Syrup, USP 27 page 273-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40618-8

## Brompheniramine Maleate and Pseudoephedrine Sulfate Syrup

(Current title_not to change until June 1, 2005)
Monograph title change-to become official June 1, 2005
See Brompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution

## Add the following:

${ }^{\boldsymbol{4}}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR SYRUP PACKAGED IN SINGLE-UNIT CONTAINERS: meets
the requirements. $\triangle$ USP28

## Add the following:

${ }^{\Delta}$ Deliverable volume $\langle 698\rangle$ -
FOR SYRUP PACKAGED IN MULTIPLE-UNIT CONTAINERS:
meets the requirements. $\triangle U S P 28$

## BRIEFING

Butalbital, Acetaminophen, and Caffeine Tablets, USP 27 page 287 and page 615 of $P F$ 29(3) [May-June 2003]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-20

## Change to read:

Dissolution Procedure for a Pooled Sample
$\Delta$
$\left\langle\mathbf{7 1 1 1}^{\text {USP28 }}\right.$
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle$ USP28
Mobile phase and Chromatographic system-Prepare as directed in the Assay.
Standard preparation-Prepare a solution in methanol having known concentrations of about 0.02 A mg of USP Acetaminophen RS per mL, $0.02 B \mathrm{mg}$ of USP Butalbital RS per mL, and $0.02 C \mathrm{mg}$ of USP Caffeine RS per mL , in which $A, B$, and $C$ are the labeled amounts, in mg, of acetaminophen, butalbital, and caffeine, respectively, per Tablet. Transfer 5.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Procedure-Filter apertion the solution under test
${ }^{\Delta}$ the pooled sample ${ }_{\Delta U S P 28}$
through a suitable filter having a porosity of $10 \mu \mathrm{~m}$ or finer. Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the filtrate and the Standard preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantities, in mg, of butalbital $\left(\mathrm{C}_{11} \mathrm{H}_{16} \mathrm{~N}_{2} \mathrm{O}_{3}\right)$, acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$, and caffeine $\left(\mathrm{C}_{8} \mathrm{H}_{10} \mathrm{~N}_{4} \mathrm{O}_{2}\right)$ dissolved by the same formula:

$$
900 C\left(r_{U} / r_{S}\right),
$$

in which $C$ is the concentration, in mg per mL , of the appropriate USP Reference Standard in the Standard preparation, and $r_{U}$ and $r_{s}$ are the peak responses of the corresponding analyte obtained from the solution under test and the Standard preparation, respectively.
Tolerances-Not less than $80 \%(Q)$ of the labeled amounts of $\mathrm{C}_{11} \mathrm{H}_{16} \mathrm{~N}_{2} \mathrm{O}_{3}, \mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$, and $\mathrm{C}_{8} \mathrm{H}_{10} \mathrm{~N}_{4} \mathrm{O}_{2}$ are dissolved in 30 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results
conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number |
| :---: | :---: | :--- |
| Stage | Tested |$\quad$| Acceptance Criteria |
| :---: |
| $\mathrm{S}_{1}$ |$\quad 6 \quad$| Average amount dissolved is not less |
| :--- |
| than $Q+10 \%$. |

## BriEfing

Calcium Lactate Tablets, USP 27 page 310-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40315-3

Change to read:
Dissolution Proedure for a Pooted Sample

Medium: water, 500 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle U S P 28$
Determine the amount of $\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{CaO}{ }_{6} \cdot 5 \mathrm{H}_{2} \mathrm{O}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{CaO}_{6} \cdot 5 \mathrm{H}_{2} \mathrm{O}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :--- |
| Stage | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{2}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## BRIEFING

Calcium Pantothenate Tablets, USP 27 page 312—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40315-1

## Change to read:

Dissolution Procedure for a Pooled Sample

Medium: water, 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.

## Procedure-

${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.
Determine the amount of $\mathrm{C}_{18} \mathrm{H}_{32} \mathrm{CaN}_{2} \mathrm{O}_{10}$ dissolved, employing the procedure set forth in the Assay for calcium pantothenate, Method 1, under Water-Soluble Vitamins Tablets, except to omit the Internal standard preparation, using filtered pertions of the selution under test,
$\Delta$ the pooled sample,
suitably dilu sample, USSP28
suitably diluted with Dissolution Medium if necessary, in comparison with a Standard solution having a known concentration of USP Calcium Pantothenate RS in the same Medium.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{18} \mathrm{H}_{32} \mathrm{CaN}_{2} \mathrm{O}_{10}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :--- |
| Stage | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> $\mathrm{S}_{2}$ |
| $\mathrm{~S}_{3}$ | 12 | equal to or greater than $Q+5 \%$. <br> Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## BRIEFING

Carboprost Tromethamine, USP 27 page 337 and page 1436 of $P F$ 29(5) [Sept.-Oct. 2003]. It is proposed to revise the new section on Other requirements that was presented in PF 29(5). Requirements are provided for Bacterial endotoxins when Carboprost Tromethamine is labeled as sterile or as being subject to further processing during the preparation of injectable dosage forms. The requirements for Bacterial endotoxins are derived from the monograph on Carboprost Tromethamine Injection, for which a Bacterial endotoxins requirement was adopted via the First Supplement to USP 26 (see page 2948).
(PA2: C. Anthony) RTS-40565-1

## Add the following:

${ }^{\Delta}$ Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. $\triangle$ USP28

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Carboprost Tromethamine $R S$.
${ }^{\boldsymbol{4}}$ USP Endotoxin RS. .USP28

## Add the following:

${ }^{\Delta}$ Other requirements-Where the label states that Carboprost Tromethamine is sterile, it meets the requirements der for Sterility Fest- $\langle 74\rangle$ ): and for Bacterial endotoxins under Carboprost Tromethamine Injection. Where the label states that Carboprost Tromethamine must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Carboprost Tromethamine Injection. $\mathbf{\Delta U S P 2 8}$

## BRIEFING

Cefpodoxime Proxetil, USP 27 page 377. It is proposed to revise the test for Heavy metals by replacing Method I with Method $I I$. Method $I$ is applied to articles that yield clear, colorless Test Preparations. Method II is applied to substances that do not yield clear, colorless solutions or to substances that interfere with the precipitation of metals by the sulfide ion. Method II is also used
for fixed and volatile oils. Because Cefpodoxime Proxetil does not dissolve in water, it is proposed to use Method II, which involves igniting the specimen under test to obtain a sulfated residue that is then dissolved in hydrochloric acid.
(PA7a: W. Wright) RTS-40517-1

Change to read:
Heavy metals, M $I\langle z 34\rangle$;
${ }^{\mathbf{\Delta}}$ Method II $\langle 231\rangle$ : $_{\mathbf{\Delta S S P 2 8}}$
$0.002 \%$.

## BriEfing

Cefprozil for Oral Suspension, USP 27 page 380-See briefing under Amoxicillin and Clavulanate Potassium for Oral Suspension.
(PA7: W. Wright) RTS-40663-2

## Add the following:

${ }^{\Delta}$ Deliverable volume $\langle 698\rangle$ -
FOR POWDER PACKAGED IN MULTIPLE-UNIT CONTAINERS:
meets the requirements. $\triangle U S P 28$

Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules, USP 27 page 417-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40315-2

## Change to read:

Dissolution Procedure for a Pooled Sample
${ }_{\langle }^{4}$ U 411$\rangle-$
Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 30 minutes.
Determine the amounts of chlordiazepoxide hydrochloride $\left(\mathrm{C}_{16} \mathrm{H}_{14} \mathrm{ClN}_{3} \mathrm{O} \cdot \mathrm{HCl}\right)$ and clidinium bromide $\left(\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{BrNO}_{3}\right)$ dissolved using the following method.

- Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\qquad$ Solution $A$-Dissolve 1.92 g of sodium 1-pentanesulfonate in
900 mL of water. Adjust the solution with dilute sulfuric acid (1 in 100 ) to a pH of $3.8 \pm 0.1$, dilute with water to 1.0 liter, and mix.
Mobile phase-Prepare a filtered and degassed mixture of Solution $A$, tetrahydrofuran, and methanol (75:18:6). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Chromatographic system-The liquid chromatograph is equipped with a $212-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph replicate injections of the Standard solution, and record the peak responses as directed for Procedure: the resolution between the two components is not less than 5.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about $100 \mu \mathrm{~L}$ ) of the Standard solution and aflered portion of the solution under test
$\Delta_{\text {the pooled sample }}^{\text {USSP28 }}$
into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.6 for clidinium bromide and 1.0 for chlordiazepoxide hydrochloride. Calculate the amounts of chlordiazepoxide hydrochloride ( $\mathrm{C}_{16} \mathrm{H}_{14} \mathrm{ClN} \mathrm{N}_{3} \mathrm{O} \cdot \mathrm{HCl}$ ) and clidinium bromide $\left(\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{BrNO}_{3}\right)$ dissolved in comparison with a Standard solution having known concentrations of USP Chlordiazepoxide Hydrochloride RS and USP Clidinium Bromide RS, similarly prepared and chromatographed.
Tolerances- Not less than $75 \%(Q)$ each of the labeled amounts of $\mathrm{C}_{16} \mathrm{H}_{14} \mathrm{ClN}_{3} \mathrm{O} \cdot \mathrm{HCl}$ and $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{BrNO}_{3}$ are dissolved in 30 minutes:
$\Delta$ the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
|  | Number |  |
| Stage | Tested | Acceptance Criteria |

## BRIEFING

Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Oral Solution, USP 27 page 432 -See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40618-9

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle-$
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\quad$ USP28

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-

TAINERS: meets the requirements. $\triangle U S P 28$

## Briefing

Clarithromycin for Oral Suspension, USP 27 page 463-See briefing under Amoxicillin and Clavulanate Potassium for Oral Suspension.
(PA7a: W. Wright) RTS-40663-3

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR POWDER PACKAGED IN SINGLE-UNIT CONTAINERS:
meets the requirements. $\triangle U S P 28$

## Change to read:

Deliverable volume $\langle 698\rangle$ -
© FOR POWDER PACKAGED IN MULTIPLE-UNIT CONTAIN-
ERS: $\triangle U S P 28$
meets the requirements.

## BRIEFING

Clonidine Transdermal System, page 1441 of $P F$ 29(5) [Sept.-Oct. 2003]. On the basis of comments received, it is proposed to revise the Identification, Chromatographic purity, and Assay sections. It is also proposed to revise the Reference standards section to add new Clonidine Related Compound B RS. Analyses were performed with a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ Capcell-UG 120 (Shiseido) column that contains $5-\mu \mathrm{m}$ L1 packing. Typical retention times are about 3.5 for clonidine and 5.6 minutes for clonidide related compound B .
(PA5: A. Wilk) RTS-40494-1

## Add the following:

## ${ }^{\wedge}$ Clonidine Transdermal System

» Clonidine Transdermal System contains not less than 80.0 pereent and not more than 120.0 pereent ef the labeled amount ofelonidine $\left(\mathrm{C}_{2} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}\right) \cdot 2.0 \mathrm{mg}$ and net more than 3.0 mg
ef clonidine, if labeled to deliver 0.1 mg of clonidine per day for one week; not less than 4.0 mg and not more than 6.0 mg of clonidine, if labeled todeliver 0.2 mg of clonidine per day for one week; and not less than 6.0 mg and not more than 9.0 mg of clenidine, if labeled to deliver 0.3 mg of elonidine per day for one week. 80.0 percent and not more than 120.0 percent of the labeled amount of clonidine $\left(\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}\right)$.

Packaging and storage-Preserve in sealed, single-dose containers at a temperature not exceeding $30^{\circ}$.

Labeling-The label states the total amount of clonidine in the Transdermal System and the release rate, in mg per day, for the duration of the application of one system.

USP Reference standards $\langle 11\rangle$ —USP Clonidine Hydrochloride RS. USP Clonidine Related Compound B RS.

NOTE-Throughout the following procedures avoid the use of tetrahydrofuran stabilized with butylated hydroxytoluene (BHT). In the presence of peroxides, BHT may react with clonidine, producing impurity peaks.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
pH 9.2, 2M Tris buffer-Dissolve 121.14 g of tris(hydroxymethyl)aminomethane in 500 mL of water. Adjust pH to 9.2 using dilute hydrochloric acid.

Sample preparation-Carefully peel the release liner from each Transdermal System and place a number of Transdermal Systems, equivalent to about 25 mg of clonidine into a $50-\mathrm{mL}$ screw-capped centrifuge tube. Add 5 mL of chloroform and vortex for 5 minutes. Let stand for 30 minutes, vortexing intermittently. Transfer the chloroform solution to another $50-\mathrm{mL}$ centrifuge tube and wash the residue with an additional 3 mL of chloroform, combining the extracts. Add 2 mL of 0.5 N hydrochloric acid to the
extract, vortex for 1 minute, and centrifuge at about 1000 rpm for 4 minutes. Remove and discard the bottom chloroform layer. Extract the aqueous layer with 4 mL of chloroform. Centrifuge at about 1000 rpm for an additional 5 minutes and again discard the bottom chloroform layer. Add 5 mL of pH 9.2 , 2M Tris buffer and 3 mL of methylene chloride. Vortex for 1 minute. Centrifuge at about 1000 rpm for 4 minutes. Transfer the bottom methylene chloride layer into a $100-\mathrm{mL}$ beaker and dry the methylene chloride with anhydrous sodium sulfate (about $1 / 4$ liquid height). Decant and evaporate to dryness with a stream of nitrogen. Dry at $105^{\circ}$ for 30 minutes and allow to cool in a desiccator. Determine the infrared absorption spectrum of the residue obtained from the Sample preparation and USP Clonidine Hydrochloride RS in the wavelength region of 3500 to $3600 \mathrm{~cm}^{-1}$.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Uniformity of dosage units $\langle 905\rangle$ : meets the requirements.
Drug release $\langle 724\rangle$ -
Medium: 0.001 M phosphoric acid; 80 mL for systems containing 5 mg or less of clonidine; 160 mL 200 mL for systems containing more than 5 mg of clonidine.

Time: 8, 24, 96, and 168 hours.
Apparatus 7 Proceed directed in the chapter. [Size of sample holder to come.]

Apparatus 7-Proceed as directed in the chapter, using the transdermal system holder-angled disk (see Figure $7 a)$. The appropriate size of the holder, 1.42 or 1.98 inches, should be chosen based on the size of the system to prevent overhang. Use $100-\mathrm{mL}$ beakers for Medium volumes of $80-$ mL and $300-\mathrm{mL}$ beakers for Medium volumes of 200 mL . Gently press the transdermal system to a dry, smooth, square
piece of cellulose membrane ${ }^{*}$, or equivalent, with the adhesive side against the membrane. Attach the membrane/system to a suitable inert sample holder with a Viton O-ring, or equivalent, such that the backing of the system is adjacent to, and centered on, the bottom of the sample holder. Trim the excess of cellulose membrane with scissors. Suspend each sample holder from the arm of a reciprocating shaker such that each system is continuously immersed in a beaker containing the specified volume of Medium. The filled beakers are weighed and pre-equilibrated to $32.0 \pm 0.3^{\circ}$ prior to immersing the test sample. Agitate the sample in an updown motion at a frequency of 30 cycles per minute with an amplitude of $2.0 \pm 0.1 \mathrm{~cm}$. The Medium must be added daily to the beakers during each interval to maintain sample immersion. At the end of each time interval, transfer the test sample to a fresh beaker containing the appropriate volume of Medium, weighed and pre-equilibrated to $32.0 \pm 0.3^{\circ}$.

Determine the amount of $\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}$ released by employing the following method.

Solvent Dissolve 2.04-g of menebasic petassium phesphate and 2.88 g of 1 - pentanesulfonic acid sodium 1- pentanesulfenate in 300 mL of water. Adjust with phespheric acid to a pH of 3.5 .
Mobile phase -Prepare a filtered and degassed mixture of Solvent and methanol (26:14). Make adjustments if neeessary (see Systen Suitability under Chromatography $\langle 624\rangle$ ). Use a filtered and degassed $0.1 \%$ solution of triethylamine in a mixture of water and methanol (70:30), adjust with phosphoric acid to a pH of $6.0 \pm 0.2$. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Fest solution At each of the test times, withdraw a 10
mL aliquet of the solution from each container.

[^9]Standard solution Prepare a solution of USP Clonidine Hydrochloride RS in 0.001 M phosphoric acid having a known concentration of elonidine similar to that of the Test solution.

System suitability solution-Prepare a solution of USP Clonidine Hydrochloride RS in 0.001 M phosphoric acid having a known concentration of about $10 \mu \mathrm{~g}$ per mL .

Standard solutions-Prepare a minimum of four standard solutions of USP Clonidine Hydrochloride RS in 0.001 M phosphoric acid having known concentrations of clonidine similar to those of the Test solutions.

Test solutions-At the end of each release interval, allow the beakers to cool to room temperature and make up for evaporative Medium losses by adding Medium to obtain the original weight. Mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210-\mathrm{mm} 220-$ nm detector and a $4.0-\mathrm{mm} \times 30-\mathrm{cm} 4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the tailing factor is not more than $\mathcal{Z 2 . 0}$; the capacity factor is not less than 0.5 ; the column efficiency is not less than 2000 theoretical plates; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure—Separately inject equal volumes (about 50 $\mu \mathrm{L} 25 \mu \mathrm{~L}$ ) of filtered portions of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Construct a standard curve of concentration ( $\mu \mathrm{g}$ per mL ) of clonidine in the Standard solutions versus peak area by linear regression analysis. The correlation coefficient is
not less than 0.995 . Calculate the release rate of clonidine by the formula:

## CV/TA,

in which $C$ is the concentration, $\mu \mathrm{g}$ per mL , of clonidine in the sample obtained from the standard curve; $V$ is the volume, in mL , of the Medium; $T$ is the time, in hours; and $A$ is the area, in $\mathrm{cm}^{2}$, of the transdermal system.

Tolerances The amer $\mathrm{C}_{2} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}$ released,as a per centage of the labeled amount of the dose absorbed in vive, as $\mu \mathrm{g}$ per hour per $\mathrm{cm}^{2}$, at the times specified conforms to Aceeptane Table 4.

| Fime (hours) | Amount dissolved |
| :---: | :---: |
| 8 | between 28\% and 68\% |
| 96 | between 116\% and 288\% |
| 168 | between 170\% and 357\% |
| Time (hems) | Amount dissolved (Hg/h |
|  | ( $\mathrm{m}^{2}$ ) |
| 8 | between 7.5 and 16.0 |
| 24 | between 1.5 and 6.0 |
| 96 | between 1.5 and-4.6 |
| 168 | between 1.5 and 3.3 |

The amoun of $\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}$ released, as a percentag of the tabeled ameunt of the dose absorbedin vive, as us per hour per $\mathrm{cm}^{2}$, at the time specified conforms to Aceeptance Table 4. The release rate of $\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}$ from the Transdermal System, expressed as $\mu \mathrm{g}$ per hour per $\mathrm{cm}^{2}$ at the times specified, conforms to Acceptance Table 4.

| Time <br> (hours) | Time for sampling <br> (hours) | Ament Release rate $\left(\mu \mathrm{g} / \mathrm{h} / \mathrm{cm}^{2}\right)$ |
| :---: | :---: | :---: |
| $0-8$ | 8 | between 7.5 and 16.0 |
| $8-24$ | 24 | between 1.5 and 4.6 |
| $24-96$ | 96 | between 1.5 and 4.6 |
| $96-168$ | 168 | between 1.5 and 3.3 |

## Chromatographic purity-

Buffer solution Dissolve 2.0 of of sodium 1-pentanesul fenate, 13.61 g of menobasic potassium phosphate, and 2 mL of triethylamine in abou 1000 mL of water in a 2 - liter velumetric flask, adjust with phosphoric acid to a pHef 4.0 $\pm 0.1$, dilute with water to volume, and mix.

Mobile phase Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $1: 1$ ), and, if neeessary, adjust with phosphoric acid to a pH of $4.5 \pm 0.1$. Make ad justments if neersary (see System Suitability under Chromatay (621)).
Biltuent 1 Dissolve 1 mL of triethylamine in about 800 mL of water in a 1 liter volumetric flask, adjust with phes phoric acid to a pH of $10.0 \pm 0.1$, dilute with water to wot tume, and mix. Transfer this solution to a 2 - liter volumetrie flask, dilute with aee itrile to volume, and mix.
Biltuent 2 Dissolve 1 mL of triethylamine and 4.36 g of dibasic petassium phesphate in about 800 mL of water in a 1- liter velumetric flask, adjust with phespheric acid to a pH of $10.0 \pm 0.1$, dilute with water to velume, and mix. Transfer this solution to a 2 - liter velumetrie flask, dilute with acetonitrile to volume, and mix.

Standar solution Dissolve an aceurately weighed quantity of USP Clonidine Hydrochloride RS in Diltent + to obtain a solution having a known concentration of about 0.1 mg per mL . Dilute an aceurately meastred volume of this solution quantitatively with Piltent 2 to obtain a solu-
tion having aknown concentration of about 16.2 нg of USP Glenidine Hydrechloride RS per mL (equivalent to about 14.0 нe of clenidine per mL).

Fest solution Carefully peel the release liner from each Transdermal System, and place a number of Transdermal Systems, equivalent abou 15 mg of elonidine, into a 150 mL polytef lined serew-cap tube. Add 30 mL of $n$ heptane, cap, and mix on a vortex mixer for 2 minutes. Allow to stand for about 3 hours, but every 30 minutes during this period mix on a vertex mixer until the Transdermal Systems are delaminated. Add 0.3 mL of methanol and 45 mL of 0.01 N sulfuric acid, shake for at least 2 minutes, and cen trifuge. Retain the $n$-heptane layer, and transfer the aqueous supernatant layer to a secend $150-\mathrm{mL}$ pelytef lined serew eap ube. Add 9 mL of ammenium hydroxide to the queous supernatant layer, and mix. Extract the $n$ heptane layer with an additional 45 mL of 0.01 N sulfuric acid for at least 2 minutes, and combine this queous supernatant layer with the first aqueous layer in the 150 mL polytef lined serew equ tube. [NOTE-The length of time of extration with 0.01 N sulfuric acid should not exceed 1 heur to avoid degradation of any related impurity that may be present.] Ex tract the aqueus layer by shaking vigorously for 2 minutes with of of 30 mL pertions of chloreform, collecting the chloreformextracts in a 150 - mL polytef lined serew eap tube. Evaperate the chloreform extracts under nitregen to dryness, and dissolve the residue in 15.0 mL of Diltuent 2.

Chromagraphic system (see Chromatography- (624)) The liquidehrematograph is equipped with a 210 - mm detec tor and a $-4.6 \mathrm{~mm} \times 25 \mathrm{~cm}$ column that contains packing E10. The flow rate is about 1 mL per minnte. Chromatograph the Statedard solution, and record the peak responses as directed for Proedtre: the column efficiency is not less
than 4000 theoretieal plater; the tailing factor is not more than 1.5 ; and the relative standard deviation for replieate injections is not more than $2.0 \%$.

Procedure Separately inject equal volumes (about 20 $\mu L)$ of the Staturd solution and the Test solution into the ehromatograph, record the chromatograms, and measure the peak responses. Caleulate the percentage of each impurity in the Transdermal Systems taken by the formula:-

$$
(230.10 / 266.56)(1.5 \mathrm{C} / N L)\left(r_{4} \psi_{s}\right),
$$

in which 230.10 and 266.56 are the moleeular weights of elenidine and-clonidine hydrochloride, respectively; $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Clenidine Hydroehloride RS in the Standard solution, $N$ is the number of Transdermal Systems taken to prepare the Test solution; $L$ is the labeled amount, in me, of clonidine in each Transdermal System taken; $r_{t}$ is the peak respense for each impurity ebtained from the Test solution; and $\Psi_{s}$ is the clonidine peak respense obtained frem the Standatd solution: not more than $1.4 \%$ of total impurities is found. not more than $1.4 \%$ of any impurity is found, and not more than $2.4 \%$ of total impurities is found.

Mobile phase, Diluent, System suitability solution, and Chromatographic system—Proceed as directed in the Assay.
Standard solution-Dissolve an accurately weighed quantity of USP Clonidine Related Compound B RS in tetrahydrofuran, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 1 mg per mL . Prepare a minimum of four Standard solutions in Diluent that bracket the expected clonidine related compound B concentration in the sample. The standard concentrations should be within the range of 0.2 to 10.0 $\mu \mathrm{g}$ per mL . Standard solutions are stable for up to 2 days if stored at $4^{\circ}$.

Test solution-Use the Test preparation as directed in the Assay.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of at least three Standard solutions that will bracket the expected sample concentration range and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the clonidine related compound B. Calculate the peak response ratios of the analyte, and plot the results. Determine the linear regression equation of the standards by the mean-square method, and record the linear regression equation and the correlation coefficient; it should be not less than 0.995 . Determine the concentration of the clonidine related compound B. Calculate the amount, in $\mu \mathrm{g}$ per $\mathrm{cm}^{2}$, of the clonidine related compound B in the portion of the Transdermal System taken by the formula:

## $C V / A$,

in which $C$ is the concentration of clonidine related compound B , in $\mu \mathrm{g}$ per mL , obtained from the linear regression analysis, $V$ is the volume of the Test solution in mL , and $A$ is the area of the sample system in $\mathrm{cm}^{2}$. Not more than $10.0 \mu \mathrm{~g}$ per $\mathrm{cm}^{2}$ of clonidine related compound $B$ is found.

Assay-
Hobile phase Prepare a fllered and degassed mixture of sedium 1 pentanesulfenate and methanol ( $63: 36$ ). Make adjustments if neessary (see-System Suitability under Chremay (621)).
Mobile phase-Prepare a filtered and degassed mixture of sodium 1 pentanesulfenate and methanol (63:36). Make ad justments if neessary (see System Suitability under Chromagraphy (621)).

Standerd preparation Dissolve an aceurately weighed quantit USP Clenidine Hydrochloride RS in 0.01 Nsut furie acid, and dilute quantitatively, and stepwise if neeessary, with 0.01 N sulfuric acid to obtain a solution having
a known coneentration of about 46 kg per mL. $0.046 T$ per mL (equivalent to abet $0.040 T$ of clonidine per mL ), $T$ being the total ameunt, in mg, of elonidine in each Transdermal System.

Assay preparation Carefully peel the release liner from 1 Transdermal System, and eut the Transdermal System inte segments. Quantitatively transfer the segments into an appropriate polytef lined serew cap centrifuge tube, add-10 mL of 0.01 N sulfuric acid saturated with $n$ heptane, ac eurately meastred, eap, and heat to $60^{\circ}$ for 3 hours. Add 10 mL of $n$ heptane, cap, shake vigorously for 1 minute, and heat to $60^{\circ}$ for about 16 hours. Allow the solution to eool to reom temperature, add 15 mL of 0.01 N sulfuric acid saturated with $n$ heptane, cap, and mix in a vortex mixer for about 2 minutes. Allow to separate, and filter the aqueous layer. [NOTE-If backing membrane has not delaminated, repeat with a new Transdermal System.] Use the aqueous fayer as the Assay preparation.

Chromatggraphic system (see Chromatgraphy (624)) The liquid chromatograph is equipped with a 210 - mm detec ter, a $3.9 \mathrm{~mm} \times 2 \mathrm{~cm}$ grard column that eontains packing L2, and a $3.9 \mathrm{~mm} \times 30 \mathrm{~cm}$ column that contains packing E1. The flow rate is 1.5 mL per minute. Chromato graph the Statated preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 ; and the relative standard deviation for replieate injections is net more than $2.0 \%$.

Proedure Separately inject equal volumes (about 50 $\mu \mathrm{L})$ of the Stated preparation and the -sssay preparation into the chromatograph, record the chromatograms, and measure the respenses for the major peaks. Caleulate the
quantity, in $\mathrm{K}_{\mathrm{g}}$, of elonidine $\left(\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{C}_{2} \mathrm{~N}_{3}\right)$ in the Transtermat
System taken by the formula:-

$$
21.58 \mathrm{C}\left(r_{4}+r_{s}\right)
$$

## $(230.10 / 266.56)(25 C)\left(F_{4}++_{5}\right)$,

in which 230.10 and 266.56 are the molecular weights of elonidine and clonidine hydrochloride, respectively; $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Clonidine Hydro-ehloride-RS in the Standtard prepatation; and $\Psi_{t}$ and $\Psi_{s}$ are the peak respenses obtained frem the Assay preparation and the Standard preparation, respectively.

Mobile phase-Dissolve 4 mL of triethylamine in 1.6 L of water and adjust with phosphoric acid to a pH of 3.0 . Add 2.4 L of acetonitrile, stir the solution for 30 minutes, filter, and degas. Make adjustments if necessary (see System suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare a mixture of tetrahydrofuran and methanol (1:1).
Standard preparation-Dissolve a suitable amount, accurately weighed, of USP Clonidine Hydrochloride RS in tetrahydrofuran to obtain a solution having a known concentration of about 1 mg per mL . Prepare a minimum of four Standard solutions in Diluent that bracket the expected clonidine concentration in the sample. The standard concentrations should be within the range of 50 to $300 \mu \mathrm{~g}$ per mL . Standard preparations are stable for up to 2 days if stored at $4^{\circ}$.

Test preparation-Remove each Transdermal System from its package, discard the release liner from each system, and transfer into a $50-\mathrm{mL}$ centrifuge tube with a Teflon-lined screw cap. Add the appropriate volume of tetrahydrofuran.

| For systems containing about 2.5 mg of clonidine | 7.0 mL |
| :---: | :---: |
| For systems containing about 5.0 mg of clonidine | 14.0 mL |
| For systems containing about 7.5 mg of clonidine | 21.0 mL |

Vortex vigorously until the systems are washed down and fully submerged in the tetrahydrofuran. Let the systems soak in tetrahydrofuran for about 5 minutes and vortex until the systems are completely delaminated. Allow the systems to remain submerged for an additional 60 minutes, vortexing every 30 minutes. Add methanol in a volume equal to the volume of tetrahydrofuran and vortex vigorously. The solution turns milky. Centrifuge for ten minutes at 2000 rpm. Use the supernatant as the Test preparation.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a detector capable of measuring at 210 nm and 242 nm , and a $4.6-\mathrm{mm} \times$ $15-\mathrm{cm}$ column that contains packing L10. The flow rate is about 1 mL per minute. The detector is programmed initially to 242 nm and 210 nm after the elution of the clonidine peak but prior to the elution of the clonidine related compound $B$. The relative retention time is 1.0 for clonidine and 1.5 for clonidine related compound B. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution between clonidine and clonidine related compound $B$ is not less than 2.0 ; the capacity factor, $k^{\prime}$, is not less than 0.6 for clonidine; and the tailing factor for both clonidine and clonidine related compound $B$ is not more than 3.0. The relative standard deviation of the clonidine peak area for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of at least three Standard solutions that will bracket the expected sample concentration range and the Test preparation into the chromatograph, record the chromatograms, and measure the responses for the clonidine. Calculate the peak response ratios of the analyte and plot the results. Determine the linear regression equation of the standards by the mean-square method, and record the linear regression equation and the correlation coefficient; it should be not less than 0.995. Calculate the amount, in mg , of $\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}$ in the Transdermal System taken by the formula:
CV/1000,
in which $C$ is the concentration of clonidine, in $\mu \mathrm{g}$ per mL , obtained from the linear regression analysis, $V$ is the volume of the Test preparation in mL per sample system. $\Delta$ USP28

Briefing
Colchicine Tablets, USP 27 page 508-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40315-4

## Change to read:

Dissolution, Pree for Pomple
${ }^{\Delta}$ USP2 28
$\left\langle{ }^{\mathbf{1}}{ }^{\text {USP2 }} 11\right\rangle$ - NOTE-Conduct this procedure without delay, under subdued light, and using low-actinic glassware.]
Medium: water; 500 mL .
Apparatus 1: 100 rpm .
Time: 30 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle$ USP28

Determine the amount of $\mathrm{C}_{22} \mathrm{H}_{25} \mathrm{NO}_{6}$ dissolved, employing the procedure set forth in the Assay under Colchicine, making any necessary modifications.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{25} \mathrm{NO}_{6}$ is dissolved in 30 minutes:
the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
|  | Number |  |
| Stage | Tested | Acceptance Criteria |

## UUSP28

## BRIEFING

Cyclizine Hydrochloride Tablets, USP 27 page 525-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40315-5

## Change to read:

Dissolution, Preedre for a Pooled Sample
${ }^{\mathbf{A}}\langle 711\rangle-28$
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution
Determine the amount of $\mathrm{C}_{18} \mathrm{H}_{22} \mathrm{~N}_{2} \cdot{ }^{U S 28} \cdot \mathrm{HCl}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{18} \mathrm{H}_{22} \mathrm{~N}_{2} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :---: | | Stage | Average amount dissolved is not less <br> than $Q+10 \%$. <br> $\mathrm{S}_{1}$ | 6 |
| :---: | :---: | :--- |

## BRIEFING

Cyclosporine Oral Solution, USP 27 page 533; Demeclocycline Oral Suspension, USP 27 page 547. To improve the standards in these monographs, it is proposed to add requirements for Uniformity of dosage units to apply to single-unit containers and Deliverable volume to apply to multiple-unit containers.
(PA7a: W. Wright) RTS-40664-1

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\mathbf{\Delta}$ USP28

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements. $\triangle$ USP28

## BRIEFING

Demeclocycline Oral Suspension, USP 27 page 547—See briefing under Cyclosporine Oral Solution.
(PA7: W. Wright) RTS-40664-3

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle-$
FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\Delta$ USP28
Add the following:
${ }^{\text {and }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\triangle U S P 28$

## BRIEFING

Desflurane, USP 27 page 549. It is proposed to revise the Packaging and storage requirement to include a recommended temperature range, in accordance with the policies of the USP Packaging, Storage, and Distribution (PSD) Expert Committee. In the Assay it is proposed to specify the use of USP Halothane RS in the preparation of the Internal standard solution. In addition, minor editorial style changes have been made.
(PA1: K. Russo; PSD: C. Okeke) RTS-40455-1; 40649-1

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers.
${ }^{\star}$ Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.
Replace the cap securely after each use. $\begin{aligned} & \text { USSP28 }\end{aligned}$

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Desflurane RS. USP Desflurane Related Compound A RS.
©USP Halothane RS.
USP Sodium Fluoride RSP28

## Change to read:

## Assay-

Internal standard solution-Transfer 2.0 mL of hatethane
${ }^{\boldsymbol{\Delta}}$ USP Halothane $\mathrm{RS}_{\Delta U S P 28}$
to a $100-\mathrm{mL}$ volumetric flask, dilute with $p$-xylene to volume, and mix.

Standard preparation-Transfer 1.0 mL of Internal standard solution to a $2.0-\mathrm{mL}$ septum-capped vial, cap, seal, and weigh accurately. Using a cold syringe, inject about $25 \mu \mathrm{~L}$ of USP Desflurane RS, previously cooled to $0^{\circ}$ to $5^{\circ}$, into the vial. Allow the vial to come to ambient temperature, accurately weigh it, and calculate the quantity, in mg , of USP Desflurane RS added.

Assay preparation-Transfer 1.0 mL of Internal standard solution to a $2.0-\mathrm{mL}$ septum-capped vial, cap, seal, and weigh accurately. Using a cold syringe, inject about $25 \mu \mathrm{~L}$ of Desflurane, previously cooled to $0^{\circ}$ to $5^{\circ}$, into the vial. Allow the vial to come to ambient temperature, accurately weigh it, and calculate the quantity, in mg , of Desflurane added.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The gas chromatograph is equipped with a flame-ionization detector and a $2.4-\mathrm{mm} \times 3.7-\mathrm{m}$ stainless steel column coated with polytef and packed with $10 \%$ phase G31 and $15 \%$ phase G18 on 80 - to $100-$ mesh support S1A. Helium is used as the carrier gas at a flow rate of about 24 mL per minute. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at about $80^{\circ}$ for 2.5 minutes, then increased at a rate of $2^{\circ}$ per minute, to $88^{\circ}$, maintained at $88^{\circ}$ for 3 minutes, then increased to $175^{\circ}$ at a rate of $70^{\circ}$ per minute, and maintained at $175^{\circ}$ for 4 minutes. The injector port is maintained at about $200^{\circ}$, and the detector at about $250^{\circ}$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are 1.0 for desflurane and about 2.8 for halothane; the resolution, $R$, between the desflurane peak and the halothane peak is not less than 8 ; and the relative standard deviation for the ratios of the desflurane peak response to the halothane peak response obtained for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak area responses for the halothane and desflurane peaks. Calculate the percentage of $\mathrm{C}_{3} \mathrm{H}_{2} \mathrm{~F}_{6} \mathrm{O}$ in the Desflurane taken by the formula:

$$
100\left(W_{S} / W_{U}\right)\left(R_{U} / R_{S}\right)
$$

in which $W_{S}$ is the quantity, in mg, of USP Desflurane RS used to prepare the Standard preparation; $W_{U}$ is the quantity, in mg , of Desflurane used to prepare the Assay preparation; and $R_{U}$ and $R_{S}$ are the ratios of the peak area responses of desflurane to that of halothane obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Dexamethasone Oral Solution, USP 27 page 560-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40618-10

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\quad$ USP28

## Add the following:

${ }^{\text {s }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP28

## Briefing

Dexbrompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution, USP 27 page 567-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40618-11

## Add the following:

${ }^{\boldsymbol{4}}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP28
Add the following:
${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP28

## Briefing

Dextroamphetamine Sulfate Capsules, USP 27 page 577See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40311-2

## Change to read:

Dissolution Procedure for a Pooled Sample-
${ }^{\Delta}$ (711) USP28
Medium: water, 500 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled sample as the test solution.
Determine the amount of $\left(\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{~N}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\left(\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{~N}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform
at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## BRIEFING

Dextroamphetamine Sulfate Tablets, USP 27 page 579—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40311-3

## Change to read:

Dissolution Proedtre for a Pooled Sample

Medium: water; 500 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Determine the amount of $\left(\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{~N}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ dissolved by employing the following method.

Mobile phase-Dissolve 1.1 g of sodium 1-heptanesulfonate in 575 mL of water. Add 25 mL of dilute glacial acetic acid (14 in $100)$ and 400 mL of methanol. Adjust by the dropwise addition of glacial acetic acid to a pH of $3.3 \pm 0.1$, if necessary, filter, and degas the solution. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph replicate injections of the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation is not more than $2.0 \%$.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. AUSP28
Inject a volume (about $100 \mu \mathrm{~L}$ ) of the solution under test
${ }^{\Delta}$ pooled sample ${ }_{\Delta U S P 28}$
into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $\left(\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{~N}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ dissolved in comparison with a Standard solution having a known concentration of USP Dextroamphetamine Sulfate RS in the same Medium and similarly chromatographed.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\left(\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{~N}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

| Number <br> Stage |  |  |
| :---: | :---: | :---: |
| $\mathrm{S}_{1}$ | 6 | Tested <br> Average amount dissolved is not less <br> than $Q+10 \%$. <br> $\mathrm{S}_{2}$ |
| $\mathrm{~S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

Briefing
Dextromethorphan Hydrobromide Oral Solution, USP 27 page 581-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-1

## Dextromethorphan Hydrobromide Oral Solution

## (Monograph under this new title-to become official June 1, 2005) <br> (Current monograph title is Dextromethorphan Hydrobromide Syrup)

## Add the following:

${ }^{\boldsymbol{4}}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements. $\triangle U S P 28$

## Add the following:

${ }^{\Delta}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements._uSP28

## BRIEFING

Dextromethorphan Hydrobromide Syrup, USP 27 page 581-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-1

## Dextromethorphan Hydrobromide Syrup

(Current title—not to change until June 1, 2005)
Monograph title change-to become official June 1, 2005
See Dextromethorphan Hydrobromide Oral Solution

## Add the following:

${ }^{\boldsymbol{\Delta}}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR SYRUP PACKAGED IN SINGLE-UNIT CONTAINERS: meets
the requirements. $\triangle$ USP28
Add the following:
${ }^{\Delta}$ Deliverable volume $\langle 698$ -
FOR SYRUP PACKAGED IN MULTIPLE-UNIT CONTAINERS:
meets the requirements. $\triangle$ USP28

## Briefing

Diazepam, USP 27 page 587 and page 1869 of PF29(6) [Nov.Dec. 2003]. Because the name of the Reference Standard USP 3-Amino-6-chloro-1-methyl-4-phenylcarbostyril RS has been changed to USP Diazepam. Related Compound B RS, [see USP Reference Standards $\langle 11\rangle$ in the Sixth Interim Revision Announcement published in PF 29(6)], it is proposed to make the corresponding change wherever the name of this Reference Standard appears in the text of the monograph. In addition, minor editorial style changes have been made.
(PA3: S. Salado) RTS-40444-1

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers.
$\square$ Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ} \cdot \mathbf{m} 2 \mathrm{~S}$ (USP27)

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of in-
jectable dosage forms. $\quad$ 2S (USP27)

## Change to read:

USP Reference standards $\langle 11\rangle$ _USP Diazepam RS. USP Diazepam Related Compound A RS. ${ }^{\bullet}$ USP Diazepam Related Compound $B R S_{\bullet 6}$
-USP Endotoxin $R$. $_{\text {■ }}$ 2S (USP27) $^{\text {( }}$
USP Nordazepam RS.

## Change to read:

## Related compounds-

Mobile phase, System suitability solution, and Chromatographic system-Proceed as directed in the Assay.

Standard solution-Dissolve accurately weighed quantities of USP 3-Amine 6-hlore-1 methyl-4 phenylearbostyril PS,
${ }^{\Delta}$ USP Diazepam Related Compound B RS,
USP Diazepam Related Compound A RS, and USP Nordazepam RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having known concentrations of about $1 \mu \mathrm{~g}$ per $\mathrm{mL}, 0.1 \mu \mathrm{~g}$ per mL , and $3 \mu \mathrm{~g}$ per mL , respectively.
Test solution-Transfer about 10 mg of Diazepam, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with methanol to volume, and mix.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of 3 amine 6 chloro 1 methyl 4 phenylearbestyil,
${ }^{\Delta}$ diazepam related compound B
diazepam related compound B, , $U S P 28$
diazepam related compound A , and nordazepam in the portion of Diazepam taken by the formula:

$$
\left(C_{R} / W\right)\left(r_{U} / r_{S}\right)
$$

in which $C_{R}$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP 3 Amine 6 ehlore-1 methyl-4 phenylearbostyril PS,
${ }^{\wedge}$ USP Diazepam Related Compound B RS, ${ }_{\text {USP28 }}$
USP Diazepam Related Compound A RS, or USP Nordazepam RS in the Standard solution; $W$ is the weight, in mg, of Diazepam taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Test solution and the Standard solution, respectively: not more than $0.01 \%$ of diazepam related compound A, not more than $0.1 \%$ of 3 amine- 6 ehlore- 1 meth Y4 phenylearbostyil,
${ }^{\boldsymbol{\Delta}}$ diazepam related compound $\mathrm{B},{ }_{\mathbf{\triangle S S P 2 8}}$ and not more than $0.3 \%$ of nordazepam are found.

Calculate the percentage of any other impurity in the portion of Diazepam taken by the formula:

$$
\left(C_{S} / W\right)\left(r_{i} / r_{S}\right)
$$

in which $C_{S}$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP 3 Amine 6 ehlore 1 methyl 4 phenylearbestyril Rs
${ }^{\mathbf{\Delta}}$ USP Diazepam Related Compound $\mathrm{BRS}_{\Delta U S P 28}$ in the Standard solution; $r_{i}$ is the peak response for any other impurity obtained from the Test solution; and $r_{S}$ is the peak response of USP 3-Amine 6-chlere-1 methyl-4 phenylearbestyril RS
${ }^{\boldsymbol{A}}$ USP Diazepam Related Compound B RS ${ }_{\mathbf{A S P 2 8}}$ obtained from the Standard solution: not more than $0.1 \%$ of any other impurity is found, and not more than $1.0 \%$ of the total impurities is found.

## Add the following:

-Other requirements-Where the label states that Diazepam is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Diazepam Injection. Where the label states that Diazepam must be subjected to further
processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Diazepam Injection.■2S (USP27)

## BRIEFING

Diethylcarbamazine Citrate Tablets, USP 27 page 602—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40311-4

Change to read:
Dissolution Preedure for a Pooled Sample
$\left\langle\begin{array}{l}\text { A } \\ \langle 711\rangle-28\end{array}\right.$
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\text {4 }}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled
sample as the test solution. ${ }^{\text {USP28 }}$
Determine the amount of $\mathrm{C}_{10} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O} \cdot \mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7}$ dissolved as directed in the Assay, preparing test solutions by quantitatively diluting filtered portions of the solution under test
${ }^{\Delta}$ portions of the pooled sample ${ }_{\Delta U S P 28}$
with phosphate buffer (1:1) containing 62.48 g of monobasic potassium phosphate in 1000 mL of water.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{10} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O} \cdot \mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7}$ is dissolved in 45 minutes:
the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$, or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labled content.

Acceptance Table for a Pooled Sample

|  | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :--- |
| Stage | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> $\mathrm{S}_{2}$ |
| $\mathrm{~S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## BriEfing

Diphenhydramine Hydrochloride Capsules, USP 27 page 638-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40311-5

## Change to read:

Dissolution, Proedure for a Pooled Semple
$\langle\mathbf{A} 11\rangle-28$
Medium: water; 500 mL .
Apparatus 1: 100 rpm .
Time: 30 minutes.
Determine the amounts of $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{HCl}$ dissolved by employing the following method.

Mobile phase and Chromatographic system-Prepare as directed in the Assay.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\Delta$ USP28
Inject a measured volume (about $50 \mu \mathrm{~L}$ ) of a filtered pertion of the solution under test
$\boldsymbol{\Delta}_{\text {the pooled sample }}^{\mathbf{\Delta S P 2 8}}{ }_{\text {th }}$
into the chromatograph, record the chromatogram, and measure the response for the major peak. Determine the quantity of $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{HCl}$ dissolved in comparison with a Standard solution having a known concentration of USP Diphenhydramine Hydrochloride RS in the same Medium and similarly chromatographed.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{HCl}$ is dissolved in 30 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number |  |
| :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> $\mathrm{S}_{3}$ |

## BRIEFING

Diphenhydramine and Pseudoephedrine Capsules, USP 27 page 639 -See briefing under Acetaminophen and Aspirin Tablets.

$$
\text { (BPC: M. Marques) } \quad \text { RTS-40311-6 }
$$

## Change to read:

Dissolution Proedure for a Ported Sample
$\Delta$
〈711 M USP28
Medium: water, 900 mL .
Apparatus 1: 100 rpm .
Time: 30 minutes.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle$ USP28
Inject a measured volume (about $50 \mu \mathrm{~L}$ ) of a filtered pertion of the solution under test
${ }^{4}$ portion of the pooled sample ${ }_{\mathbf{A} U S P 28}$
into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Determine the quantities of $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{HCl}$ and of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ dissolved by employing the procedures set forth in the Assay, making any necessary modifications.

Tolerances-Not less than 75\% (Q) of the labeled amounts of $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{HCl}$ and of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ are dissolved in 30 min utes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$, or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labled content.

## Acceptance Table for a Pooled Sample

|  | Number |  |
| :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> $\mathrm{S}_{3}$ |

## Briefing

Dorzolamide Hydrochloride, USP 27 page 662. On the basis of comments received, it is proposed to change the calculation and the theoretical plates specification in the test for Limit of dorzolamide hydrochloride related compound $A$ to better reflect the procedure used in the validation of the method. It is also proposed to simplify the buffer preparation and to revise the calculation in the test for Chromatographic purity to reflect the original submission that is based on percent area. In addition, editorial changes are proposed in the Assay.
(PA6: L. Evans) RTS—39833-1; 39833-2; 39833-3; 39833-4

## Change to read:

Limit of dorzolamide hydrochloride related compound A-
Mobile phase-Prepare a filtered and degassed mixture of tertbutyl methyl ether, chromatographic $n$-heptane, acetonitrile, and water ( $63: 35: 2: 0.2$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Transfer about 18 mg of USP Dorzolamide Hydrochloride RS and 2 mg of USP Dorzolamide Hydrochloride Related Compound A RS, each accurately weighed, to a $15-\mathrm{mL}$ centrifuge tube, dissolve in 4 mL of 0.5 N ammonium hydroxide, add 4 mL of ethyl acetate, and mix. Separate the ethyl acetate layer, and transfer to a $15-\mathrm{mL}$ centrifuge tube. Add 4 mL of ethyl acetate to the aqueous layer, mix, separate the ethyl acetate layer, and combine it with the first extract. Evaporate the combined organic layers to dryness on a water bath maintained at $50^{\circ}$ under a stream of nitrogen. Dissolve the residue in 3 mL of acetonitrile, add 3 drops of (S)-(-)- $\alpha$-methylbenzyl isocyanate
${ }^{\boldsymbol{\Delta}}$ [NOTE-Discard the reagent if it is colored.], $]_{\text {USP } 28}$
and allow to react for 5 minutes on a water bath maintained at $50^{\circ}$. under a stream of nitrogen. [NOTE-Diseard the solution if it is fored.]
$\Delta$
EvUSP28
Evaporate the mixture to dryness on a water bath maintained at $50^{\circ}$ under a stream of nitrogen. Dissolve the residue in 10 mL of a mixture of tert-butyl methyl ether, glacial acetic acid, and acetonitrile (87:10:3).

Test solution-Transfer about 20 mg of Dorzolamide Hydrochloride, accurately weighed, to a $15-\mathrm{mL}$ centrifuge tube, and proceed as directed for System suitability solution beginning with "dissolve in 4 mL ".

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L3. The flow rate is about 2 mL per minute. Chromatograph the System suitability solution, and record the peak respenses
areas $_{\triangle U S P 28}$
as directed for Procedure: the relative retention times are about 1.0 for dorzolamide and 1.5 for dorzolamide hydrochloride related compound A ; the resolution, $R$, between dorzolamide and dorzolamide hydrochloride related compound A is not less than 4.0; the column efficiency
${ }^{\boldsymbol{\Delta}}$ for the dorzolamide hydrochloride peak $\mathbf{\Delta U S P 2 8}$ is not less than 6000
44000 ${ }_{\text {USP } 28}$
theoretical plates; the tailing factor is not more than 1.4; and the relative standard deviation for replicate injections determined from the dorzolamide peak is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the System suitability solution and the Test solution into the chromatograph, record the chromatograms, and measure the respenses for
$\Delta^{\text {areas of }}{ }_{\triangle U S P 28}$
the major peaks. Calculate the percentage of dorzolamide hydrochloride related compound $A$ in the portion of Dorzolamide Hydrochloride taken by the formula:

$$
6100\left(r_{i}+r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, Of USP Dorzolamide Hydrochloride Related Compound $A$ PS in the System suit ability solttion; andriandrsare the peak respenses of dorzolamide hydrochloride related compound $A$ obtained from the Test solution and the System suitability solution, respectively: not more that $0.5 \%$ is found.

$$
\mathbf{\Delta} 100 r_{i}\left(r_{i}+r_{S}\right)
$$

in which $r_{i}$ is the peak area of dorzolamide hydrochloride related compound A obtained from the Test solution; and $r_{S}$ is the peak area of dorzolamide hydrochloride obtained from the Test solution: not more than $0.5 \%$ is found. -USP28

## Change to read:

Chromatographic purity-
${ }^{\wedge}$ Phosphate buffer, ${ }_{\text {Solution }}{ }^{\boldsymbol{U}}{ }^{28}$
Solution A, Solution B, Mobile phase, and Chromatographic system-Proceed as directed in the Assay.

Standard solution Use the Standard preparation as prepared in the Assay.

- $\Delta S P 28$

Test solution-Use the Assay preparation.
Procedure-Separately inject equal volumes (about 10- 10 L) of the Standerd solution and
${ }^{\boldsymbol{\Delta}}$ Inject a volume (about $10 \mu \mathrm{~L}$ ) of $\boldsymbol{A}_{\text {USP28 }}$ the Test solution into the chromatograph, record the chromatogram, and measure all of the peak respenses.
areas. $\quad$ USP28
Calculate the percentage of each impurity in the portion of Dorzolamide Hydrochloride taken by the formula:

$$
10,000(C / H)\left(r_{i}-r_{s}\right)
$$

in which $C$ is the eoncentration, in mg per mL, of USP Derzola mide Hydrochloride PS in the Staterd solution; Wis the weight, in mes, of Dorzolamide-Hydrochloride taken to prepare the Test solution; $r_{i}$ is the peak respense for each impurity obtained from
 tained from the Standetrd solution: not mere than $0.1 \%$ of any im purity with a relative retention time of 0.92 is found; not more than $0.1 \%$ of any individual impurity is found; and not more than $0.3 \%$ of total-impurities is found.
in which $r_{i}$ is the peak area of each individual impurity obtained from the Test solution; and $r_{s}$ is the sum of all the peak areas obtained from the Test solution: not more than $0.1 \%$ of any individual impurity is found; and not more than $0.5 \%$ of total impurities is found. $\triangle$ USP28

## Change to read:

## Assay-

Solution 4
${ }^{\mathbf{\Delta}}$ Phosphate buffer ${ }_{\mathbf{\Delta U S P} \text { U } 28}$
-Dissolve 3.7 g of potassium phosphate in 100 mL of a mixture-
$\triangle 1000 \mathrm{~mL}_{4}$ USP28
of water. and acenitrile (94:0).
${ }^{\Delta}$ Solution A-Prepare a filtered and degassed mixture of
Phosphate buffer and acetonitrile (94:6)._USP28 Solution B-Use acetonitrile.
Mobile phase-Use variable mixtures of Solution $A$ and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard preparation-Dissolve suitable quantities of USP Dorzolamide Hydrochloride RS in Solution $A$ to obtain a solution having a known concentration of about 0.6 mg per mL .
Assay preparation-Transfer about 60 mg of Dorzolamide Hydrochloride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Solution $A$ to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $35^{\circ}$. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0-15$ | 100 | 0 | isocratic |
| $15-30$ | $100 \rightarrow 50$ | $0 \rightarrow 50$ | linear gradient |
| $30-37$ | $50 \rightarrow 100$ | $50 \rightarrow 0$ | linear gradient |
| $37-44$ | 100 | 0 | isocratic |

Chromatograph the Standard preparation, and record the peak spenses
$\Delta_{\text {areas }_{\triangle U S P 28}}$
as directed for Procedure: the column efficiency is not less than 6500 theoretical plates; the tailing factor is not less than 0.6 and not more than 1.2; and the relative standard deviation for replicate injections is not more than $1.0 \%$.
Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the
$\Delta_{\text {areas }_{\triangle U S P 28}}$
for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{10} \mathrm{H}_{16} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S}_{3} \cdot \mathrm{HCl}$ in the portion of Dorzolamide Hydrochloride taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Dorzolamide Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Dyphylline and Guaifenesin Tablets, $U S P 27$ page 682—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) $\quad$ RTS-40311-7

## Change to read:

Dissolution Proecture for a Pooted Semple-
${ }^{\boldsymbol{4}}$ 〈 A USP28
Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.nUSP28
Determine the amounts of dyphylline $\left(\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{~N}_{4} \mathrm{O}_{4}\right)$ and guaifene$\sin \left(\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{O}_{4}\right)$ dissolved, using the procedure set forth in the $A s$ say, making any necessary modifications.
Tolerances-Not less than $75 \%(Q)$ of the labeled amounts of $\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{~N}_{4} \mathrm{O}_{4}$ and $\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{O}_{4}$ are dissolved in 45 minutes:
$\Delta_{\text {the requirements are met if the quantities of active ingredi- }}$ ents dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

|  | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :--- |
| Stage | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{2}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## BRIEFING

Ephedrine Sulfate Syrup, USP 27 page 709. It is proposed to revise the Identification test to eliminate an obsolete cross-reference. The procedure and acceptance criterion are added to the monograph.
(PA1: K. Russo) RTS-40568-1

## Ephedrine Sulfate Syrup

(Current title_not to change until June 1, 2005)
Monograph title change-to become official June 1, 2005
See Ephedrine Sulfate Oral Solution

## Change to read:

Identification,
${ }^{\Delta}$ Angular rotation $\langle 781 \mathrm{~A}\rangle-{ }_{\Delta}$ USP28
${ }^{\triangle}$ Use ${ }_{\text {USP28 }}$
the $0.1 \stackrel{U S P 28}{\mathrm{~N}}$ sulfuric acid extract of the chloroform solution obtained as directed under Assay preparation: respends to Identifion test 6 under Ephedrine Sulfate Injection
${ }^{\Delta}$ The angular rotation is levorotatory. $\mathbf{\Delta U S P 2 8}$

## Briefing

Conjugated Estrogens Tablets, USP 27 page 749. It is proposed to add another tablet strength to Drug Release Test 1. In addition, minor editorial style changes have been made.
(BPC: M. Marques) RTS-40514-1

## Change to read:

Drug release $\langle 724\rangle$ —Proceed as directed for Extended-Release Articles-General Drug Release Standard.

TEST 1 (for products labeled as 0.3-,
${ }^{\Delta} 0.45$ -
and $0.625-\mathrm{mg}$ tablets)-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 1.

Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Mobile phase-Prepare a filtered and degassed mixture of 0.025 M monobasic potassium phosphate and acetonitrile (3:1). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Transfer 10 Tablets to a $1000-\mathrm{mL}$ volumetric flask, dilute with water to volume, and stir vigorously by mechanical means for at least 3 hours. Pipet a filtered $100-\mathrm{mL}$ aliquot of the solution into a $900-\mathrm{mL}$ volumetric flask, and dilute with water to volume.

Test solution-Filter a portion of the solution under test. [NOTEIt is recommended that the filters selected be tested for binding affinity.]

Chromatographic system-The liquid chromatograph is equipped with a $205-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 3.0-\mathrm{cm}$ column that contains $3-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. Chromatograph replicate injections of the Standard solution, and record the responses as directed for Procedure: the relative retention times are about 0.9 for equilin sulfate and 1.0 for estrone sulfate, the estrone sulfate peak being the last major peak in the chromatogram; the resolution, $R$, between equilin sulfate and estrone sulfate is not less than 1.5; and the relative standard deviation for the estrone sulfate peak is not more than $1.5 \%$. [NOTE-If estrone is present it may be retained on the column for a period longer than 50 minutes and interfere in later chromatographic runs.]
Procedure-Separately inject equal volumes (between 20 and $200 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the estrone sulfate peaks. Calculate the percentage of estrone sodium sulfate released by the formula:

$$
100\left(r_{U} / r_{S}\right)
$$

in which $r_{U}$ and $r_{S}$ are the peak responses obtained from the Test solution and the Standard solution, respectively.

Times and tolerances-The percentages of estrone sodium sulfate dissolved at the times specified conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 2 | between $19 \%$ and $49 \%$ |
| 5 | between $66 \%$ and $96 \%$ |
| 8 | not less than $80 \%$ |

TEST 2 (for products labeled as $0.9-\mathrm{mg}$ tablets)-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 2.

Medium, Apparatus, Mobile phase, Standard solution, Test solution, Chromatographic system, and Procedure-Proceed as directed for Test 1 .

Times and tolerances-The percentages of estrone sodium sulfate dissolved at the times specified conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 2 | between $12 \%$ and $37 \%$ |
| 5 | between $57 \%$ and $85 \%$ |
| 8 | not less than $80 \%$ |

TEST 3 (for products labeled as $1.25-$ and $2.50-\mathrm{mg}$ tablets)-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 3.

Medium, Apparatus, Mobile phase, Standard solution, Test solution, Chromatographic system, and Procedure-Proceed as directed for Test 1 .

Times and tolerances-The percentages of estrone sodium sulfate dissolved at the times specified conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 2 | between 3\% and $22 \%$ |
| 5 | between $37 \%$ and $67 \%$ |
| 8 | between $66 \%$ and $96 \%$ |
| 12 | not less than $80 \%$ |

## BRIEFING

Ethosuximide Capsules, USP 27 page 763 -See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40311-8

Change to read:
Dissolution Procedure for a Pooled Sample
$\Delta$

Medium: pH 6.8 phosphate buffer (see Buffer Solutions in the section Reagents, Indicators, and Solutions); 900 mL .

Apparatus 1: 50 rpm .
Time: 30 minutes.
Mobile phase-Prepare a degassed and filtered mixture of water and acetonitrile (80:20).

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph replicate injections of the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation is not more than $2.0 \%$.

Procedure-
${ }^{\mathbf{\Delta}}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. UUSP28
Inject an accurately measured volume (about $50 \mu \mathrm{~L}$ ) of filtered pertion of the solution under test
${ }^{\Delta}$ the pooled sample ${ }_{\mathbf{n}_{U S P 28}}$
into the chromatograph, record the chromatogram, and measure the response for the major peak. Determine the amount of $\mathrm{C}_{7} \mathrm{H}_{11} \mathrm{NO}_{2}$ dissolved by comparison with a Standard solution, having a known concentration of USP Ethosuximide RS in the same Medium, similarly chromatographed.
Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{7} \mathrm{H}_{11} \mathrm{NO}_{2}$ is dissolved in 30 minutes:
${ }^{\boldsymbol{\Delta}}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

Number

| Stage | Tested | Acceptance Criteria |
| :---: | :---: | :---: |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> $\mathrm{S}_{3}$ |
| 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |  |

## BriEfing

Etoposide, USP 27 page 772. It is proposed to revise the calculation in the test for Related compounds to accurately determine the level of impurity found.
(PA6: L. Evans) RTS-40445-1

## Change to read:

Related compounds-
Buffer solution-Prepare as directed in the Assay.
Solution A-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (80:20).

Solution $B$-Prepare a filtered and degassed mixture of acetonitrile and Buffer solution (60:40).

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed under Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluting solution-Prepare a filtered mixture of 0.02 M sodium acetate, previously adjusted with acetic acid to a pH of 4.0 , and acetonitrile (70:30).

Standard solution-Dissolve an accurately weighed quantity of USP Etoposide RS in Diluting solution to obtain a Stock standard solution having a known concentration of about 2.0 mg per mL . Dilute this Stock standard solution quantitatively, and stepwise with Diluting solution to obtain a solution having a known concentration of about $10 \mu \mathrm{~g}$ per mL .

System suitability solution-Transfer about 20 mg of $n$-propylparaben, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with Diluting solution to volume. Transfer 5 mL of this solution and 5 mL of the Stock standard solution to a $50-\mathrm{mL}$ volumetric flask, and dilute with Diluting solution to volume. Transfer 5.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with Diluting solution to volume, and mix.

Test solution-Transfer about 100 mg of Etoposide, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with Diluting solution to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L11 having a diameter of less than $5 \mu \mathrm{~m}$. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution using Solution A, and record the peak responses as directed for Procedure: the relative retention times are about 0.20 for lignan $\mathrm{P}, 1.0$ for etoposide, and 1.43 for picroetoposide; and the resolution, $R$, between propylparaben and etoposide is not less than 1.1. The chromatograph is programmed for Procedure as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-15$ | 100 | 0 | isocratic |
| $15-30$ | $100 \rightarrow 40$ | $0 \rightarrow 60$ | linear gradient |
| $30-40$ | 40 | 60 | isocratic |
| $40-42$ | $40 \rightarrow 0$ | $60 \rightarrow 100$ | linear gradient |
| $42-45$ | 0 | 100 | isocratic |
| $45-47$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $47-50$ | 100 | 0 | re-equilibration |

Procedure-Separately inject equal volumes (about $25 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms for at least 40 minutes, and measure the peak responses. Calculate the percentages of lignan P and picroetoposide in the portion of Etoposide taken by the formula:

$$
50\left(r_{i}+r_{s}\right),
$$

$$
\Delta^{\Delta} 5000(C / W)\left(r_{i} / r_{s}\right)_{\mathbf{\Delta U S P 2 8}}
$$

in which $C$ is the concentration, in mg per mL , of USP Etoposide RS in the Standard solution;
${ }^{\wedge} W$ is the weight, in mg , of Etoposide taken to prepare the

## Test solution; ${ }_{\mathbf{\Delta U S P} 28}$

$r_{i}$ is the peak response for each related compound obtained from the Test solution; and $r_{S}$ is the peak response for etoposide obtained from the Standard solution: not more than $0.5 \%$ of lignan P and $1.0 \%$ of picroetoposide is found. Calculate the quantity of any other impurity observed in the chromatogram of the Test solution by the same formula: not more than $2.0 \%$ of all related compounds and other impurities is found.

## BRIEFING

Fluconazole. Because there is no existing $U S P$ monograph for this drug substance, a new monograph is being proposed based on data submitted to USP. The liquid chromatographic procedures in the test for Related compounds are based on analyses performed with a Symmetry ${ }^{\mathbb{B}}$ (Waters) brand of L1 column. Typical retention times are about 4.9 minutes for fluconazole related compound A 8.0 minutes for fluconazole related compound B 8.5 minutes for fluconazole related compound C and 9.9 minutes for fluconazole.
(PA7b: B. Davani) RTS-40268-1

## Add the following:

©Fluconazole

$\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{~F}_{2} \mathrm{~N}_{6} \mathrm{O} \quad 306.27$
1H-1,2,4-Triazole-1-ethanol, 1-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-ylmethyl)-.

# 2,4-Difluoro-1', $1^{\prime}$-bis( 1 H -1,2,4-triazol-1-ylmethyl)benzyl alcohol [86386-73-4]. 

» Fluconazole contains not less than 98.5 percent and not more than 101.5 percent of $\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{~F}_{2} \mathrm{~N}_{6} \mathrm{O}$, calculated on the dried basis.

Packaging and storage-Preserve in tight containers and store below $30^{\circ}$.

USP Reference standards $\langle 11\rangle-U S P$ Fluconazole $R S$. USP Fluconazole Related Compound A RS. USP Fluconazole Related Compound B RS. USP Fluconazole Related Compound C RS.

Clarity and color of solutions-Dissolve sample in methanol to obtain a 5 in 100 solution (w/v): the solution is clear and colorless.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle-$
Solution: $200 \mu \mathrm{~g}$ per mL .
Medium: alcohol.
Melting range $\langle 741\rangle$ : between $138^{\circ}$ and $142^{\circ}$.
Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 3 hours: it loses not more than $0.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on a 0.5 g sample.

Iron $\langle 241\rangle$ —Accurately weigh 0.5 g of sample into a test tube. Dissolve in 5 mL of alcohol, add 5 mL of distilled water, and mix. The limit is $0.002 \%$.

## Related compounds-

Mobile phase-Prepare a mixture of water and acetonitrile (80:20)

System suitability solution-Use the Standard solution.

Standard solution-Transfer accurately weighed quantities of USP Fluconazole RS, USP Fluconazole Related Compound A RS, USP Fluconazole Related Compound B RS, and USP Fluconazole Related Compound C RS to a suitable volumetric flask, dissolve in acetonitrile, dilute quantitatively, and stepwise if necessary, with Mobile phase, to volume and mix to obtain a solution having known concentrations of $10 \mu \mathrm{~g}$ per mL of each.
Test solution-Transfer about 30 mg of Fluconazole, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase, to volume and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $260-\mathrm{nm}$ detector, and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $3.5-\mu \mathrm{m}$ packing L1. The flow rate is about 0.5 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: typical retention times are about 4.9 minutes for fluconazole related compound $\mathrm{A}, 8.0$ minutes for fluconazole related compound $\mathrm{B}, 8.5$ minutes for fluconazole related compound C , and 9.9 minutes for fluconazole; the resolution, $R$, between fluconazole related compound $B$ and fluconazole related compound $C$ is not less than 1.5 ; and the relative standard deviation of each peak for replicate injections is not more than $5.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of fluconazole related compound A, fuconazole related compound B , fluconazole related compound C , and any other impurities in the portion of Fluconazole taken by the formula:

$$
1000(C / W)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Fluconazole Related Compound A RS, USP Fluconazole Related Compound B RS, USP Fluconazole Related Compound C RS, or USP Fluconazole RS, respectively, in the Standard solution; $W$ is the weight, in mg, of Fluconazole taken to prepare the Test solution; $r_{U}$ is the peak response obtained from Test solution; and $r_{S}$ is the average peak response of fluconazole related compound A , fluconazole related compound B , fluconazole related compound C or fluconazole obtained from replicate injections of the Standard solution: not more than $0.1 \%$ of any individual impurity is found; and not more than $0.3 \%$ of total impurities is found.

Assay—Dissolve about 200 mg of Fluconazole, accurately weighed, in 100 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, using a suitable anhydrous electrode system. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 15.31 mg of $\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{~F}_{2} \mathrm{~N}_{6} \mathrm{O}_{\mathbf{\Delta} \text { USP } 28}$

## BRIEFING

Fluoxymesterone Tablets, USP 27 page 826. It is proposed to replace the reagent norethindrone used in the Internal standard solution in the Dissolution test by the use of the USP Norethindrone RS.
(BPC: M. Marques) RTS-40521-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Fluoxymesterone $R S$.
${ }^{\mathbf{4}}$ USP Norethindrone $R S_{.}{ }_{\mathbf{\Delta S P 2 8}}$

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: 0.01 N hydrochloric acid; 900 mL .

Apparatus 2: 75 rpm .
Time: 60 minutes.
Determine the amount of $\mathrm{C}_{20} \mathrm{H}_{29} \mathrm{FO}_{3}$ dissolved by employing the following method.
Mobile phase-Prepare a degassed and filtered solution of water and acetonitrile ( $58: 42$ ). Make adjustments if necessary (see Chromatography (621>).
Internal standard solution-Dissolve a quantity of drane
${ }^{\mathbf{4}}$ USP Norethindrone RS $_{\mathbf{\Delta U S P 2 8}}$
in alcohol to obtain a solution having a final concentration of about $46 \mu \mathrm{~g}$ per mL .
Standard solution-Transfer about 28 mg of USP Fluoxymesterone RS, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with alcohol to volume, and mix. Pipet 5 mL of the resulting solution into a $250-\mathrm{mL}$ volumetric flask, dilute with Dissolution Medium to volume, and mix. Pipet 5 mL of this solution and 2 mL of Internal standard solution into a $25-\mathrm{mL}$ volumetric flask, dilute with Dissolution Medium to volume, and mix.
Test solution-Pipet a filtered $20-\mathrm{mL}$ aliquot of the solution under test and 2 mL of Internal standard solution into a $25-\mathrm{mL}$ volumetric flask, dilute with Dissolution Medium to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph replicate injections of the Standard solution, and measure the peak responses as directed for Procedure: the relative retention times are 0.5 for fluoxymesterone and 1.0 for norethindrone; the resolution, $R$, between fluoxymesterone and norethindrone is not less than 2 ; and the relative standard deviation is not more than $2.0 \%$.
Procedure-Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the responses for the major peaks. Calculate the amount of $\mathrm{C}_{20} \mathrm{H}_{29} \mathrm{FO}_{3}$ dissolved by comparison with the Standard solution, similarly chromatographed.
Tolerances-Not less than $70 \%(Q)$ of the labeled amount of $\mathrm{C}_{20} \mathrm{H}_{29} \mathrm{FO}_{3}$ is dissolved in 60 minutes.

## BRIEFING

Glycopyrrolate Tablets, USP 27 page 878—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40311-10

## Change to read:

Dissolution Proedure for a Pooted Sample
-
〈711 USP28
Medium: water; 500 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.

## Procedure-

${ }^{\mathbf{\Delta}}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle U S P 28$
Determine the amount of $\mathrm{C}_{19} \mathrm{H}_{28}{ }_{2} \mathrm{BrNO}_{3}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications.

Tolerances-Not less than $75 \%$ ( $Q$ ) of the labeled amount of $\mathrm{C}_{19} \mathrm{H}_{28} \mathrm{BrNO}_{3}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient, expressed as a percentage of the labeled content.


## Change to read:

Dissolution Procedure for a Pooled Sample
4
$\langle 711\rangle$ USP28
Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure-
${ }^{\mathbf{4}}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle$ USP28
Determine the amount of $\mathrm{C}_{10}{ }_{0} \mathrm{H}_{14} \mathrm{O}_{4}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications.
Tolerances-Not less than 75\% (Q) of the labeled amount of $\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{O}_{4}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |
|  |  | \USP28 |

## Briefing

Guaifenesin Oral Solution, USP 27 page 888 —See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-2

## Guaifenesin Oral Solution

(Monograph under this new title—to become official June 1, 2005)
(Current monograph title is Guaifenesin Syrup)

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle-$ FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-

TAINERS: meets the requirements. $\mathbf{\Delta U S P 2 8}$

## Add the following:

${ }^{\Delta}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements. $\mathbf{\triangle}$ USP28

## BRIEFING

Guaifenesin Syrup, USP 27 page 888—See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-2

## Guaifenesin Syrup

(Current title_not to change until June 1, 2005)
Monograph title change-to become official June 1, 2005
See Guafenesin Oral Solution

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR SYRUP PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements. $\triangle U S P 28$

## Add the following:

${ }^{4}$ Deliverable volume $\langle 698\rangle$ FOR SYRUP PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements. USPP28

## BRIEFING

Guaifenesin Tablets, USP 27 page 888-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40311-12

Change to read:
Dissolution Proedure for a Pooled Sample
〈
( 711 USP28
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.
Determine the amount of $\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{O}_{4}$ dissolved in filtered pertions of the solution under test
${ }^{\Delta}$ the pooled sample ${ }_{\Delta U S P 28}$
from UV absorbances at the wavelength of maximum absorbance at about 274 nm in comparison with a Standard solution having a known concentration of USP Guaifenesin RS in the same medium. Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{O}_{4}$ is dissolved in 45 minutes:
the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform
at either $\mathrm{S}_{1}$, or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :--- |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |

## BriEfing

Guaifenesin and Codeine Phosphate Oral Solution, USP 27 page 889 -See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-3

## Guaifenesin and Codeine Phosphate Oral Solution

(Monograph under this new title-to become official June 1, 2005)
(Current monograph title is Guaifenesin and Codeine Phosphate Syrup)

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle-$
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\Delta$ USP28

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP28

## BRIEFING

Guaifenesin and Codeine Phosphate Syrup, USP 27 page 890-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-3

## Guaifenesin and Codeine Phosphate Syrup <br> (Current title-not to change until June 1, 2005)

Monograph title change-to become official June 1, 2005
See Guaifenesin and Codeine Phosphate Oral Solution

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR SYRUP PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements. $\triangle$ USP28

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -
FOR SYRUP PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements. $\triangle$ USP28

## BRIEFING

Homosalate, USP 27 page 913. On the basis of comments received and of data included in the original submission, it is proposed to specify that the Refractive index is determined at $20^{\circ}$.
(PA6: L. Evans) RTS-40627-1; 40627-2

## Change to read:

Refractive index $\langle 831\rangle$ : between 1.516 and 1.519
$\Delta_{\text {at }} 20^{\circ}{ }^{\circ}{ }_{\Delta U S P 28}$

Hydrocodone Bitartrate and Acetaminophen Tablets, USP 27 page 920 and page 633 of $P F 29(3)$ [May-June 2003]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40311-13

## Delete the following:

■Phammey Equivalent Name: Co hyeodAPAP Tablets ${ }_{1 S}$ (USP27)
Change to read:
Dissolution Proedure for a Pooled Samaple -
-
$\langle 711\rangle-$
TEST 1-If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 1.

Medium: pH $5.8 \pm 0.05$ phosphate buffer (see Buffer Solutions
in the section Reagents, Indicators, and Solutions); 900 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle$ USP28
Proceed as directed in the Assay, making any necessary modifications.

Tolerances-Not less than $80 \%(Q)$ each of the labeled amounts of acetaminophen ( $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ ) and hydrocodone bitartrate $\left(\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{3} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6} \cdot 2^{\frac{1}{2}} \mathrm{H}_{2} \mathrm{O}\right)$ are dissolved in 30 minutes:
the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

|  | Number |
| :---: | :---: | :---: |
| Stage | Tested |$\quad$| Acceptance Criteria |
| :---: |

TEST 2-If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.
Medium: 0.1 N hydrochloric acid; 900 mL .
Apparatus, Time, and Procedure-Proceed as directed under Test 1 .
Tolerances-Not less than $80 \%(Q)$ each of the labeled amounts of acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$ and hydrocodone bitartrate $\left(\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{3} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6} \cdot 2 \frac{1}{2} \mathrm{H}_{2} \mathrm{O}\right)$ is dissolved in 30 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content. $\triangle$ USP28

## Briefing

Ibuprofen Oral Suspension, USP 27 page 954—See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-4

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\quad U S P 28$

## Change to read:

Deliverable volume $\langle 698\rangle$-meets the requirements.
© FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements. $\triangle$ USP 28

## Briefing

Indomethacin Oral Suspension, USP 27 page 978-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-5

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle-$
FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\quad$ USSP28
Add the following:
${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-

TAINERS: meets the requirements. $\Delta U S P 28$

## BRIEFING

Irbesartan, page 1034 of $P F$ 29(4) [July-Aug. 2003]. On the basis of data received, it is proposed to add a new reference standard and revise the methods in the test for Related compounds and the Assay. The proposed method was validated using MachereyNagel, $7 \mu \mathrm{~m}$ Nucleosil 120 brand of L1 packing. The typical retention time for Irbesartan is about 23 minutes. It is also proposed to add storage conditions to the Packaging and storage section.
(PA5: A. Wilk) RTS-35777-1

## Add the following:

## ©Irbesartan


$\mathrm{C}_{25} \mathrm{H}_{28} \mathrm{~N}_{6} \mathrm{O} \quad 428.54428 .53$
1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tet-razol-5-yl)[1, 1'-biphenyl]-4-yl]methyl]-.
2-Butyl-3-[ $p$-(o-1H-tetrazol-5-ylphenyl)benzyl]-1,3-diazas-piro[4.4]non-1-en-4-one [138402-11-6].
» Irbesartan contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{25} \mathrm{H}_{28} \mathrm{~N}_{6} \mathrm{O}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight containers, and store at a temperature below $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Irbesartan RS. USP
Irbesartan Related Compound A RS.

Identification-Infrated Absorption- $\langle 197 \mathrm{~K}\rangle=$
A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Water, Method $I\langle 921\rangle$ : not more than $0.5 \%$.
Heavy metals, Method II $\langle 231\rangle$ : 0.002\%

## Limit of azide-

Mobile phase-Prepare a filtered and degassed 0.1 N sodium hydroxide solution (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Transfer about 25 mg of sodium azide, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix. Pipet $250 \mu \mathrm{~L}$ of this solution into a $200-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. This solution contains about $0.312 \mu \mathrm{~g}$ of sodium azide per mL .

Test solution-Transfer about 100 mg of Irbesartan, accurately weighed, to a $5-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a conductimetric detector, and a $4.0-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L46. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the signal to noise ratio for the azide peak is not less than 10.

Procedure-Separately inject equal volumes (about 200 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak area for azide peak. Calculate the amount of azide in ppm in the portion of Irbesartan taken by the formula:

$$
1000\left(C_{S} / C_{T}\right)(42.02 / 65.01)\left(r_{U} / r_{S}\right),
$$

in which $C_{S}$ is the concentration, in $\mu \mathrm{g}$ per mL , of sodium azide in the Standard solution; $C_{T}$ is the concentration, in mg per mL , of Irbesartan in the Test solution; $r_{U}$ is the peak area for azide obtained from the Test solution; and $r_{S}$ is the peak area for azide obtained from the Standard solution: not more than 10 ppm of azide is found.

## Chromatographie purity -

Diluent, Triethylamine solution, Mobile phase, and Chromagraphic system Proee directed in the Assaly:
Fest solution Use the Assaly preparation.
Procedure Inject volume (about $20-\mu L$ ) of the Test solution inte the chrematograph, record the chromatogram, and measure the peak respenses. Calculate the pereentage of each impurity in the pertion of Irbesartan taken by the for mula:-

$$
100\left(x_{i}+x_{t}\right),
$$

in which $r_{i}$ is the peak respense for each impurity, and $r_{t}$ is the sum of the respenses of all the peaks: not more than $0.5 \%$ of any individual impurity is found, and not more than $1.0 \%$ of total impurities is found.

## Related compounds-

pH 3.2 Phosphate buffer, Mobile phase, and Dilute standard solution-Proceed as directed in the Assay.

Standard solution-Prepare as directed for the System suitability solution in the Assay.

Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay. Chromatograph the Standard solution and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the
area for irbesartan related compound A peak. Calculate the percentage of irbesartan related compound A in the portion of Irbesartan taken by the formula:

$$
100\left(C_{S} / C_{T}\right)\left(r_{U} / r_{S}\right)
$$

in which $C_{S}$ is the concentration, in mg per mL , of USP Irbesartan Related Compound A RS in the Standard solution; $C_{T}$ is the concentration, in mg per mL , of Irbesartan in the Test solution; $r_{U}$ is the peak response for irbesartan related compound A obtained from the Test solution; and $r_{S}$ is the peak response for irbesartan related compound A obtained from the Standard solution: not more than $0.2 \%$ of irbesar$\tan$ related compound A is found, not more than $0.1 \%$ of any other impurity is found; and not more than $0.5 \%$ of total impurities is found.

Organic volatile impurities, Methot $I V(467) \div$ meets the requirements.

## Assay -

Diluent Prepare a solution of phespheric acid (1 in 100). Triethylamine solution Add 1.0 mL of triethylamine - $\theta$ 1000 mL of water, mix, and adjust with phespheric acid to a pH of 3.5

Mobile phase Prepare a filtered and degassed mixture of Friethylamine solution and acetonitrile (1:1). Make adjustments if neeessary (see Systen Suitability under Chromatograply $\langle 621$ ).).

Standard preparation- Dissolve-an aceurately weighed quantity of USP Irbesatan RS in Diltent to obtain a solut tion having a known concentration of about 0.5 mg per mL . Assay preparation Transfer about 50 mg of Irbesartan, accurately weighed, to a $100-\mathrm{mL}$ volumetric flack, dissolve in and dillte with Diluent to velume, and mix.

Chromatographic system (see Chromatography- $\langle 621\rangle$ ) The liquid chromatograph is equipped with a fluorometrie detector that has an excitation wavelength of 250 nm and an emission wavelength of 371 nm , and a $4.6 \mathrm{~mm} \times 15$
em coltumn that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chrematograph the Standard preparation, and record the peak respenses as directed for Procedure: the relative standard deviation for replicate in jections is net mere than $2.0 \%$.

Proecture Separately inject equal voltumes (about 20 $\mu \mathrm{L})$ of the Standard preparation and the Assay preparation inte the chromatograph, record the chromatograms, and measure the respenses for the irbesartan peaks. Caleulate the quantity, in mg, of $\mathrm{C}_{25} \mathrm{H}_{28} \mathrm{~N}_{6} \mathrm{O}$ in the pertion of Irbesartan taken by the formula:

$$
100 C\left(r_{t}+r_{s}\right)
$$

in which $C$ is the concentration, in mg per $m L$, of USP Ir besartan RS in the Standard preparation; and $r_{t}$-and $\Psi_{s}$ are the peak respenses obtained frem the $A s s a y$ preparation and the Standard preparation, respectively.

## Assay-

pH 3.2 Phosphate buffer-Mix 5.5 mL of phosphoric acid with about 950 mL of water, and adjust pH to 3.2 with triethylamine.

Mobile phase-Prepare a filtered and degassed mixture of pH 3.2 phosphate buffer and acetonitrile (67:33). Make adjustments if necessary (see System Suitability under Chromatography (621〉).

System suitability solution-Dissolve accurately weighed quantities of USP Irbesartan RS and USP Irbesartan Related Compound A RS in methanol to obtain a solution having a known concentration of about 0.05 mg per mL of each USP Reference Standard.
Dilute standard solution-Dissolve an accurately weighed quantity of USP Irbesartan RS in methanol to obtain a solution having a known concentration of about $1 \mu \mathrm{~g}$ per mL.

Standard preparation-Dissolve an accurately weighed quantity of USP Irbesartan RS in methanol to obtain a solution having a known concentration of about 0.5 mg per mL . Assay preparation-Transfer about 50 mg of Irbesartan, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with methanol to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.8 for irbesartan related compound A and 1.0 for irbesartan; the resolution, R , between irbesartan and irbesartan related compound A is not less than 2.0. Chromatograph the Standard preparation, and record the peak response as directed for Procedure: the standard deviation for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in mg, of $\mathrm{C}_{25} \mathrm{H}_{28} \mathrm{~N}_{6} \mathrm{O}$ in the portion of Irbesartan taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Irbesartan RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\Delta$ USP28

## Briefing

Isosorbide Dinitrate Sublingual Tablets, USP 27 page 1048See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40311-15

## Change to read:

Dissolution Procedure for a Pooled Sample

Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 20 minutes.
Mobile phase-Prepare a suitable degassed and filtered mixture of $\mathrm{pH} 3.0,0.1 \mathrm{M}$ ammonium sulfate and methanol ( $50: 50$ ).

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 5-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, prepared as directed below, and record the peak responses as directed for Procedure: the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0\%.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled samples as the test solution. $\triangle$ USP28
Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and an flltered
${ }^{\Delta}$ AUSP28
aliquot of the selution under
${ }^{\Delta}$ pooled sample ${ }_{\Delta U S P 28}$
into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{~N}_{2} \mathrm{O}_{8}$ dissolved in comparison with a Standard solution having a known concentration of USP Isosorbide Dinitrate RS, similarly prepared and chromatographed.
Tolerances-Not less than $80 \%$ ( $Q$ ) of the labeled amount of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{~N}_{2} \mathrm{O}_{8}$ is dissolved in 20 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$, or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## Briefing

Ivermectin, page 1519 of $P F 29(5)$ [Sept.-Oct. 2003]. Storage temperatures have been added to the Packaging and storage statement.
(VET: I. DeVeau; PSD: C. Okeke) RTS-40446-1

## Add the following:

## A Ivermectin




Component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ :
Avermectin $\mathrm{A}_{1 \mathrm{a}}$, 5-O-demethyl-22,23-dihydro-
( $2 \mathrm{a} E, 4 E, 8 E$ )-(5'S, $6 S, 6^{\prime} R, 7 S, 11 R, 13 R, 15 S, 17 \mathrm{a} R, 20-$
$R, 20$ a $R, 20 \mathrm{~b} S)-6^{\prime}-(S)-s e c-\mathrm{Buty}-$ $3^{\prime}, 4^{\prime}, 5^{\prime}, 6,6^{\prime}, 7,10,11,14,15,17 \mathrm{a}, 20,20 \mathrm{a}, 20 \mathrm{~b}-$ tetradecahy-dro-20,20b-dihydroxy[11,15-methano- $2 H, 13 H, 17 H$ furo $[4,3,2-p q][2,6]$ benzodioxacyclooctadecin-13, $2^{\prime}$ -[2H]pyran]-7-yl 2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl- $\alpha$-L-arabino-hexopyranosyl)-3-O-methyl- $\alpha-\mathrm{L}-$ arabino-hexopyranoside [70161-11-4].

Component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ :
Avermectin $\mathrm{A}_{1 \mathrm{a}}$, 5-O-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-.
( $2 \mathrm{a} E, 4 E, 8 E$ )-( $5^{\prime} S, 6 S, 6^{\prime} R, 7 S, 11 R, 13 R, 15 S, 17 \mathrm{a} R, 20-$ $R, 20 \mathrm{a} R, 20 \mathrm{~b} S)-3^{\prime}, 4^{\prime}, 5^{\prime}, 6,6^{\prime}, 7,10,11,-$ oxospiro[11,15-methano- $2 H, 13 H, 17 H$-furo[4,3,2-pq][2,6]benzodioxa-cyclooctadecin-13, $2^{\prime}[2 H]$ pyran $]-7-y l 2,6$-dideoxy-4-O-(2,6-dideoxy-3-O-methyl- $\alpha$-L-arabino-hexopyrano-syl)-3-O-methyl- $\alpha$-L-arabino-hexopyranoside [70209-81-3].

H-Ivermectin is a mixture of 5- $\theta$-demethyl-22,23dihydreavermectin $A_{14}$ (compenent $B_{4+}$ ) and 5- demethyl 25-de( 1 methylpropyl) 22, 23-dihydre-25-( 1 methylethyl)avermectin $\Lambda_{\text {tb }}$ (component $\mathrm{B}_{46}$. It contains not less than 95.0 pereent of compenent $B_{46}$ plus compenent $B_{t a}$-caleulated on the water, ethanol aleohel, and formamide free basis.
» Ivermectin is a mixture of Avermectin $\mathrm{A}_{1 \mathrm{a}}$, 5-$O$-demethyl-22,23-dihydro-(component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ ) and Avermectin $\mathrm{A}_{1 \mathrm{a}}, 5-O$-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methyl-ethyl)-(component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ ). It contains not less than 90.0 percent of component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$, and the sum of component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ plus component $\mathrm{H}_{2} \mathrm{~B}_{1 \text { b }}$ is not less than 95.0 percent and not more than 100.5 percent, calculated on the anhydrous and al-cohol- and formamide-free basis. It may contain a small amounts of suitable antioxidant and chelating agents.

Packaging and storage-Preserve in tight containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-If it is intended for veterinary use only, it is so labeled. Label it to state the name(s) and amount(s) of any added substance(s). Label it also to state that it is for manufacturing, processing, or repackaging.

USP Reference standards $\langle 11\rangle$ —USP Ivermectin RS.
Clarity of solution-Transfer 1 g to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with toluene to volume, and mix: the solution is clear.

Color of solution-Pass a portion of the solution prepared in the test for Clarity of solution through a fine-porosity, sin-tered-glass filter. Determine the absorbance of the filtrate at 440 nm in a $1-\mathrm{cm}$ cell using toluene as the blank: the absorbance is not more than $0.024(1-0.01 V)$, in which $V$ is the sum of the percentages of water, alcohol, and formamide in the Ivermectin taken.

## Identification-

A: The-chrematogram of the Assay preparation, obtained as directed in the Assat, exhibits major peaks for eompenent $B_{t+a}$ and compenent $B_{t b}$, the retention times-of
which correspend to these exhibited in the chromategram of the Standared preparation, obtained as directed in the $A s$ say, and the ratio of compenent $\mathrm{B}_{1+}$ to compenent $\mathrm{B}_{4 \mathrm{~m}}$ is not less than-9.0:1 9.0:1.0. Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.

B: Ultraviolet Absorption $\langle 197 U\rangle$ -
Solution: $20 \mu \mathrm{~g}$ per mL.
Medium: methanol. The spectrum exhibits maxima at about 238 nm and 245 nm and a shoulder at about 253 nm, and the absorptivity at the wavelength of maximmm abserption at about 245 nm is between 37.2 and 39.2 , caleu lated on the water, ethanol aleohol, and formamide free basis. The retention times of the component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ peak and the component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ peak in the chromatogram of the Assay preparation correspond to those in the chromatogram of the Standard preparation, as obtained in the Assay.

Clarity and-color of solution Dissolve 1.0 g of it in tol Hene to obtain 50 mL of solution: the solution is clear and its abserbance at 440 nm in a $1-\mathrm{em}$ eell is net mere than 0.024 , toluene being used as the blank.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $-17^{\circ}$ and $-20^{\circ}$, deter mined at $20^{\circ}$ and calculated on the water-, ethanet alco-hol-, and formamide-free basis.

Test solution: 255 mg per mL , in methanol.
Water, Method $I\langle 921\rangle$ : not more than $1.0 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : 0.002\%.
Limit of ethanol alcohol and formamide-
Standerd solutions. Transfer 3.0 mL of dehydrated aleo-
hol to a $100-\mathrm{mL}$ volumetric flask, dilute with water to vol ume, and mix (Solution A). Transfer 1.0 mL of formamide to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix (Solution B). Transfer 3.0 mL of Solution 4 and 3.0 mb Of Solution B to a $100-\mathrm{mL}$ volumetric flask, dilute-with water to volume, and mix to obtain a solution having concentrations of ethanol aleohol and formamide of 0.0009 and
0.0003 mL per mL , respectively (Solution C). Transfer 8.0 mL of Solution $A$ and 8.0 mL of Solution B-10-100-mE velumetric flask, dilute with water to volume, and mix to ebtain a solution having concentrations of ethanel alcehel and formamide of 0.0024 and 0.0008 mL per mL , respectively (Solution D). Transfer 4.0 mL of Solution $C$ and- 4.0 mL of Solution $D$ to separate $15-\mathrm{mL}$ centrifuge tubes, add 2.0 mL of $m$ xylene to each tube, stopper, mix, centrifuge, and diseard the upper m-xylene-layers. The retained lower fayers are Standard solutions $C$ and $P$.

Fest solution Transfer 120 mg of Ivermectin, aceurately weighed, to a 15 mL centrifuge tube, and dissolve in 2.0 mb of $m$-kylene. Add 2.0 mL of water, mix, and centrifugeTransfer the $m-x y l e n e$ layer to a $15-\mathrm{mL}$ centrifuge tube, and extract again with 2.0 mL of water. Diseard the $m-x y$ lene layer, and combine the two aqueous layers to obtain the Fest solution.

Chromatographic system (see Chromatography $\langle 621$ )) The gas chrematograph is equipped with a flame ionization detector and contains a $1.8-\mathrm{ml} \times 3.2-\mathrm{mm}$ column packed with 80-10-100-mesh support S2. The injection pert is maintained at about $190^{\circ}$, and the detector is maintained at about $250^{\circ}$. Helimm is used as the carrier gas at a flow rate of about 40 mL per mintute. The coltumn is maintained at about $150^{\circ}$ fer 12 mintutes after injection, then raised at a rate of $20^{\circ}$ per minute to $180^{\circ}$, and then held for 20 minutes.

Precedure Separately inject equal volumes (about $2 \mu \mathrm{HL}$ ) Of Standard solutions $C$ and $D$ and the Test solution inte the ehromatograph, record the chromatograms, and measure the ethanel aleohol and formamide peak respenses. Plet the peak respenses for ethanol aleohol and formamide versus eoncentrations, in mL per mL, of ethanol aleohol and forma mide, respectively, obtained from Standard solutions $C$ and D. From the graphs so obtained, determine the concentrations of ethanol aleohol and formamide in the Test solution.
[NOTE-In the event that the peak respenses of the Test solthfion are-signifieantly outside the ranger of peak respenses ebtained with Standard solutions $C$ and $D$, prepare additional Standard solutions, and chrematograph them to obtain peak responses bracketing those obtained with the Fest solution.] Caleulate the pereentages of ethanol aleohel and formamide in the pertion of Ivermectin taken by the for-mula:-

## $400,000 \mathrm{Cd} / \mathrm{H}$,

in which $C$ is the cencentration of ethanelaleohelor formamide, in mL per mL, of the Test solution, $d$ is the density of ethanel aleehel ( 0.79 ) or formamide- $(1.13)$, and $W$ is the weight, in mg, of Ivermectin taken: not more than $5.0 \%$ of ethanel alcohel $\left(\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}\right)$ and $3.0 \%$ of formamide-are found.

Internal standard solution-Dilute 0.5 mL of isopropyl alcohol with water to 100 mL , and mix.

Standard solution 1—Transfer 3.02 .0 mL of dehydrated alcohol to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Standard solution 2-Transfer 1.0 mL of formamide to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Standard solution 3-Transfer 5.0 mL of Standard solution 1 and 5.0 mL of Standard solution 2 to a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of formamide and alcohol of 0.001 and 0.0030 .002 mL per mL , respectively. Transfer 2.0 mL of this solution to a $15-\mathrm{mL}$ centrifuge tube, add 2.0 mL of $m$-xylene, insert the stopper, mix, and centrifuge. Remove the upper $m$-xylene layer, and extract it with 2.0 mL of water. Discard the upper layer, combine the two retained lower aqueous layers, add 1.0 mL of Internal standard solution, and mix. Each mL of this solution contains about 0.00120 .0008 mL of alcohol and 0.0004 mL of formamide.

Standard solution 4-Transfer 10.0 mL of Standard solution 1 and 10.0 mL of Standard solution 2 to a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of alcohol and formamide of 0.0060 .004 and 0.002 mL per mL , respectively. Transfer 2.0 mL of this solution to a $15-\mathrm{mL}$ centrifuge tube, add 2.0 mL of $m$-xylene, insert the stopper, mix, and centrifuge. Remove the upper $m$-xylene layer, and extract it with 2.0 mL of water. Discard the upper layer, combine the two retained lower aqueous layers, add 1.0 mL of Internal standard solution, and mix. Each mL of this solution contains about 0.00240 .0016 mL of alcohol and 0.0008 mL of formamide.

Test solution-Transfer 120 mg of Ivermectin, accurately weighed, to a $15-\mathrm{mL}$ centrifuge tube, and dissolve in 2.0 mL of $m$-xylene, heating in a water bath at $45 \pm 5^{\circ}$, if necessary. Add 2.0 mL of water, mix, and centrifuge. Transfer the $m$ xylene layer to a $15-\mathrm{mL}$ centrifuge tube, and extract with 2.0 mL of water. Discard the upper $m$-xylene layer, combine the two retained lower aqueous layers, add 1.0 mL of Internal standard solution, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and a $0.53-\mathrm{mm} \times 30-\mathrm{m}$ fused-silica analytical column coated with a $3-\mu \mathrm{m}$ G43 stationary phase. The carrier gas is helium, with a $1: 5$ split ratio and a linear velocity of about 35 cm per second. The chromatograph is programmed as follows. The column temperature is maintained at about $40^{\circ}$ for 5 minutes after injection, and then increased at a rate of $20^{\circ}$ per minute to $180^{\circ}$, and maintained at $180^{\circ}$ for 2 minutes. The injection port temperature is maintained at about $140^{\circ}$, and the detector temperature is maintained at about $250^{\circ}$.

Procedure-Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of Standard solution 3, Standard solution 4, and the Test solution into the chromatograph, record the chromatograms,
and measure the peak responses for alcohol, formamide, and isopropyl alcohol. Plot the ratios of the peak responses for alcohol and isopropyl alcohol and for formamide and isopropyl alcohol versus concentrations, in mL per mL , of alcohol and formamide, respectively, obtained from Standard solution 3 and Standard solution 4. From the graphs so obtained, and using the ratios of the peak responses for alcohol and isopropyl alcohol and for formamide and isopropyl alcohol obtained from the chromatogram of the Test solution, determine the concentrations, $C$, of alcohol and formamide in the Test solution. [NOTE-In the event that the peak responses of the Test solution are significantly outside the ranges of peak responses obtained from Standard solution 3 and Standard solution 4, prepare additional Standard solutions, and chromatograph them to obtain peak responses bracketing those obtained with the Test solution.] Calculate the percentages of alcohol and formamide in the portion of Ivermectin taken by the formula:

$$
500,000 C D / W
$$

in which $C$ is the concentration of alcohol or formamide, as appropriate, in mL per mL , in the Test solution; $D$ is the density of alcohol (0.79) or formamide (1.13); and $W$ is the weight, in mg, of Ivermectin taken: not more than $5.0 \%$ of alcohol and $3.0 \%$ of formamide is found.

Related sthbstances compounds-Using the chromato gram of the Assaly preparation obtained as direeted in the Assay, caleulate the percentage of each related substance compound in the Ivermectin taken by the formula:-

$$
100 r_{i}+r_{i}
$$

in which $r_{i}$ is the respense of each individual peak, exeept thes of compenent $B_{t a}$ and compenent $B_{4}$, and $r_{t}$ is the sum of the respense of all of the peaks in the chrematogram.

Not more than 2\% of any individual related substance com pound is found, and the sum of all related substances is not mere than $4 \%$.

Mobile phase and Chromatographic system—Proceed as directed in the Assay.

Standard stock solution-Proceed as directed for Standard preparation in the Assay.

Standard solution 1-Transfer 1.0 mL of the Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with methanol to volume, and mix.

Standard solution 2-Transfer 5.0 mL of Standard solution 1 to a $100-\mathrm{mL}$ volumetric flask, dilute with methanol to volume, and mix.

Test solution-Use the Assay preparation.
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of Standard solution 1, Standard solution 2, and the Test solution into the chromatograph, record the chromatogram of the Test solution for a period of time equivalent to twice the retention time of the prineipal main peak in the chromatogram obtained from Standard solution 1, and measure the respenses for the major peaks. In the-chremategram obtained from the Test solution, the area of any peak with at retention time of 1.3 to 1.5 about 1.2 to 1.4 , relative to the prineipal peak, is net greater than twiee 2.5 times the area-of the prineipal peak in the chromatogram obtained from Stat dard selution $1(2.0 \%$ 2.5\%); the area of any other peak, aside-from the twe principal peaks, is not greater than the area of the principal peak in the chromatogram obtained from Standard solution $1(1.0 \%)$; and the sum of the areas of all the peaks, apart from the two principal peaks, is not greater than four times the area of the principal peak in the ehromagram obtained from Sta solut solion-1 (4.0\%) $(4 \%)$. Disregard any peak with an area less than that of
the prineipal peak in the chrematogram of Statheded solution $\mathcal{Z}(0.05 \%)$ ) peak areas. Calculate the percentage of each impurity by the formula:

$$
100 r_{i} /\left(r_{s}-r_{b}\right)
$$

in which $r_{i}$ is the peak area for each individual impurity in the Test solution chromatogram; $r_{s}$ is the sum of all peaks in the Test solution chromatogram; and $r_{b}$ is the total area of all peaks in a blank chromatogram: not more than $2.5 \%$ is found for the sum of all peaks with a relative retention time of about 1.3 to 1.4 (corresponding to $\mathrm{H}_{4} \mathrm{~B}_{1 \mathrm{a}}$ isomers and $\Delta^{2,3}$ $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ ); not more than $1 \%$ is found for the peak with a relative retention time of about 0.7 (corresponding to 8 a -oxo$\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ ); not more than $0.7 \%$ is found for the peak with a relative retention time of about 0.5 (corresponding to Avermectin $\mathrm{B}_{1 \mathrm{a}}$ ); not more than $0.5 \%$ is found for any other individual impurity peak; not more than $1 \%$ is found for the sum of all other individual peaks; and not more than $4 \%$ is found for the sum of the areas of all the peaks, apart from the two main peaks $\left(\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}\right.$ and $\left.\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}\right)$. Disregard any peak with an area less than that of the two main peaks $\left(\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}\right.$ and $\left.\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}\right)$ in the chromatogram of Standard solution 2 ( $0.05 \%$ ).

## Assay-

Mobile phase Prepare a mixture of acetonitrile, metha nol, and water ( $530: 350: 120$ ), filter through a filter having a peresity of $1 \mu \mathrm{~m}$-r less, and degas. Make adjustments if neeessary (see System Suitability under Chromatography〈 624$\rangle$ ).

Standard preparation Dissolve an aceurately weighed quantity of USP Ivermectin RS quantitatively in Mobile phase to obtain a-solution having a-known concentration of about 0.5 mg per mL .
Assay preparation Transfer about 40 mg of Ivermeetin, aceurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in methanol, dilute with Mobile phase to volume, and mix.

Chromatographie system (see-Chromatography $\langle 621\rangle$ )
The liquid chrematograph is equipped with a 254 -nm detecfor and a $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chrematograph the Standard preparation, and record the peak respenses as directed under Procedure: compenent $\mathrm{B}_{46}$ is eluted at a retention time of about 14 minutes, followed by compenent $B_{1+1}$-at a retention time of about 17 minutes. The resolution, $R$, between the peaks for component $B_{4 b}$ and eompenent $\mathrm{B}_{\text {tut }}$ is not less than 3.0 , the column effieiency determined frem the compenent $B_{1+n}$ peak is net less than 2000 theoretical plates, the tailing factor for the compenent $B_{1+}$ peak is not more than 2.5 , and the relative standard deviation of the peak respenses for compenent $B_{\text {tet }}$ for replieate injections is not mere than $1.0 \%$.

Proedure [NOTE-Use peak areas where peak respenses are indicated.] Separately inject equal volumes (about $50-\mu \mathrm{L}$ ) of the Standerd preparation and the Assay preparation into the chromatograph, record the chromategrams over a period of time that is wice the retention time Of the peak for compenent $B_{1+n}$, and measure the peak respenses for compenent $B_{t+}$ and compenent $B_{4 b}$. Caleulate the pereentage of compenent $B_{14}$ plus component $B_{40}$ in the portion of Ivermectin taken by the formula:-

$$
100(C P / H)\left(F_{\downarrow}++_{s}\right)
$$

in which $C$ is the concentration, in mg per $m L$, of USP Ivermectin RS in the Standard preparation, $P$ is the designated percentage of the sum of compenent $B_{t+n}$ and compenent $B_{t h}$ in the USP Ivermectin RS, $W$ is the weight, in mg, of Ivermectin taken to prepare the $A s s a y$ preparation, and $r_{t}$ and $r_{s}$ are the sums of the peak respenses for compenent $B_{\text {ten }}$ and eomponent $\mathrm{B}_{\mathrm{tb}}$-obtained from the Assay preparation and the Standard preparation, respectively.

Mobile phase-Prepare a mixture of acetonitrile, methanol, and water (53:35:12), pass through a filter having a $1-$ $\mu \mathrm{m}$ or finer porosity, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ). Increasing the proportion of water increases the elution times and allows better separation of impurities.

Standard preparation-Dissolve an accurately weighed quantity of USP Ivermectin RS in methanol to obtain a solution having a known concentration of about 0.8 mg per mL .

Assay preparation-Transfer about 80 mg of Ivermectin, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with methanol to volume, and mix. Sonicate, if necessary.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.8 for component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ and 1.0 for component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$; the resolution, $R$, between component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ and component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ is not less than 3.0; the column efficiency determined from the component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ peak is not less than 5000 theoretical plates; the tailing factor for component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ peak is not more than 2.5 ; and the relative standard deviation for replicate injections is not more than $1.0 \%$ determined from the component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ peak.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses for component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ and component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$. Calculate the quantity, in mg , of component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}\left(\mathrm{C}_{48} \mathrm{H}_{74} \mathrm{O}_{14}\right)$ and component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}\left(\mathrm{C}_{47} \mathrm{H}_{72} \mathrm{O}_{14}\right)$ in the portion of Ivermectin taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ or component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses for component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ or component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta U S P 2 8}$

## BRIEFING

Kanamycin Sulfate Capsules, USP 27 page 1053-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-1

## Change to read:

Dissolution Proedtre for a Pooled Sample
$\Delta$
〈711 USP28
Medium: 0.01 N hydrochloric acid; 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure-
${ }^{\text {® }}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle U S P 28$
Determine the amount of kanamycin $\left(\mathrm{C}_{18} \mathrm{H}_{36} \mathrm{~N}_{4} \mathrm{O}_{11}\right)$ dissolved by employing the procedure set forth in the Assay, making any necessary modifications.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{18} \mathrm{H}_{36} \mathrm{~N}_{4} \mathrm{O}_{11}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform
at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :--- |
| Stage | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{2}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## BRIEFING

Levothyroxine Sodium Tablets, USP 27 page 1085 and the Fifth Interim Revision Announcement on page 1394 of PF 29(5) [Sept.-Oct. 2003]. The Note "Do not use paddle stirrers with synthetic coating" applies only to Test 4 under Dissolution.
(BPC: M. Marques) RTS-40525-1

## Change to read:

Dissolution $\langle 711\rangle$ - [NOTE-All containers that are in contact with solutions containing levothyroxine sodium are to be made of glass.
${ }^{6}$ Pe net use paddle-stirrers with synthetic enating.os]
$\triangle$ USP28
TEST 1 -
Medium: 0.01 N hydrochloric acid containing $0.2 \%$ sodium lauryl sulfate; 500 mL .

Apparatus 2: 50 rpm .
Time: 45 minutes.
Determine the amount of $\mathrm{C}_{15} \mathrm{H}_{10} \mathrm{I}_{4} \mathrm{NNaO}_{4}$ dissolved by employing the following method.

Mobile phase-Prepare a filtered and degassed mixture of methanol and $0.1 \%$ phosphoric acid ( $60: 40$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ). $\bullet 5$

Standard solution-Prepare a stock solution of USP Levothyroxine RS in methanol having a known concentration of about 0.1 mg per mL . Dilute this stock solution with Dissolution Medium to obtain a solution having a concentration similar to that expected in the Test solution.

Test solution-[NOTE-Prior to use, check the filters for absorptive loss of drug.] Use a filtered portion of the solution under test.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $225-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor is not more than 1.5 ; and the relative standard deviation is not more than $4.0 \%$.

Procedure-Separately inject equal volumes (about $800 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $\mathrm{C}_{15} \mathrm{H}_{10} \mathrm{I}_{4} \mathrm{NNaO}_{4}$ dissolved.

Tolerances-Not less than $70 \%(Q)$ of the labeled amount of $\mathrm{C}_{15} \mathrm{H}_{10} \mathrm{I}_{4} \mathrm{NNaO}_{4}$ is dissolved in 45 minutes.

TEST 2-If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium, Apparatus, Mobile phase, Standard solution, Test solution, Chromatographic system, and Procedure-Proceed as directed for Test 1.
$\Delta_{\text {TEST } 3-[T o ~ c o m e .] ~}^{\mathbf{\Delta U S P 2 8}}$

- TEST 4-If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 4.
${ }^{\Delta}$ [NOTE-Do not use paddle stirrers with synthetic coating. $]_{\text {Medium }}$.

Medium: 0.01 N hydrochloric acid; 500 mL for tablets labeled to contain between $25 \mu \mathrm{~g}$ and $175 \mu \mathrm{~g}$ of levothyroxine sodium; 900 mL for tablets labeled to contain $200 \mu \mathrm{~g}$ or $300 \mu \mathrm{~g}$ of levothyroxine sodium.

Apparatus 2: 75 rpm .
Time: 45 minutes.
Determine the amount of $\mathrm{C}_{15} \mathrm{H}_{10} \mathrm{I}_{4} \mathrm{NNaO}_{4}$ dissolved by employing the following method.

Mobile phase-Prepare a filtered and degassed mixture of water, acetonitrile, and $85 \%$ orthophosphoric acid (700:500:2). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Prepare a stock solution by transferring about 100 mg of USP Levothyroxine RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Add 80 mL of alcohol and 1 mL of 1 N hydrochloric acid, sonicate for about 2 minutes, dilute with alcohol to volume, and mix. Dilute this stock solution with a mixture of alcohol and water (1:1) to obtain a solution having a concentration of 0.01 mg of levothyroxine per mL . Dilute this intermediate solution with Dissolution Medium to obtain a solution having a concentration similar to that expected in the Test solution.

Test solution-Use a centrifuged portion of the solution under test.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $225-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 12.5-\mathrm{cm}$ column that contains packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor is not more than 1.5; and the relative standard deviation is not more than $4.0 \%$.

Procedure-Separately inject equal volumes (about $500 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $\mathrm{C}_{15} \mathrm{H}_{10} \mathrm{I}_{4} \mathrm{NNaO}_{4}$.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{15} \mathrm{H}_{10} \mathrm{I}_{4} \mathrm{NNaO}_{4}$ is dissolved in 45 minutes. 05

Briefing
Lisinopril Tablets, USP 27 page 1097—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-2

## Change to read:

Dissolution Procedure for a Pooled Sample
-
〈 $\mathbf{A} 11\rangle$ USP28
(
Medium: 0.1 N hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
Determine the amount of lisinopril dissolved using the following method.

Mobile phase and Chromatographic system-Prepare as directed in the Assay.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled sample as the test solution. $\Delta$ USP28
Inject a volume of a filtered portion of the solution under test
${ }^{\Delta}$ the pooled sample $\boldsymbol{a}_{U S P 28}$
into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $\mathrm{C}_{21} \mathrm{H}_{31} \mathrm{~N}_{3} \mathrm{O}_{5}$ dissolved in comparison with a Standard solution having a known concentration of USP Lisinopril RS in the same medium and similarly chromatographed.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{21} \mathrm{H}_{31} \mathrm{~N}_{3} \mathrm{O}_{5}$ in the Tablets is dissolved in 30 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform
at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

| Number |  |  |
| :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved ( $\mathrm{S}_{1}+\mathrm{S}_{2}+$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## BRIEFING

Loperamide Hydrochloride Tablets, USP 27 page 1103-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-3

## Change to read:

Dissolution Proedtre for a Porled Sample
A UUSP28
$\langle 711\rangle-$
Medium: 0.01 N hydrochloric acid; 900 mL . Apparatus 2: 50 rpm .
Time: 30 minutes.
Determine the amount of $\mathrm{C}_{29} \mathrm{H}_{33} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot \mathrm{HCl}$ dissolved by employing the following method.

Mobile phase and Chromatographic system—Proceed as directed in the Assay.

Procedure-
${ }^{\mathbf{\Delta}}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\begin{aligned} \text { USP28 }\end{aligned}$

Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of a filtered pertion of the solution under test
$\Delta_{\text {the pooled sample }}^{\Delta U S P 28}$
into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $\mathrm{C}_{29} \mathrm{H}_{33} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot \mathrm{HCl}$ dissolved in comparison with a Standard solution having a known concentration of USP Loperamide Hydrochloride RS in the same Medium and similarly chromatographed. Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{29} \mathrm{H}_{33} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot \mathrm{HCl}$ is dissolved in 30 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity $Q$, is the amount of dissolved active ingredient, expressed as a percentage of the labeled content.

|  | Acceptance Table for a Pooled Sample |  |
| :--- | :---: | :--- |
|  | Number |  |
| Stage | Tested | Acceptance Criteria |

## Add the following:

## ■ Loratadine Oral Solution

» Loratadine Oral Solution contains not less than 94.0 percent and not more than 105.0 percent of the labeled amount of loratadine $\left(\mathrm{C}_{22} \mathrm{H}_{23} \mathrm{ClN}_{2} \mathrm{O}_{2}\right)$.

## Change to read:

Packaging and storage-Preserve in tight containers, and store between $2^{\circ}$ and $30^{\circ} 25^{\circ} \cdot \mathbf{\Delta U S P 2 8}$

USP Reference standards $\langle 11\rangle-U S P$ Loratadine $R S$.

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ —

Test solution-Place a volume of Oral Solution, equivalent to about 10 mg of loratadine, in a centrifuge tube. Add 10 mL of 0.2 N sodium hydroxide and 2.0 mL of dichloromethane. Rotate for 10 minutes. Centrifuge, and discard the aqueous phase.

Standard solution-Dissolve an accurately weighed quantity of USP Loratadine RS in dichloromethane to obtain a solution having a known concentration of about 5 mg per mL .

Developing solvent system: ethyl ether and diethylamine (40:1), in a paper-lined tank.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, as obtained in the Assay.

Antimicrobial effectiveness test $\langle 51\rangle$ : meets the requirements.

Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total aerobic microbial count does not exceed 100 per mL ; and the total combined molds and yeasts count does not exceed 50 cfu per mL.

Deliverable volume $\langle 698\rangle$ : meets the requirement.
$\mathbf{p H}\langle 791\rangle$ : between 2.5 and 3.1.

## Related compounds-

Mobile phase-Prepare a mixture of 15 mmol sodium dodecyl sulfate in a mixture of water and acetonitrile (1:1). Adjust with phosphoric acid to a pH of $2.6 \pm 0.1$, filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare a mixture of Mobile phase and water (2:1).

System suitability solution 1-Dissolve an accurately weighed quantity of USP Loratadine RS, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.002 mg per mL .

System suitability solution 2-Quantitatively transfer 5.0 mL of System suitability solution 1 into a suitable container, dilute with Diluent to 50 mL , and mix.

Resolution solution-Transfer an amount of Oral Solution, equivalent to 20 mg of loratadine, into a screw-cap, glass container. Add 1 mL of $3 \%$ aqueous hydrogen peroxide, and mix. Cap, and heat at $65^{\circ}$ for 18 to 24 hours.

Test solution-Transfer an accurately measured volume of Oral Solution, equivalent to about 5 mg of loratadine, to a $25-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The flow rate is about 2 mL per minute. The column temperature is maintained between $30^{\circ}$ and $40^{\circ}$.

Chromatograph the Resolution solution, and record the peak areas as directed for Procedure: the relative retention times are about 0.70 for ethyl 4-[8-chloro-5,6-dihydro-4-(hydro-xymethyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yli-dene]-1-piperidinecarboxylate, 0.84 for ethyl 4-[8-chloro-5,6-dihydro-2-(hydroxymethyl)-11 H -benzo[5,6]cyclohep-ta[1,2-b]pyridin-11-ylidene]-1-piperidinecarboxylate, and 1.0 for loratadine; and the resolution, $R$, between loratadine and ethyl 4-[8-chloro-5,6-dihydro-2-(hydroxymethyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene]-1-piperidinecarboxylate is not less than 3.0. Chromatograph System suitability solution 1, and record the peak area response of the loratadine peak as directed for Procedure: the tailing factor is not less than 0.7 and not greater than 1.1. Chromatograph System suitability solution 2, and record the peak area response of the loratadine peak as directed for Procedure: the relative standard deviation for replicate injections of System suitability solution 2 is not more than $10 \%$.

Procedure-Inject about $50 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure all of the peak area responses. Calculate the percentage of each individual related compound in the portion of Oral Solution taken by the formula:

$$
100\left(r_{i} / r_{s}\right),
$$

in which $r_{i}$ is the individual peak response of each related compound in the Test solution; and $r_{s}$ is sum of the responses of all of the peaks, excluding excipient peaks: not more than $0.3 \%$ of ethyl 4-[8-chloro-5,6-dihydro-4-(hydro-xymethyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yli-dene]-1-piperidinecarboxylate is found; not more than $0.3 \%$ of ethyl 4-[8-chloro-5,6-dihydro-2-(hydroxymethyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene]-1-piperidinecarboxylate is found; not more than $0.2 \%$ of any other individual impurity is found; and the sum of all impurities is not more than $0.5 \%$.

Assay-
0.05 M Monobasic potassium phosphate solution-Transfer about 6.8 g of monobasic potassium phosphate, accurately weighed, to a 1-liter volumetric flask, dissolve in and dilute with water to volume, and mix. Adjust with phosphoric acid to a pH of $3.0 \pm 0.1$.

Mobile phase-Prepare a filtered and degassed mixture of 0.05 M Monobasic potassium phosphate solution and acetonitrile (7:3). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard preparation-Dissolve an accurately weighed quantity of butylparaben in a mixture of water and acetonitrile (7:3), and dilute quantitatively, and stepwise if necessary, with a mixture of water and acetonitrile (7:3) to obtain a solution having a concentration of about 0.3 mg per mL .

Standard stock peparation-Dissolve an accurately weighed quantity of USP Loratadine RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 1.0 mg per mL .
Standard preparation-Transfer 5.0 mL of Internal standard preparation, 5.0 mL of Standard stock preparation, and 12 mL of water into a $50-\mathrm{mL}$ volumetric flask. Dilute with a mixture of water and acetonitrile (7:3), and mix.

Assay preparation-Transfer an accurately measured quantity of Oral Solution, equivalent to 5 mg of loratadine, into a $50-\mathrm{mL}$ volumetric flask. Pipet 5.0 mL of Internal standard preparation into the flask, dilute with a mixture of water and acetonitrile (7:3) to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L11. The flow rate is about 2 mL per minute. The column temperature is maintained between $20^{\circ}$ and $30^{\circ}$.

Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.78 for butylparaben and 1.0 for loratadine; the resolution, $R$, between loratadine and butylparaben is not less than 1.9; the tailing factor is not more than 1.6 for the loratadine and butylparaben peaks; and the relative standard deviation for replicate injections is not more than $2 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg of loratadine $\left(\mathrm{C}_{22} \mathrm{H}_{23} \mathrm{ClN}_{2} \mathrm{O}_{2}\right)$ in the portion of Oral Solution taken by the formula:

$$
50 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Loratadine RS in the Standard preparation; and $R_{U}$ and $R_{S}$ are the ratios of loratadine to the internal standard peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP27)

## Add the following:

## ©Losartan Potassium


$\mathrm{C}_{22} \mathrm{H}_{22} \mathrm{ClKN}_{6} \mathrm{O} \quad 461.00$
$1 H$-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tet-razol-5-yl)[1, 1'-biphenyl]-4-yl]methyl]-, monopotassium salt.

2-Butyl-4-chloro-1-[p-(o-1 H -tetrazol-5-ylphenyl)benzyl] imidazole-5-methanol, monopotassium salt [124750-99-8].
» Losartan Potassium contains not less than 98.5 percent and not more than 101.0 percent of $\mathrm{C}_{22} \mathrm{H}_{22} \mathrm{ClKN}_{6} \mathrm{O}$ calculated on the anhydrous, sol-vent-free basis.

Packaging and storage-Preserve in well-closed containers. Store at controlled room temperature

USP Reference Standards $\langle 11\rangle$ —USP Losartan Potassium $R S$.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$ -
B: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle-$
Solution: $10 \mu \mathrm{~g}$ per mL .
Medium: methanol.
C: It meets the requirements of the test for Potassium $\langle 191\rangle$.

Water, Method $I\langle 921\rangle$ : not more than $0.5 \%$.
Heavy metals, Method II $\langle 231\rangle$ : 0.001\%.

## Limit of cyclohexane and isopropyl alcohol-

Standard solution-Accurately prepare a solution having a known concentration of about 0.05 mg per mL of cyclohexane and 0.05 mg per mL of isopropyl alcohol in dimethylformamide.

Test solution-Transfer 500 mg of Losartan Potassium to a $10-\mathrm{mL}$ volumetric flask that contains 5 mL of dimethylformamide, dissolve using a vortex mixer, dilute with dimethylformamide to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and contains a $0.53-\mathrm{mm} \times 30-\mathrm{m}$ column containing packing G27 of $1.5-\mu \mathrm{m}$ film thickness. The carrier gas is helium, flowing at a rate of about 6 mL per minute. The chromatograph is programmed as follows. Initially the column is maintained at $50^{\circ}$ for 5 minutes, then the temperature is increased at a rate of $30^{\circ}$ per minute to $200^{\circ}$, and maintained at $200^{\circ}$ for 5 minutes. The injection port and detector block temperature are each maintained at $220^{\circ}$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the retention times are about 2 minutes for isopropyl alcohol and 4 minutes for cyclohexane; the resolution, $R$, between cyclohexane and isopropyl alcohol is not less than 4.0; and the relative standard deviation for replicate injections is not more than $8.0 \%$.

Procedure-Inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Test solution and the Standard solution into the gas chromatograph, record the chromatogram, and measure the responses for the major peaks. Calculate the percentage of cyclohexane and isopropyl alcohol taken by the formula:

$$
100(C / /)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of cyclohexane or isopropyl alcohol in the Standard solution; $I$ is the concentration, in mg per mL , of Losartan in the Test solution; and $r_{U}$ and $r_{S}$ are the responses of cyclohexane or iso-
propyl alcohol in the Test solution and the Standard solution, respectively: not more than $0.1 \%$ of cyclohexane; and not more than $0.2 \%$ of isopropyl alcohol is found.

## Chromatographic purity-

Solution A-Prepare a $0.1 \%$ solution of phosphoric acid in water.

Solution B-Use acetonitrile.
Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$.

System suitability solution-Dissolve an accurately weighed quantity of USP Losartan Potassium RS and triphenylmethanol in methanol, and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 0.3 mg per mL and 0.002 mg per mL , respectively.

Test solution-Transfer about 30 mg of Losartan Potassium, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with methanol to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 25-\mathrm{cm}$ column containing packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 75 | 25 | equilibration |
| $0-25$ | $75 \rightarrow 10$ | $25 \rightarrow 90$ | linear gradient |
| $25-35$ | 10 | 90 | isocratic |
| $35-45$ | $10 \rightarrow 75$ | $90 \rightarrow 25$ | linear gradient |
| $45-50$ | 75 | 25 | re-equilibration |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.0 for losartan and 1.9 for triphenylmethanol; and the tailing factor for losartan is not more than 1.6. [NOTE-The typical retention time for triphenylmethanol is about 20 minutes.]

Procedure-Inject a volume (about $10 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure all the peak responses. Calculate the percentage of each impurity in the portion of Losartan Potassium taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for each impurity; and $r_{s}$ is the sum of the responses for all the peaks: not more than $0.2 \%$ of any individual impurity is found; and not more than $0.5 \%$ of total impurities is found.

## Assay-

Solution A and Solution B-Proceed as directed for Chromatographic purity.

Mobile phase-Prepare a filtered and degassed mixture of Solution $A$ and Solution B (3:2). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation - Dissolve an accurately weighed quantity of USP Losartan Potassium RS in methanol, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.25 mg per mL.

Assay preparation-Transfer about 25 mg of Losartan Potassium, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with methanol to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at about $35^{\circ}$. Chromatograph the

Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 5600 theoretical plates; the tailing factor is not more than 1.4 ; and the relative standard deviation for replicate injections is not more than $0.5 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{22} \mathrm{H}_{22} \mathrm{ClKN}_{6} \mathrm{O}$ in the portion of Losar$\tan$ Potassium taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Losartan Potassium RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak areas for the losartan peak obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta U S P 2 8}$

## BRIEFING

Meclizine Hydrochloride Tablets, USP 27 page 1146-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-4

## Change to read:

Dissolution, Preedure for a Pooled Sample

Medium: 0.01 N hydrochloric acid; 900 mL . Apparatus 1: 100 rpm .
Time: 45 minutes.
Determine the amount of $\mathrm{C}_{25} \mathrm{H}_{27} \mathrm{ClN}_{2} \cdot 2 \mathrm{HCl}$ dissolved by employing the following method.
Mobile phase-Prepare a suitable degassed and filtered mixture of water and methanol ( $55: 45$ ) that contains 0.69 g of monobasic sodium phosphate in each 100 mL and is adjusted with phosphoric acid, if necessary, to a pH of 4.0 .

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $230-\mathrm{nm}$ detector, a 4.6$\mathrm{mm} \times 25-\mathrm{cm}$ precolumn positioned between the pump and the injection valve that contains packing L27, and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ analytical column that contains packing L9. The flow rate is about 2 mL per minute. Chromatograph replicate injections of the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation is not more than $2.0 \%$.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled
sample as the test solution. $\begin{aligned} & \text { USP28 }\end{aligned}$
Inject about $100 \mu \mathrm{~L}$ of a filtered

- 4 USP28
portion of the solution under test,
$\Delta_{\text {pooled sample }}^{{ }_{U U S 28}}$
suitably diluted with Mobile phase, if necessary, into the chromatograph, record the chromatogram, and measure the response for the major peak. Determine the amount of $\mathrm{C}_{25} \mathrm{H}_{27} \mathrm{ClN}_{2} \cdot 2 \mathrm{HCl}$ dissolved from the peak response obtained in comparison with the peak response obtained from the Standard solution having a known concentration of USP Meclizine Hydrochloride RS in a mixture of Dissolution Medium and Mobile phase (1:1), similarly chromatographed. An amount of alcohol not to exceed $1 \%$ of the total volume of the Standard solution may be used to dissolve USP Meclizine Hydrochloride RS prior to dilution.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{25} \mathrm{H}_{27} \mathrm{ClN}_{2} \cdot 2 \mathrm{HCl}$ is dissolved in 45 minutes:
$\Delta_{t}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

| Number |  |  |
| :--- | :---: | :--- |
| Stage | Tested | Acceptance Criteria |


| Stage | Tested | Acceptance Criteria |
| :---: | :---: | :---: |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$ |
| $\mathrm{~S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> $\mathrm{S}_{3}$ |
|  | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

BRIEFING
Meperidine Hydrochloride Oral Solution, USP 27 page 1161-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-6

## Meperidine Hydrochloride Oral Solution

## (Monograph under this new title-to become official June 1, 2005) <br> (Current monograph title is Meperidine Hydrochloride Syrup)

Add the following:
${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP 28

## Add the following:

${ }^{\boldsymbol{4}}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\triangle U S P 28$

## BRIEFING

Meperidine Hydrochloride Syrup, USP 27 page 1161—See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-6

## Meperidine Hydrochloride Syrup

(Current title—not to change until June 1, 2005)
Monograph title change-to become official June 1, 2005
See Meperidine Hydrochloride Oral Solution

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle-$ FOR SYRUP PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements. $\triangle$ USP28

## Add the following:

${ }^{\text {t}}$ Deliverable volume $\langle 698\rangle$ -
FOR SYRUP PACKAGED IN MULTIPLE-UNIT CONTAINERS:
meets the requirements. $\triangle$ USP28

## BRIEFING

Meprobamate Tablets, USP 27 page 1167—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-5

Change to read:
Dissolution, Proedure for a Pooled Sample
-
〈711 USP28
Medium: deaerated water; 900 mL
Apparatus 1: 100 rpm .
Time: 30 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.
Determine the amount of $\mathrm{C}_{9} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{4}$ dissolved using the method set forth for the Assay, making any necessary volumetric adjustments.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{9} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{4}$ is dissolved in 30 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for Pooled Sample. Continue testing through the three stages unless the results conform to either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for Pooled Sample |  |  |  |
| :---: | :---: | :---: | :---: |
| Number |  |  |  |
| Stage | Tested | Acceptance Criteria |  |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |  |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. | 10 <br> $\mathbf{\circ}$ <br> $\$$ <br> 8 |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. | 20 <br> 0 <br> 0.0 <br> 0 <br> 0 |
| ⓊSP28 |  |  |  |

## Briefing

Methadone Hydrochloride Oral Solution, USP 27 page 1186-See briefing under Acetaminophen Oral Solution.

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(PA2: C. Anthony) RTS-40619-7
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## Add the following:

${ }^{4}$ Uniformity of dosage units $\langle 905\rangle$ FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-

TAINERS: meets the requirements. $\quad$ USP28

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements. $\quad$ USP28

## BRIEFING

Methenamine Tablets, USP 27 page 1193—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-6

## Change to read:

Dissolution Preedure for a Pooled Sample
${ }_{\langle }^{\Delta}$ U ${ }^{\text {USPP28 }}$
Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure-
${ }^{\mathbf{\Delta}}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.
Determine the amount of $\mathrm{CH}_{12} \mathrm{~N}_{4}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{~N}_{4}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. <br> $\mathrm{S}_{2}$ |
| $\mathrm{~S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## BRIEFING

Methocarbamol Tablets, USP 27 page 1197—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) $\quad$ RTS - 40313-7

## Change to read:

Dissolution Procedure for a Pooled Sample
${ }^{\Delta}$ 〈 $\mathbf{A 1 1}$ USP28
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.
Determine the amount of $\mathrm{C}_{11} \mathrm{H}_{15} \mathrm{NO}_{5}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{11} \mathrm{H}_{15} \mathrm{NO}_{5}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform to either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

| Stage | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :--- |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> $\mathrm{S}_{3}$ |
| 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |  |

Briefing
Methylphenidate Hydrochloride Tablets, USP 27 page 1217-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-8

## Change to read:

Dissolution, Proedure for Pood Sample

Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\Delta U S P 28$
Determine the amount of $\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{NSO}_{2} \cdot \mathrm{HCl}$ dissolved by employing the procedure set forth in the Assay, making any necessary volumetric adjustments.
Tolerances-Not less than $75 \%$ (Q) of the labeled amount of $\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
$\Delta_{\text {the requirements are met if the quantities of active ingredi- }}$ ent dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested |  |

## BriEfing

Nadolol and Bendroflumethiazide Tablets, USP 27 page 1270. See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-10

## Change to read:

Dissolution Preedure for a Porled Sample
〈 711 USP28 [NOTE-_Protect solutions from light throughout this test.] Medium: 0.1 N hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed under Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets (Dissolution $\langle 711\rangle$ ). Combine equal volumes of the filtered solutions of the 6 or 12 individual specimines withdrawn, and use the
pooled sample as the test solution. $\triangle U S P 28$
Determine the amounts of $\mathrm{C}_{17} \mathrm{H}_{27} \mathrm{NO}_{4}$ and $\mathrm{C}_{15} \mathrm{H}_{14} \mathrm{~F}_{3} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{~S}_{2}$ dissolved, employing the procedure set forth in the Assay, using fit tered portions of the solution under test
© portions of the pooled sample, ${ }_{\text {USP2 }}$
suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having known concentrations of USP Nadolol RS and USP Bendroflumethiazide RS, prepared by dissolving them in the minimal amount of methanol and diluting to the desired concentrations with Dissolution Medium.

Tolerances-Not less than $80 \%(Q)$ of the labeled amounts of nadolol $\left(\mathrm{C}_{17} \mathrm{H}_{27} \mathrm{NO}_{4}\right)$ and bendroflumethiazide $\left(\mathrm{C}_{15} \mathrm{H}_{14} \mathrm{~F}_{3} \mathrm{~N}_{3} \mathrm{O}_{4} \mathrm{~S}_{2}\right)$ are dissolved in 30 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |
| :---: | :---: |
|  | Number |
| Stage | Tested |


| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. <br> $\mathrm{S}_{2}$ |
| :---: | :---: | :--- |
| $\mathrm{~S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5$ <br> Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## BRIEFING

Nalidixic Acid, USP 27 page 1274. It is proposed to specify the solvent employed to prepare the titrant used in the Assay.
(BPC: M. Marques) RTS-40477-2

## Change to read:

Assay-Dissolve about 250 mg of Nalidixic Acid, accurately weighed, in 30 mL of dimethylformamide that previously has been neutralized to thymolphthalein TS, and titrate with 0.1 N lithium methoxide VS
$\boldsymbol{\Delta}^{\boldsymbol{i n}}$ methanol, $\mathbf{A S S P 2 8}$
using a magnetic stirrer and taking precautions against absorption of atmospheric carbon dioxide. Each mL of 0.1 N lithium methoxide is equivalent to 23.22 mg of $\mathrm{C}_{12} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{3}$.

Briefing
Naproxen Oral Suspension, USP 27 page 1283—See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-8

## Add the following:

${ }^{4}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP28

## Add the following:

${ }^{\Delta}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\mathbf{\triangle}$ USP28

## BRIEFING

Neomycin Sulfate Oral Solution, USP 27 page 1289; Nystatin for Oral Suspension, USP 27 page 1351; Vancomycin Hydrochloride for Oral Solution, USP 27 page 1932. To improve the standards in these monographs, it is proposed to add requirements for Uniformity of dosage units to apply to single-unit containers and Deliverable volume to apply to multiple-unit containers.
(PA7a: W. Wright) RTS-40665-1

## Add the following:

${ }^{\boldsymbol{4}}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\quad$ USSP28

## Add the following:

${ }^{\Delta}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-

Briefing
Neostigmine Bromide Tablets, USP 27 page 1311—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-13

## Change to read:

Dissolution, Procedure for a Pooled Sample
${ }^{\Delta}\langle\mathbf{A}$ USP28
Medium: water; 500 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\text {® Proceed as directed for Procedure for Capsules, Uncoated }}$ Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle$ USP28
At the speified time interval, withdraw 30 mL of the solution under test, and filter.
$\Delta$
AUSP28
Pipet 10 mL each of the filtered test solution,
${ }^{\Delta}$ of the Pooled Sample,,$_{\Delta U S P 28}$
a Standard solution having a known concentration of USP Neostigmine Bromide RS, and water to provide a blank, into respective $125-\mathrm{mL}$ separators. Proceed as directed for Procedure in the Assay, beginning with "Add 15 mL of a solution."
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{12} \mathrm{H}_{19} \mathrm{BrN}_{2} \mathrm{O}_{2}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

TAINERS: meets the requirements. $\mathbf{\triangle}$ USP28

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :--- |
|  | Number |  |
| Stage | Tested | Acceptance Criteria | S1

has a potency equivalent to not less than $595 \mu \mathrm{~g}$ of netilmicin $\left(\mathrm{C}_{21} \mathrm{H}_{41} \mathrm{~N}_{5} \mathrm{O}_{7}\right)$ per mg ., caleulated on the dried basis.
${ }^{\wedge} \mathbf{\Delta} U S P 28$

## Change to read:

USP Reference standards $\langle 11\rangle —$ USP Netilmicin Sulfate RS.
${ }^{\star}$ USP Sisomicin Sulfate $R S{ }_{\mathbf{\Delta U S P 2 8}}$

## Change to read:

## Identification-

A: Prepare a solution containing 10 mg of netilmicin per mL . Apply $5 \mu \mathrm{~L}$ of this solution, $5 \mu \mathrm{~L}$ of a Standard solution of USP Netilmicin Sulfate RS containing 10 mg of netilmiein per mL , and $5 \mu \mathrm{~L}$ of a $1: 1$ mixture of the two solutions to a suitable thin layer ehrematographic plate (see-Chromatography (621)) coated with a 0.25 mm layer of chromatographic siliea gel mixture. Allow the spots to dry, place the plate in a developing chamber fitted for con tinuous flow, thin layer chromatography, develop the chromatogram in a solvent system consisting of a mixture of methanol, ammonium hydroxide, and chloroform ( $60: 30: 25$ ) for 1.5 hours. Remove the plate from the developing chamber, allow the selvent to evaperate, and heat the plate at $110^{\circ}$ for 15 minutes. Spray the plate with a 1 in 100 solution of ninhydrin in butanol to whieh 1 mL of pyridine has been added: netilmicin appears as a brown spot, and the spots obtained from the test solution and from the mixture of test solution and Standard solution, respectively, correspond in distance from the origin to that of the spet from the Standard solution.
${ }^{\Delta}$ The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the As-
say. USP28
B: ${ }^{\text {It }}$ USP28 responds to the tests for Sulfate $\langle 191\rangle$.

## Add the following:

${ }^{\Delta}$ Chromatographic purity-
Dilute phosphoric acid, Mobile phase, Resolution solution, Assay preparation, and Chromatographic sys-tem-Proceed as directed in the Assay.

Test solution-Use the Assay preparation.
Reference solution-Transfer 1.0 mL of the Assay preparation to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Test solution and the Reference solution into the chromatograph, and measure the area responses for all
${ }^{\wedge}$ previously dried in a vacuum at a pressure not exceeding 5 mm mercury for 1 hour, $\boldsymbol{\Delta U S P 2 8}$
the peaks, except those due to the solvent. Calculate the percentage of each impurity in the portion of Netilmicin Sulfate taken by the formula:

$$
\left(r_{i} / r_{s}\right),
$$

in which $r_{i}$ is the peak response of each impurity peak in the chromatogram obtained from the Test solution, and $r_{S}$ is the netilmicin peak response in the chromatogram obtained from the Reference solution. Not more than $1 \%$ of any individual impurity is found, and the total of all impurities is not more than 5\%. ${ }^{\text {UUSP28 }}$

## Change to read:

Assay Preceed as directed under Antibioties Mierobial Asseys: $\langle 81\rangle=$
${ }^{\Delta}$ Dilute phosphoric acid-Dilute 5.0 mL of phosphoric acid to 1000 mL with water, and mix.

Mobile phase-Dissolve 20.22 g of sodium heptaneslfonate in Dilute phosphoric acid, dilute with Dilute phosphoric acid to 1000 mL , and mix. To 620 mL of this solution add 380 ml of acetonitrile, mix, and pass through a $0.45-\mathrm{nm}$ porosity filter. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Resolution solution-Prepare a solution in Mobile phase containing about 1 mg of USP Netilmicin Sulfate RS and 1 mg of USP Sisomicin Sulfate RS per mL.

Standard preparation-Transfer about 50 mg of USP Netilmicin Sulfate RS to a low-actinic, previously accurately tared, $50-\mathrm{mL}$ volumetric flask. Place the flask in a vacuum desiccator under a vacuum of less than 5 mm of mercury for 1 hour. Accurately weigh the flask, and determine the dry weight of the USP Netilmicin Sulfate RS taken. Dissolve in, and dilute with, Mobile phase to volume, and mix.

Assay preparation-Transfer about 50 mg of Netilmicin Sulfate to a low-actinic, previously accurately tared, 50mL volumetric flask. Place the flask in a vacuum desiccator under a vacuum of less than 5 mm of mercury for 1 hour.

Accurately weigh the flask, and determine the dry weight of the Netilmicin Sulfate taken. Dissolve in, and dilute with, Mobile phase to volume, and mix.

Chromatographic system-(see Chromatography $\langle 621\rangle)$-The chromatograph is equipped with a $205-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed under Procedure: the resolution of the sismicin and netilmicin peaks is not less than 1 . Chromatograph the Standard preparation, and record the peak responses as directed under Procedure: The column efficiency is not less than 3000 theoretical plates, the tailing factor is not more than 2, and the relative standard deviation for replicate injections is not more than $1 \%$.

Procedue-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, and measure the area responses for the main peaks. Calculate the quantity, in $\mu \mathrm{g}$, of netilmicin $\left(\mathrm{C}_{21} \mathrm{H}_{41} \mathrm{~N}_{5} \mathrm{O}_{7}\right)$ per mg of Netilmicin Sulfate taken by the formula:

$$
\left(W_{S} P / W_{U}\right)\left(r_{U} / r_{S}\right),
$$

in which $W_{S}$ is the dry weight, in mg , of USP Netilmicin Sulfate RS taken to prepare the Standard preparation; $P$ is the designated potency, in $\mu \mathrm{g}$ of netilmicin $\left(\mathrm{C}_{21} \mathrm{H}_{41} \mathrm{~N}_{5} \mathrm{O}_{7}\right)$ per mg, of the USP Netilmicin Sulfate RS; $W_{U}$ is the dry weight, in mg , of the Netilmicin Sulfate taken to prepare the Assay preparation; and $r_{U}$ and $r_{S}$ are the netilmicin peak responses obtained from the Assay preparation and the Standard preparation, respectively. USPP28 $^{\text {U }}$

## BriEfing

Netilmicin Sulfate Injection, USP 27 page 1312—See briefing under Netilmicin Sulfate.
(PA7:W. Wright) RTS-40546-2

## Change to read:

USP Reference standards $\langle 11\rangle —$ USP Endotoxin RS. USP Netilmicin Sulfate RS.
${ }^{\wedge}$ USP Sisomicin Sulfate RS. ${ }_{\mathbf{\Delta U S P 2 8}}$

## Change to read:

Assay - Proeed as directed under Antibies Mied Assays〈81, using an aceurately measured volume of Injection diluted quantitatively and stepwise with Buffer No. 3 to yield a Test Dilt tion having a concentration assumed to be equal to the median dose level of the Standard:
${ }^{\triangle}$ Dilute phosphoric acid, Mobile phase, Resolution solution, Standard preparation, and Chromatographic sys-tem-Proceed as directed in the Assay under Netilmicin Sulfate.

Assay preparation-Transfer an accurately measured volume of Netilmicin Sulfate Injection, equivalent to about 100 mg of netilmicin, to a low-actinic, $100-\mathrm{mL}$ volumetric flask.

Dilute with Mobile phase to volume, and mix.
Procedure-Proceed as directed for Procedure in the $A s$ say under Netilmicin Sulfate. Calculate the quantity, in mg, of netilmicin $\left(\mathrm{C}_{21} \mathrm{H}_{41} \mathrm{~N}_{5} \mathrm{O}_{7}\right)$ in each mL of Netilmicin Sulfate Injection taken by the formula:

$$
0.1\left(W_{S} P / 50 V\right)\left(r_{U} / r_{S}\right)
$$

in which $V$ is the volume, in mL, of Netilmicin Sulfate Injection taken to prepare the Assay preparation, and the other terms are as defined therein. $\Delta$ USP28

Briefing
Nevirapine, page 1054 of $P F$ 29(4) [July-Aug. 2003]. On the basis of new information received, the following modifications have been proposed. (1) The term "Specified and unspecified impurities" rather than "Related compounds" is used in accordance with ICH terminology. (2) For Organic volatile impurities, Method $V$ rather than Method 1 is used. (3) The water determination for the anhydrous form is performed by Method la rather than Method 1c. Additional editorial changes are made to clarify the injection volumes as well as the system suitability criteria for the Resolution solution.
(PA7b: B. Davani) RTS-40312-1

## Add the following:

## ${ }^{\Delta}$ Nevirapine


$\mathrm{C}_{15} \mathrm{H}_{14} \mathrm{~N}_{4} \mathrm{O} \quad 266.30$
$6 H$-Dipyrido[3,2-b:2', $\left.3^{\prime}-e\right][1,4]$ diazepin-6-one, 11-cyclo-
propyl-5,11-dihydro-4-methyl-.
11-Cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-
$\left.b: 2^{\prime}, 3^{\prime}-e\right][1,4]$ diazepin-6-one [129618-40-2].

Hemihydrate 275.31
» Nevirapine is anhydrous or contains net mere tham one-half molecule of water of hydration. It contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{15} \mathrm{H}_{14} \mathrm{~N}_{4} \mathrm{O}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight containers.
Store ben $15^{\circ}$ and $30^{\circ}$, at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-Label it to indicate whether it is anhydrous or the hemihydrate.

USP Reference standards $\langle 11\rangle — U S P$ Nevirapine Anhydrous RS. USP Nevirapine Hemihydrate RS. USP Nevirapine Related Compound A RS. USP Nevirapine Related Compound B RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$ —Do not dry the specimens.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Water, Method I $\langle 921\rangle$-For Nevirapine anhydrous: preeeed directed for Mether not more than $0.2 \%$. For Nevirapine hemihydrate: preas direed for Method between $3.1 \%$ and $3.9 \%$.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $0.001 \%$.
Related-empounds Specified and unspecified impurities -
0.025 M Ammonium phosphate buffer, Mobile phase, Standard stock solution 1, Standard stock solution 2, Standard stock solution 3, and Resolution solution-Proceed as directed in the Assay.

Standard solution-Transfer 2.0 mL of the Standard stock solution 1 to a $200-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. Transfer 5.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Test solution-Transfer an accurately weighed quantity of Nevirapine, equivalent to about 24 mg of nevirapine anhydrous, to a $100-\mathrm{mL}$ volumetric flask. Add 4 mL of acetonitrile and 80 mL of Mobile phase, and sonicate for at least 15 minutes. Allow to cool to room temperature, dilute with Mo bile phase to volume, and mix.

Chromatographic system-Proceed as directed in the Assay. Chromatograph the Resolution solution (approximately $25 \mu \mathrm{~L}$ ), and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for nevirapine related compound $\mathrm{B}, 1.0$ for nevirapine, 1.5 for nevirapine related compound A , and 2.8 for nevirapine impurity C ; the resolution, $R$, between nevirapine related compound B and nevirapine is not less than 5.0; and the resolution between nevirapine and nevirapine related compound A is not less than 7.4. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $5.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms for at least 80 minutes, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Nevirapine taken by the formula:

$$
10,000(1 / F)(C / W)\left(r_{i} / r_{S}\right)
$$

in which $F$ is the relative response factor for each impurity, which is equal to 1.3 for nevirapine related compound $B$ and 1.0 for all other impurities; $C$ is the concentration, in mg per mL, of USP Nevirapine Anhydrous RS in the Standard solution; $W$ is the weight of Nevirapine, in mg , taken to prepare the Test solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the nevirapine peak response obtained from the Standard solution: not more than $0.2 \%$ each of nevirapine related compound A, nevirapine related compound B , and the impurity having a relative retion of 2.8 is found; nevirapine impurity C is found; not more than $0.1 \%$ of any other individual unspecified impurity is found; and not more than $0.6 \%$ of total impurities is found.

Organic volatile impurities, $I$ Method $V\langle 467\rangle$ : meets the requirements.

## Assay-

0.025 M Ammonium phosphate buffer-Transfer 2.88 g of monobasic ammonium phosphate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in 800 mL of water, adjust with 1 N sodium hydroxide to a pH of about 5.0, dilute with water to volume, and mix.

Mobile phase-Prepare a filtered and degassed mixture of 0.025 M Ammonium phosphate buffer and acetonitrile (4:1).

Standard stock solution 1-Transfer an accurately weighed quantity of USP Nevirapine Anhydrous RS to a volumetric flask, add a volume of a mixture of Mobile phase and acetonitrile (20:1), sonicate for at least 15 minutes, allow to cool to room temperature, dilute with Mobile phase to volume, and mix to obtain a solution having a known concentration of about 0.24 mg per mL . [NOTE-Do not use after 78 hours.]

Standard stock solution 2-Transfer an accurately weighed quantity of USP Nevirapine Related Compound A RS to a volumetric flask, add a volume of a mixture of Mobile phase and acetonitrile (3:1), sonicate for at least 15 minutes, allow to cool to room temperature, dilute with Mobile phase to volume, and mix to obtain a solution having a known concentration of about 0.24 mg per mL .

Resolution solution-Transfer 3.0 mL of Standard stock solution 1, 3.0 mL of Standard stock solution 2, and 6.0 mL of Standard stock solution 3 to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Standard preparation-Transfer 3.0 mL of Standard stock solution 1 to a $25-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. [NOTE-Do not use after 78 hours.]

Assay preparation-Transfer an accurately weighed quantity of Nevirapine, equivalent to about 24 mg of nevirapine anhydrous, to a $100-\mathrm{mL}$ volumetric flask. Add 4 mL of acetonitrile and 80 mL of Mobile phase, sonicate for at least 15 minutes, allow to cool to room temperature, dilute with Mobile phase to volume, and mix. Transfer 3.0 mL of this solution to a $25-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L57. L\#\# (see Chromatography $\langle 621\rangle$ ). The flow rate is about 1 mL per minute. The column temperature is maintained at $35^{\circ}$. Chromatograph the Resolution solution (approximately $25 \mu \mathrm{~L}$ ), and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for nevirapine related compound $\mathrm{B}, 1.0$ for nevirapine, 1.5 for nevirapine related compound A , and 2.8 for nevirapine impurity C ; the resolution, $R$, between nevirapine related compound B and nevirapine is not less than 5.0 ; and the resolution between nevirapine and nevirapine related compound A is not less than 7.4. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.0 \%$. $2.0 \%$.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{15} \mathrm{H}_{14} \mathrm{~N}_{4} \mathrm{O}$ in the portion of Nevirapine taken by the formula:

$$
833.33 C\left(r_{U} / r_{S}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Nevirapine Anhydrous RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta U S P 2 8}$

## BRIEFING

Niacinamide Tablets, USP 27 page 1314 -See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-14

Change to read:
Dissolution Proedtre for a Pooted Sample
$\Delta$
〈711) ${ }^{\text {USP28 }}$
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled
sample as the test solution. USP28 $^{2}$
Determine the amount of $\mathrm{C}_{6} \mathrm{H}_{6} \mathrm{~N}_{2} \mathrm{O}$ dissolved, employing the procedure set forth in the Assay for niacin or niacinamide, pyridoxine hydrochloride, riboflavin, and thiamine under Water-soluble Vitamins Tablets, using fllered the solution under test,
$\Delta_{\text {portions of the pooled sample }}^{\text {ASSP28 }^{28}}$
suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Niacinamide RS in the same Medium.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{6} \mathrm{H}_{6} \mathrm{~N}_{2} \mathrm{O}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :--- |
| Stage | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{2}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## Briefing

Nitrofurantoin Capsules, USP 27 page 1324 and page 1545 of $P F 29(5)$ [Sept.-Oct. 2003]. It is proposed to slightly modify the preparation of the Test solution in the test for Uniformity of dosage units and in the preparation of the Assay preparation in the Assay to allow for sample homogenization if needed. In addition, editorial style changes have been made.
(PA7b: B. Davani) RTS-40480-1

## Change to read:

Labeling-Capsules that contain the macrocrystalline form of Ni trofurantoin are so labeled.
-When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.■2S (USP27)

Change to read:
Dissolution $\langle 711\rangle$ -
-TEST 1■2S (USP27)
(where labeled as containing Nitrofurantoin macrocrystals) Medium: $\mathrm{pH} 7.2( \pm 0.05)$ phosphate buffer; 900 mL . Apparatus 1: 100 rpm.
Times: 1, 3, and 8 hours.
Procedure-Determine the amount of $\mathrm{C}_{8} \mathrm{H}_{6} \mathrm{~N}_{4} \mathrm{O}_{5}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 375 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Nitrofurantoin RS in the same Medium.

Tolerances-The percentage of the labeled amount of $\mathrm{C}_{8} \mathrm{H}_{6} \mathrm{~N}_{4} \mathrm{O}_{5}$ dissolved at the 1-hour time point conforms to Acceptance Table 1 under Drug Release $\langle 724\rangle$, and the percentages dissolved at the 3and 8-hour time points conform to the criteria for the final test time in Acceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $20 \%$ and $60 \%$ |
| 3 | not less than $45 \%$ |
| 8 | not less than $60 \%$ |

-TEST 2 (where labeled as containing both Nitrofurantoin macrocrystalline and monohydrate forms)-If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Acid medium: 0.01 N hydrochloric acid for 1 hour; 900 mL .

$$
\text { pH 7.5 Buffer medium—Prepare a pH } 7.5 \text { buffer concen- }
$$ trate by dissolving 62.2 g of potassium hydroxide and 129.3 g of monobasic potassium phosphate in water, dilute with water to 1 L , and mix. After 1 hour change the Acid medium to pH 7.5 Buffer medium by adding 50 mL of pH 7.5 buffer concentrate, and operate for an additional 6 hours.

Apparatus 2: 100 rpm , with sinkers made of teflon-coated steel wire prepared by forming a coil approximately 22 mm long from a $13-\mathrm{cm}$ length of 20 -gauge wire (See Figure 1).


Fig. 1. Sinker.
Times: 1, 3, and 7 hours.
Acid-stage standard solution-Prepare a solution of USP Nitrofurantoin RS in Acid medium to obtain a solution having a known concentration of about 0.025 mg per mL .

Buffer-stage standard solution-Prepare a solution of USP Nitrofurantoin RS in $p H$ 7.5 Buffer medium to obtain a solution having a known concentration of about 0.075 mg per mL.
Procedure-Determine the amount of $\mathrm{C}_{8} \mathrm{H}_{6} \mathrm{~N}_{4} \mathrm{O}_{5}$ dissolved from UV absorbances at the isosbestic wavelength at about 375 nm on filtered portions of each solution under test suitability diluted, if necessary, with Acid medium or pH 7.5 Buffer medium when appropriate in comparison with the appropriate Standard solution.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{8} \mathrm{H}_{6} \mathrm{~N}_{4} \mathrm{O}_{5}$ dissolved at the specified times conform to the following tables.

| Time <br> (hours) | Amount dissolved <br> (individual) | Amount dissolved <br> (mean) |
| :---: | :--- | :--- |
| 1 | between $2 \%$ and $16 \%$ | between $5 \%$ and $13 \%$ |
| 3 | between $27 \%$ and between $39 \%$ and |  |
|  | $69 \%$ | $56 \%$ |
| 7 | not less than $68 \%$ | not less than $81 \%$ |

Number
Level

Tested
Criteria

L2 12 The mean percentage of dissolved label claim lies within the range for

12

The mean percentage of dissolved label claim lies within the range for the means at each interval and is not less than the stated amount at the final test time. All individual values lie within the ranges for the individuals at each interval and are not less than the stated amount at the final test time. the means at each interval and is not less than the stated amount at the final test time. Not more than 2 of the 24 individual values lie outside the stated ranges for individual values at each interval, and not more than 2 of the 24 individual values is less than the stated amount at the final test time.

## -2S (USP27)

## Change to read:

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements. PROCEDURE FOR CONTENT UNIFORMITY-
Test solution-Transfer the contents of 1 Capsule to a suitable flask, and add a volume of dimethylformamide to obtain a solution having a concentration of about 1.2 mg of nitrofurantoin per mL . Shake the flask for 15 minutes.
${ }^{\boldsymbol{\Delta}}$ [nOTE-If necessary, the sample may be homogenized using a disperser.] $]_{\triangle S P 28}$
In the case of a $50-$ or $100-\mathrm{mg}$ Capsule transfer 40.0 mL of this solution to a suitable flask, and proceed as directed for Assay preparation in the Assay, beginning with "add 50.0 mL of Internal standard solution." In the case of a $25-\mathrm{mg}$ Capsule, transfer 20.0 mL of the solution to a suitable flask, and add 25.0 mL of Internal standard solution instead of 50.0 mL .

Procedure-Proceed as directed in the Assay, using the follow-
ing Test solution instead of the Assay preparation.

## Change to read:

## Assay-

pH 7.0 phosphate buffer, Mobile phase, Internal standard solution, Standard preparation, and Chromatographic systemProceed as directed in the Assay under Nitrofurantoin.

Assay preparation-Transfer, as completely as possible, the contents of 20 Capsules to a $500-\mathrm{mL}$ flask. Place the emptied capsules in a beaker, add 25 mL of dimethylformamide, and agitate for 1 minute. Decant into the flask containing the Capsule contents. Rinse the emptied capsules with another two $25-\mathrm{mL}$ portions of dimethylformamide, and decant into the flask. Add sufficient dimethylformamide to bring the volume to about 250 mL . Insert the stopper in the flask, and shake by mechanical means for 15 minutes. Dilute with dimethylformamide to volume, and mix.
${ }^{\boldsymbol{\Delta}}$ [NOTE-If necessary, the sample may be homogenized using a disperser.] $]_{\Delta U S P 28}$

## Add the following:

## ${ }^{4}$ Composition-

Solution $A$-Prepare a mixture of 0.05 M ammonium acetate and acetonitrile (71:29).

Solution B-Prepare a mixture of acetonitrile and 0.05 M ammonium acetate (60:40).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Quantitatively dissolve an accurately weighed quantity of USP Nystatin RS in dimethyl sulfoxide to obtain a solution having a known concentration of about 0.4 mg per mL . [NOTE-Protect this solution from light and use within 24 hours, if stored in the refrigerator.]

Test solution-Transfer about 20 mg of Nystatin, accurately weighed, to a low-actinic $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with dimethyl sulfoxide to volume, and mix. [NOTE-Use this solution within 24 hours, if stored in the refrigerator.]
System suitability solution-Dissolve about 20 mg of Ny statin in 25 mL of methanol, dilute with water to 50 mL , and mix. To 10.0 mL of this solution add 2.0 mL of diluted hydrochloric acid, and allow to stand at room temperature for 1 hour.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $304-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains base-deactivated end-capped $5-\mu \mathrm{m}$ packing L1. The column is
maintained at a constant temperature of about $30^{\circ}$. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0-25$ | 100 | 0 | isocratic |
| $25-35$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | gradient |
| $35-40$ | 0 | 100 | isocratic |
| $40-45$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | gradient |
| $45-50$ | 100 | 0 | equilibrium |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the two major peaks is not less than 3.5. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the main nystatin A1 peak elutes at about 14 minutes.

Procedure-Inject about $20 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure the peak area responses for all of the peaks, disregarding any peaks eluting in less than 2 minutes. Calculate the percentage of each peak by the formula:

$$
100 r_{i} / r_{T},
$$

in which $r_{i}$ is the response of an individual peak; and $r_{T}$ is the total of all of the responses, any peaks eluting in less than 2 minutes being disregarded. Not less than $85.0 \%$ of nystatin A1 is found; and not more than $4.0 \%$ of any other individual component is found. $\triangle U S P 28$

## BRIEFING

Nystatin for Oral Suspension, USP 27 page 1351—See briefing under Neomycin Sulfate Oral Solution.
(PA7: W. Wright)

$$
\text { RTS }-40665-2
$$

## Add the following:

${ }^{\boldsymbol{4}}$ Uniformity of dosage units $\langle 905\rangle$ FOR POWDER PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements. $\triangle U S P 28$

## Add the following:

${ }^{\text {© }}$ Deliverable volume $\langle 698\rangle$ FOR POWDER PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements. $\triangle U S P 28$

[^10](PA4: E. Gonikberg; BPC: M. Marques) RTS-40646-1 ; 40215-1; 40104-1

## Add the following:

## ©Omeprazole Delayed-Release Capsules

» Omeprazole Delayed-Release Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of omeprazole $\left(\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}\right)$.

Packaging and storage-Preserve in tight, light-resistant containers. Store between $15^{\circ}$ and $30^{\circ}$.

Labeling-When more than one Drug Release test is given, the labeling states the Drug Release test used only if Test 1 is not used.

USP Reference standards $\langle 11\rangle$ —USP Omeprazole $R S$.

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -

Adsorbent: $0.25-\mathrm{mm}$ chromatographic silica gel mixture, prewashed with methanol.
Diluent: a mixture of methylene chloride and methanol (1:1).

Test solution-Transfer the contents of not fewer than 5 Capsules to a mortar, grind the Capsules, and mix. Transfer a weighed quantity of the powder, equivalent to about 10 mg of omeprazole, to a suitable container. Add 2 mL of Diluent, sonicate for 5 minutes, and allow to settle for 20 minutes before applying to the plate.
Standard solution-Dissolve an accurately weighed quantity of USP Omeprazole RS in Diluent to obtain a solution having a known concentration of about 5 mg per mL .

Developing solvent system: a mixture of methylene chloride saturated with ammonia, methylene chloride, and isopropyl alcohol (2:2:1).

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Drug release, Meth A $\langle 724\rangle$ -

```
ACID_STAGE-
    Medium: 0.1 N hydrechloric acid; 500 mL.
    Apparatus 2: paddles constructed of, or coated with, poly
#f,100 rpm.
```

Time: 2 hours.

## Procedure: Proceed as directed for Buffer stage.

TEST 1, METHOD A $\langle 724\rangle$ -
ACID RESISTANCE STAGE-
Medium: 0.1 N hydrochloric acid; 500 mL .
Apparatus 2: 100 rpm .
Time: 2 hours.
pH 7.6 phosphate buffer, Mobile phase, and
Chromatographic system and Proce-Proceed as directed under Buffer stage.

Standard solution-Transfer about 50 mg of USP Omeprazole RS, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask, dissolve in 50 mL of alcohol, dilute with 0.01 M sodium borate solution to volume, and mix. Transfer 10.0 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, add 20 mL of alcohol, dilute with 0.01 M sodium borate solution to volume, and mix.

Test solution-After 2 hours, filter the Dissolution Medium containing the pellets through a sieve with an aperture of not more than 0.2 mm . Collect the pellets on the sieve, and rinse them with water. Using approximately 60 mL of 0.01 M sodium borate solution, carefully transfer the pellets quantitatively to a $100-\mathrm{mL}$ volumetric flask. Sonicate for about 20 minutes until the pellets are broken up. Add 20 mL of alcohol to the flask, dilute with 0.01 M sodium borate solution to volume, and mix. Dilute an appropriate amount of this solution with 0.01 M sodium borate solution to obtain a solution having a concentration of about 0.02 mg per mL .

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of omeprazole $\left(\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}\right)$ dissolved in the Medium by the formula:

$$
T-C D\left(r_{U} / r_{S}\right)
$$

in which $T$ is the labeled quantity, in mg , of omeprazole in the capsule; $C$ is the concentration, in mg per mL , of USP Omeprazole RS in the Standard solution; $D$ is the dilution factor used in preparing the Test solution; and $r_{U}$ and $\mathrm{r}_{S}$ are the omeprazole peak responses obtained from Test solution and Standard solution, respectively.

Tolerances-Level $\mathrm{L}_{1}$ : no individual value exceeds $10 \%$ $15 \%$ of omeprazole dissolved. Level $\mathrm{L}_{2}$ : the average of 12 units is not more than $10 \% 20 \%$ of omeprazole dissolved, and no individual unit is greater than $25 \% 35 \%$ of omeprazole dissolved. Level $L_{3}$ : the average of 24 units is not more than $10 \% 20 \%$ of omeprazole dissolved, not more than 2 units are greater than $35 \%$ of omeprazole dissolved, and no individual unit is greater than $25 \% 45 \%$ of omeprazole dissolved.

## BUFFER STAGE- <br> Medium: pH 6.8 phosphate buffer, 900 mL , prepared by

 adding 400 mL of 0.235 M dibasic sedium phesphate to the vessel and adjusting, if necessary, with 2 N hydrechlerie acid or 2 N sodium hydroxide to a pH of $6.8 \pm 0.05$ -Medium: pH 6.8 phosphate buffer, 900 mL .
Proceed as directed under Acid resistance stage with a new set of capsules from the same batch. After 2 hours, add 400 mL of 0.235 M dibasic sodium phosphate to the 500 mL of 0.1 N hydrochloric acid medium in the vessel. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of $6.8 \pm 0.05$.

Apparatus 2: 100 rpm .

## Proedtre-

At the end of 30 minutes, determine the amount of $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}$ dissolved in pH 6.8 Phosphate buffer by employing the following method.
pH 10.4, 0.235 M Dibasic sodium phosphate—Dissolve 33.36 g of anhydrous dibasic sodium phosphate in 1000 mL of water, and adjust with 2 N sodium hydroxide to a pH of $10.4 \pm 0.1$.
pH 6.8 Phosphate buffer-Add 400 mL of 0.1 N hydrochloric acid to 320 mL of pH 10.4, 0.235 M Dibasic sodium phosphate, and adjust with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of $6.8 \pm 0.05$.
pH 7.6 Phosphate buffer-Dissolve 0.718 g of monobasic sodium phosphate and 4.49 g of dibasic sodium phosphate in 1000 mL of water. Adjust with 2 N hydrochloric acid or 2 N sodium hydroxide, if necessary, to a pH of $7.6 \pm 0.1$. Dilute 250 mL of this solution with water to 1000 mL .
Mobile phase-Transfer 340 mL of acetonitrile to a 1000mL volumetric flask, dilute with $p H$ 7.6 Phosphate buffer to volume, and pass through a membrane filter having a 0.5 $\mu \mathrm{m}$ or finer porosity. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution 1 (for Capsules labeled 10 mg )-Dissolve an accurately weighed quantity of USP Omeprazole RS in alcohol to obtain a solution having a known concentration of about 2 mg per mL . Dilute with pH 6.8 Phosphate buffer quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.01 mg per mL . To 10 mL of this solution immediately add 2 mL of 0.25 M sodium hydroxide, and mix. [NOTE-Do not allow the solution to stand before adding the sodium hydroxide solution.]

Standard solution 2 (for Capsules labeled 20 mg and 40 mg )—Proceed as directed for Standard solution 1, except to obtain a solution having a known concentration of about 0.02 mg per mL before mixing with 2 mL of 0.25 M sodium hydroxide.

Test solution 1 (for Capsules containing 10 mg and 20 mg )-Transfer immediately 5.0 mL of the solution under test to a test tube containing 1.0 mL of 0.25 M sodium hydroxide. Mix well, and pass through a membrane filter having a $1.2-\mu \mathrm{m}$ or finer porosity. Protect from light.
Test solution 2 (for Capsules labeled 40 mg )—Transfer immediately 5.0 mL of the solution under test to a test tube containing 2.0 mL of 0.25 M sodium hydroxide and 5 mL of pH 6.8 Phosphate buffer. Mix well, and pass through a membrane filter having a $1.2-\mu \mathrm{m}$ or finer porosity. Protect from light.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 12.5-\mathrm{cm}$ analytical column that contains $5-\mu \mathrm{m}$ packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the appropriate Standard solution, and record the peak responses as directed for Procedure: the column efficiency is not less than 2000 theoretical plates, and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the appropriate Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of omeprazole $\left(\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}\right)$ dissolved by the formula:

$$
V C D\left(r_{U} / r_{S}\right)
$$

in which $V$ is the volume of Medium in each vessel; $C$ is the concentration, in mg per mL, of USP Omeprazole RS in the appropriate Standard solution; $D$ is the dilution factor used in preparing the appropriate Test solution; and $r_{U}$ and $r_{S}$ are the omeprazole peak responses obtained from the appropriate Test solution and Standard solution, respectively.

Tolerances-For Capsules labeled 10 and 20 mg , not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}$ is dissolved in 30 minutes. For Capsules labeled 40 mg , not less than $70 \%(Q)$ of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}$ is dissolved in 30 minutes.

TEST $2\langle 711\rangle$ —
If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 2.

## ACID RESISTANCE STAGE-

Medium: 0.1 N hydrochloric acid; 900 mL .
Apparatus 1: 100 rpm .
Time: 2 hours.
Procedure-After two hours, remove each sample from the basket, and transfer quantitatively into separate volumetric flasks to obtain a solution having a final concentration of about 0.2 mg per mL . Proceed as directed under Assay, Assay preparation starting with "Add about 50 mL of Diluent ...". Calculate the quantity, in mg , of omeprazole $\left(\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}\right)$ dissolved in the Medium by the formula:

$$
T-C D\left(r_{U} / r_{S}\right)
$$

in which $T$ is the assayed quantity, in mg , of omeprazole in the capsule; $C$ is the concentration, in mg per mL , of USP Omeprazole RS in the Standard solution; $D$ is the dilution factor used in preparing the Test solution; and $r_{U}$ and $r_{S}$ are the omeprazole peak responses obtained from Test solution and Standard solution, respectively.

Tolerances-It complies with the following Acceptance Table:

Acceptance Table
Level Criteria
$L_{1} \quad$ the average of the 6 units is not more than $10 \%$ of omeprazole dissolved
$\mathrm{L}_{2}$ the average of the 12 units is not more than
$10 \%$ of omeprazole dissolved
$L_{3}$ the average of the 24 units is not more than $10 \%$ of omeprazole dissolved

## BUFFER STAGE-

Medium: 0.05 M pH 6.8 phosphate buffer; 900 mL (see Reagents, Indicators, and Solutions).

Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure-Proceed as directed under Acid resistance stage with a new set of capsules from the same batch. After 2 hours, replace the acid medium with the buffer medium and continue the test for 45 more minutes. Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 305 nm of portions of the solutions under test filtered through a $0.2 \mu \mathrm{~m}$ nylon filter, in comparison with a Standard solution having a known concentration of USP Omeprazole RS in the same Medium.

Tolerances-It complies with the Acceptance Table under Dissolution $\langle 711\rangle$. Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}$ is dissolved in 45 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Chromatographic purity-

Diluent, Solution A, Solution B, Mobile phase, and Chromatographic system - Proceed as directed in the Assay.

Standard solution-Prepare as directed for the Standard preparation in the Assay.

Test solution-Use the Assay preparation.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Capsules taken by the formula:

$$
(10 C / F A)\left(r_{i} / r_{S}\right),
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Omeprazole RS in the Standard solution; $F$ is the relative response factor (see Note below for values); $A$ is the quantity, in mg , of omeprazole in the portion of Capsules taken, as determined in the Assay; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the peak response for omeprazole obtained from the Standard solution: not more than $0.5 \%$ of any individual impurity is found, and not more than $2.0 \%$ of total impurities is found. [NOTE-The relative response factor, $F$, equals 1.6 and 3.1 for peaks with a relative retention time of about 0.33 and 0.64 , respectively; and equals 1.0 for peaks obtained from all other impurities.]

## Assay-

Diluent-Dissolve 7.6 g of sodium borate decahydrate in about 800 mL of water. Add 1.0 g of edetate disodium, and adjust with $50 \%$ sodium hydroxide solution to a pH of 11.0 $\pm 0.1$. Transfer the solution to a $2000-\mathrm{mL}$ volumetric flask, add 400 mL of dehydrated alcohol, and dilute with water to volume.

Solution A-Prepare a filtered and degassed solution of 6.0 g of glycine in 1500 mL of water. Adjust with $50 \%$ sodium hydroxide solution to a pH of 9.0 , and dilute with water to 2000 mL .

Solution B-Use a filtered and degassed mixture of acetonitrile and methanol (85:15).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make
adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard preparation-Dissolve, by sonicating, an accurately weighed quantity of USP Omeprazole RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 0.2 mg per mL .

Assay preparation-Weigh and mix the contents of not fewer than 20 Capsules. Transfer an accurately weighed portion of the mixture, equivalent to about 20 mg of omeprazole, to a $100-\mathrm{mL}$ volumetric flask, add about 50 mL of Diluent, and sonicate for 15 minutes. Cool, dilute with Diluent to volume, mix, and pass through a membrane filter having $0.45-\mu \mathrm{m}$ or finer porosity. [NOTE-Bubbles may form just before bringing the solution to volume. Add a few drops of dehydrated alcohol to dissipate the bubbles if they persist for more than a few minutes.]
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $305-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ basedeactivated packing L7. The flow rate is about 1.2 mL per minute. The chromatograph is programmed as follows.

| Time | Solution A | Solution B |  |
| :---: | :---: | :---: | :--- |
| (minutes) | $\%$ | $\%$ | Elution |
| $0-20$ | $88 \rightarrow 40$ | $12 \rightarrow 60$ | linear gradient |
| $20-21$ | $40 \rightarrow 88$ | $60 \rightarrow 12$ | linear gradient |
| $21-25$ | 88 | 12 | isocratic |

Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 20,000 theoretical plates; the tailing factor is not less than 0.8 and not more than 2 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg , of omeprazole $\left(\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}\right)$ in the portion of Capsules taken by the formula:

$$
\begin{aligned}
& 100 C\left(r_{4}+r_{s}\right), \\
& D C\left(r_{U} / r_{S}\right)
\end{aligned}
$$

in which $D$ is the dilution factor of the Assay preparation; $C$ is the concentration, in mg per mL , of USP Omeprazole RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta U S P 2 8}$

## BriEfing

Oxandrolone, USP 27 page 1366 and page 1835 of $P F 28(6)$ [Nov.-Dec. 2002]. It is proposed to replace the liquid chromatographic procedure in the test for Related compounds with a gradient elution method that provides greater sensitivity to the impurities.
(PA1: C. Anthony) RTS-40102-1

## Change to read:

» Oxandrolone contains not less than 97.0
${ }^{\wedge} 98.0_{\Delta U S P 28}$
percent and not more than 100.5
-102.0 ${ }_{\Delta U S P 28}$
percent of $\mathrm{C}_{19} \mathrm{H}_{30} \mathrm{O}_{3}$, calculated on the dried basis.

## Change to read:

Identification-
A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Prepare a solution in chloroform containing 5 mg per mL. Apply $10 \mu \mathrm{~L}$ each of this solution and a solution of USPOxandrotone RS in chloroform, containing 5 mg per mL to a suitable thinlayer chromatographic plate (see Chromatography $\langle 621$ ) ) eonted with a 0.25 mm layer of chromategraphic siliea gel. Allow the
spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of chloroform and methanol (19:1) until the solvent from has moved about three fourths of the length of the plate. Remove the plate frem the developing chamber, mark the solvent fromt, and allow the solvent to evaporate. Loeate the spets on the plate by lightly spraying with dilute sulfuric acid ( 1 in 2) and heating on a hot plate or under a lamp until spets appear: the $R_{f}$ value of the prineipal spet obtained from the test solution eorrespends to that obtained from the Standard solution.
${ }^{\Delta}$ The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the As-
say. $\triangle$ USP28

## Delete the following:

${ }^{\Delta}$ Ordinary impurities $\langle 466\rangle$ -
Fest solution: methanel.
Standard solution: methanel.
Application valane: $10 \mu \mathrm{~L}$.
Elutat: a mixture of toluene and isopropylateohol ( $90: 10$ ), in a nenequilibrated chamber.

Yistalization: 5- $\mathbf{A S S P}^{\text {U }}$

## Add the following:

## ${ }^{4}$ Related compounds-

Mobile phase, Standard preparation, and
Chromatographic system Proceed as directed in the Assay.
Fest solution Prepare as directed for Assay preparation
in the Assaty.
Proedure-Inject a volume (about $25 \mu \mathrm{~L}$ ) of the Test solut
fimn into the chromatograph, record the chromatogram, and measure the peak respenses. Caleulate the pereentage of each impurity in the pertion of $\Theta x a n d r o l e n e$ taken by the fermata:-

$$
100\left(r_{i}+r_{s}\right)
$$

in which $r_{i}$ is the respense of each impurity; and $r_{s}$ is the sum of the respensec of all the peaks-in the chrematogram: net more than $0.5 \%$ of any individual impurity having relative retention times of about $0.43,0.89$, and 1.82 , respectively, is found, not more than $0.5 \%$ of total unknown impurities is found; and not more than $2.0 \%$ of total impurities is found.

Solution A: acetonitrile.

Solution B: water (adjusted with 1 to 2 drops of phosphoric acid to a pH of 3.0 ). [NOTE-The pH of this solution must not be below 3.0.]

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Oxandrolone RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.035 mg per mL . [NOTE-Use this solution within 24 hours.]

Test solution-Transfer about 175 mg of Oxandrolone, accurately weighed, to a $5-\mathrm{mL}$ volumetric flask, dilute with methanol to volume, and mix in a heated ultrasonic bath at $50^{\circ}$ to $60^{\circ}$ for 1 to 2 minutes. [NOTE-Samples must be maintained at $40^{\circ}$ in a temperature-controlled auto sampler and injected within 5 minutes of preparation.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $198-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The column, sample, and injector temperatures are maintained at $40^{\circ}$. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

## Time Solution A Solution B

| (minutes) | $(\%)$ | $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 27 | 73 | equilibration |
| $0-3$ | 27 | 73 | isocratic |
| $3-35$ | $27-50$ | $73-50$ | linear gradient |
| $35-40$ | 27 | 73 | re-equilibration |

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $10 \%$.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Oxandrolone taken by the formula:

$$
500(1 / F)(C / W)\left(r_{i} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Oxandrolone RS in the Standard solution; $W$ is the weight, in mg , of Oxandrolone taken to prepare the Test solution; $F$ is the relative response factor and is equal to the value for the individual peak listed in the table below; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the oxandrolone peak response obtained from the Standard solution: the impurities meet the requirements specified in the table below.

| Compound | Relative <br> Reten- <br> tion <br> Time | Relative <br> Re- <br> sponse <br> Factor | Limit <br> (\%) |
| :---: | :---: | :---: | :---: |
| Seco-acid oxandrolone $\begin{aligned} & \text { (17 } \beta \text {-Hydroxy-17 }- \\ & \text { methyl-1-hydroxy-1,2- } \\ & \text { seco-A-nor-5 } \alpha- \\ & \text { androstan-2-oic acid) } \end{aligned}$ | 0.55 | 0.45 | 0.3 |
| 4-Lactone oxandrolone <br> (17 $\beta$-Hydroxy-17 $\alpha$ - <br> methyl-4-oxa-andro- <br> stan-3-one) | 0.95 | 1.71 | 0.3 |
| 17-epi-Oxandrolone <br> ( $17 \alpha$-Hydroxy-17 $\alpha$ - <br> methyl-2-oxa-5 $\alpha$ - <br> androstan-3-one) | 1.37 | 0.91 | 0.3 |
| Specified impurity | 1.35 | 1.0 | 0.5 |
| Unknown impurities | - | 1.0 | 0.1 |


|  |  |  |  |
| :--- | :---: | :---: | :---: |
|  | Relative | Relative |  |
|  | Reten- | Re- |  |
|  | tion | sponse | Limit |
| Compound | Time | Factor | $(\%)$ |
| Total unknown | - | - | 0.5 |
| Total impurities | - | - | 1.0 |

## Change to read:

Assay-Transfer about 500 mg of $\Theta$ xandrolone, aceurately weighed, to a 250 mL conieal flack, and add 25.0 mL of 0.1 Nat eoholic potassium hydroxide VS. Insert into the neek of the flask, by means of a perforated stopper, an wir condenser consisting of a glass tube 70 to 80 cm in length and 5 to 8 mm in diameter, and heat the flask on a steam bath for 30 minutes, frequently rotating the contents. Cool, add 1 mL of phenelphthalein TS, and titrate the exess alkali with-0.1 N hydrechloric acid VS. Perform a blank determination, and make any neeessary correction. Each mL of 0.1 N alcoholic potassium hydroxide is equivalent to 30.64 mg of $\mathrm{C}_{49} \mathrm{H}_{30} \Theta_{3}$ :
${ }^{\Delta}$ Mobile phase-Prepare a filtered and degassed mixture of $0.01 \%(\mathrm{v} / \mathrm{v})$ glacial acetic acid in water and acetonitrile (64:36). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Oxandrolone RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 5 mg per mL . [NOTE-Sonicate if necessary to dissolve.]
Assay preparation-Transfer to a suitable volumetric flask an accurately weighed quantity of Oxandrolone, and dissolve in and dilute with acetonitrile to volume to obtain a solution having a concentration of about 5 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $198-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure. The column efficiency
is not less than 2000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{19} \mathrm{H}_{30} \mathrm{O}_{3}$ taken by the formula:

$$
V C\left(r_{U} / r_{S}\right)
$$

in which $V$ is the final volume in per mL , of the Assay preparation; $C$ is the concentration, in mg per mL , of USP Oxandrolone RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\begin{aligned} & \text { USP28 } \\ & \text {. }\end{aligned}$

## BRIEFING

Oxycodone Hydrochloride Oral Solution, USP 27 page 1376-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-9

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP28

## Add the following:

${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP28

## Briefing

Oxycodone and Acetaminophen Capsules, USP 27 page 1377 and page 645 of $P F$ 29(3) [May-June 2003]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-15

## Delete the following:

-Pharma Equivalent Name: Co-oxyedAPAP Capsules.IS (USP27)

## Change to read:

Dissolution Proedure for a Pooled Santle
-
ムUUSP28
$\langle 711\rangle-2$
Medium: 0.1 N hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle$ USP28
Determine the amounts of oxycodone $\left(\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{4}\right)$ and acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$ dissolved, employing the procedure set forth in the Assay, making any necessary volumetric adjustments, including adjusting the solution under test to a pH of about 5.5 before injecting.

Tolerances-Not less than $75 \%(Q)$ of the labeled amounts of $\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{4}$ and $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ are dissolved in 45 minutes:
$\Delta_{\text {the requirements are met if the quantities of the active in- }}$ gredient dissolved from the pooled sample conform ot the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

| Number |  |  |
| :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved ( $\mathrm{S}_{1}+\mathrm{S}_{2}+$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## BRIEfing

Oxycodone and Acetaminophen Tablets, USP 27 page 1378 and page 645 of $P F$ 29(3) [May-June 2003]-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-16

## Delete the following:

■Phammary Equivalent Name: Co oxyeod APAP Tablets 1 IS (USP27)

## Change to read:

Dissolution Procedure for a Pooled Sample
${ }_{\langle 711}{ }^{\text {USP2 }}{ }^{\text {US }}$
Medium: 0.1 N hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered soutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\mathbf{U S P 2 8}$
Determine the amounts of oxycodone $\left(\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{4}\right)$ and acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$ dissolved, employing the procedure set forth in the Assay, making any necessary volumetric adjustments, including adjusting the pH of the solution under test to about 5.5 before injecting.

Tolerances-Not less than $75 \%$ (Q) of the labeled amounts of $\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{4}$ and $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ are dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

| Number <br> Tested |  |  |
| :---: | :---: | :--- |
| Stage | Acceptance Criteria |  |

## BriEFING

Oxycodone and Aspirin Tablets, USP 27 page 1378—See briefing under Acetaminophen and Aspirin Tablets.

$$
\text { (BPC: M. Marques) } \quad \text { RTS-40313-17 }
$$

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution
Determine the amount of $\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{4}$ dissolved using the method for Assay for oxycodone, making any necessary volumetric adjustments. Determine the amount of $\mathrm{C}_{9} \mathrm{H}_{8} \mathrm{O}_{4}$ dissolved from UV absorbances at the wavelength of the isobestic point of aspirin and salicylic acid at about 265 nm of filtered pertions of the solution under test
$\Delta^{\text {the pooled sample }}{ }_{\Delta U S P 28}$
, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Aspirin RS in the same Medium. [NOTE-Prepare the Standard solution at the time of use. An amount of alcohol not to exceed $1 \%$ of the total volume of the Standard solution may be used to bring the Reference Standard into solution prior to dilution with Dissolution Medium.]

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{4}$ is dissolved in 30 minutes and not less than $75 \%$ (Q) of the labeled amount of $\mathrm{C}_{9} \mathrm{H}_{8} \mathrm{O}_{4}$ is dissolved in 30 minutes
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through these three stages unless the results conforma at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient, expressed as a percentage of the labeled content.
Acceptance Table for a Pooled Sample

|  | Number |
| :---: | :---: | :--- |
| Stage | Tested |$\quad$| Acceptance Criteria |
| :---: | :--- |

Change to read:
Dissolution Proedure for a Pooled Sample

Medium: 0.05 M acetate buffer, prepared by mixing 2.99 g of sodium acetate trihydrate and 1.66 mL of glacial acetic acid with water to obtain 1000 mL of a solution having a pH of $4.50 \pm 0.05$; 500 mL .

Apparatus 1: 50 rpm .
Time: 30 minutes.

## BriEfing

Oxytocin Injection, USP 27 page 1393. On the basis of stability data received, a more specific storage temperature has been added to the Packaging and storage statement.
(BNT: I. DeVeau) RTS-40692-1

## Change to read:

Packaging and storage-Preserve in single-dose or in multipledose containers, preferably of Type I glass. De not freeze.
${ }^{\Delta}$ Store between $2^{\circ}$ and $8^{\circ} \cdot \mathbf{\Delta U S P 2 8}$

## BRIEFING

Penicillamine Capsules, USP 27 page 1413-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-18

## Change to read:

Dissolution Preedure for a Porled Sample
$\triangle$
〈711) ${ }^{\text {USP28 }}$
Medium: 0.1 N hydrochloric acid; 900 mL .
Apparatus 1: 100 rpm .
Time: 30 minutes.
Dilute hydrochloric acid-Dilute 37 mL of hydrochloric acid with water to 1 L .

Ammonium sulfamate reagent-Dissolve 250 mg of ammonium sulfamate in 100 mL of Dilute hydrochloric acid.
$N$-(1-Naphthyl)ethylenediamine dihydrochloride reagent-Dissolve 100 mg of N -(1-naphthyl)ethylenediamine dihydrochloride in 100 mL of Dilute hydrochloric acid.

Sulfanilamide-mercuric chloride reagent-Dissolve 100 mg of sulfanilamide and 100 mg of mercuric chloride in 100 mL of Dilute hydrochloric acid.

Sodium nitrite reagent-Dissolve 200 mg of sodium nitrite in 100 mL of dilute sulfuric acid (1 in 50). Prepare fresh.

Standard preparation-Dissolve an accurately weighed quantity of USP Penicillamine RS in 0.1 N hydrochloric acid to obtain a solution having a known concentration of about $250 \mu \mathrm{~g}$ per mL .

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the Test solution. $\mathbf{4 S P 2 8}$
Pipet an aliquot of the filtered test solution,
${ }^{\Delta}$ pooled sample ${ }_{\text {aUSP28 }}$
estimated to contain about $278 \mu \mathrm{~g}$ of penicillamine, into a $100-\mathrm{mL}$ volumetric flask. Into a similar flask pipet an equivalent volume of 0.1 N hydrochloric acid to provide a reagent blank, and into a third $100-\mathrm{mL}$ volumetric flask pipet 1 mL of Standard preparation. Treat each flask as follows. Add by pipet 3 mL of Sodium nitrite reagent, and mix by swirling occasionally. After 5 minutes, add 10 mL of Ammonium sulfamate reagent, swirl, and allow to stand for an additional 5 minutes. Add 5 mL of Sulfanilamide-mercuric chloride reagent, swirl, and immediately add 10 mL of N -(1Naphthyl)ethylenediamine dihydrochloride reagent. Dilute with water to volume, and mix. Determine the absorbances of both solutions in $1-\mathrm{cm}$ cells at the wavelength of maximum absorbance at about 540 nm , with a suitable spectrophotometer, against the reagent blank. Calculate the percentage dissolution of the Capsule taken by the formula:

$$
90(C / W V)\left(A_{U} / A_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Penicillamine RS in the Standard preparation; $W$ is the labeled quantity, in mg , of penicillamine in the Capsule; $V$ is the volume, in mL , of the aliquot of test solution used; and $A_{U}$ and $A_{S}$ are the absorbances of the solutions from the test solution and the Standard preparation, respectively.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{5} \mathrm{H}_{11} \mathrm{NO}_{2} \mathrm{~S}$ is dissolved in 30 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

| Number |  |  |
| :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved ( $\mathrm{S}_{1}+\mathrm{S}_{2}+$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## Briefing

Penicillin G Potassium for Injection, USP 27 page 1420. It is proposed to revise the $p H$ ranges specified in these monographs to reflect the pH standards for products intended for injection that do not contain any added substances, in addition to the current pH ranges that more properly apply to products that contain sodium citrate. The $p H$ range of 5.0 to 7.5 is proposed for Penicillin G Potassium for Injection and for Penicillin G Sodium for Injection, respectively, when they contain no added substances. This reflects the limits previously provided in the corresponding monographs for Sterile Penicillin G Potassium and Sterile Penicillin G Sodium included in USP 23, pages 1170 and 1179, respectively, which contained no added substances.
(PA7: W. Wright) RTS-40463-2

## Change to read:

$\mathbf{p H}\langle 791\rangle$ : between 6.0 and 8.5 ,
${ }^{\mathbf{4}} 5.0$ and $7.5, \mathbf{\Delta U S P 2 8}$
in a solution containing 60 mg per mL , or, where packaged for dispensing, in the solution constituted as directed in the labeling,
© except where it is labeled as containing sodium citrate it is between 6.0 and 8.5 . $\quad$ USP28

## BriEFING

Penicillin G Sodium for Injection, USP 27 page 1429—See briefing under Penicillin $G$ Potassium for Injection.
(PA7: W. Wright) RTS-40463-1

## Change to read:

$\mathbf{p H}\langle 791\rangle$ : between 6.0 and 7.5,
${ }^{\mathbf{4}} 5.0$ and $7.5, \mathbf{\Delta}$ USP.28. in a solution containing 60 mg per mL ;
${ }^{\Delta}$ except, where it is labled as containing sodium citrate, it is between 6.0 and 7.5. $\mathbf{\Delta S P 2 8}$

## BRIEFING

Pentobarbital, USP 27 page 1440 and page 1956 of $P F$ 29(6) [Nov.-Dec. 2003]; Pentobarbital Sodium, USP 27 page 1441 and page 1959 of $P F 29(6)$ [Nov.-Dec. 2003]. It is proposed to identify and include an acceptance criterion for a known impurity, 5-ethyl-5-(1-ethylpropyl) barbituric acid (3-isomer). According to data received, this impurity can be detected in the proposed method, and when the material is for veterinary use, the limit has been approved up to $3 \%$. The monograph has been revised accordingly. It is proposed to delete the test for Isomer content because the 3-isomer is detected and quantified in the test for Related compounds.
(PA3: S. Salado) RTS-40386-1

## Change to read:

» Pentobarbital contains not less than 98.5
${ }^{\wedge} 98.0_{\Delta U S P 28}$
percent and not more than 101.0
${ }^{\Delta} 102.0_{\text {aUSP28 }}$
percent of $\mathrm{C}_{11} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{3}$, calculated on the dried basis.

## Change to read:

Packaging and storage-Preserve in tight containers.
-Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and
$30^{\circ} \cdot \mathbf{m} 2 \mathrm{~S}$ (USP27)

## Add the following:

${ }^{\boldsymbol{\Delta}}$ Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. Pentobarbital intended for veterinary use only is so labeled. $\triangle$ USP28

## Change to read:

USP Reference standards $\langle 11\rangle$ -
${ }^{\mathbf{4}}$ USP Endotoxin RS. ${ }_{\text {nUSP28 }}$
USP Pentobarbital RS.

## Change to read:

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~S}\rangle$ -
Solution: 7 in 100.
Medium: chloroform.
B: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ -
Solution: $16 \mu \mathrm{~g}$ per mL.
Medium: 0.1 N sodium hydroxide. Absitien 240 mm , ealeulated on the dried basis, do not differ by more than 3.0\%.

- $\triangle$ USP28

CUSP28 Shake about 300 mg with_ 5 mL of sodium hydrexide selut tion (1 in 125) for 2 minutes, filter, and to 1 mL of the filtrate add about 1.2 mL of silver nitrateTS: a whiteprecipitate is formed, and it is seluble in 6 N ammenium hydroxide. Te-secend 1 mL per tion of the filtrate ade 3-drops of mereuric chloride TS: a white precipitate-is formed, and it is seluble-in-6N ammenium hydrex ide-
${ }^{\Delta}$ The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the $A s$ say. $\triangle U S P 28$

## Add the following:

${ }^{4}$ Related compounds-
Mobile phase-Prepare as directed in the Assay.
Standard solution-Dissolve an accurately weighed quantity of USP Pentobarbital RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.001 mg per mL .

Test solution-Transfer about 100 mg of Pentobarbital, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, add about 80 mL of Mobile phase, and sonicate until dissolved. Dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ ) The liquid chromatograph is equipped with a $214-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 2.5; the column efficiency is not less than 15,000 theoretical plates; the tailing factor is not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $15.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of any impurity in the portion of Pentobarbital taken by the formula:

$$
(10,000 / F)(C / W)\left(r_{i} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Pentobarbital RS in the Standard solution; $F$ is the relative response factor of the impurity according the table below; $W$ is the weight, in mg, of pentobarbital, on dried basis, used to prepare the Test solution; $r_{i}$ is the peak area for any impurity in the Test solution; and $r_{S}$ is the peak area for pentobarbital
in the Standard solution: the impurities meet the requirements given in the table below:

| Compound name | Relative <br> retention <br> time | Relative <br> Response <br> Factor | Limit <br> (\%) |
| :---: | :---: | :---: | :---: |
| $\begin{gathered} \text { 6-Imino-5-ethyl-5- } \\ \text { (1-methylbutyl) } \\ \text { barbituric acid } \end{gathered}$ | about 0.39 | 1.5 | 0.2 |
| 5-Ethyl-5-(1-ethylpropyl) barbituric acid * | about 0.93 | 1.0 | 0.1 |
| Pentobarbital | 1.0 | - | - |
| $\begin{gathered} \text { 5-Ethyl-5-(1,3-di- } \\ \text { methylbutyl) } \\ \text { barbituric acid } \end{gathered}$ | about 1.5 | 0.9 | 0.3 |
| Unknown impurities | - | 1.0 | 0.1 |
| Total | - | - | 0.5 |

* Where the material is labeled as intended solely for veterinary use, the limit of 5-ethyl-5-(1-ethylpropyl) barbituric acid is $3.0 \%{ }_{\mathbf{\triangle} U S P 28}$


## Delete the following:

${ }^{4}$ Isomer eontent Transfer $300 \pm 5$ mg to a round bottom flack equipped with a standard taper, sround glass joint, and add 4 mL of water. Add, dropwise, sodium hydroxide solution ( 4 in 10 ) just to dissolve the specimen (about 3 or 4 dreps), then add 10 mL of aleohol. Add $300 \pm 5$ me of $p$ nitrobenzyl bromide, mix, attacha condenser, and reflux for 30 minutes. Cool, filter under reduced pressure, and wash the residue with four 5 mL pertions of water. Transfer the residue, asempletely as pessible, to a small flack, add 25 mL of aleohol, and reflux for 10 minutes: the solid dissolves completely. Coul, and filter under redueed pressure: the $p$ nitroben zylderivative so obtained, after being dried at $105^{\circ}$ for 30 minutes, melts empletely between $136^{\circ}$ and $146^{\circ}$, when determined by the procedure for Class Ia (see Melting Range or Temperature $\langle 744\rangle)_{\Delta U S P 28}$

## Add the following:

${ }^{\Delta}$ Other requirements-Where the label states that Pentobarbital is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Pentobarbital Sodium Injection. Where the label states that Pentobarbital must be
subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Pentobarbital Sodium Injection. $\mathbf{\triangle}$ USP28
Change to read:
Assay-
Q.1 N Tetrabuthanminm hydroxide in ehlorabenzene- Dilute 100 mL of 1 N tetrabutylammonium hydroxide VS with ehlore benzene to 1000 mL , and mix.
Standardization of 0.1 N tetrabutlammanium hydroxide in ehlorobenzene Dissolve abeut 180 mg, aceurately weighed, of primary standard benzoic acid in about 100 mL of acetone, and titrate with - 0.1 N Tetrabutlammenium hydroxide in chloroben zene, determining the endpoint potentiometrically, using a glass electrode and a calomel electrodecontaining 0.1 N methanolic tetrabutylammenium chloride (see Titrinnetry (544)). Each mL of Q.1 N Tetrabulylammitan hydroxide in chlorobenzene is equivalent to 12.21 mg of benzoic acid.
Preedure Transfer about 330 mg of Pentobarbital, aceurately weighed, to a suitable beaker, and dissolve in 100 mL of acetone. Titrate with 0.1-N Tetrabuthlammanium hydroxide in chlorobenzene, determining the endpeint petentiometrieally, using a glass electrode and acalomel electrode entaining 0.1 N methanolic tetrabutylammenium chloride. Each mL of 0.1 N Tetrabur yhan hydrux in ehlorobenzene is equivalent to 22.63 mg of $\mathrm{C}_{44} \mathrm{H}_{48} \mathrm{H}_{2} \mathrm{O}_{3}$ :
${ }^{\text {4 }}$ Mobile phase-Prepare a filtered and degassed pH 3.5 mixture of 0.01 M monobasic potassium phosphate and acetonitrile (65:35). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Pentobarbital RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.1 mg per mL .

Assay preparation-Transfer about 100 mg of Pentobarbital, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, add about 80 mL of Mobile phase, and sonicate until dissolved. Dilute with Mobile phase to volume, and mix. Transfer 10.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask. Dilute with Mobile phase to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ ) The liquid chromatograph is equipped with a $214-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the capacity factor,
$k^{\prime}$, is not less than 2.5 ; the column efficiency is not less than 15,000 theoretical plates; the tailing factor is not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses for the major peak. Calculate the quantity, in mg, of $\mathrm{C}_{11} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{3}$ in the portion of Pentobarbital taken by the formula:

$$
1000 C\left(r_{U} / r_{S}\right),
$$

in which $C$ is the concentration, in mg per mL, of USP Pentobarbital RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{U S P} 28$

## BRIEFING

Pentobarbital Sodium, USP 27 page 1441 and page 1959 of PF 29(6) [Nov.-Dec. 2003]-See briefing under Pentobarbital.
(PA3: S. Salado) RTS-40386-2

## Change to read:

" Pentobarbital Sodium contains not less than 98.5
${ }^{\wedge} 98.0^{\text {aUSP28 }}$
percent and not more than 101.0
-102.0 ${ }_{\Delta U S P 28}$
percent of $\mathrm{C}_{11} \mathrm{H}_{17} \mathrm{~N}_{2} \mathrm{NaO}_{3}$, calculated on the dried basis.

## Change to read:

Packaging and storage-Preserve in tight containers.

- Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$. 2 (USP27)


## Add the following:

${ }^{\boldsymbol{\Delta}}$ Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. Pentobarbital Sodium intended for veterinary use only is so labeled. $\triangle$ USP28

## Change to read:

USP Reference standards $\langle 11\rangle$ -
${ }^{\mathbf{4}}$ USP Endotoxin RS. ${ }_{\text {.USP28 }}$
USP Pentobarbital RS.

## Change to read:

Identification-
A: The WVabserption spectrum of the Assay preparation correspends to that of the Standard preparation, as obtained in the Assity:
${ }^{\text {© }}$ Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ -
Solution: $10 \mu \mathrm{~g}$ per mL .
Medium: dilute ammonium hydroxide (1 in 200). $\mathbf{\Delta U S P 2 8}$ B:
${ }^{\Delta}$ The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the $A s$ say.

C: ${ }^{\text {USP28 }}$
Ignite about 200 mg : the residue effervesces with acids, and meets the requirements of the tests for Sodium $\langle 191\rangle$.

## Add the following:

${ }^{4}$ Related compounds-
Mobile phase-Prepare as described in the Assay.
Standard solution-Dissolve an accurately weighed quantity of USP Pentobarbital RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.001 mg per mL .

Test solution-Transfer about 110 mg of Pentobarbital Sodium, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, add about 80 mL of Mobile phase, and sonicate until dissolved. Dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $214-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 2.5; the column efficiency is not less than 15,000 theoretical plates; the tailing factor is not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $15.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of any impurity in the portion of Pentobarbital Sodium taken by the formula:

$$
(248.25 / 226.27)(10,000 / F)(C / W)\left(r_{i} / r_{S}\right),
$$

in which 248.25 and 226.27 are the molecular weights of pentobarbital sodium and pentobarbital, respectively; $C$ is the concentration, in mg per mL, of USP Pentobarbital RS in the Standard solution; $F$ is the relative response factor of the impurity according to the table below; $W$ is the weight, in mg , of Pentobarbital Sodium, on the dried basis, used to prepare the Test solution; $r_{i}$ is the peak area for any impurity in the Test solution; and $r_{S}$ is the peak area for Pentobarbital
in the Standard solution: the impurities meet the requirements given in the table below:

| Compound | Relative | Relative |  |
| :---: | :---: | :---: | :---: |
|  | Retention | Response |  |
| Name | Time | Factor | Limit (\%) |
| 6-Imino-5-ethyl- | about 0.39 | 1.5 | 0.2 |
| 5-(1-methyl- |  |  |  |
| butyl)barbituric |  |  |  |
| acid |  |  |  |
| 5-Ethyl-5-(1- | about 0.93 | 1.0 | 0.1 |
| ethylpropyl) |  |  |  |
| barbituric acid ${ }^{*}$ |  |  |  |
| Pentobarbital | 1.0 | - | - |
| 5-Ethyl-5-(1,3- | about 1.5 | 0.9 | 0.3 |
| dimethylbutyl) |  |  |  |
| barbituric acid |  |  |  |
| Unknown | - | 1.0 | 0.1 |
| impurities |  |  |  |
| Total | - | - | 0.5 |

${ }^{*}$ Where the material is labeled as intended solely for veterinary use, the limit of 5-ethyl-5-(1-ethylpropyl) barbituric acid is $3.0 \%$. $\mathbf{\perp}$ USP28

## Delete the following:

${ }^{4}$ Isomer content Dissolve $300 \pm 5 \mathrm{mg}$ in 5.0 mL of water, and dissolve $300 \pm 5$ mg of $p$ nitrobenzyl bromide in 10.0 mL of at eehel. Mix the solutions, reflux for 30 minutes, coel to $25^{\circ}$, and fitter by suetion. Wash the cellected selid with four 5 mL per tiens of water, transfer as completely as practicable to a small flask, add 25.0 mL of aleohel, and reflux for 10 minutes: the selid dissolves completely. Cool the solution to $25^{\circ}$, and filter by suction: the collected solid, after being dried at $105^{\circ}$ for 30 minutes, melts ermpletely between $136^{\circ}$ and $146^{\circ}$, when determined by the procedure for Class Ia (see Melting Range or Temperatare $\langle 744\rangle$ ). $\mathbf{A}$ USP28

## Add the following:

${ }^{\Delta}$ Other requirements-Where the label states that Pentobarbital Sodium is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Pentobarbital Sodium Injection. Where the label states that Pentobarbital Sodium must be subjected fo further processing during the prepara-
tion of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Pentobarbital Sodium Injection. $\triangle$ USP28

## Change to read:

## Assay-

Biluting solvent Use freshly prepared dilute-ammonium hy droxide (1 in 200).

Standard preparation Dissolvenan aeeurately weighed quantity of USP Pentobarbital RS in Diluting selvent to obtain a selution having a known concentration of about $10 \mu \mathrm{~g}$ per mL .

Assay preparation Transfer about 25 me of pentebarbital se dium, previeusly dried and uceurately weighed, in a 50 mL volu metric flack, immediately dilute with Diluting solvent to volume, and mix. Pipet 2 mL of this solution into a 100 mL volumetrie flack, add Diluting solvent to volume, and mix.

Procedure Coneomitantly determine the absorbances of the Assay preparation and the Standard preparation in 1 em cells at the wavelength of maximum absorbance at about 240 nm, with a suitable spectrophotometer, using Diluting solvent as the blank. Calculate the quantity, in mor, of $\mathrm{C}_{4} \mathrm{H}_{47} \mathrm{~N}_{2} \mathrm{NaO}_{3}$ in the pertion of Pentebarbital Sodium taken by the formala:

$$
2.56(248.26 / 226.28)\left(A_{\downarrow}+A_{\&}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP PentobarbitalPS in the Standard preparation; 248.26 and 226.28 are the $m e-$ lecular weights of pentobarbital sodium and pentobarbitat, respectively; and $A_{t}$ and $A_{s}$ are the abserbances of the $4 s s a y$ preparation and the Standard preparation, respectively.
${ }^{\Delta}$ NOTE-Use the value for Loss on drying obtained at the same time as the preparation of the Test solution in the test for Related compounds and the Assay preparation in the Assay.

Mobile phase, Standard preparation, and Chromatographic system-Proceed as described in the Assay under

## Pentobarbital.

Assay preparation-Transfer about 110 mg of Pentobarbital Sodium, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, add about 80 mL of Mobile phase, and sonicate until dissolved. Dilute with Mobile phase to volume, and mix. Transfer 10.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask. Dilute with Mobile phase to volume, and mix.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses for the major peak. Calculate
the quantity, in mg , of $\mathrm{C}_{11} \mathrm{H}_{17} \mathrm{~N}_{2} \mathrm{NaO}_{3}$ in the portion of Pentobarbital Sodium taken by the formula:

$$
(248.25 / 226.27) 1000 C\left(r_{U} / r_{S}\right)
$$

in which 248.25 and 226.27 are the molecular weights of pentobarbital sodium and pentobarbital, respectively; $C$ is the concentration, in mg per mL , of USP Pentobarbital RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{A U S P 2 8}^{\text {. }}$

BRIEFING

Phentermine Hydrochloride Capsules, USP 27 page 1466See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40315-8

## Change to read:

Dissolution Procedure for a Pooled Sample

Medium: water, 900 mL . Use 500 mL for Capsules containing 15 mg of phentermine hydrochloride or less.
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.
Determine the amount of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{~N} \cdot \mathrm{HCl}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications including concentration of the analyte in the volume of test solution taken.
Tolerances-Not less than $75 \%$ (Q) of the labeled amount of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{~N} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue
testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table a Pooled Sample

| Acceptance Table |  |  |
| :--- | :---: | :--- |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |

$\mathrm{S}_{1} 6 \quad$ Average amount dissolved is not less than $Q+10 \%$.
$\mathrm{S}_{2} \quad 6 \quad$ Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$.
$\mathrm{S}_{3} \quad 12 \quad$ Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ $\mathrm{S}_{3}$ ) is equal to or greater than $Q$.

## BRIEFING

Phentermine Hydrochloride Tablets, USP 27 page 1467See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40313-20

Change to read:
Dissolution Preedure for a Pooled Sample

Medium: water; 900 mL . Use 500 mL for Tablets containing 15 mg of phentermine hydrochloride or less.
Apparatus 2: 50 rpm .
Time: 45 minutes.
Determine the amount of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{~N} \cdot \mathrm{HCl}$ dissolved by employing the following method.

Ion-pair solution-Dissolve 1.1 g of sodium 1-heptanesulfonate in 1 liter of water. Add 3.5 mL of glacial acetic acid, and mix.
Mobile phase-Prepare a filtered and degassed mixture of methanol and Ion-pair solution (21:19). Adjust with phosphoric acid to a pH of 2.5 . Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Phentermine Hydrochloride RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration approximately equivalent to the Test solution.

Test solution-Use a filtered portion of the pooled sample under test.
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\Delta$ USP28

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $208-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $25 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Determine the amount, in mg , of phentermine hydrochloride $\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{~N} \cdot \mathrm{HCl}\right)$ dissolved by the formula:

$$
V C\left(r_{U} / r_{S}\right)
$$

in which $V$ is the volume of dissolution media used per vessel; $C$ is the concentration, in mg per mL , of USP Phentermine Hydrochloride RS in the Standard solution; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Test solution and the Standard solution, respectively.

Tolerances-Not less than $75 \%$ (Q) of the labeled amount of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{~N} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform
at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

| Number |  |  |
| :---: | :---: | :---: |
| Stage | Tested |  |$\quad$| Acceptance Criteria |
| :---: |

## BRIEFING

Phenylpropanolamine Hydrochloride Capsules, USP 27 page 1475-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-1

Change to read:
Dissolution Proedtre for a Pooled Sample-
${ }^{\Delta}$ (711) USP28
Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled sample as the test solution. $\Delta$ USP28
Determine the amount of phenylpropanolamine hydrochloride dissolved, employing the procedure set forth in the Assay, making any necessary volumetric adjustments.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

| Acceptance Table for a Pooled Sample |  |  |  |
| :---: | :---: | :---: | :---: |
|  | Number |  |  |
| Stage | Tested |  |  |$\left.\quad \begin{array}{l}\text { Acceptance Criteria }\end{array}\right]$| Average amount dissolved is not less |
| :--- | :---: | :--- |
| than $Q+10 \%$. |

## BriEfing

Phenylpropanolamine Hydrochloride Oral Solution, USP 27 page 1477 -See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-10

## Add the following:

${ }^{\boldsymbol{4}}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\mathbf{\Delta S S P 2 8}$

## Add the following: <br> ${ }^{\text {a }}$ Deliverable volume $\langle 698\rangle$ -

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements. $\triangle$ USP28

## BRIEFING

Phenylpropanolamine Hydrochloride Tablets, USP 27 page 1477-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-2

## Change to read:

Dissolution Proedur for a Pored Sample
4 $4 U S P 28$
$\langle 711\rangle-$
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\text {® }}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle U S P 28$
Determine the amount of phenylpropanolamine hydrochloride dissolved, employing the procedure set forth in the Assay, making any necessary volumetric adjustments.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

|  | Number |
| :---: | :---: | :---: |
| Stage | Tested |$\quad$| Acceptance Criteria |
| :---: | -USP28

## BRIEFING

Phenyltoloxamine Dihydrogen Citrate, page 1062 of $P F$ 29(4) [July-Aug. 2003]. It is proposed to revise the official title of the monograph to Phenyltoloxamine Citrate in accordance with the current policies and procedures of the USP Nomenclature and Labeling (NL) Expert Committee. It is proposed to change the name of the related compound Reference Standard to USP Phenyltoloxamine Related Compound A RS. Also, it is proposed to remove the room temperature storage condition from the Packaging and storage statement.
(PA1: K. Russo; NL: C. Barnstein) RTS-40542-1

## Add the following:

## ©Phenyltoloxamine Dihydrogen Citrate

(1:1) salt.
$\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7} \quad 447.47$
$\mathrm{~N}, \mathrm{~N}$-Dimethyl-2-( $\alpha$-phenyl-o-tolyloxy)ethylamine, citrate
2-(2-Dimethylaminoethoxy)diphenylmethane, citrate (1:1)
shenyltoloxamine dihydrogen citrate
[1176-08-5].
» Phenyltoloxamine Bihydrogen Citrate contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7}$, calculated on the dried basis.

Packaging and storage-Preserve in well closed containers and store at room temperature. Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle$ —USP Phenyltoloxamine Dilydrogen Citrate RS. USP Phenyltoloxamine Dihydrogen Gitrate Related Compound A RS.

## Identification,

$$
\begin{aligned}
& \text { A: Infrared Absorption-〈197K }\rangle \text { : } \\
& \text { B: Ultraviolet Absorption }\langle 197 \mathrm{H}\rangle \text { - } \\
& \text { Selution: } 100 \text { Hg per mL. } \\
& \text { Medium: } 0.1 \text { N hydrechleric acid. }
\end{aligned}
$$

C: Dissolve 0.5 g of Phenyltoloxamine Dihydrogen Ci
trate in 15 mL of het water, add a-slight excess of $5 \mathrm{M}-\mathrm{se}$ dium hydroxide, filter, and add 2 N hydrochloric acid untit the filtrate is neutral to litmus paper: the solution meets the requirements of the test for Citrate $\langle 194\rangle$ =Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.

Melting range, Class $1 a\langle 741\rangle$ : between $137^{\circ}$ and $143^{\circ}$. $\mathbf{p H}\langle 791\rangle$ : between 3.2 and 4.2, in a solution (1 in 100).

Loss on drying $\langle 731\rangle$-Dry it in vacuum at $80^{\circ}$ for 3 hours: it loses not more than $0.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method $I\langle 231\rangle: 20 \mu \mathrm{~g}$ per g .

## Related compounds-

Resolution solution-In a separatory funnel dissolve about 10 mg each of USP Phenyltoloxamine Pihydrogen Citrate RS and USP Phenyltoloxamine Bihydrogen Citrate Related Compound A RS, accurately weighed, in 50 mL of water. Add 5 mL of ammonium hydroxide, and extract with three $10-\mathrm{mL}$ portions of ethylether methylene chloride.

Combine the extracts, dry the solution over anhydrous sodium sulfate, and gently evaporate to dryness. Dissolve the residue in 20 mL of ehlorem methylene chloride.

Test solution-In a separatory funnel dissolve about 800 mg 400 mg of Phenyltoloxamine Bihydrog Citrate, accurately weighed, in 50 mL of water. Proceed as directed for Resolution solution, beginning with "Add 5 mL of ammonium hydroxide."
Chromatographic system (see Chromatography $\langle 621\rangle$ ) The gas chromatograph is equipped with a split injection system, a flame-ionization detector, and a $0.32-\mathrm{mm} \times 25$ m column coated with a $0.45-\mu \mathrm{m}$ film of phase G27. The carrier gas is helium, flowing at a rate of about 29 cm per second, with a split flow rate of about 25 mL per minute. The column temperature is programmed as follows. Initially the temperature of the column is equilibrated at $190^{\circ}$ for 3 minutes, then the temperature is increased at a rate of $4^{\circ}$ per minute to $240^{\circ}$, and maintained at $240^{\circ}$ for 8 minutes. The injection port and the detector temperatures are maintained at $280^{\circ}$. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between phenyltoloxamine dihydrege itrate and phenyltoloxamine dihydrege citrate related compound A is not less than z.0 1.5.

Procedure-Inject a volume (about $1 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Phenyltoloxamine BihydreCitrate taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response of each impurity; and $r_{s}$ is the sum of the responses of all the peaks, excluding the solvent peaks: not more than $0.2 \%$ of phenyltoloxamine dihy
drogen citrate related compound A ; not more than $0.1 \%$ of any other individual impurity; is found; and not more than $1.0 \%$ of total impurities is found.

Organic volatile impurities, Method $1\langle 467\rangle$ : meets the requirements.

Assay-Dissolve about 0.5 g of Phenyltoloxamine Pihy dregen Citrate, accurately weighed, in 80 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Each mL of 0.1 N perchloric acid is equivalent to 44.75 mg of $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7 \cdot \mathbf{\Delta} \text { USP28 }}$

BRIEFING
Pimozide Tablets, USP 27 page 1492 —See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-3

Change to read:
Dissolution Procedure for a Pooled Sample
${ }^{\text {4 }}$ (711SP28
Medium: 0.01 N hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
Standard preparation-Transfer about 27 mg of USP Pimozide RS, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask containing 1 mL of lactic acid. Heat on a steam bath to dissolve, add about 80 mL of hot water, and shake. Cool, dilute with water to volume, and mix. Dilute the solution quantitatively with 0.01 N hydrochloric acid to obtain a solution having a known concentration approximately the same as that of the solution under test (assuming complete dissolution).

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solu-
tion. $\triangle$ USP28

Transfer a portion of the solution under test
${ }^{\Delta}$ pooled sample ${ }_{\mathbf{A} U S P 28}$
to a suitable container, and centrifuge until clear. Pipet a volume of the supernatant liquid, estimated to contain about $110 \mu \mathrm{~g}$ of pimozide (assuming complete dissolution), into a suitable container. Pipet an equal volume of the Standard preparation into a second container. To each container add 20 mL of 1 N sodium hydroxide and 20.0 mL of chloroform. Shake each mixture by mechanical means for 15 minutes, and centrifuge. Aspirate and discard the aqueous layers, and transfer the chloroform layers to separate clean beakers. Determine the amount of $\mathrm{C}_{28} \mathrm{H}_{29} \mathrm{~F}_{2} \mathrm{~N}_{3} \mathrm{O}$ dissolved from absorbances of the chloroform layers obtained from the solution under test and the Standard preparation, in $5-\mathrm{cm}$ cells at the wavelength of maximum absorbance at about 277 nm .
Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{28} \mathrm{H}_{29} \mathrm{~F}_{2} \mathrm{~N}_{3} \mathrm{O}$ is dissolved in 30 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

|  | Number |  |
| :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. <br> $\mathrm{S}_{2}$ |
| $\mathrm{~S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## BriEfing

Pindolol Tablets, USP 27 page 1494—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-4

## Change to read:

Dissolution Procedure for a Pooled Sample
4 4 USP28
$\langle 711\rangle-$
Medium: 0.1 N hydrochloric acid; 500 mL .
Apparatus 2: 50 rpm .
Time: 15 minutes.
Mobile phase and Chromatographic system-Proceed as directed in the Assay.

Standard solution-Dissolve an accurately weighed quantity of USP Pindolol RS in Dissolution Medium to obtain a solution having a known concentration of about $0.002 J \mathrm{mg}$ per mL , $J$ being the labeled quantity, in mg , of pindolol in each Tablet. Mix equal volumes of this solution and of Mobile phase to obtain the Standard solution.

Resolution solution-Dissolve a quantity of nortriptyline hydrochloride in Standard solution to obtain a solution having a concentration of about 0.005 mg of nortriptyline hydrochloride per mL . Test solution Filter a portion of the solution under test.
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.

Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. |  |
| :--- |
| USP28 |

Mix equal volumes of the filtate-
${ }^{\Delta}$ pooled sample ${ }_{\Delta U S P 28}$
and of Mobile phase to obtain the Test solution.
Procedure-Proceed as directed for Procedure under the Assay. Calculate the quantity of $\mathrm{C}_{14} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{O}_{2}$ dissolved by the formula:

$$
500 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Pindolol RS in the Standard solution; and $r_{U}$ and $r_{S}$ are the pindolol peak responses obtained from the Test solution and the Standard solution, respectively.
Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{14} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{O}_{2}$ is dissolved in 15 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform
at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## BRIEFING

Piperazine Citrate Tablets, USP 27 page 1498—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-5

## Change to read:

Dissolution Proedtre for a Pooted Sample
(ti11)
Medium: water; 900 mL . Apparatus 2: 50 rpm . Time: 45 minutes.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle U S P 28$
Determine the amount of piperazine hexahydrate $\left(\mathrm{C}_{4} \mathrm{H}_{10} \mathrm{~N}_{2} \cdot 6 \mathrm{H}_{2} \mathrm{O}\right)$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{4} \mathrm{H}_{10} \mathrm{~N}_{2} \cdot 6 \mathrm{H}_{2} \mathrm{O}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

| Number |  |  |
| :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## Briefing

Platelets. Because there is no existing USP monograph for this product, a new monograph is being proposed.
(BBP: R. Tirumalai) RTS-40379-1

## Add the following:

## ©Platelets

» Platelets is the portion of blood that contains platelet cells. It is derived from human whole blood from which red blood cells and a portion of the plasma are removed by centrifugation, sedimentation, or apheresis. In the apheresis removal method, the red blood cells and plasma are automatically removed and returned directly to the donor. Platelets derived from whole blood must be prepared within 4 hours after collecting the whole blood from which it is derived, or within the time frame specified for the blood collecting, processing, and storage system used.

Platelets may be derived from whole blood collected in any approved anticoagulant solution (see USP monographs for anticoagulant solutions). Platelets prepared by apheresis must be collected using Anticoagulant Citrate Dextrose Solution A as the anticoagulant solution.

Platelets derived from whole blood must have a minimum of $5.5 \times 10^{10}$ platelet cells suspended in a volume of 40 to 70 mL of original plasma. Platelets produced by apheresis must have a mini-
mum of $3.0 \times 10^{11}$ platelet cells, suspended in 100 to 500 mL of original plasma or in an approved additive solution.

Platelets derived from whole blood or by apheresis may be further processed by filtration for removal of leukocytes, or by irradiation to inactivate lymphocytes. Platelets derived from whole blood may be pooled from multiple donors to form one dose of platelets.

Leukocytes may be removed from platelets by filtration using an approved platelet leukoreduction filter. Platelets derived from whole blood must contain less than $8.3 \times 10^{5}$ leukocytes after filtration.

The source blood for platelets must be tested for syphilis, hepatitis $B$, and human T-cell virus (HTLV) Type I and Type II, using FDA approved and licensed commercially available test kits. The test results must be below the limits of detection specified by the manufacturers of the respective test kits. The source blood must also be tested for hepatitis C and HIV Type 1 and Type 2, using FDA approved nucleic acid assays. The test results must be below the approved limits of detection for the tests used.

Packaging and storage-Store platelets in an approved container. Platelets may be stored in plasma or in an approved additive solution at $20^{\circ}$ to $24^{\circ}$ with continuous gentle agitation for no more than 5 days after date of preparation.

Labeling-Label the container to indicate the collection date, the donation number or other coding means to uniquely identify the unit and to provide traceability to the donor, approximate volume, storage temperature, and its expiration date. Indicate the anticoagulant solution used and any additive solutions added subsequent to collection. Also label the container to identify donor status (for example, volunteer or paid). Label it also with the following statements: "See Circular of Information for the Use of Human Blood and Blood Components for indications, contraindications, cautions, and methods of infusion;" "Properly identify intended recipient;" "This product may transmit infectious agents;" and "Rx only." In addition, label the container to indicate the product name as indicated in Table 1. [NOTE-The name is determined by the method of platelets preparation (derived from whole blood or by apheresis) and by performing the necessary testing to ensure that the product meets the minimum requirements for the named products, as indicated in Table 1.]

Table 1. Names of Platelet Preparations

| Product Name | Method of Preparation |
| :--- | :---: |
| Platelets | Prepared from a single unit of whole human blood within 8 hours of |
|  | collection. |
| Platelets, Pooled | Individual platelet units derived from whole human blood and pooled |
|  | by sterile techniques. [NOTE-Label this preparation with a unique |
|  | identifying number related to the number of individual units pooled, |
|  | and with an expiration date of 4 hours after pooling of the individual |
|  | units.] |
| Platelets, Pheresis | Prepared by apheresis from a single donor. |
| Platelets, Leukocyte Reduced | Contains less than $8.3 \times 10^{5}$ leukocytes, either from the method of |
|  | separation from whole blood by filtration. |
| Platelets, Pheresis, Leukocyte Reduced | Contains not more than $5 \times 10^{6}$ white blood cells, prepared by filtration. |

[NOTE-Platelets prepared by apheresis should be labeled with the donor's ABO blood group and Rh factors. Test the donor's whole blood or red blood cells as directed under Whole Blood or Red Blood Cells, respectively.]

Identification-Dilute a small volume of platelets 1:1000 with $0.9 \%$ sodium chloride solution. Place a small drop of the diluted platelets onto the end of a clean glass microscope slide. Obtain a second clean glass microscope slide and draw its edge across the drop of platelets so that capillary action spreads the drop across the first slide. Push the second slide in one smooth motion across the first slide to make a smear of platelets. Allow the smear to dry. Apply a liberal amount ( 1 to 2 mL ) of Wright's stain to the platelet smear and allow to stand for 2 minutes. Dip the slide in deionized water and gently blot dry with absorbent paper. Examine the slide using a microscope at $100 \times$ with bright illumination. Platelets appear as anuclear, round, or oval shapes approximately 0.1 to $0.2 \mu \mathrm{~m}$ in diameter, with some fine purple granulation. The platelets may occasionally appear to have a purple center with clear cytoplasm at the periphery.

Platelet count-Use a commercially available, validated hematology analyzer to determine platelet count. Proceed as directed in the instrument's operating manual.

Residual leukocyte count-Place $100 \mu \mathrm{~L}$ of platelets into a suitable test tube. Add $400 \mu \mathrm{~L}$ of $0.01 \%$ ( $\mathrm{w} / \mathrm{v}$ ) crystal violet in $15 \%(\mathrm{v} / \mathrm{v})$ acetic acid, and mix thoroughly. Fit a hemocytometer with a $50-\mu \mathrm{L}$ counting volume and a bright background with a cover slip. Load the counting chamber with the mixture until the counting area is completely covered, but do not overfill. Cover the counting chamber with a suitable moist lid to prevent evaporation, and allow to settle undisturbed for 10 to 15 minutes. Remove the lid and place the chamber on the stage of a light microscope fitted with a $10 \times$ ocular lens and $20 \times$ objective. Count the leukocytes in the entire $50-\mu \mathrm{L}$ counting volume. Calculate the leukocyte count in the platelets, expressed in leukocytes per $\mu \mathrm{L}$,
by dividing the observed leukocyte count by 10 . Calculate the total number of leukocytes in the red blood cell unit as follows:

Total leukocytes $=$ leukocytes $/ \mu \mathrm{L} \times 10^{3} \times$ volume of the platelet unit in mL .

$\mathbf{p H}\langle 791\rangle$ (for stored Platelets)—Transfer aseptically a volume appropriate for the equipment: pH must be greater than 6.2 throughout the storage period. | USP28 |
| :--- |

BriEfing
Prednisone Oral Solution, USP 27 page 1545-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-11

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle-$
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\Delta U S P 28$

## Add the following:

${ }^{\text {s }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP28

## Change to read:

Dissolution Procedure for a Pooled Sample

Medium: water, 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution
Determine the amount of $\mathrm{C}_{19} \mathrm{H}_{29} \mathrm{H}_{2} \mathrm{NO} \cdot \mathrm{HCl}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{19} \mathrm{H}_{29} \mathrm{NO} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.


Procyclidine Hydrochloride Tablets, USP 27 page 1564 -See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-7

## Briefing

Propantheline Bromide Tablets, USP 27 page 1574—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-8

Change to read:
Dissolution Proce for a Pooled Sample
$\Delta$ USSP28
$\langle 711)^{-}$
Medium: $\mathrm{pH} 4.5( \pm 0.05)$ acetate buffer prepared by mixing 1.64 g of anhydrous sodium acetate and 1.25 mL of glacial acetic acid with 500 mL of water, and diluting with water to obtain 1000 mL of solution having a pH of $4.50 \pm 0.05 ; 500 \mathrm{~mL}$.

Apparatus 2: 50 rpm .
Time: 45 minutes.
Determine the amount of $\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{BrNO}_{3}$ dissolved by employing the following method.
pH 3.5 Buffer solution, Mobile phase, and Chromatographic system-Prepare as directed in the Assay.

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle U S P 28$
Inject a volume (about $50 \mu \mathrm{~L}$ ) of a filtered pertion of the solution under test
$\Delta_{\text {the pooled sample }}^{\mathbf{A}_{\text {USP28 }}}$
into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{BrNO}_{3}$ dissolved in comparison with a Standard solution having a known concentration of USP Propantheline Bromide RS in the same Medium and similarly chromatographed.

Tolerances-Not less than $75 \%$ ( $Q$ ) of the labeled amount of $\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{BrNO}_{3}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample


## Change to read:

Dissolution Proedure for a Pooled Sample
〈 $\mathbf{4} 11$ USP28
Medium: pH 4.5 acetate buffer, prepared as directed in the test for Dissolution under Propoxyphene Hydrochloride, Aspirin and Caffeine Capsules; 700 mL .

Apparatus 2: 50 rpm .
Time: 30 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled
sample as the test solution. $\triangle U S P 28$
Proceed as directed in the Assay, using a-filtered pertion of the solution under test,
$\Delta_{a}$ portion of the pooled sample $\mathbf{A}_{\mathbf{A S P 2 8}}$
diluted with Mobile phase, and a Standard solution having accurately known concentrations of USP Propoxyphene Hydrochloride RS and USP Acetaminophen RS in Mobile phase. Calculate the amounts of propoxyphene hydrochloride $\left(\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{NO}_{2} \cdot \mathrm{HCl}\right)$ and acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$ dissolved.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ and not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ are dissolved in 30 minutes:
$\Delta$ the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

|  | Number |  |
| :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. <br> $\mathrm{S}_{2}$ |
| $\mathrm{~S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |

## BriEfing

Propoxyphene Napsylate Oral Suspension, USP 27 page 1583-See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-12

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle-$
FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\triangle U S P 28$
Add the following:
${ }^{\text {A }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\quad$ USP28

## BRIEFING

Pseudoephedrine Hydrochloride Oral Solution, USP 27 page 1599 -See briefing under Acetaminophen Oral Solution.
(PA2: C. Anthony) RTS-40619-13

## Pseudoephedrine Hydrochloride Oral Solution <br> (Monograph under this new title—to become official June 1, 2005) <br> (Current monograph title is Pseudoephedrine Hydrochloride Syrup)

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle-$ FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements. $\quad$ USP ${ }^{\text {I }}$

## Add the following:

${ }^{\text {at }}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\quad$ USP28

## BRIEFING

Pseudoephedrine Hydrochloride Syrup, USP 27 page 1599See briefing under Acetaminophen Oral Solution.

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(PA2: C. Anthony) RTS-40619-13
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## Pseudoephedrine Hydrochloride Syrup

## (Current title_not to change until June 1, 2005) <br> Monograph title change-to become official June 1, 2005

See Pseudoephedrine Hydrochloride Oral Solution

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR SYRUP PACKAGED IN SINGLE-UNIT CONTAINERS: meets
the requirements. $\triangle U S P 28$

## Add the following:

${ }^{4}$ Deliverable volume $\langle 698\rangle$ -
FOR SYRUP PACKAGED IN MULTIPLE-UNIT CONTAINERS:
meets the requirements. $\triangle$ USP28

## Briefing

Pseudoephedrine Hydrochloride Tablets, USP 27 page 1600-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-10

Change to read:
Dissolution Proedtre for a Pooled Sample
-
〈711 USP28
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Determine the amount of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ dissolved by employing the following method.

Mobile phase-Proceed as directed in the Assay.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $214-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L3. The flow rate is about 1.5 mL per minute. Chromatograph the Standard solution,
and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-
${ }^{\mathbf{\Delta}}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\triangle U S P 28$ Inject a volume of a filtered

portion of the selution under test
${ }^{\mathbf{\Delta}}$ pooled sample ${ }_{\mathbf{\Delta U S P 2 8}}$
into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ dissolved in comparison with a Standard solution having a known concentration of USP Pseudoephedrine Hydrochloride RS in the same medium and similarly chromatographed.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## Briefing

Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution, USP 27 page 1601 -See briefing under Acetaminophen Oral Solution.

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(PA2: C. Anthony) RTS-40619-14
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## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements. $\mathbf{\Delta U S P 2 8}$

## Add the following:

${ }^{\text {s }}$ Deliverable volume $\langle 698\rangle$ FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-

TAINERS: meets the requirements. $\triangle$ USP28

## BRIEFING

Psyllium Hemicellulose. Because there is no existing USP monograph for this article, a new monograph is being proposed.
(DSB: G. Giancaspro) RTS-40087-1

## Add the following:

## ©Psyllium Hemicellulose

» Psyllium Hemicellulose is the alkali soluble fraction of the husk from Plantago ovata Forssk. It consists of a combination of highly substituted arabinoxylan polysaccharides. These polysaccharides are linear chains of xylose units ( $\beta$ $(1 \rightarrow 4)$-xylan) to which are attached single units of arabinose and additional xylose. Rhamnose, galactose, glucose, and rhamnosyluronic acid re-
sidues are also present as minor constituents. It contains not less than 75.0 percent of dietary soluble fiber, calculated on the dried basis.

Packaging and storage-Preserve in tight containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

## Identification-

A: The powdered mucilage stains red with ruthenium red TS and lead acetate TS.

B: It meets the requirements of the test for Swell vol-

## ите.

Total acidity-To a beaker, transfer 40 mL of the supernatant as obtained below in the test for Swell volume without disturbing the gel. Add 1 mL of phenolphthalein TS, and titrate with 0.03 N sodium hydroxide. Not more than 1.8 mL is consumed.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed $10^{3}$ per $g$ and the total combined molds and yeasts count does not exceed $10^{2}$ per g . It meets the requirements of the tests for absence of Salmonella species and Escherichia coli.

Loss on drying $\langle 731\rangle$-Dry at $105^{\circ}$ for 3 hours: it loses not more than $12.0 \%$ of its weight.

Total ash $\langle 561\rangle$ : not more than $5.0 \%$.
Acid-insoluble ash $\langle 561\rangle$ : not more than $1.0 \%$.

## Limit of alcohol-

Internal standard solution-Transfer 5.0 mL of $n$-propyl alcohol into a $500-\mathrm{mL}$ volumetric flask containing approximately 450 mL of water. Dilute with water to volume, insert the stopper into the flask, and mix well.
Standard stock solution-Transfer 5.0 mL of absolute alcohol at $20 \pm 2^{\circ}$ into a $500-\mathrm{mL}$ volumetric flask containing approximately 450 mL of water. Dilute with water to volume, insert the stopper into the flask, and mix well.

Standard solution-Transfer 10.0 mL of the Standard stock solution and 10.0 mL of Internal standard solution into a $100-\mathrm{mL}$ volumetric flask. Dilute with water to volume, insert the stopper into the flask, and mix well.

Test solution-Transfer 0.5 g of Psyllium Hemicellulose, accurately weighed, into a $150-\mathrm{mL}$ conical flask. Add about 90 mL of water, insert the stopper into the flask, and stir rapidly for 3 hours using a magnetic stirrer. Add 10.0 mL of the Internal standard solution, and mix well. Pass the sample through a filter having a $0.45-\mu \mathrm{m}$ porosity.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and a $0.53-\mathrm{mm} \times 30-\mathrm{m}$ fused silica analytical column coated with $3.0-\mu \mathrm{m}$ G43 stationary phase. A $0.53-\mathrm{mm}$ $\times 2-\mathrm{m}$ fused silica guard column may be used. The chromatograph is programmed as follows. Initially, the column temperature is equilibrated at $40^{\circ}$ for 5 minutes. The temperature is then increased at a rate of $10^{\circ}$ per minute to $230^{\circ}$, and is maintained at $230^{\circ}$ for 3 minutes. The injection port temperature is maintained at $250^{\circ}$, and the detector is maintained at $300^{\circ}$. The carrier gas is helium. The split flow ratio is about $10: 1$, and the flow rate is maintained at about 4.0 mL per minute. Inject the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2 \%$.

Procedure-Separately inject equal volumes (about 0.5 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the percentage of alcohol in the portion of Psyllium Hemicellulose taken by the formula:

$$
1000(C / W)\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of alcohol in the Standard stock solution; $W$ is the weight, in mg , of Psyllium Hemicellulose taken; and $R_{U}$ and $R_{S}$ are the ratios of the peak responses of alcohol to those of $n$-propyl alcohol from the Test solution and the Standard solution, respectively: not more than $12.0 \%(\mathrm{w} / \mathrm{w})$ is found.

Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

Heavy metals, Method II $\langle 231\rangle: 10 \mu \mathrm{~g}$ per g.
Swell volume-Add 0.50 g of Psyllium Hemicellulose to a glass-stoppered, $100-\mathrm{mL}$ graduated mixing cylinder. To avoid material clumping, hold the cylinder at a $45^{\circ}$ angle, and gently rotate it while using a wash bottle to forcefully add about 30 mL of water. Add water to bring the total volume to 100 mL , and cap the cylinder. Invert the cylinder several times until a uniform suspension is achieved, and allow to stand. Gently invert the cylinder several times again at 4 hours and 8 hours after the initial sample preparation, and allow to stand. Allow the gel to settle for 16 hours. Determine the volume of the gel: not less than 80 mL per g of Psyllium Hemicellulose is found.

## Content of soluble dietary fiber-

Alcohol solution -Transfer 82.0 mL of alcohol to a 100mL volumetric flask, dilute with water to volume, and mix.

Buffer solution-Dissolve 1.95 g of 2-( N -morpholino)ethanesulfonic acid and 1.22 g of tris(hydroxymethyl)aminomethane in 170 mL of water. Adjust with 6 N sodium hydroxide to a pH of 8.2 , dilute with water to 200 mL , and mix. [NOTE-It is important to adjust the pH to 8.2 at $24^{\circ}$. If the Buffer solution temperature is $20^{\circ}$, adjust the pH to 8.3 ; if the temperature is $28^{\circ}$, adjust the pH to 8.1 . For deviations between $20^{\circ}$ and $28^{\circ}$, adjust by interpolation.]
Acid solution-Prepare 0.561 N hydrochloric acid by dissolving 9.35 mL of 6 N hydrochloric acid in 70 mL of water. Dilute with water to 100.0 mL , and mix.

Phosphate buffer-Prepare a pH 6.0 phosphate buffer (see Buffer Solutions under Reagents, Indicators, and Solutions).

Protease solution-Dissolve 5 mg of protease in 0.1 mL of Phosphate buffer.

Enzyme purity-To ensure the absence of undesirable enzymatic activities and the presence of desirable enzymatic activities, proceed as directed for Test preparations and Procedure using the substrates listed in the following table in place of Psyllium Hemicellulose. The enzyme preparation is suitable if more than $90 \%$ of the original weight of pectin, arabinogalactan, and $\beta$-glucan is recovered; not more than $2 \%$ of the original weight of casein and corn starch is recovered; and not more than $1 \%$ of the original weight of wheat starch is recovered. [NOTE-Test the enzyme purity of every new lot of enzyme and at 6-month intervals thereafter.]

| Substrate | Weight in g | Activity Tested |
| :--- | :---: | :--- |
| Pectin | 0.2 | Pectinase |
| Arabinogalac- | 0.2 | Hemicellulase |
| tan | 0.2 | $\beta$-Glucanase |
| $\beta$-Glucan | 1.0 | $\alpha$-Amylase and <br> amyloglucosidase |
| Wheat starch | 1.0 | $\alpha$-Amylase and <br> amyloglucosidase |
| Corn starch | 0.3 | Protease |
| Casein |  |  |

Blank preparations-Using two $400-\mathrm{mL}$ tall-form beakers, appropriately labeled, proceed as directed for Procedure without Psyllium Hemicellulose.

Test preparations-Weigh accurately, in duplicate, approximately 0.2 g of Psyllium Hemicellulose, previously milled to very fine powder. [NOTE-Duplicates should differ
by less than 1 mg in weight.] Transfer duplicate samples to appropriately labeled $400-\mathrm{mL}$, tall-form beakers, and proceed as directed for Procedure.

Procedure-Treat each preparation in the following manner. Add 40 mL of Buffer solution to the beaker. [NOTEFor the Test preparation, stir until Psyllium Hemicellulose is completely dispersed.] Add $125 \mu \mathrm{~L}$ of heat-stable $\alpha$-amylase solution, and stir to ensure uniform mixing. Cover the beaker with aluminum foil, and incubate over a water bath maintained at $95^{\circ}$ to $100^{\circ}$ for 15 minutes, with continuous agitation. [NOTE-Start timing once the water bath temperature reaches $95^{\circ}$; a total time of 35 minutes is usually sufficient.] Remove the beaker from the water bath, and cool to $60^{\circ}$. Remove the aluminum foil, scrape any ring from inside the beaker, and disperse any gels in the bottom of the beaker with a spatula. Rinse the walls of the beaker and the spatula with 10 mL of water, collecting the rinsings in the beaker. Add $500 \mu \mathrm{~L}$ of Protease solution. Cover with aluminum foil, and incubate over a water bath maintained at $60 \pm$ $3^{\circ}$ for 30 minutes with continuous agitation. [NOTE-Start timing when the bath temperature reaches $60^{\circ}$.] Remove the foil, and transfer 5 mL of Acid solution while stirring. Adjust, if necessary, with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of $4.28 \pm 0.07$ at $60^{\circ}$. [NOTE-It is important to adjust the pH to 4.28 while the solution in the beaker is maintained at $60^{\circ}$, otherwise the pH will increase at lower temperatures.] Add $150 \mu \mathrm{~L}$ of amyloglucosidase solution with stirring. Cover with aluminum foil, and incubate over a water bath maintained at $60 \pm 3^{\circ}$ for 30 minutes with constant agitation. [NOTE-Start timing once the water bath reaches $60^{\circ}$.] Transfer approximately 40 mL of the beaker contents to a $50-\mathrm{mL}$ centrifuge tube, and sonicate the tube contents for 3 minutes. ${ }^{*}$ Centrifuge at 10,000-14,000

[^11]rpm for 10 minutes. Carefully pour the supernatant into an appropriately labeled $600-\mathrm{mL}$ tared beaker. Do not disturb any pellet in the bottom of the centrifuge tube. Add the remaining sample from the original $400-\mathrm{mL}$ beaker into the centrifuge tube still containing the pellet. Rinse the 400mL beaker with $15-20 \mathrm{~mL}$ of water, and add the rinsing to the $50-\mathrm{mL}$ centrifuge tube. Centrifuge the sample at $10,000-14,000 \mathrm{rpm}$ for 10 minutes. Carefully pour the supernatant into the $600-\mathrm{mL}$ beaker containing the first supernatant. Add 390 mL (measured before heating) of alcohol at $60^{\circ}$ to the $600-\mathrm{mL}$ beaker. Cover the beaker, and allow to stand for at least 1 hour to form a precipitate.

Place 3 g of chromatographic siliceous earth into a clean air-dried crucible with a fritted disk. Heat the crucible containing chromatographic siliceous earth at $525^{\circ}$ in a muffle furnace for at least 4 hours. Cool. Pass deionized water through the crucible while applying constant suction. Rinse with acetone, and allow to air-dry. Store the crucible in a convection oven at approximately $130^{\circ}$ for at least 2 hours before use. Weigh the prepared crucible to 0.1 mg before use. Wet the chromatographic siliceous earth in the crucible using a stream of Alcohol solution from a washing bottle, and apply suction to evenly distribute the chromatographic siliceous earth over the fritted disk. Maintaining the suction, transfer the supernatant and precipitate from the beaker to the crucible, and filter. Transfer any solid residue in the beaker with the aid of Alcohol solution. [NOTE-In some cases, gums may form during filtration, trapping liquid in the residue. If so, break the surface film with a spatula to improve filtration.] Wash the residue in the crucible sequentially with 30 mL of Alcohol solution, 20 mL of alcohol, and 20 mL of acetone. Dry the crucible containing the residue at $100^{\circ}$ in a convection oven for at least 4 hours, cool to room temperature in a desiccator.

Determine the weight of the residue $(R)$.

Use one of the duplicate residues from the Test preparations and one of the blank residues from the Blank preparations to determine the protein content, in mg, by placing the residue in a $500-\mathrm{mL}$ Kjeldahl flask, and proceeding as directed for Method I under Nitrogen Determination $\langle 461\rangle$. The protein content is determined by multiplying the content of nitrogen found by 6.25 . Incinerate the residue from the remaining duplicate of the Test preparation and the Blank preparation as directed for Total Ash under Articles of Botanical Origin $\langle 561\rangle$ at a reduced temperature of $525^{\circ}$, and determine the ash content as directed. Calculate the corrected average weight of the blank, in $\mathrm{mg}, B$, by the formula:

$$
R_{B}-P_{B}-A_{B}
$$

in which $R_{B}$ is the weight, in mg , of the average blank residue for duplicate blank determinations; $P_{B}$ is the content, in mg , of protein found in the blank; and $A_{B}$ is the content, in mg , of ash found in the blank. Calculate the content of soluble dietary fiber, in percentage, by the formula:

$$
100\left(R_{U}-P_{U}-A_{U}-B\right) / W_{U},
$$

in which $R_{U}$ is the the weight, in mg , of average residue for the duplicate Test preparations; $P_{U}$ is the content of protein, in mg , found in the Psyllium Hemicellulose; $A_{U}$ is the content of ash, in mg , found in the Psyllium Hemicellulose; $B$ is the average weight of the blank as calculated above; and $W_{U}$ is the average weight, in mg , of the Psyllium Hemicellulose taken. $\Delta$ USP28

## BriEfing

Pyridoxine Hydrochloride Tablets, USP 27 page 1609—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-12

Change to read:
Dissolution Procedure for a Pooled Sample
4 4 USP28
$\langle 711\rangle-$
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\angle$ USP28
Determine the amount of $\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{NO}_{3} \cdot \mathrm{HCl}$ dissolved employing the procedure set forth in the Assay for niacin or niacinamide, pyridoxine hydrochloride, riboflavin, and thiamine under Water-Soluble Vitamins Tablets by using filtered portion the thent
$\Delta_{\text {portions of the pample }}^{\text {USP28 }}$
suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Pyridoxine Hydrochloride RS in the same Medium.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{NO}_{3} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample


## Change to read:

Dissolution, Procedure for a Poded Sample

Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.
Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{H}_{3} \mathrm{~N}_{3} \mathrm{O} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{~N}_{3} \mathrm{O} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform
at either $\mathrm{S}_{1}$, or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## Briefing

Sevoflurane, page 1571 of $P F$ 29(5) [Sept.-Oct. 2003]. It is proposed to revise the Packaging and storage section to include a recommended storage temperature range in accordance with the current policies of the USP Packaging, Storage, and Distribution (PSD) Expert Committee. It is also proposed to revise the names of two of the Reference Standards: USP Sevomethyl Ether RS is changed to USP Sevoflurane Related Compound B RS, and USP Hexafluoroisopropanol RS is changed to USP Sevoflurane Related Compound C RS.
(PA1: K. Russo; PSD: C. Okeke) RTS-40649-2
» Sevoflurane contains not less than 99.9 99.97 percent and not more than 100.0100 .00 percent of $\mathrm{C}_{4} \mathrm{H}_{3} \mathrm{~F}_{7} \mathrm{O}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight, light-resistant containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$. Replace the cap securely after each use.

USP Reference standards $\langle 11\rangle-U S P$ Sevoflurane $R S$. USP Sevoflurane Related Compound A RS.USP Sevenethyl Ether (SAEE) RS. USP He RS. USP Sevoflurane Related Compound B RS. USP Sevoflurane Related Compound C RS.

Identification, Infrared Absorption-The IR absorption spectrum of Sevoflurane, obtained using a gas cell, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Sevoflurane RS.

Refractive index $\langle 831\rangle$ : between 1.2745 and 1.2760 , at $20^{\circ}$.

Acidity or alkalinity-Transfer 20.0 mL of Sevoflurane and 20.0 mL of carbon dioxide-free water to a separatory funnel, shake for 3 minutes, and allow the layers to separate: the aqueous layer requires not more than 0.10 mL of 0.010 N sodium hydroxide or not more than 0.60 mL of 0.010 N hydrochloric acid for neutralization, bromocresol purple TS being used as the indicator.

Water, Method $I\langle 921\rangle$ : 0.03\% and 0.2\%. not more than $0.2 \% ; 0.1 \%$. and, when packeged in glas eontainers, not less than $0.03 \%$.

Limit of fluoride-[NOTE-Use plastic utensils throughout this test.]
Buffer solution-Transfer 110 g of sodium chloride and 1 g of sodium citrate to a $2000-\mathrm{mL}$ volumetric flask, and dissolve in 700 mL of water. Carefully add 150 g of sodium hydroxide, and shake to dissolve. Cool to room temperature, and carefully add 450 mL of glacial acetic acid while stir-
ring. Cool, add 600 mL of isopropyl alcohol, dilute with water to volume, and mix. [NOTE-The pH of this solution is between 5.0 and 5.5 . This solution may be used for six weeks when stored at room temperature.]

Solution A-Transfer about 221 mg of sodium fluoride, previously dried at $150^{\circ}$ for 4 hours and accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Add about 20 mL of water, and mix to dissolve. Add 1.0 mL of 0.01 N sodium hydroxide, and dilute with water to volume. Each mL of this solution contains 1 mg of fluoride. Store in a tightly closed plastic container. [NOTE-This solution may be used for two weeks when stored in a refrigerator.]

Standard stock solutions-Quantitatively transfer accurately measured volumes of Solution $A$ to separate 100mL volumetric flasks, and dilute with water to obtain solutions having known concentrations of about 5, 2, 0.5 , and $0.2 \mu \mathrm{~g}$ of fluoride per mL .

Standard solutions-Transfer 25.0 mL of each of the Standard stock solutions to separate $50-\mathrm{mL}$ volumetric flasks, dilute with Buffer solution to volume, and mix.

Test solution-Pipet 50.0 mL of Sevoflurane and 50.0 mL of water into a separatory funnel, shake vigorously for 3 minutes, and allow the liquids to separate completely. Transfer 25.0 mL of the aqueous top layer to a $50-\mathrm{mL}$ volumetric flask, dilute with Buffer solution to volume, and mix.

Procedure-Concomitantly measure the potentials, in mV, of the Standard stock solutions, Standard solutions, and Test solution with a pH meter (see $\mathrm{pH}\langle 791\rangle$ ) capable of a minimum reproducibility of $\pm 0.2 \mathrm{mV}$ and equipped with a fluoride-specific ion-indicating electrode and a glass-sleeved calomel reference electrode. [NOTE-When taking measurements, transfer the solution under test to a $100-\mathrm{mL}$ beaker containing a polytef-coated stirring bar, and immerse the electrodes. Allow to stir on a magnetic stirrer having an insulated top until equilibrium is attained in
about 2 to 3 minutes, and record the potential. Rinse the electrodes with the Buffer solution, and dry, taking care to avoid damaging the crystal of the specific-ion electrode. A satisfactory response is achieved if the difference between the potentials obtained with the Standard stock solutions having fluoride concentrations of 5 and $0.5 \mu \mathrm{~g}$ per mL is in the range between 50 and 60 mV .] Plot the logarithms of the fluoride concentrations, in $\mu \mathrm{g}$ per mL , of the Standard solutions versus potentials, in mV. From the graph so obtained and the measured potential of the Test solution, determine the concentration, in $\mu \mathrm{g}$ per mL , of fluoride in the Test solution: not more than $2 \mu \mathrm{~g}$ per mL is found.

Limit of nonvolatile residue-Transfer 10.0 mL of Sevoflurane to an accurately weighed evaporating dish, evaporate to dryness on a steam bath, and dry the residue at $105^{\circ}$ for 2 hours: the weight of the residue does not exceed 1.0 mg .

## Limit of peroxide-

Titanium tetrachloride solution-Separately cool 1.0 mL of 6 N hydrochloric acid and 1.0 mL of titanium tetrachloride in small beakers surrounded by crushed ice. Add titanium tetrachloride dropwise to the chilled acid. Allow to stand at ice-bath temperature until all of the yellow solid dissolves, dilute with 6 N hydrochloric acid to 100 mL , and mix.

Standard stock solution-Prepare a solution of 30 percent hydrogen peroxide in water ( 1 in 400).
Standard solution-Transfer 15.0 mL of the Standard stock solution to a $1000-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of the solution so obtained and 5.0 mL of Titanium tetrachloride solution to a $10-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Test solution-Transfer 50.0 mL of Sevoflurane and 5.0 mL of Titanium tetrachloride solution to a separatory funnel, shake vigorously, allow the layers to separate, drain, and discard the lower layer. Carefully collect the top layer in a $10-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Procedure-Concomitantly determine the absorbances of the Standard solution and the Test solution at a wavelength of about 410 nm , with a suitable spectrophotometer, using a $1-\mathrm{cm}$ cell and a mixture of Titanium tetrachloride solution and water (1:1) as the blank. Calculate the peroxide concentration, in $\mu \mathrm{g}$ per mL , in the portion of Sevoflurane taken by the formula:

$$
0.22\left(A_{U} / A_{S}\right)
$$

in which $A_{U}$ and $A_{S}$ are the absorbances obtained from the Test solution and the Standard solution, respectively: not more than $0.22 \mu \mathrm{~g}$ per mL is found.

## Chromatographic purity -

Internal stated solution-Use dimethoxymethane.
Standerd solutions Prepare solutions, proceeding for each as follows. Transfer 2.0 mL of ethylene dichloride into a serew capped vial, immediately seal with a cap and septum, and place on a balanee. Using a mierosyringe, transfer about $20 \mu \mathrm{~L}$ of USP Sevellurane RS, aceurately measured, to the vial by inserting the syringe needle through the septum. Record the quantity, in me, of USP Sevollurane RS added. Using the same method, transfer about $20 \mu \mathrm{~L}$ of Internal stataderd soldtion to the vial, and record the quantity, in mg, of the Internal standard solution added.

Fest solution Transfer 20.0 mL of Seveflurane to a vial, and insert the stopper. Using a mierosyringe, add $5 \mu \mathrm{~L}$ of Internal standed solution, aceurately measured, to the vial. Chromagraphic system (see Chromatgraphy (624)) The gas chromatograph is equipped with a flame-ionization detector and a $0.32 \mathrm{~mm} \times 30 \mathrm{~m}$ fused silica capillary col
umnerat with $3.0-\mu \mathrm{m}$ film of liguid phase G19. Prior to use, condition the column overnight at a temperature of $250^{\circ}$. The column temperature is programmed as follows. Initially it is maintained at $40^{\circ}$ for 10 minutes, then in ereased a rate of $10^{\circ}$ per minte to $200^{\circ}$, and maintained at $200^{\circ}$ for at least 14 minutes. The injection port temperature is maintained at $200^{\circ}$. The detector temperature is maintained at $225^{\circ}$. The split ratio is $1: 20$. Helium is used as the earrier gas, flowing at a rate of about 1.0 mL per minute. Chromatograph one of the Staterd solutions, and reeord the chromatograms as directed for Procedure, adjusting the recorder sensitivity to obtain the sevollurane peak on seale: the relative retentime are 0.57 for $1,1,3,3$ pentafluoroisopropenyl fluoremethyl ether, 0.62 for methyl 2,2,2-triflure-1 (triflueremethy) ethyl ether, 0.74 for seveflur ane, and 1.0 for the internal standard; the column efficiency is not less than 6000 theoretieal plates; and the relative standard deviation for replicate injections is not more than $2.0 \%$. Chromatograph the Test solution, adjusting the recorder sensitivity to obtain peak heights of at least $10 \%$ of full seale for the two impurities, and record the ehromatograms as directed for Procedure: the resolution, $R$, between these iw im purities is not less than 2.0 .

Proedtre Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of the Statedard solutions and the Test solution int the chromatograph, record the ehromatograms, and measure the areas of the major peaks. Caleulate the relative respense factor, $F$, for each of the Staturd solutions by the formula:

$$
\left(W_{f}+W_{s}\right) R_{s}
$$

in which $H_{f}$ is the weight, in mg, of the intemal standard in the Standard solution; $W_{s}$ is the weight, in mg, of USP Seweflurane RS in the Standerd solution; and $R_{s}$ is the average respense ratio of the seveflurane peak to that of the internal standard obtained from the Standard solutions: the relative respense factors for the Standerd solutions do not differ by
more than $3.0 \%$ frem their average. Caleulate the quantity, in $\mu \mathrm{y}$ per g , of each impurity in the pertion of Sevelturane taken by the formula:

$$
250(0.859 / 1.525)\left(R_{i}+F\right)
$$

in which 0.859 and 1.525 are the specific gravities of the internal standard and seveflurane, respectively; $R_{i}$ is the re spenseratio of the impurity peak to that of the internalstan dard obtained from the Test solution; and $F$ is the average relative response facter obtained as directed above: not more than 25 kg per of of $1,1,3,3$-pentafluoroisopropenyt flueromethylether, not more than 50 fig per gof methyt 2,2,2-trifluere-1 (triflueremethyl) ethylether, and not mere than $25 \mu$ gis per of of any other individualimpurity are found; and not more than 50 pg per of of totalimpurities, exeluding the nomed above, is found.

## Intern stan Use dimethoxymethane.

Standard solution - Transfer 2.0 mL of ethylene
dichloride to serew eapped vial, immediately seal with a eap and septum, and place on a balanee. Inject about $20 \mu \mathrm{~L}$ of USP Seveflurane PS and $20 \mu \mathrm{~L}$ of the Internal statard solution, beth aceurately measured, into the vial through the septum, and weigh the vial after each injection.
Standard solution 2 Transfer 2.0 mL of ethylene dichloride to serew eapped vial, immediately seal with a eap and septum, and place on a balanee. Inject about $20-\mu \mathrm{L}$ ef USP Sevelluane Related Compound A RS and $20 \mu \mathrm{~L}$ of the Internal standerd solution, both aceurately measured, into the vial through the septum, and weigh the vial after each injection.

Fest solution Transfer 20.0 mL of Seveflurane to a vial, and insert the stopper. Using a microsyringe, add about $5 \mu \mathrm{~L}$ of the Internal standard solution, aceurately measured, to the vial.

Chromatigraphic system (see Chromatography (621)) The gas chromatograph is equipped with a flame ionization detectrond contains $0.32 \mathrm{~mm} \times 30 \mathrm{~m}$ fused-silicacapil lary column coated with a $3.0 \mu \mathrm{~m}$ film of liquid phase G43. Prior to use, condition the column overnight at a temperature of $250^{\circ}$. The earrier gas is helium, flowing at a rate of about $1.0-\mathrm{mL}$ per minute. The chromatograph is programmed as follows. Initially the column temperature is maintained at $40^{\circ}$ for 10 minutes, then it is inereased at a rate of $10^{\circ}$ per minute to $200^{\circ}$, and maintained at $200^{\circ}$ for not less than 14 minutes. The injection port temperature is maintaine at $200^{\circ}$, and the detector temperature is maintained at $225^{\circ}$. The split ratio is $1: 20$. Chrematograph Standard solution 1 and Statadard soldtion 2, and record the peak respense directed for Proedure, adjusting the recorder sensitivity to obtain the seveflurane peak on seale: the relative retention times are about 0.57 for seveflurane related eompernd $\Lambda, 0.74$ for seveflurane, and 1.0 for the internat standard; the resolution, $R$, between seveflurane and seveflurane related compound $\Lambda$ is not less than 2.0; the column efficieney is not less than 6000 theoretieal plates; and the relative standard deviation for replieate injections, determined from the peak area ratio of seveflurane to the internal standard, is not more than $2.0 \%$.

Procedure Separately injec equal volumes (about $2 \mu \mathrm{~L}$ ) of Stand solution 1, Stand solution 2, and Test solution into the chromatograph, record the chrematograms, and measure the areas of the major peaks. Caleulate the relative respense factor, $F$, for each Standetrd solution taken by the fermela:

$$
R_{s}\left(H_{f}+H_{s}\right),
$$

in which $R_{s}$ is the peak are ratio of seveflurane to the internal standard obtained from the chromatogram; $H_{t}$ is the weight, in mg, of the internal standard in the partieular Standatrd solution; and $H_{s}$ is the weight, in mg, ofUSP Sevellur-
ane RS-or USP Seveflurane Related Compound $A$ RS in the eorrespending Standard solution. Caleulate the quantity, in Hg per g , of sevellurane related compound $A$ in the pertion
of Seveflurane taken by the formula:

$$
250\left(R_{i}+F\right)
$$

in whieh $R_{i}$ is the peak respense ratio of sevoflurane related empound $A$ to the internal standard obtained from the Test solution; and $F$ is the relative respense factor obtained as directed above: not more than 25 - $\mu$ g per g of sevellurane related compound $A$ is found. Caleulate the quantity, in Hg per g, of each impurity, other than sevoflurane related eompound $\Lambda$, in the pertion of Seveflurane taken by the for mula:-

$$
250\left(R_{i}+F\right)
$$

in which $R_{i}$ is the peak respense ratio of each impurity to the internal standard obtained from the Test solution; and $F$ is the average relative-respense facter obtained as directed above: not more than 100 ug per of of any impurity, other than sevoflurane related compound $A$, is found; and not more than 300 pg per g of totalimpurities is found.

## Related compounds-

Standard stock solution-Accurately weigh $10 \mathrm{~mL}(15 \mathrm{~g})$ of USP Sevoflurane RS in a suitable vial fitted with a septum, and successively add $25 \mu \mathrm{~L}(\sim 0.0375 \mathrm{~g})$ each of USP Sevoflurane Related Compound A RS, USP Sevomethyt Ether (SME) RS, and USP Hexafluoroisopropanol RS. USP Sevoflurane Related Compound B RS, and USP Sevoflurane Related Compound C RS. Record the weight after addition of each impurity.

Standard solution-Accurately weigh about 20 mL of USP Sevoflurane RS in a suitable vial fitted with a septum, and add $0.2 \mathrm{~mL}(\sim 0.3 \mathrm{~g})$ of the Standard stock solution. Record the exact weight of Standard stock solution added.

Test solution-The test sample is used as is.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and contains a $2.1-\mathrm{mm} \times 4-\mathrm{m}$ silicosteel column packed with $5 \%$ G35 on 80 - to 100 -mesh support S12. The carrier gas is helium, flowing at a rate of 25 mL per minute. Initially the column temperature is maintained at $70^{\circ}$ for 20 minutes, then it is increased at a rate of $8^{\circ}$ per minute to $170^{\circ}$, and maintained at $170^{\circ}$ for 17.5 minutes. The injection port temperature is maintained at $175^{\circ}$, and the detector temperature is maintained at $200^{\circ}$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are 0.67 for sevoflurane related compound $\mathrm{A}, 1.0$ for sevemethylether, and 2.88 for hexaftureisopropanel; sevoflurane related compound B and 2.88 for sevoflurane related compound C ; the resolution, $R$, between sevoflurane related compound A and se vemethyl ether sevoflurane related compound B is not less than 6; and the relative standard deviation, determined from the semethylether sevoflurane related compound B peak, for replicate injections is not more than $2 \%$.

Procedure—Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas of all the peaks. Record the chromatogram for at least 50 minutes. Calculate the relative response factors, $F$, of sevoflurane related compound $A$ and hewafluereiseprepanel relative to that of sevemethyl ether sevoflurane related compound $C$ relative to that of sevoflurane related compound $B$ taken by the formula:

$$
\left(\epsilon_{s}+\epsilon_{\text {shaf }}\right)\left(r_{\text {sumf }}+r_{s}\right) \text {, }
$$

$$
\left(C_{S} / C_{B}\right)\left(r_{B} / r_{S}\right)
$$

in which $C_{S}$ and $r_{S}$ are the concentration and the peak area for either sevoflurane related compound A or her propal sevoflurane related compound C in the Standard solution; and $\mathrm{G}_{\text {and }} \mathrm{C}_{B}$ and $r_{B}$ are the concentration and the peak area for enethy sevoflurane related compound B in the Standard solution. The calculated relative response factors for sevoflurane related compound A and hexallureispropand sevoflurane related compound C must be in the range of 1.08 to 1.31 and 2.28 to 2.79 , respectively.

Calculate the percentages ( $\mathrm{w} / \mathrm{w}$ ) of impurities present in the Test solution, which are also found in the Standard solution, by the formula:

$$
C_{S}\left(r_{i} / r_{S}\right),
$$

in which $r_{i}$ and $r_{S}$ are the peak responses of impurities in the Test solution and in the Standard solution; and $C_{S}$ is the concentration ( $w / w$ ) of the impurities in the Standard solution. The other known impurities, that are not present in the Standard solution, are identified by their relative retention times and their amounts present are determined using their respective relative response factors (Table 1) by the formula:


Use relative response factor of SME sevoflurane related compound B to calculate the unknown impurities. $F$ is the relative response factor of the known impurity not present in
the Standard solution; $\epsilon C_{B}$ is the concentration (w/w) of SME sevoflurane related compound B in the Standard solution; and $\Psi r_{B}$ is the peak area of SME sevoflurane related compound B in the Standard solution. Not more than $0.0025 \%$ of sevoflurane related compound A is found; not more than $0.01 \%$ of any other single impurity is found; and not more than $0.03 \%$ of total impurities is found.

Table 1

|  | Relative <br> Retention | Relative <br> Response <br> Time |
| :--- | :---: | :---: |
| Impurity | 1 | 1 |
| Sactor |  |  |
| flurane related com- |  |  |
| $\quad$ pound B |  |  |
| 2-Chloropropane | 0.48 | 0.4092 |
| Dichloromethane | 0.76 | 1.5141 |
| Chlorosevo ether | 2.23 | 1.0884 |
| Hexafluoroisopropyl | 1.47 | 1.3068 |
| $\quad$ formate |  |  |
| Unknown impurities | - | 1 |

Assay-Using the results from the test for Related compounds, calculate the percentage of $\mathrm{C}_{4} \mathrm{H}_{3} \mathrm{~F}_{7} \mathrm{O}$ in the volume of Sevoflurane taken by subtracting the sum of percentages for all impurities found from $100.0 \% 100.00 \%$. $\mathbf{\triangle U S P 2 8}$

## Briefing

Simethicone, USP 27 page 1689 and page 1078 of $P F$ 29(4) [July-Aug. 2003]. It is proposed to clarify that in the Identification test, the blank should be prepared using the procedure in the Assay, to be consistent with the preparation of the Test solution and the Standard solution.
(PA4:E. Gonikberg) RTS-40638-1

## Change to read:

Identification, Infrared Absorption $\langle 197 \mathrm{~S}\rangle$ -
© [NOTE-Use toluene as a blank the procedural blank, pre-
pared as directed in the Assay, to set the instrument.] $]_{U U S P 28}$ Test solution-Prepare as directed for Assay preparation in the Assay.

Standard solution-Prepare as directed for Standard preparation in the Assay.

Cell size: 0.5 mm .

Briefing

Simethicone Emulsion, USP 27 page 1690—See briefing under Simethicone.
(PA4: E. Gonikberg) RTS-40638-2

## Change to read:

Identification-The IR absorption spectrum, determined in a 0.5 mm cell, of the solution of Emulsion prepared as directed in the Assay, the dilute hydrochloric acid being omitted, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Polydimethylsiloxane RS.
${ }^{\boldsymbol{\Delta}}$ [NOTE—Prepare a procedural blank by similarly treating 25.0 mL of toluene, and use this blank to set the instrument.] ${ }_{\mathbf{\Delta S S P 2 8}}$

BRIEFING
Sumatriptan, page 116 of $P F$ 29(1) [Jan.-Feb. 2003]. Several modifications are made to this proposed monograph to clarify the name of the compounds quantified and to correct the chemical formula and chemical name.
(PA3: S. Salado) RTS-40055-1; 40243-1

## Add the following:

## ©Sumatriptan


$\mathrm{C}_{14} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S} \quad 295.40$
1 H -Indole-5-methanesulfonamide, 3-[2-(dimethylami-no)ethyl]-N-methyl-.
3-[2-(dimethylamino)ethyl]-N-methy-1 H -indole-5-methanesulfonamide [103628-46-2].
» Sumatriptan contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{14} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S}$, calculated on the anhydrous and solvent-free basis.

Packaging and storage-Preserve in tight, light resistant containers. Protect from freezing, and store below $30^{\circ}$.

USP Reference standards $\langle 11\rangle-U S P$ Sumatriptan $R S$. USP Sumatriptan Succinate RS. USP Sumatriptan Succinate Related Compound A RS. USP Sumatriptan Succinate Related Compound B C RS. USP Sumatriptan Succinate Related Impurities $R S$.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Water, Method $I\langle 921\rangle$ : not more than $1.0 \%$.
Limit of sumatriptan stecinate related compound $A$ -
10 M Ammonium acetate solution-Dissolve 77.1 g of ammonium acetate in 100 mL of water.

Mobile phase_Prepare a filtered and degassed mixture of methanol and 10 M Ammonium acetate solution (9:1). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Sumatriptan Succinate Related Compound A RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.00625 mg per mL .

Test solution-Transfer about 100 mg of Sumatriptan, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $282-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L3. The flow rate is about 2.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $5 \%$.

Procedure—Separately inject equal volumes (about 20 $\mu \mathrm{L})$ of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of
sumatriptan suceinate related compound A in the portion of Sumatriptan taken by the formula:

$$
100(495.7 / 613.8)\left(C_{S} / C_{U}\right)\left(r_{U} / r_{S}\right)
$$

in which 495.7 and 613.8 are the molecular weights of sumatriptan related compound $A$ and sumatriptan succinate related compound A , respectively; $C_{S}$ is the concentration, in mg per mL, of USP Sumatriptan Succinate Related Compound A RS in the Standard solution; $C_{U}$ is the concentration, in mg per mL , of Sumatriptan in the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses for sumatriptan suecinate related compound A obtained from the Test solution and the Standard solution, respectively: not more than $0.6 \%$ is found.

## Chromatographic purity Related compounds-

Piltent and Mobile phase-Prepare as directed in the As say.

Resolution solution-Prepare as directed for the System suitability solution in the $A$ ssay.

Diluent and System suitability solution-Proceed as directed in the Assay.

Buffer solution-Dissolve about 1.7 mL of dibutylamine, about 0.6 mL of phosphoric acid, and about 3.9 g of monobasic sodium phosphate dihydrate in water. Adjust to a pH of about 7.5 with a solution of $50 \%(\mathrm{w} / \mathrm{v})$ sodium hydroxide, and dilute with water to 1000 mL , and mix.
Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (3:1). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).
Identification solution-Prepare a solution of USP Sumatriptan Succinate Related Impurities RS in Mobile phase having a concentration of about 3 mg per mL .

Test solution-Dissolve an accurately weighed quantity of Sumatriptan in Diluent to obtain a solution having a concentration of about 2 mg per mL .


#### Abstract

Chromatographic system (see Chromatography- $\langle 621\rangle$ )Prepare as directed in the Assaly. Chromatograph the Resotution solution, and record the peak respenses as directed for Procedure: the relative retention times are about 0.8 for sumatriptan succinate related compound $B$ and 1.0 for suma triptan; and the reselution, $R$, between sumatriptan suceinate related compeund $B$ and sumatriptan is not less than 1.5 .

Procedure Inject a volume (about $10 \mu \mathrm{~L}$ ) of the Test solution inte the chromatograph, record the chremategram, and measure all of the peak areas. Caleulate the pereentage of each impurity in the pertion of Sumatriptan taken by the formula:- $$
100\left(x_{i}+r_{s}\right)
$$ in which $r_{i}$ is the peak response for each impurity; and $r_{s}$ is the sum of the respenses of all of the peaks: not more than $0.2 \%$ of any impurity with a relative retention time of about 0.26 is found; not more than $0.5 \%$ of any impurities with


relative retention times of about 0.58 or about 0.79 are found; net mere than $0.3 \%$ of any other impurity is found; and the total of all impurities, including the amount found in the test for Limit of sumatriptan succinate related compound $A$, is net more than $1.5 \%$

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $282-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for sumatriptan succinate related compound C and 1.0 for sumatriptan; the resolution, $R$, between sumatriptan succinate related compound $C$ and sumatriptan is not less than 1.5. Chromatograph the Identification solution, and record the peak responses as directed for Procedure: identify the peaks according to Table 1.

Table 1

| Compound name | Relative retention time | Limit (\%) |
| :---: | :---: | :---: |
| [3-[2-(dimethylamino $N$-oxide)ethyl]-1H-indol-5-yl]- N -methylmethanesulfona- | about 0.3 | 0.2 |
| mide |  |  |
| [3-[2-(methylamino)ethyl]-1 $H$-indol-5-yl]- N -methylmethanesulfonamide | about 0.6 | 0.5 |
| Sumatriptan succinate related compound C | about 0.9 | 0.5 |
| Sumatriptan suceinate | 1.0 | - |
| [3-[2-(aminoethyl)-1H-indol-5-yl]-N-methylmethanesulfonamide | about 0.4 | 0.1 |
| Unknown impurities | - | 0.1 |
| Total | - | 1.5 |

[NOTE-The calculation of total impurities includes the amount of sumatriptan related compound A, determined in the test for Limit of sumatriptan related compound $A$.]

Procedure-Inject a volume (about $10 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Sumatriptan taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for each impurity, and $r_{s}$ is the sum of the responses of all the peaks: meet the requirements given in Table 1.

Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

Assay-
Diluent Dissolve 2.59-g of menebasic sedium phesphate in 600 mL of water, adjust to a pH of 6.5 with a solut tion of $50 \%$ (w/v) sodium hydroxide, dilute to 750 mL with water, add 250 mL of acetonitrile, and mix.

AObile phase Dissolve-0.97g of dibutylamine, 0.735 g of phosphoric acid, and 2.59 g of menobasic sodium phosphate in 750 mL of water, adjust to a pH of 6.5 with a solut tion of $50 \%$ (w/v) sodium hydroxide, and dilute to 1000 mL with water. Mix 750 mL of the solution so obtained with 250 mL of acetonitrile, mix, filter, and degas. Make adjustments if necessury (see System Suitability under Chrematography (621)).

Diluent-Dissolve 3.9 g of monobasic sodium phosphate dihydrate in water. Adjust with a solution of $50 \%(\mathrm{w} / \mathrm{v})$ sodium hydroxide to a pH of about 6.5 , and dilute to 1000 mL with water. Mix 750 mL of this solution with 250 mL of acetonitrile.

Buffer solution-Dissolve about 1.7 mL of dibutylamine, about 0.6 mL of phosphoric acid, and about 3.9 g of monobasic sodium phosphate dihydrate in water. Adjust with a solution of $50 \%(\mathrm{w} / \mathrm{v})$ sodium hydroxide to a pH of about 6.5 , and dilute with water to 1000 mL , and mix.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (3:1). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).
System suitability solution-Dissolve accurately weighed quantities of USP Sumatriptan Succinate RS and USP Sumatriptan Succinate Related Compound B C RS in Diluent to obtain a solution having known concentrations of about 0.140 .28 mg per mL and 0.070 .14 mg per mL , respectively.

Standard preparation-Dissolve an accurately weighed quantity of USP Sumatriptan Succinate RS, and dissolve in Diluent to obtain a solution having a known concentration of about 0.14 mg per mL .
Assay preparation-Transfer about 10 mg of Sumatriptan, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Diluent to volume, and mix.

$$
\text { Elaromatographie system (see-Chromatography }\langle 621\rangle \text { ) }
$$

The liquid chromategraphis equipped with a 282 nm deteeErand a $4.6 \mathrm{~mm} \times 25 \mathrm{~mm}$ eolumn that contains 5 mm packing L1. The flow rate is about 1.5 mL per minute. Chremategraph the System suitability solution and the Standard preparation, and record the peak respenses as directed for Procedure: the relative retention times are about 0.8 for su matriptan succinate related compeund B and 1.0 for sumat triptan; the resolution, $R$, between sumatriptan-suceinate related compeund $B$ and sumatriptan is not less than 1.5; and the relative standard-deviation for replicate injections of the Staded preparation is not more than $1.5 \%$.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $282-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for sumatriptan succinate related com-
pound C and 1.0 for sumatriptan; the resolution, $R$, between sumatriptan succinate related compound C and sumatriptan is not less than 1.5. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the amount of $\mathrm{C}_{14} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S}$, in mg, in the portion of Sumatriptan taken by the formula:

$$
(295.4 / 413.5) 100 C\left(r_{U} / r_{S}\right)
$$

in which 295.4 and 413.5 are the molecular weights of sumatriptan and sumatriptan succinate, respectively; $C$ is the concentration, in mg per mL, of USP Sumatriptan Succinate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses for sumatriptan obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta U S P 2 8}$

## Change to read:

Dissolution Pwe for Polle
${ }_{\langle }^{\boldsymbol{A}} \mathbf{7 1 1}$ USP28
Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
BRIEFING
Terbutaline Sulfate Tablets, USP 27 page 1787-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40315-6

Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\quad$ USP28
Determine the amount of $\left(\mathrm{C}_{12} \mathrm{H}_{19} \mathrm{NO}_{3}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ dissolved, em-
Determine the amount of $\left(\mathrm{C}_{12} \mathrm{H}_{19} \mathrm{NO}_{3}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ dissolved, em-
ploying the procedure set forth in the Assay, making any necessary modifications.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\left(\mathrm{C}_{12} \mathrm{H}_{19} \mathrm{NO}_{3}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ is dissolved in 45 minutes:
$\Delta$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

Number

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
|  | Number |  |
| Stage | Tested |  |$\quad$| Acceptance Criteria |
| :---: |


| Number |  |  |
| :---: | :---: | :---: |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. |

## BriEfing

Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets, USP 27 page 1816-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-14

## Change to read:

Dissolution Preedure for a Pooled Sample
$\triangle$
〈 ${ }^{\text {A }}$ USP 11$\rangle-\frac{1}{-}$
Medium: water; 900 mL
Apparatus 1: 100 rpm .
Time: 30 minutes.
Determine the amounts of $\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{~N}_{4} \mathrm{O}_{2}, \mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$, and $\mathrm{C}_{12} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{3}$ dissolved by employing the following procedure.

Mobile phase-Dissolve accurately weighed quantities of monobasic potassium phosphate and sodium 1-hexanesulfonate in water, and dilute quantitatively with water to obtain a solution having concentrations of 0.953 mg per $\mathrm{mL}(0.007 \mathrm{M}$ monobasic potassium phosphate) and 0.564 mg per $\mathrm{mL}(0.003 \mathrm{M}$ sodium 1hexanesulfonate), respectively. Adjust, if necessary, with 0.3 M phosphoric acid or 0.2 M monobasic potassium phosphate to a pH of $3.0 \pm 0.05$, to obtain a Phosphate buffer. The Mobile phase is a mixture of Phosphate buffer and methanol (75:25).

Standard solution-Dissolve accurately weighed quantities of USP Theophylline RS, USP Ephedrine Sulfate RS, and USP Phenobarbital RS in water, and dilute quantitatively and stepwise with water to obtain a solution having known concentrations of about $145 \mu \mathrm{~g}$ of anhydrous theophylline per $\mathrm{mL}, 28 \mu \mathrm{~g}$ of ephedrine sulfate per mL , and $9 \mu \mathrm{~g}$ of phenobarbital per mL .
${ }^{\mathbf{\Delta}}$ Test solution-Proceed as directed for Procedure for
Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the Test solu-

## tion. $\mathbf{H}$ USP28

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 3.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the theophylline and phenobarbital peaks is not less than 4.0 ; the tailing factors for the ephedrine and phenobarbital peaks are not more than 3.0 and 2.0 , respectively; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject an accurately measured volume (about $75 \mu \mathrm{~L}$ ) of a filtered portion of the solution under test
${ }^{\Delta}$ the Standard solution and the Test solution ${ }_{\Delta U S P 28}$ into the chromatograph, record the chromatogram, and measure the responses for the major peaks. The elution order is theophylline, ephedrine, and phenobarbital (last). Calculate the quantity, in mg , of $\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{~N}_{4} \mathrm{O}_{2}$ dissolved by the formula:

$$
(0.9 C)\left(r_{U} / r_{S}\right),
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Theophylline RS in the Standard solution, and $r_{U}$ and $r_{S}$ are the peak responses for theophylline obtained from the solution under test
${ }^{\Delta}$ Test solution ${ }_{\Delta U S P 28}$
and the similarly chromatographed Standard solution, respectively. Calculate the quantity, in mg , of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ dissolved by the formula:

$$
(201.69 / 214.27)\left(0.9 C^{\prime}\right)\left(r_{U}^{\prime} / r_{S}^{\prime}\right)
$$

in which 201.69 is the molecular weight of ephedrine hydrochloride; 214.27 is one-half the molecular weight of ephedrine sulfate; $C^{\prime}$ is the concentration, in $\mu \mathrm{g}$ per mL of USP Ephedrine Sulfate RS in the Standard solution; and $r_{U}^{\prime}$ and $r_{S}^{\prime}$ are the peak responses for ephedrine obtained from the solution under test
${ }^{\mathbf{\Delta}}$ Test solution ${ }_{\mathbf{\Delta U S P 2 8}}$
and the similarly chromatographed Standard solution, respectively. Calculate the quantity, in mg, of $\mathrm{C}_{12} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{3}$ dissolved by the formula:

$$
\left(0.9 C^{\prime \prime}\right)\left(r^{\prime \prime}{ }_{U} / r^{\prime \prime}{ }_{S}\right),
$$

in which $C^{\prime \prime}$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Phenobarbital RS in the Standard solution, and $r^{\prime \prime}{ }_{U}$ and $r^{\prime \prime}{ }_{S}$ are the peak responses for phenobarbital obtained from the selution under test
${ }^{\wedge}$ Test solution $\mathbf{A U S P 2 8}$
and the similarly chromatographed Standard solution, respectively. Tolerances-Not less than $75 \%(Q)$ of the labeled amounts of $\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{~N}_{4} \mathrm{O}_{2}, \mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$, and $\mathrm{C}_{12} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{3}$ are dissolved in 30 minutes:
$\Delta$ the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

## Acceptance Table for a Pooled Sample

Number
Stage Tested Acceptance Criteria

| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| :--- | :--- | :--- |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |
|  |  |  |

## Briefing

Thiamine Hydrochloride Tablets, USP 27 page 1825—See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-15

Change to read:
Dissolution Procedure for a Pooled Sample
${ }^{\mathbf{A}}\langle 711\rangle$ USP28
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-
${ }^{\Delta}$ Proceed as directed for Procedure for Capsules, Uncoated
Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$.
Combine equal volumes of the filtered solutions of the 6 or
12 individual specimens withdrawn, and use the pooled sample as the test solution
Determine the amount of $\mathrm{C}_{12} \mathrm{H}_{17} \mathrm{ClN}_{4} \mathrm{OS} \cdot \mathrm{HCl}$ dissolved, employing the procedure set forth in the Assay for niacin or niacinamide, pyridoxine hydrochloride, riboflavin, and thiamine under WaterSoluble Vitamins Tablets using filtered pertions of the solution under test,
${ }^{\Delta}$ the pooled sample ${ }_{\triangle U S P 28}$
suitably diluted with Dissolution Medium if necessary, in comparison with a Standard solution having a known concentration of USP Thiamine Hydrochloride RS in the same Medium.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{12} \mathrm{H}_{17} \mathrm{ClN}_{4} \mathrm{OS} \cdot \mathrm{HCl}$ is dissolved in 45 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

|  | Number <br> Stage | Acceptance Criteria |
| :---: | :---: | :--- |

## BRIEFING

Tiamulin Fumarate, USP 27 page 1842. It is proposed to change the name of the Reference Standard USP Tosyl Pleuromutilin RS to USP Tiamulin Related Compound A RS and to make the corresponding change in the text of the monograph. In addition, minor editorial style changes have been made.
(VET: I. DeVeau) RTS-40592-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Tiamulin Fumarate RS. USP Tosyl Pletromutilin RS.
${ }^{\Delta}$ USP Tiamulin Related Compound $A$ RS. $\mathbf{\Delta U S P 2 8 ~}$

## Change to read:

Chromatographic purity-
Dilute perchloric acid solution, Buffer solution, Mobile phase, System suitability solution, and Chromatographic system-Proceed as directed in the Assay.
Standard solution-Use the Standard preparation prepared as directed in the Assay.

Test solution-Use the Assay preparation prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatogram, identify the tiamulin fumarate peak, and measure all of the peak responses. [NOTE-Possible tiamulin fumarate impurities include, but are not limited to, pleuromutilin, mutilin, 14-acetyl mutilin, 11-monoacetyl mutilin, tosyl pleuromatilin,
$\Delta_{\text {tiamulin related compound A, }}$ USP28
11,14-diacetyl mutilin, 8-dimethylderivative, bisdimethylderivative, and 11-ketoderivative, their retention times, relative to tiamulin fumarate, being about $0.25,0.3,0.5,0.6,0.8,1.1,1.3,1.4$, and
2.3 , respectively.] Calculate the area percentage of each impurity, relative to tiamulin fumarate, in the portion of Tiamulin Fumarate taken by the formula:

$$
100\left(r_{i} / r_{U}\right)
$$

in which $r_{i}$ and $r_{U}$ are the peak responses of each impurity and tiamulin fumarate, respectively: not more than $1.0 \%$ of any identified impurity is found; not more than $0.5 \%$ of any unidentified impurity is found; and not more than $2.0 \%$ of total impurities is found.

## Change to read:

## Assay-

Dilute perchloric acid solution-Prepare a solution containing $6 \%$ of perchloric acid.

Buffer solution-Transfer 10 g of ammonium carbonate to a $1000-\mathrm{mL}$ volumetric flask, and dissolve in about 800 mL of water. Add 24 mL of Dilute perchloric acid solution, dilute with water to volume, mix, and filter.

Mobile phase-Prepare a mixture of methanol, Buffer solution, and acetonitrile, (49:28:23), filter, and degas.

System suitability solution-Dissolve accurately weighed quantities of USP Tiamulin Fumarate RS and USP Tosyl Pleuromutilim RS
${ }^{\boldsymbol{\Delta}}$ USP Tiamulin Related Compound $\mathrm{A} \mathrm{RS}_{\mathbf{\Delta U S P 2 8}}$
in Mobile phase to obtain a solution having known concentrations of about 0.08 mg of each per mL .

Standard preparation-Dissolve an accurately weighed quantity of USP Tiamulin Fumarate RS in Mobile phase to obtain a solution having a known concentration of about 4 mg per mL .

Assay preparation-Transfer about 200 mg , accurately weighed, to a 50 mL -volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $212-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at $30 \pm 3^{\circ}$. Chromatograph the Standard preparation and the System suitability solution, and record the peak responses as directed for Procedure: pleuremutilin
${ }^{\boldsymbol{\Delta}}$ the tiamulin related compound $\mathrm{A}_{\mathbf{\Delta U S P 2 8}}$
peak elutes prior to the tiamulin fumarate peak; the resolution, $R$, between pleuremutilin
$\boldsymbol{\Delta}_{\text {tiamulin related compound }} \mathrm{A}_{\mathbf{\Delta} U S P 28}$
and tiamulin fumarate is not less than 2.0 ; the capacity factor, $k^{\prime}$, determined from the tiamulin fumarate peak, is not less than 2.0 ; the column efficiency is not less than 14,000 ; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{28} \mathrm{H}_{47} \mathrm{NO}_{4} \mathrm{~S} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$ in the portion of Tiamulin Fumarate taken by the formula:

$$
50 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Tiamulin Fumarate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the tiamulin fumarate peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Timolol Maleate Tablets, USP 27 page 1851 —See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-16

## Change to read:

Dissolution Proedure for a Pooled Sample
$\Delta$
〈711 USP 28
Medium: 0.1 N hydrochloric acid; 500 mL .
Apparatus 1: 100 rpm .
Time: 20 minutes.
Procedure-
${ }^{\mathbf{\Delta}}$ Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution
Determine the amount of $\mathrm{C}_{13} \mathrm{H}_{24} \mathrm{~N}_{4} \mathrm{O}_{3} \mathrm{~S} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$ in solution in fit tered pertions of the solution under test,
${ }^{\boldsymbol{\Delta}}$ in the pooled sample $\quad$ USP28
in comparison with a Standard solution having a known concentration of USP Timolol Maleate RS in the same Medium, employing the procedure set forth in the Assay, making any necessary modifications.
Tolerances-Not less than $80 \%(Q)$ of the labeled amount of timolol maleate $\left(\mathrm{C}_{13} \mathrm{H}_{24} \mathrm{~N}_{4} \mathrm{O}_{3} \mathrm{~S} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right)$ is dissolved in 20 minutes:
${ }^{\Delta}$ the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |

## BRIEFING

Triprolidine and Pseudoephedrine Hydrochlorides Tablets, USP 27 page 1911-See briefing under Acetaminophen and Aspirin Tablets.
(BPC: M. Marques) RTS-40314-18

## Change to read:

Dissolution Preedure for a Porled Sample
©
$\langle 711\rangle$ USP28
Medium: water, 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Determine the amounts of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ and $\mathrm{C}_{19} \mathrm{H}_{22} \mathrm{~N}_{2} \cdot \mathrm{HCl} \cdot \mathrm{H}_{2} \mathrm{O}$ dissolved using the following method.

Mobile phase and Chromatographic system-Proceed as directed in the Assay under Triprolidine and Pseudoephedrine Hydrochlorides Syrup (Oral Solution, Official June 1, 2005).

- Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. $\begin{aligned} & \text { USP28 }\end{aligned}$
Procedure-Inject an accurately measured volume (about 200 $\mu \mathrm{L}$ ) of a filtered portion of the solution under test
${ }^{\Delta}$ the pooled sample ${ }_{\Delta U S P 28}$
into the chromatograph by means of a microsyringe or a sampling valve, record the chromatogram, and measure the responses for the major peaks. Calculate the quantities of pseudoephedrine hydrochloride $\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}\right)$ and triprolidine hydrochloride $\left(\mathrm{C}_{19} \mathrm{H}_{22} \mathrm{~N}_{2} \cdot \mathrm{HCl} \cdot \mathrm{H}_{2} \mathrm{O}\right)$ dissolved in comparison with a Standard solution having known concentrations of USP Pseudoephedrine Hydrochloride RS and USP Triprolidine Hydrochloride RS in the same Medium and similarly chromatographed.
Tolerances - Not less than $75 \%(Q)$ of the labeled amounts of $\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{NO} \cdot \mathrm{HCl}$ and $\mathrm{C}_{19} \mathrm{H}_{22} \mathrm{~N}_{2} \cdot \mathrm{HCl} \cdot \mathrm{H}_{2} \mathrm{O}$ is dissolved in 45 minutes:
the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredients specified, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
| Number |  |  |
| Stage | Tested | Acceptance Criteria |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less <br> than $Q+10 \%$. |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is <br> equal to or greater than $Q+5 \%$. <br> $\mathrm{S}_{3}$ |
| 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\left.\mathrm{S}_{3}\right)$ is equal to or greater than $Q$. |  |

## BRIEFING

Vancomycin Hydrochloride for Oral Solution, USP 27 page 1932-See briefing under Neomycin Sulfate Oral Solution.
(PA7: W. Wright) RTS-40665-3

## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle$ FOR POWDER PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements. $\triangle U S P 28$

## Add the following:

${ }^{\Delta}$ Deliverable volume $\langle 698\rangle$ -
FOR POWDER PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements. $\triangle U S P 28$

## Briefing

Vecuronium Bromide, page 1886 of $P F 28$ (6) [Nov.-Dec. 2002]. It is proposed to include a HPLC method in the test for Related compounds instead of TLC. This method was validated using a Altima C18 brand of L1 column. In a typical chromatogram, the vecuronium bromide peak appears at about 18 minutes. The name of vecuronium bromide related compound D has been modified for this proposal, and the water content has been updated to accommodate approved products.
(PA3: S. Salado) RTS-39775-1

## Add the following:

## © Vecuronium Bromide


$\mathrm{C}_{34} \mathrm{H}_{57} \mathrm{BrN}_{2} \mathrm{O}_{4} \quad 637.75637 .73$
Piperidinium, $1-[(2 \beta, 3 \alpha, 5 \alpha, 16 \beta, 17 \beta)-3,17$-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide. 1 -(3 $\alpha, 17 \beta$-Dihydroxy- $2 \beta$-piperidino- $5 \alpha$-androstan- $16 \beta, 5 \alpha$ -yl)-1-methylpiperidinium bromide, diacetate [50700-72-6].
» Vecuronium Bromide contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{34} \mathrm{H}_{57} \mathrm{BrN}_{2} \mathrm{O}_{4}$, calculated on the dried basis.

Packaging and storage-Preserve in tight containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Endotoxin RS. USP Pancuronium Bromide RS. USP Vecuronium Bromide RS. USP Vecuronium Bromide Related Compound A RS. USP Vecuronium Bromide Related Compound B RS. USP Vecuronium Bromide Related Compound C RS. USP Vecuronium Bromide Related Compound $\boxminus F$ RS. USP Vemin Bro mide Related Compound ERS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.
Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $-16^{\circ}$ and $-20^{\circ}$, at $20^{\circ}$.
Test solution: 10 mg per mL , in dehydrated alcohol.
Bacterial endotoxins $\langle 85\rangle$ : not more than 10 USP Endotoxin Units per mg of vecuronium bromide.

Loss on drying $\langle 731\rangle$ - Dry it $80^{\circ}$ for 2 hours to constant weight: it loses net mere than $2.0 \%$ of its weight. Dry it at $105^{\circ}$ for two hours: it loses not more than $2.0 \% 2.5 \%$ of its weight.

## Related compounds-

Solution A, Solution B, Mobile phase, and Diltuent Preeeed as directed in the Assety.

System suitability solution Dissolve aceurately weighed quantities of USP Vecurenium Bromide RS andUSP Veeurenium Bromide Related Compeund $A$ RS in Diltent to-obfain a solution having known concentrations of about 0.5 mgs per mL and 0.4 mg per mL , respectively.

Festsoltion Dissolvean aceurately weighedquantity of Vecurenium Bremide in Diltent to obtain a solution having a concentration of about 4 mg per mL .

Ghromatographic system Prepare as directed in the As say. Chromatograph the System suitability solution, andreeord the peak respenses as directed for Proedtre: the relative retention times are about 0.85 for vecurenium bremide related compeund $\Lambda$ and 1.0 for vecurenium bremide; the resolution, $R$, between vecurenium bromide and veeurenium bremide related compound $A$ is not less than 5.0 ; the eolumn efficiency is not less than 5000 theoretical plates; the tailing factors for vecurenium bromide and vecuronium bromide related compeund $A$ are net more than 2.0 ; and the relative standard deviation for replicate injections is not mere than $2.0 \%$

Proedure Inject a volume (about $20 \mu \mathrm{LL}$ ) of the Test solution inte the chremategraph, record the chrematogram, and measure the peak respenses. Calculate the percentage of any impurity in the pertion of Vecurenium Bromide taken by the formula:

$$
100\left(r_{i} \not r_{s}\right)
$$

in which $r_{i}$ is the peak respense for each individual impurity, and $r_{s}$ is the sum of the responses of all the peaks: not more than 2\% of total impurities is found.

TEST 1-
Dragendorff's reagent Mix 850 mg of bismuth subnitrate with 40 mL of water and 10 mL of glacial acetic acid (Solution 4). Dissolve-8 g of petassitum iodide in 20 mL of water (Solution B). Mix Solution $A$ and Solution B. Dilute 1.0 mL of the solution so-obtained with 10 mL of $50 \%$ (v) *) glacial acetic acid solution.
$5 \%$ Hydrogen peroxide solution Dilute about 16.6 mL of $30 \%$ hydregen peroxide with water to 100 mL .

Sodium iodide solution Dissolve 1.5 g of sodiumiodide in 50 mL of acetone.

Piltent Preparea mixture of acetonitrile and chloroform $(9: 1)$.
Adsorbent: 0.1 mm layer of chromatographic 5 Hm-silica gel mixture (see-Chrematography $\langle 621\rangle$ ).

Fest solution Transfer about 50 mg of Vecurenitum Bremide, aceurately weighed, to a $5-\mathrm{mL}$ volumetric flack. Dis solve in and dilute with Diltent to volume, and mix.

Standard solution 1 Dissolve-an aceurately weighed pertion of USP Vecurenium Bromide RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a-solution having a known concentration of 10 He per mL.

Standard solution 2 Dissolve aceurately weighed portions of USP Vecurenium Bromide Related Compound D A RS, USP Veeurenitm Bremide-Related-Compound B RS, USP Vecurenium Bromide Related Compeund E D RS, and USP Paneurenium Bromide RS in Diluent, and dilete quantitatively, and stepwise if necessary, with Diltent to obtain a solution having known concentrations of about $20 \mu \mathrm{~g}$ per $\mathrm{mL}, 20 \mu \mathrm{~g}$ per $\mathrm{mL}, 20 \mu \mathrm{~g}$ per mL , and $10 \mu \mathrm{~g}$ per mL , respectively.

Application volume: 10 mL .
Developing solvent syistem: a mixture of Sodiun iodide seltition, acetone, and methyl ethyl ketone (5:5:1).

Procedure Proced as directed for Thin Layer Chromatography under Chromatography- $\langle 621$ ). Dry the plate for 2 minutes in acurrent of cold air, and spray it with $5 \%$ Hydrogen peroxide solution. Dry it in a current of air and then spray with Dragendorff's reagent. Repent the procedure beginning with "spray it with $5 \%$ Hydrogen peroxide solttion": the spetcorrespending to the prineipalspet ebtained from Standard solution 1 is visible; the $R_{F}$ values of analytes are as follows:

| Analyte | $\mathrm{R}_{\text {F }}$ |
| :---: | :---: |
| pancuronium bremide | about 0.25 |
| vecuronium bromide | about 0.50 |
| vecuronium bromide related |  |
| empernd D-A | about 0.70 |
| vecurenitum bremide related |  |
| compound B- | about 0.60 |
| veeuronium bromide related |  |
| eompound ED | about 0.85 |

Any spet in the chromategram obtained frem the Test solut fion, except for the principal spet, is net more intense that the correspending spet in the chromategram obtained from Standard solution 2: not more than-0.2\% each of vecurenium bremide related compeund $D \Lambda$, vecurenium bremide related compernd $B$, and vecuronium bremide related com peund E $D$ is found; and net more than $0.1 \%$ of paneurenium bromide is found. Any unknown spet obtained in the chromatogram of the Test solution is not more-intense than the principal spet in the chromategram obtained from the Standard solution 1 : net mere than $0.1 \%$ of any indivi dual unknown impurity is found.

## TEST $2-$

Pragendorff's reagent, Diltent, Test solution, and 5\%
Hydrogen peroxide solttion- Proced as directed in Test 1. Sodium iodide solution 1- Dissolve 1.5 g of sodium io dide in 95 mL of iseprepyl aleohel.

Sodium iodide solution 2 Proceed as directed for Sodium iodide solution in Test 1.

Adsorbent: 0.1 mm layer of ehrematographic 5 - mm silica gel mixture (see Chromatography $\langle 621\rangle$ ).

Standard solution Dissolve an aceurately weighed por tion of USP Vecurenitm Bremide RelatedCompeundC RS in Diluent to obtain a solution having a known concentration of 20 mg per mL .

Application volume: $10 \mu \mathrm{HL}$.
Peveloping solvent system 1: a mixture of Sodiun iodide solution 1 and water (95:5).

Developing solvent system 2: a mixture of Sodium iodide solution 2, aeetone, and methyl ethyl ketone ( $5: 5: 1$ ).

Procedtre Apply the Test soltution on the rightcorner of the plate at 1.5 cm frem each side. Intreduce the plate inte the unsaturated developing chamber containing Developing solvent systen 1. Cover, and maintain the system until the solvent fremt has moved to a point about 10 cm above the initial applieation. Dry the plate in acurrent of cold air untit the isepropyl alcohol odor disappears. Retate the plate $90^{\circ}$, eensidering the-side of the previous deposition of the Test solution as base. Apply the Standtrd solution at 1.5 cm frem the base and at not less than 1.5 cm from the line to which the solvent front has moved previously. Introduce the plate inte the saturated developing chamber containing Developing solvent system 2. Cover, and maintain the system until the solvent ascends to a peint about 8 cm above the initiat spets. Dry the plate for 2 minutes in acurrent of cold air, and spray it with $5 \%$ Hydrogen peroxide solution. Dry it in a eurrent of cold air, and then spray with Dragendorff's reagent. Repeat the procedure, starting from'"spray it with 5\% Hydrogen peroxide solution", the spot correspending to the prineipal spet obtained from the-Standard solution is visible. Any spet in the chromatogram obtained from the Test solution is not more intense than the respective spet in the-chremategram obtained from the Standerd solution:
net more than $0.2 \%$ of vecurenitum bremide related compound $C$ is found; and not mere than $1.0 \%$ of totalimpurities is found, the results of Test 1 and Test 2 being added.

Cation suppressor regeneration solution: 0.02 M tetrabutylammonium hydroxide.

Mobile phase-Mix 1500 mL of water, 250 mL of methanol, 45 mL of tetrahydrofuran, and 1 mL of hydrochloric acid in a $2000-\mathrm{mL}$ volumetric flask. Leave at room temperature for few minutes, and dilute with water to volume. Mix, filter, and degas. [NOTE-Avoid evaporation of tetrahydrofuran during degassing.]

Standard solution-Dissolve an accurately weighed quantity of USP Vecuronium Bromide RS, USP Pancuronium Bromide RS, USP Vecuronium Bromide Related Compound A RS, USP Vecuronium Bromide Related Compound B RS, USP Vecuronium Bromide Related Compound C RS, and USP Vecuronium Bromide Related Compound F RS in 0.0025 N hydrochloric acid, and dilute quantitatively and stepwise if necessary, to obtain a solution having a known concentration of about $5 \mu \mathrm{~g}$ of each compound per mL .

Test solution-Transfer about 25 mg of Vecuronium Bromide, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with 0.0025 N hydrochloric acid to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid ion chromatograph is equipped with a conductivity detector, a $4-\mathrm{mm}$ cation suppressor and a $4.6-\mathrm{mm} \times 25-$ cm column that contains packing L1. The flow rate is about 1.5 mL per minute. The flow rate for the cation suppressor is about 2 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are given in Table 1; the ratio of the height of the vecuronium bromide related compound A peak to the height of the valley between the vecur-
onium bromide related compound A peak and the pancuronium bromide peak is not less than 2.0 ; and the relative standard deviation for replicate injections is not more than $10.0 \%$ for each compound.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each vecuronium bromide related compound in the portion of Vecuronium Bromide taken by the formula:

$$
2.5(C / W)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL of the relevant USP Reference Standard in the Standard solution; $W$ is the weight, in mg , of Vecuronium Bromide taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak areas for the correspondent vecuronium bromide related compound obtained from the Test solution and Standard solution, respectively: the limits of impurities are specified in Table 1. [NOTE-Use the peak area of vecuronium bromide in the Standard solution as $r_{S}$ to calculate any unknown impurity.]

|  | Relative |  |
| :--- | :---: | :---: |
| Compound <br> Name | Retention <br> Time | Limit <br> $\%$ |
| Pancuronium bromide | about 0.5 | 0.5 |
| Vecuronium bromide related | about 0.6 | 0.5 |
| compound F |  |  |
| Vecuronium bromide related <br> compound C | about 0.86 | 0.5 |
| Vecuronium bromide <br> Vecuronium bromide related <br> compound A | about 2.0 | 0.3 |
| Vecuronium bromide related | about 2.6 | 0.5 |
| compound B |  |  |


|  |  |  |
| :--- | :---: | :---: |
|  |  | Relative |
|  | Compound | Retention |
|  | Limit |  |
|  | Name | Time |

## Assay-

Solution A-Transfer 8.0 g of sodium perchlorate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in 6.0 mL of water, dilute with acetonitrile to volume, and mix.

Solution B-Prepare a mixture of methanol and $25 \%$ ammonium hydroxide containing 0.03 M ammonium chloride (992:8).

Mobile phase-Prepare a filtered and degassed mixture of Solution $A$ and Solution B (3:2). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Diluent-Pipet 10.0 mL of 1 M hydrochloric acid into a $1000-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix.
Standard preparation-Dissolve an accurately weighed quantity of USP Vecuronium Bromide RS in Diluent to obtain a solution having a known concentration of about 0.5 mg per mL .
Assay preparation-Dissolve an accurately weighed quantity of Vecuronium Bromide in Diluent to obtain a solution having a concentration of about 0.5 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L3. The flow rate is about 0.5 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Standard preparation, and record the peak re-
sponses as directed for Procedure: the column efficiency is not less than 5000 theoretical plates; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{34} \mathrm{H}_{57} \mathrm{BrN}_{2} \mathrm{O}_{4}$ in the portion of Vecuronium Bromide taken by the formula:

$$
C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Vecuronium Bromide RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\Delta$ USP28

## DIETARY SUPPLEMENTSMONOGRAPHS

## Briefing

Chondroitin Sulfate Sodium, USP 27 page 1980 and page 1270 of $P F 29(4)$ [July-Aug. 2003]. It is proposed to modify the titration procedure in the test for Content of chondroitin sulfate sodium by dissolving the test specimens in a more concentrated buffer solution containing polysorbate 80. The introduction of a pH 7 phosphate buffer into the diluent at the final concentration of 5 mM results in improved method performance in the presence of pH modifying matrices. The addition of polysorbate 80 significantly improves the titration curve shape by preventing rapid curve falloff due to self-aggregation of the particles. Concentrations of the Standard solutions for the calibration curve were modified to fit nominal volumes of standard volumetric equipment usually available in analytical laboratories. In protein determination, Folin-Ciocalteu phenol TS must be further diluted before use. In response to suggestions received from interested parties that the requirement for the demonstration of the absence of Clostridium spp. be deleted, the USP Analytical Microbiology Expert Committee determined that because there is no potential risk to the consumer from Clostridium in the use of the substance, except for infants, there is no need to test for this organism. The Expert Committee decided to concur with the proposed deletion of this test. A new procedure for the test for Electrophoretic purity is proposed to re-
place the current procedure using nitrocellulose membranes. This revision is based on the difficulties of handling nitrocellulose membranes and the fact that they become overloaded with the $10-\mu \mathrm{L}$ application volume making it difficult to detect glycosaminoglycans (GAGs) impurities with mobilities close to that of the chondroitin sulfate anion. Cellulose acetate membranes are easier to handle, and they do not require a cooling plate. Comments regarding these proposed monograph revisions are invited and should be submitted by February 29, 2004.
(DSB: G. Giancaspro; AMB: D. Porter) RTS—40235-1; 39812-1; 39888-2

Change to read:

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$. Pred in the ehapter, except to record the spectrum from 3800 to $1000 \mathrm{em}^{+}$-
$\square_{\text {■1S (USP27) }}$
B: AS ASP27) requirements of the test for Sodium $\langle 191\rangle$.

## Delete the following:

${ }^{\Delta}$ Test for absence of clostridiun-species-
Fest Preparation Provide separate-10-s specimens for each of the tests called for below. Dissolve Chendreitin Sulfate-Sodium in pH 7.2 Phosphate buffer. [NOTE-On the basis of results for Pre paraty Testing, modify the Test Preparan as appropriate.]

Preparatory. Testing Ineubate Clostridium sporeggenes (ATCG No. 11437) for 18 to 24 hours, and then dilute with pH 7.2 Phos phate Buffer. Inoeulate the Test Preparation, to obtain a final coneentration of less than 100 -fu per mL . Controls containing the inoculum but without the material under test are prepared at the same time. Proce as directed under Proedure, making sure-to evaluat the growth after each time a medium is added.

Results Preeed as direeted for Preparatery Testing under Miembial Limil Tests Dietty Supplements $\langle 2024\rangle$ -

REINFORCED-MEDHM FOR-CLOSTRIDIA

| Beef Extract . . . ........................ | 10.0-8 |
| :---: | :---: |
| Peptone . . . . . . . . . . . . . . . . . . . . | $10.0{ }^{\text {\% }}$ |
| Yeast Extraet | 3.0 年 |
| Soluble Starch | 1.0-8 |
| Glueese Menehydrate. | 5.0-8 |
| Eysteine Hydrechleride-. | - 5-9 |
| Sodium Chloride | 5.0-8 |
| Sodium-Acetate | 3.0 \% |
| Agear .......................................... | $0.5-\frac{8}{8}$ |
| Water | 1000 mL |

Pissolve agar in water by heating to beiling, while stirring eon tinmeusly. Adjust the pH if neessary, and sterilize.
pH after sterilization: $6.8 \pm 0.2$.

GOLUMBIA AGAR

| Pancreatic Digest of Casein. | 10.0 - |
| :---: | :---: |
| Ment Peptic digest ................. | $5.0-\frac{8}{8}$ |
| Heart Pancreatic digest ................ | 3.0-8 |
| Yeast Extract | $5.0-8$ |
| Gorn Stareh | 1.0-8 |
| Sodium Chloride | 5.0 g |
| Agrar | 15.0-8 |
| Water | 000 mb |

Dissolve agar in water by heating to beiling with continuous stir ring. If necessary, adjust the pH . Sterilize, and allow to cool to $-45^{\circ}$ to $50^{\circ}$. Add gentamicin culfate, equivalent to about 20 mg of gen tamiein base, and pour into Petri dishes.
pH-after sterilization: $7.3 \pm 0.2$.
Preedure Tak equal portions of the Test Preparation, heat one $10-80^{\circ}$ for 10 minutes, and cool rapidly. Transfer 10 mL of each pertion to separate containers, each containing each 100 mL of Reinforced Medium for Clostridia, and incubate under anaerebic conditions at $35^{\circ}$ to $37^{\circ}$ for 48 hours. After ineubation subeulture each specimen on Columbia-Agat Medium to which gentamiein has been added, and ineubate under anaerobic eonditions at $35^{\circ}$ to $37^{\circ}$ for 48 hours. Examine the plates, and interpret as follows: if no growth of Gram peritive rods is detected, the test specimen meets the requirement for the absence of Clostridium species.

If growth-oeeurs, subeulture each distinct colony on Columbia Agat Mediun, and separately incubate in aerobic and in anaerebic eenditions at $35^{\circ}$ to $37^{\circ}$ for 48 hours. The ocurrence of only anaerobic growth of Gram pesitive bacilli, giving a negative catalase reaction, indieates the presence of Clostridiun sporogenes species. To perform the catalase test, transfer discretecolonies to glass slides, and apply a drop of dilute hydrogen peroxide solution: the reaction is negative if no gas bubbles evolve. If the test spect menexhibits none of the characteristies, it meets the requirement for the absence of Clestriditan -species. $\triangle$ USP28

## Change to read:

Residue on ignition $\langle 281\rangle$ : between $20.0 \%$ and $30.0 \%$, on the dried basis. emitting the addition of sulfuric acid.
$\boldsymbol{■}_{\text {■ }}$ (USP27)

## Change to read:

Electrophoretic purity (see Electrophoresis $\langle 726\rangle$ )+M
© $0.1 M_{\Delta U S P 28}$
Barium acetate buffer, pH 5.0-Dissolve about $225.43-\mathrm{f}$
${ }^{\Delta} 25.24 \mathrm{~g}_{\mathbf{\Delta S P} \text { U } 28}$
of barium acetate in water, and dilute with water to 900 mL . Adjust with acetic acid to a pH of 5.0 , dilute with water to 1 L , and mix. Q. 4 M Bariun beffer, pH 5.0. Dissolve about 90.17 ge of barium acetate in water, and dilute with water to 900 mL . Adjust with acetic acid to a pHof 5.0 , dillute with water to 1 liter, and mix.

- $\Delta U S P 28$

Staining reagent: 0.08\% azure A selution.
${ }^{\Delta} 0.1 \%$ toluidine blue in acetic acid; dissolve 1 g of toluidine
blue in 1000 mL of 0.1 M acetic acid. USPP28 $^{2}$
Standard solution 1-Prepare a solution of USP Chondroitin Sulfate Sodium RS in water having a known concentration of about 3 -ms per mb.
${ }^{\Delta} 30 \mathrm{mg}$ per mL. $\mathbf{\Delta U S P 2 8}$
Standard solution 2-Dilute 1 mL of Standard solution 1 with water to 100 mL ,
${ }^{\Delta} 50 \mathrm{~mL}, \mathbf{\Delta U S P 2 8}$
and mix.
Standard solution 3- Prepare a solution containing 1.0 g of phenol red TS in 100 mL water.
${ }^{\Delta} \triangle U S P 28$
Test solution-Transfer 150 mg of Chondroitin Sulfate Sodium, accurately weighed, to a 50 mE
${ }^{\Delta} 5.0-\mathrm{mL}_{\mathbf{\Delta} U S P 28}$
volumetric flask, dissolve in and dilute with water to volume, and mix.

Procedure-Adhere a cellophane sheet to the top of a cooling plate of the electropheretic equipment by means of some water drops. Remove any air bubbles. Soak acut $6 \times 12 \mathrm{~cm}$ cellulese nitrate gel having a $0.45 \mu \mathrm{~m}$ porosity in 0.4 M Barium acte buf fer, pH 5.0 for 5 minutes, and remove any exeess solution between the filter paper and the cellulese-strip. Apply $10 \mu \mathrm{~L}$ each of Stan dard solution 1, Standard solution 2, Standard solution 3, and the Fest solution as bands to the gel near the eathede. [NOTE Back the eellophane sheet with a plastic shee for protection to prevent the gel from breaking; otherwise use a supported nitrocellulose membrane, and place it on top of the ellophane sheet.] Attach the strip to the suppert bridge of an electrophoresis chamber containing 1 M Bariun acte buffer, pH 5.0 in each side of the chamber. Ensure that each end of the strip is in contact with 1 M Bariun acetate buffer, $\mathrm{p} H$-5.0. Connect the electrodes, clese the cover, start the water cireulation for gel cooling until the temperature of the plate is about $10^{\circ}$, and apply a 20 mA eurrent ab abeut 330 V for 1 hour. Switch off the current, diseonnect the electrodes, remove the plastic sheet, and immerse the gel in the Staining reagent for 10 min utes. Wash with water to remove any unbound Staining reagent, and compare the bands: the electropherogram obtained from the Test solution exhibits a major band that is similar in position to the band obtained from. Standard solution 1. The band obtained from Standard solution 3 remains red ( $\mathrm{p} H$ buffering apacity), and the band correspending to Stand solution 2 is clearly visible at a mobility similarto the band obtained frem Standerd solution 1. Any seendary band in the electropherogram of the Test solution is not more intense than the band obtained frem Standard solution -2. Net more than $1 \%$ of any individual impurity is found.
${ }^{\Delta}$ Fill the chambers of an electrophoresis apparatus suitable for separations on cellulose acetate membranes ${ }^{1}$ (a small submarine gel chamber or one dedicated to membrane media) with 0.1 M Barium acetate buffer, pH 5.0. Soak a cellulose acetate membrane about 5 to $6 \mathrm{~cm} \times 12$ to 14 cm in 0.1 M Barium acetate buffer, pH 5.0 for 10 minutes, or until evenly wetted, then blot dry between two sheets of absorbent paper. Using an applicator ${ }^{2}$ suitable for electrophoresis, apply equal volumes (about $0.5 \mu \mathrm{~L}$ ) of the Test solution, Standard solution 1, and Standard solution 2 to the brighter side of the membrane held in position in an appropriate applicator stand or on a separating bridge in the chamber. Ensure that both ends of the membrane are dipped in at least 0.5 - to $1.0-\mathrm{cm}$ deep into the buffer chambers. Apply a constant 60 volts (about 6 mA at the start) for 2 hours. [NOTE-

[^12]Perform the application of solutions and voltage within 5 minutes because further drying of the blotted paper reduces sensitivity.] Place the membrane in a plastic staining tray, and with the application side down, float or gently immerse in Staining reagent for 5 minutes. Then stir the solution gently for 1 minute. Remove the membrane, and destain in $5 \%$ acetic acid until the background clears. Compare the bands. The electropherogram obtained from the Test solution exhibits a major band that is identical in position to the band obtained from Standard solution 1. The band obtained from Standard solution 2 is clearly visible at a mobility similar to the band obtained from Standard solution 1. Any secondary band in the electropherogram of the Test solution is not more intense than the band obtained from Standard solution 2. Not more than $2 \%$ of any individual impurity is found. Document the results by taking a picture within 15 minutes of completion of destaining. $\Delta$ USP28

## Change to read:

## Limit of protein-

Alkaline cupric tartaric reagent-Dissolve 200 mg of sodium tartrate dihydrate in 10 mL of water, and mark as Solution A. Dissolve 100 mg of cupric sulfate in 10 mL of water, and mark as Solution B. Dissolve 2.0 g of anhydrous sodium carbonate in 0.1 M sodium hydroxide, dilute with 0.1 M sodium hydroxide to 100 mL , and mark as Solution C. Mix well 1 mL of Solution $A$ and 1 mL of Solution B, and to the mixture slowly add 100 mL of Solution $C$ with stirring. Use within 24 hours, and discard afterwards. USSP $_{27}$
Standard solution-Transfer an accurately measured volume of 7 percent bovine serum albumin certified standard to a suitable container, and dilute quantitatively and stepwise with water to obtain a solution having a known concentration of about $35 \mu \mathrm{~g}$ per mL .
Test solution-Transfer an accurately weighed amount of Chondroitin Sulfate Sodium, equivalent to 60 mg of the dried substance, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix.
Procedure—Add 2.0 mL of freshly prepared ${ }^{\mathbf{A}}$ Alkaline cupric tartaric reagent ${ }_{\text {USP } 27}$ to test tubes containing 2.0 mL of water, 2.0 mL of the Test solution, or 2.0 mL of the Standard solution, and mix. After about 10 minutes, add 1.0 mL of Folin-Ciocalteu phenol TS,
$\Delta_{\text {diluted with water (1:5) and }}^{\mathbf{\Delta U S P 2 8}}$
prepared immediately before use, to each test tube, and mix
$\Delta_{\text {immediately }}$ and vigorously. AUSP28 $^{\text {and }}$
After 30 minutes, measure the absorbance of each solution at 750 nm against the blank. The absorbance of the Test solution is not greater than the absorbance of the Standard solution: not more than $6.0 \%$ of proteins is found, calculated on the dried basis.

## Change to read:

Content of ${ }^{\mathbf{A}}$ chondroitin sulfate sodium-_USP27
Cetylpyridinium chloride solution-Prepare a solution of cetylpyridinium chloride in water having a concentration of about 1 mg per mL .
${ }^{\Delta}$ Degas before use.
Diluent-Weigh about 297 mg of monobasic potassium phosphate, 492 mg of dibasic potassium phosphate, and 250 mg of polysorbate 80 , and transfer into a $1-\mathrm{L}$ beaker.

Dissolve in 1000 mL of water, and adjust with potassium
hydroxide or phosphoric acid to a pH of $7.0 \pm 0.2$. USP 28 .
Standard solutions - Transfer abou 30 mg of USP Chendroitin Sulfate-Sodium RS, aceurately weighed, to a 25 mL volumetrie flask. Dissolve in 6 mL of water, add 1 mL of pH 7.2 phesphate buffer solution (see Buffer Solutions under Solutions in the section Reagents, Indicators, and Solutions),
${ }^{\Delta}$ Prepare a solution having a known concentration of USP
Chondroitin Sulfate Sodium RS in water, $\triangle U S P 28$
and dilute with water, quantitatively and stepwise if necessary, to obtain three Standard solutions having known concentrations of about 1.2 mg per $\mathrm{mL}, 0.8 \mathrm{mg}$ per mL , and 0.4 mg per mL , respec tively.
${ }^{\star} 1.5 \mathrm{mg}$ per $\mathrm{mL}, 1.0 \mathrm{mg}$ per mL , and 0.5 mg per mL , respectively. $\triangle U S P 28$

Test solution-Transfer about 100 mg of dried Chondroitin Sulfate Sodium, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in 30 mL of water, add 5 mL of pH 7.2 phosphate buffer solution (see Buffer Solutions under Solutions in the-section Reagents, Indieators, and Solutions),
© $U S P 28$
dilute with water to volume, and mix.
Procedure-Transfer 5.0 mL of each Standard solution and the Test solution to four separate titration vessels, and 30 mL of water. Stir until a steady reading is obtained using a photetrode to determine the endpeint furbidimetrieally, either at $420 \mathrm{~nm}, 550$ mm , of 660 nm . Set the instrument to zero if absorbance is being menitered or not less than $70 \%$ if transmittance is used. Titrate with Cetylpyridinitum ehloride solution. Frem a linear regression equation caleulatedusing the volumes of Cetylpymidinitu chloride solution consumed, and the mass, in mg, of USP Chondroitin Sut fate Sodium RS,
© and add about 25 mL of Diluent. Use a phototrode to determine the endpoint turbidimetrically, either at $420 \mathrm{~nm}, 550$ nm , or 660 nm . Stir until a steady reading is obtained. Set the instrument to zero in absorbance mode. Titrate with Ce tylpyridinium chloride solution. From a linear regression equation derived from the volumes of Cetylpyridinium chloride solution consumed, and the masses, in mg, of USP Chondroitin Sulfate Sodium RS in the aliquots of the respective Standard solutions, $\mathbf{\Delta}$ USP28
determine the mass of ${ }^{\mathbf{\Delta}} \mathbf{\Delta U S P 2 7}$ chondroitin sulfate sodium in the aliquot of the Test solution taken. Calculate the percentage of $\boldsymbol{\Delta}_{\Delta U S 27}$ chondroitin sulfate sodium in the portion ${ }_{\Delta} \mathbf{\Delta S S P 2 7}$ taken by the formula:

2000 (M/W),
in which $M$ is the mass of ${ }^{\boldsymbol{\Delta}}$ Chondroitin Sulfate Sodium $\mathbf{\Delta U S P 2 7 ~}$
${ }^{\Delta}$ found ${ }_{A U S P 28}$
in the aliquot of the Test solution; and $W$ is the weight, in mg , of Chondroitin Sulfate Sodium taken to prepare the Test solution.

## BRIEFING

Chondroitin Sulfate Sodium Tablets, USP 27 page 1982 and the Fifth Interim Revision Announcement on page 1398 of PF 29(5) [Sept.-Oct. 2003]-See briefing under Chondroitin Sulfate Sodium.
(DSB: G. Giancaspro) RTS-40251-2

## Change to read:

Identification-
f M
${ }^{\triangle} 0.1 M_{\Delta U S P 28}$
Barium acetate buffer, pH 5.0; 9.4 M Barinm bute buffer, pH 5.0;
${ }^{\wedge} \mathbf{\Delta U S P 2 8}$
Staining reagent; and Procedure—Proceed as directed in Electrophoretic purity under Chondroitin Sulfate Sodium.

Standard solution-Use the Standard solution of middle concentration in the test for Content of chondroitin sulfate sodium.

Test solution-Prepare as directed in the test for Content of chondroitin sulfate sodium. The principal spot obtained from the Test solution has the same migration as the principal spot obtained from the Standard solution.

## Change to read:

Disintegration and dissolution $\langle 2040\rangle$ : meet the requirements for Dissolution.

Medium: water; 900 mL .
Apparatus 2: 75 rpm .
Time: 60 minutes.
Cetylpyridinium chloride solution, stan,
${ }^{4}$ Standard solutions, $\mathbf{\Delta U S P 2 8}$
and Test solution-Prepare as directed in the test for Content of chondroitin sulfate sodium
^under Chondroitin Sulfate Sodium. $\mathbf{\Delta S P 2 8}$
Procedure-Proceed as directed in the test for Content of chondroitin sulfate sodium, adjusting the volume of the aliquot
$\boldsymbol{\Delta}^{\boldsymbol{a}}$ and the concentrations of the Standard solutions, $\mathbf{\Delta S P 2 8}$
if necessary. Calculate the quantity, in mg , of chondroitin sulfate sodium dissolved in the pertion of Tablets taken
A $U$ USP28
by the formula:

## $900 C$,

in which $C$ is the concentration, in mg per mL , of chondroitin sulfate sodium in the solution under test.

Tolerances-Not less than $75 \%$ of the labeled amount of chondroitin sulfate sodium is dissolved in 60 minutes.

## Change to read:

## Content of chondroitin sulfate sodium-

Cetylpyridinium chloride solution-Prepare a solution of cetylpyridinium chloride in water having a concentration of about 1 mg per mL.
${ }^{\Delta}$ Diluent-Weigh about 297 mg of monobasic potassium phosphate, 492 mg of dibasic potassium phosphate, and 250 mg of polysorbate 80 , and transfer into a $1-\mathrm{L}$ beaker. Dissolve in approximately 900 mL of water, and adjust with potassium hydroxide or phosphoric acid to a pH of $7.0 \pm 0.2$.

Dilute with water to 1 L , and mix thoroughly. $\triangle$ USP28
Standard solutions-Prepare as directed in the test for Content of
$\boldsymbol{\Delta}_{\text {chondroitin sulfate sodium }}^{\mathbf{\Delta U S P 2 7}}$ under Chondroitin Sulfate Sodium.

Test solution-Weigh and finely powder not fewer than $20 \mathrm{Tab}-$ lets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of chondroitin sulfate sodium, to a $100-\mathrm{mL}$ volumetric flask, add 30 mL of water and 5 mL of pH 7.2 phes phate buffer selution (see Buffer Solutions under Solutions in the section Reagents, Indientors, and Solutions),

## $\triangle 60 \mathrm{~mL}$ of water, ${ }_{\mathbf{\Delta U S P 2 8}}$

and shake to suspend the powder in solution. Sonicate in a $65^{\circ}$ water bath for 20 minutes. Remove from the bath, stir with a mag netic stirrer
$\Delta^{\text {or shake }}{ }_{\mathbf{A S P 2 8}}$
for 5 minutes, dilute with water to volume, and centrifuge
$\Delta_{\text {or filter through a suitable filter. }}$ USP28
Procedure-Separately transfer 5.0 mL of each Standard solution and the Test solution to separate titration vessels, and add about 30 mL of water
$\Delta_{25} \mathrm{~mL}$ of Diluent $\mathbf{\Delta U S P 2 8}$
to each. Stir until a steady reading is obtained using a phototrode to determine the endpoint turbidimetrically, either at 420,550 , or 660 nm . Set the instrument to zero if
$\Delta_{\text {in }}^{\Delta U S P 28}$
absorbance is being menitered or to net less than 70\% if transmit tanee is used.
${ }^{\Delta}$ mode. ${ }^{\text {USPP28 }}$
From a linear regression equation calculated using the volumes of Cetylpyridinium chloride solution consumed, and the mass, in mg, of USP Chondroitin Sulfate Sodium RS, determine the mass of chondroitin sulfate sodium in the aliquot of the Test solution taken. Calculate the amount, in mg , of chondroitin sulfate sodium in the portion of Tablets taken by the formula:
$20 M$,
in which $M$ is the mass of Chondroitin Sulfate Sodium in the aliquot of the Test solution.

## BRIEFING

Glucosamine and Chondroitin Sulfate Sodium Tablets, USP 27 page 2012 and the Fifth Interim Revision Announcement on page 1395 of $P F$ 29(5) [Sept.-Oct. 2003]-See briefing under Chondroitin Sulfate Sodium.
(DSB: G. Giancaspro) RTS-40251-1

## Change to read:

Disintegration and dissolution $\langle 2040\rangle$ : meet the requirements for Dissolution.

Medium: water; 900 mL .
Apparatus 2: 75 rpm .
Time: 60 minutes.
Determine the amount of glucosamine $\left(\mathrm{C}_{6} \mathrm{H}_{13} \mathrm{NO}_{5}\right)$ dissolved by employing the following method.

Diluent, 0.2 M Borate buffer, Derivatizing reagent, Mobile phase, and Chromatographic system-Proceed as directed in the test for Content of glucosamine.

Standard solution-Prepare as directed in the test for Content of glucosamine. Dilute with a suitable quantity of water, if necessary.

Test solution-Use the solution under test.
Procedure-Proceed as directed in the test for Content of glucosamine. Calculate the quantity, in mg, of glucosamine $\left(\mathrm{C}_{6} \mathrm{H}_{13} \mathrm{NO}_{5}\right)$ dissolved by the formula:

$$
(179.17 / 215.63)(900 C)\left(r_{U} / r_{S}\right)
$$

in which the terms are as defined therein.
Tolerances-Not less than $75 \%$ of the labeled amount of $\mathrm{C}_{6} \mathrm{H}_{13} \mathrm{NO}_{5}$ is dissolved in 60 minutes.

Determine the amount of chondroitin sulfate $\mathbf{s}_{\text {sodium }}^{\Delta U S P 27}{ }^{\text {dis- }}$ solved by employing the following method.

Cetylpyridinium chloride solution, Stent Test solution
${ }^{\star}$ Diluent, Standard solutions, and Test solution._USP28 —Prepare as directed in the test for Content of chondroitin sulfate sodium
©under Chondroitin Sulfate Sodium Tablets. ${ }^{\text {USSP28 }}$ Procedure-Proceed as directed in the test for Content of chondroitin sulfate sodium,
^under Chondroitin Sulfate Sodium Tablets. $\quad$ USP28 adjusting the volume of the sample,
$\boldsymbol{\Delta}^{\mathbf{a}}$ and/or the concentrations of the standards, $\boldsymbol{\Delta U S P 2 8}$ if necessary. Calculate the quantity, in mg , of chondroitin sulfate sodium dissolved by the formula:

$$
900 C
$$

in which $C$ is the concentration, in mg per mL, of chondroitin sulfate sodium in the solution under test.

Tolerances-Not less than $75 \%$ of the labeled amount of chondroitin sulfate sodium is dissolved in 60 minutes.

## Change to read:

Content of chondroitin sulfate sodium-
Cetylpyridinium chloride solution, St,
${ }^{\mathbf{\Delta}}$ Diluent, Standard solutions, $\mathbf{\Delta S P 2 8}$
Test solution, and Procedure-Proceed as directed in the test for Content of chondroitin sulfate sodium under Chondroitin Sulfate ${ }^{4}$ Sodium ${ }_{\mathbf{U S P} 27}$ Tablets.

## Briefing

Ubidecarenone Capsules, USP 27 page 2040. It is proposed to clarify the wording of Assay Preparation 1 in the Assay to indicate the solvent used in the dilution.
(DSN: L. Evans) RTS-40549-1

## Change to read:

Assay-[NOTE-Conduct this test promptly with minimum exposure to actinic light.]
Solvent-Prepare a mixture of dehydrated alcohol and n-hexane (2:5).

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile, tetrahydrofuran, and water (55:40:5). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Ubidecarenone RS in Solvent to obtain a solution having a known concentration of 1.0 mg per mL . Dilute a portion of this solution with dehydrated alcohol to obtain a solution having a known concentration of about $40 \mu \mathrm{~g}$ per mL .

Resolution solution-Dissolve an accurately weighed quantity of coenzyme $\mathrm{Q}_{9}$ in Solvent to obtain a solution having a concentration of 1.0 mg per mL . Dilute a portion of this solution with dehydrated alcohol to obtain a solution having a concentration of about $40 \mu \mathrm{~g}$ per mL . Mix equal volumes of this solution and the Standard preparation.

Assay preparation 1 (for soft gelatin Capsules)-Using a suitable cutting instrument, open an accurately counted number of Capsules, equivalent to about 200 mg of ubidecarenone. Quantitatively transfer the shells and contents to a suitable container, add 100 mL of Solvent, and shake by mechanical means for 30 minutes. Using small portions of Solvent, quantitatively transfer this mixture to a $200-\mathrm{mL}$ volumetric flask, dilute with Solvent to volume, and mix. Centrifuge a portion of this solution, transfer 1.0 mL of the supernatant to a $25-\mathrm{mL}$ volumetric flask, add 2.5 mL of a $0.1 \%$ solution of anhydrous ferric chloride in alcohol,
${ }^{\Delta}$ dilute with alcohol to volume, $\triangle U S P 28$ and mix.
Assay preparation 2 (for hard gelatin Capsules)-Empty and thoroughly mix the contents of not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of ubidecarenone, to a $100-\mathrm{mL}$ volumetric flask, add 60 mL of Solvent, and shake by mechanical means for $30 \mathrm{~min}-$ utes. Dilute with Solvent to volume, and mix. Centrifuge a portion of this solution, transfer 1.0 mL of the supernatant to a $25-\mathrm{mL}$ volumetric flask, add 2.5 mL of a $0.1 \%$ solution of anhydrous ferric chloride in alcohol, dilute with alcohol to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and an $8-\mathrm{mm} \times 10-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2.5 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between ubidecarenone and coenzyme $\mathrm{Q}_{9}$ is not less than 2.5. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $15 \mu \mathrm{~L}$ ) of the Standard preparation and Assay preparation 1 or Assay preparation 2 into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ubidecarenone $\left(\mathrm{C}_{59} \mathrm{H}_{90} \mathrm{O}_{4}\right)$ in each soft gelatin Capsule taken by the formula:

## $5000(C / N)\left(r_{U} / r_{S}\right)$,

in which $C$ is the concentration, in mg per mL , of USP Ubidecarenone RS in the Standard preparation; $N$ is the number of Capsules taken to prepare Assay preparation 1; and $r_{U}$ and $r_{S}$ are the peak responses obtained from Assay preparation 1 and the Standard preparation, respectively. Calculate the quantity, in mg , of ubidecarenone $\left(\mathrm{C}_{59} \mathrm{H}_{90} \mathrm{O}_{4}\right)$ in the portion of hard gelatin Capsules taken by the formula:

$$
2500 C\left(r_{U} / r_{S}\right)
$$

in which $r_{U}$ is the peak response obtained from Assay preparation 2 ; and the other terms are as defined herein.

## MONOGRAPHS (NF)

## BRIEFING

Alfadex, page 1092 of $P F$ 29(4) [July-Aug. 2003]. It is proposed to add requirements for combined molds and yeasts count to the test for Microbial limits.
(EMC: E. Gonikberg; AMB: D. Porter) RTS-40632-1

## Add the following:

## AAlfadex


$\left(\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{5}\right)_{6} \quad 972.85972 .84$
Alpha cyclodextrin [10016-20-3].
» Alfadex is composed of six alpha-(1-4) linked D-glucopyranosyl units. It contains not less than 98.0 percent and not more than 101.0 percent of $\left(\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{5}\right)_{6}$, calculated on the dried basis.

Packaging and storage-Preserve in tight containers. Store at to $25 \pm 2^{\circ}$. Avoideressive heat and freezing.

## Protect from moisture.

USP Reference standards $\langle 11\rangle$ —USP Alpha Cyclodextrin RS. USP Beta Cyclodextrin RS. USP Gamma Cyclodextrin $R S$.

Clarity of solution-Dissolve 1.0 g in 100.0 mL of previously boiled and cooled water: the resulting solution is clear.

## Identification-

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

B: It meets the requirements of the test for Specific rotation $\langle 781 \mathrm{~S}\rangle$.

C: Mix 0.2 g with 2 mL of iodine TS, warm in a water bath to dissolve the test specimen, and allow to stand at room temperature: a yellow-brown precipitate is formed.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $+147^{\circ}$ and $+152^{\circ}$ $\left(\mathrm{t}=20^{\circ}\right)$.

Test solution: 10 mg per mL , in water.
Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total aerobic bacterial count does not exceed 1000 cfu per g . The total combined molds and yeasts count does not exceed 100 cfu per g.
$\mathbf{p H}\langle 791\rangle$ - The pH of the mixture of 30 mL of its aqueous solution (1 in 100) and 1 mL of Potassium chloride solution is 5.0 to 8.0 .

Potassium chloride solution-Transfer 22.4 g of potassium chloride into a $100-\mathrm{mL}$ volumetric flask, and dilute with water to volume.

Loss on drying $\langle 731\rangle$ —Dry 1.0 g of it at $120^{\circ}$ for 2 hours: it loses not more than $10.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on 1.0 g .

Heavy metals, Method II $\langle 231\rangle: 10 \mu \mathrm{~g}$ per g.

## Reducing sugars-

Cupric solution-Dissolve 15 g of cupric sulfate in water to make 100 mL .

Tartrate solution-Dissolve 2.5 g of anhydrous sodium carbonate, 2.5 g of potassium sodium tartrate, 2.0 g of sodium bicarbonate, and 20 g of anhydrous sodium sulfate in water to make 100 mL .

Cupric-tartaric solution-Immediately before use, mix 1 part of Cupric solution with 25 parts of Tartrate solution.
Ammonium molybdate reagent-Mix 10 mL of a solution of disodium arsenate ( 6 in 100), 50 mL of a solution of ammonium molybdate ( 1 in 10), and 90 mL of diluted sulfuric acid, and dilute with water to 200 mL .

Test solution-Transfer about 1.0 g of Alfadex, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water that has been previously boiled and cooled to room temperature, to volume, and mix. To 1 mL of this solution add 1 mL of Cupric-tartaric solution. Heat on a water bath for 10 minutes, then cool to room temperature. Add 10 mL of Ammonium molybdate reagent, and allow to stand for 15 minutes.

Standard solution-Prepare at the same time and in the same manner as the Test solution, using 1 mL of a glucose solution that contains 20 mg in 1 liter.
Procedure-Concomitantly measure the absorbance of the Test solution and the Standard solution at the wavelength of maximum absorbance at 740 nm relative to that
of water, with a suitable spectrophotometer. The absorbance of the Test solution is not greater than that of the Standard solution ( $0.2 \%$ ).

## Related compounds-

System suitability solution-Prepare as directed for System suitability preparation in the Assay.
Standard solution-Transfer 5.0 mL of the System suitability solution into a $50-\mathrm{mL}$ volumetric flask, and dilute with water to volume.

Test solution-Use the Assay stock preparation prepared as directed in the Assay.

Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. For the Test solution, the areas of any peaks corresponding to beta cyclodextrin or to gamma cyclodextrin are not greater than half of the area of the corresponding peaks in the chromatogram of the Standard solution $(0.25 \%)$, and the sum of the areas of all the peaks, excluding the principal peak and the peaks corresponding to beta cyclodextrin or to gamma cyclodextrin, is not greater than half of the area of the peak corresponding to alpha cyclodextrin in the chromatogram of the Standard solution ( $0.5 \%$ ).

Light-absorbing impurities-
Test solution-Transfer about 1.0 g of Alfadex, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water, which has been previously boiled and cooled to room temperature, to volume, and mix.

Procedure-Determine the absorbance of the Test solution in a $1-\mathrm{cm}$ cell with a suitable spectrophotometer, after correcting for the blank: between 230 nm and 350 nm , the absorbance is not greater than 0.10 ; and between 350 nm and 750 nm , the absorbance is not greater than 0.05 .

Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of water and methanol (90:10, v/v). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Standard preparation-Transfer 25 mg of USP Alpha Cyclodextrin RS, accurately weighed, in $25-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with water to volume.
System suitability preparation-Transfer 25 mg of USP Beta Cyclodextrin RS, 25 mg of USP Gamma Cyclodextrin RS, and 50 mg of USP Alpha Cyclodextrin RS, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water, and mix.

Assay stock preparation-Dissolve 250 mg of Alfadex, accurately weighed, in water with the aid of heat. Cool, and dilute with water to 25.0 mL .

Assay preparation-Transfer 5.0 mL of the Assay stock preparation to a $50-\mathrm{mL}$ volumetric flask, and dilute with water to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ ) The liquid chromatograph is equipped with a refractive index detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $10-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability preparation, and record the chromatograms for about 3.5 times the retention time of alpha cyclodextrin. Record the peak responses as directed for Procedure: the retention time of alpha cyclodextrin is about 4.5 minutes; the relative retention times are
about 1.0 for alpha cyclodextrin, about 2.2 for beta cyclodextrin, and about 0.7 for gamma cyclodextrin; the resolution, $R$, between the gamma cyclodextrin and alpha cyclodextrin peaks is not less than 1.5 ; and for the alpha cyclodextrin peak, the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $\left(\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{5}\right)_{6}$ in the portion of Alfadex taken by the formula:

$$
2500(C / W)\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of alpha cyclodextrin in the Standard preparation, calculated on the dried basis, as determined from the concentration of USP Alpha Cyclodextrin RS corrected for the declared moisture content; $W$ is the weight, in mg, of alpha cyclodextrin taken to prepare the Assay stock preparation; and $R_{U}$ and $R_{S}$ are the peak responses of the alpha cyclodextrin peak obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta N F 2 3}^{\text {. }}$

## BriEfing


#### Abstract

L-Asparagine, page 687 of $P F$ 29(3) [May-June 2003]. Asparagine is the name now proposed for the title of this new NF monograph because letters or numbers as prefixes to names are not included in titles of USP monographs. L-Asparagine, a chemical name in which " $L$-" designates the stereochemical configuration for asparagine, is now included in the chemical information that precedes the official standards of the monograph on this amino acid. On the basis of comments received, it is also proposed to add the statement of hydration state to the Definition.


(NL: C. Barnstein; EMC: E. Gonikberg) RTS-40672-1

## Add the following:

## 4t-Asparagine Asparagine


$\mathrm{C}_{4} \mathrm{H}_{8} \mathrm{~N}_{2} \mathrm{O}_{3} \cdot \mathrm{H}_{2} \mathrm{O} \quad 150.13$

L-Asparagine
L- $\alpha$-Aminosuccinamic acid, monohydrate [5794-13-8].
Anhydrous 132.12 [70-47-3].
" E-Asparagine Asparagine is anhydrous, or contains one molecule of water of hydration. It contains not less than 98.0 percent and not more than 101.5 percent of $\mathrm{C}_{4} \mathrm{H}_{8} \mathrm{~N}_{2} \mathrm{O}_{3}$, as L-asparagine, calculated on the dried basis.

Packaging and storage-Preserve in well-closed, light-resistant containers. Store rom tomperature, and avidexeessive heat and freezing. Protect from moisture.

Labeling-Label it to indicate whether it is anhydrous or the monohydrate.

USP Reference standards $\langle 11\rangle-U S P_{ \pm-A s p a r a g i n e ~ R S . ~}^{\text {R }}$ USP Asparagine RS.

Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $+33.0^{\circ}$ and $+36.5^{\circ}$, measured at $20^{\circ}$.

Test solution: 10 mg per mL in 6 N hydrochloric acid.
Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed $10^{3}$ per g , and the total combined molds and yeasts count does not exceed $10^{2}$ cfu per $g$.

Loss on drying $\langle 731\rangle$-Dry it at $130^{\circ}$ for 3 hours: the anhydrous form loses not more than $1.0 \%$ of its weight, and the monohydrate loses between $11.5 \%$ and $12.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on 1.0 g .

Lead $\langle 251\rangle$ —Prepare a Test Preparation using a 1-g portion of E Asparagine, Asparagine, and use 5 mL of Diluted Standard Lead Solution ( $5 \mu \mathrm{~g}$ of Pb ) for the test: the limit is $5 \mu \mathrm{~g}$ per $g$.

## Chromatographic purity-

Adsorbent: $0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture.

Test solution: 10 mg per mL .
Standard solution-Prepare a solution of USP gine RS USP Asparagine RS in water having a known concentration of about 0.05 mg per mL .
Application volume: $5 \mu \mathrm{~L}$.
Developing solvent system: a mixture of butyl alcohol, water, and glacial acetic acid ( $3: 1: 1$ ).

Spray reagent-Dissolve 0.2 g of ninhydrin in 100 mL of a mixture of butyl alcohol and glacial acetic acid (95:5).
Procedure—Proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$, and then dry the plate at $80^{\circ}$ for 30 minutes. Spray the plate with the Spray reagent, heat at $80^{\circ}$ for 10 minutes, and examine under white light: no secondary spot in the chromatogram obtained from the Test solution is larger or more intense than the principal spot in the chromatogram obtained from the Standard solution ( $0.5 \%$ ); and not more than $1.0 \%$ of total impurities is found.

Assay—Dissolve about 130 mg of E -Aspagine, Asparagine, accurately weighed, in 3 mL of formic acid and 50 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS (see Titrimetry $\langle 541\rangle$ ), determining the endpoint
potentiometrically. Perform a blank determination, and make any necessary corrections. Each mL of 0.1 N perchloric acid is equivalent to 13.21 mg of $\mathrm{C}_{4} \mathrm{H}_{8} \mathrm{~N}_{2} \mathrm{O}_{3}$, calculated on the dried basis. $\Delta N F 23$

## BRIEFING

Betadex, NF 22 page 2831. It is proposed to modify the Chromatographic system in the Assay to allow for the refractive index detector to be maintained at temperatures other than $25 \pm 2^{\circ}$. This is in response to comments received that most refractive index detectors cannot maintain a constant temperature of $25^{\circ}$.
(EMC: D. Bempong) RTS-40636-1

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and water (65:35). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard solution-Dissolve 2.0 g of glycerol in water contained in a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Filter through a $0.45-\mu \mathrm{m}$ membrane filter. Use fresh or store in a freezer, thaw in hot water, and mix.

Standard preparation - Dissolve an accurately weighed quantity of USP Beta Cyclodextrin RS in water, and dilute quantitatively with water to obtain a solution having a known concentration of about 10 mg per mL. Use fresh or store in a freezer, thaw in hot water, and mix. Mix 1.0 mL of this solution with 1.0 mL of Internal standard solution.

System suitability preparation-Prepare a solution in water containing about 5 mg per mL each of USP Alpha Cyclodextrin RS and USP Beta Cyclodextrin RS. Filter through a $0.45-\mu \mathrm{m}$ membrane filter.
Assay preparation-Transfer about 1 g of Betadex, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Filter this solution through a $0.45-\mu \mathrm{m}$ membrane filter. Mix 1.0 mL with 1.0 mL of Internal standard solution.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The tiquid chromatograph is equipped with a refractive indes detector that is maintained at a constant temperature of $25^{\circ}$, a $4.6 \mathrm{~mm}-*$ 25 cm column that contains $10-\mathrm{mm}$ packing L 8 , and a gurard col umn that contains packing L8. The columms are maintained at a constant temperature of $25 \pm 2^{\circ}$, and the flow rate is about 2.0 mL per minute.
${ }^{\Delta}$ The chromatograph is equipped with a refractive index detector, a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $10-\mu \mathrm{m}$ packing L8, and a guard column that contains packing L8. The columns and, if necessary, the detector are maintained
at a constant temperature of about $25 \pm 2^{\circ}$, and the flow rate is about 2.0 mL per minute. If the column or detector is operated at a temperature other than $25 \pm 2^{\circ}$, the system also must be shown to meet all system suitability requirements. $\Delta N F 23$
Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$, and the alpha cyclodextrin and beta cyclodextrin peaks exhibit baseline separation, the relative retention times being about 0.8 and 1.0 , respectively.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Assay preparation and the Standard preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\left(\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{5}\right)_{7}$ in the portion of Betadex taken by the formula:

$$
100 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of anhydrous beta cyclodextrin in the Standard preparation, as determined from the concentration of USP Beta Cyclodextrin RS corrected for moisture content by a titrimetric water determination, and $R_{U}$ and $R_{S}$ are the peak response ratios of the beta cyclodextrin peak to the internal standard peak obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Cocoa Butter, NF 22 page 2853. On the basis of comments received, it is proposed to revise the system suitability requirement in the test for Fatty acid composition. It is proposed to change the current relative standard deviation requirement of not more than $2.0 \%$ to not more than $5.0 \%$.
(EMC: C. Sheehan) RTS-40487-1

## Change to read:

## Fatty acid composition-

Test solution-Place about 100 to 150 mg of Cocoa Butter in a $50-\mathrm{mL}$ round-bottom flask, and add 4 mL of 0.5 N sodium hydroxide solution, prepared in methanol. Add a few boiling chips to the flask, connect the round-bottom flask to a condenser, and boil the mixture under total reflux until the fat globules go into solution. Add 5.0 mL of a 2.0 M borontrifluoride in methanol solution to the boiling mixture via the condenser, and continue boiling for 2 minutes. Add 2 to 5 mL of chromatographic $n$-heptane to the boiling mixture via the condenser, and boil for another minute. Remove the flask from the source of heat, and remove the reflux condenser. Add saturated sodium chloride solution, and swirl the flask gently. Add more of the saturated sodium chloride solution to bring the liquid level into the neck of the round-bottom flask.

Transfer about 1 mL of the organic layer into a glass-stoppered test tube, add some anhydrous sodium sulfate to remove the last traces of water, and filter. Use the filtrate.
System suitability solution-Dissolve suitable quantities of methyl stearate and methyl oleate in $n$-heptane to obtain a solution having a known concentration of about 1 mg per mL for each component.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The gas chromatograph is equipped with a flame-ionization detector maintained at a temperature of about $250^{\circ}$, a $0.25-\mathrm{mm} \times 15-\mathrm{m}$ fused-silica capillary column coated with $0.25-\mu \mathrm{m}$ stationary phase G19, and a split injection system with a split ratio of about $60: 1$, maintained at a temperature of about $250^{\circ}$. The carrier gas is helium flowing at a linear velocity of about 48 cm per second. The column temperature is programmed to increase linearly from $180^{\circ}$ to $240^{\circ}$ at a rate of $10^{\circ}$ per minute, and is maintained at $240^{\circ}$ for 5 minutes. [NOTE--The components of interest elute during the temperature program. The final hold at a temperature of $240^{\circ}$ serves only to facilitate elution of higher boiling components.] Inject about $0.1 \mu \mathrm{~L}$ of the System suitability solution into the chromatograph, record the chromatogram, and measure the responses for the major peaks: the resolution, $R$, between the stearate and oleate peaks is not less than 1.5; and the relative standard deviation for replicate injections is not more than $2.0 \%$.
${ }^{4} 5.0 \%$. ${ }^{\text {AF }}$.
The relative retention times are about 0.97 for stearate and 1.0 for oleate.

Procedure-Inject about $0.1 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure the areas for the peaks of the methyl esters of the fatty acids. [NOTE-The relative retention times for palmitate, stearate, oleate, linoleate, linolenate (if present), and arachidate are about $1.0,1.55,1.60,1.72$, 1.89 , and 2.30 , respectively.] Calculate the percentage of each fatty acid methyl ester in the specimen of Cocoa Butter taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the response of each peak; and $r_{s}$ is the sum of the responses of all of the peaks: the percentages of palmitate, stearate, oleate, linoleate, linolenate (if present), and arachidate are in the ranges of 23 to 30,31 to 37,31 to $38,1.6$ to $4.8,0$ to 1.5 , and 0 to 1.5 , respectively.

2-Phenoxyethanol, page 1900 of $P F$ 28(6) [Nov.-Dec. 2002] A monograph for this article was previously proposed under the name 2-Phenoxyethanol. Phenoxyethanol is the name now proposed for the title of this monograph because numbers or letters as prefixes to names are not included in titles of $U S P$ or NF monographs. 2-Phenoxyethanol, a chemical name in which "2-" designates the position of the phenoxy-substituent on the ethyl alcohol molecule, is now included in the chemical information that precedes the official standards of the monograph for this excipient.

It is proposed to replace a spectrophotometric procedure in the test for Limit of phenol and two different gas chromatographic procedures in the Chromatographic purity test and Assay with a single gas chromatographic procedure. This gas chromatographic procedure is based on analyses performed with Chrompack CP-Sil 8 CB
brand of G27 column. The typical retention times for phenol and phenoxyethanol are about 8.4 minutes and 15 minutes, respectively.
On the basis of data supporting the antimicrobial effectiveness of this excipient, it is proposed to delete the test for Microbial limits. It is also proposed to make changes in the Definition, Labeling, and Bacterial endotoxins sections.
(EMC: E. Gonikberg; AMB: D. Porter; NL: C. Barnstein) RTS—39836-1; 40020-4; 40596-1

## Add the following:

## 42-Phenoxyethanol

$\mathrm{C}_{8} \mathrm{H}_{10} \mathrm{O}_{2} \quad 138.17$

2-Phenoxyethanol
2-Phenoxyethyl alcohol
Ethylene glycol, 2-monophenyl ether [122-99-6].
» $z$ Phenoxyethanol contains not less than 99.0
98.0 percent and not more than 100.5102 .0 percent of 2-phenoxyethanol.

Packaging and storage-Preserve in tight containers, in a cool, dry place, protected from light.

Labeling-Where it is intended for use in ecines nistered either intramuseularly or subeutaneously, articles administered parenterally, it is so labeled.

Bacterial endotoxins $\langle 85\rangle$ - Where it is intended for use in vaceines administered either intramuseularly or subeutaarsly, articles administered parenterally, it contains not more than 2.9 USP Endotoxin Units per mg.

## Limit of phenol-

Fest solution Dissolve abeut 1.0 g of 2 Phenoxyethanol, accurately weighed, in $50-\mathrm{mL}$ of methylene chloride, add 4 mL of sodium hydroxide solution ( 8.5 in 100 ) and 10 mL of water, and shake well. Separate, and diseard the lower layer. Wash the upper (aqueous) layer with two $20-\mathrm{mL}$ pertions of methylene chloride, and discard the washings. Transfer the aqueous layer to a 100 mb volumetric flask, dilute to vot ume with water, and mix.

Procedure Determine the absorbance of the Test solth fion in a 1 em cell at the maximmm at about 287 nm with a-suitable-spectrophotemeter, correcting for the blank. The abserbance is net mere than 0.27: net mere than $0.1 \%$ of phenel is found.

Phenol solution, Standard solution, Test solution, and Chromatographic system-Prepare as directed under Chromatographic purity.
Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the percentage of phenol in the portion of Phenoxyethanol taken by the formula:

$$
150(C / W)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of phenol in the Standard solution; $W$ is the weight of Phenoxyethanol, in mg , taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are peak areas of the phenol peak in the chromatograms obtained from the Test solution and the Standard solution, respectively: not more than $0.1 \%$ is found.

## Chromatographic purity-

Internal standard solution Transfer about 1.25 g of methyl latrate to a $25-\mathrm{mL}$ volumetric flask, dissolve and dilute to volume with methylene chloride, and mix.

Fest stock solution Transfer about 10.0 of of 2 Phenok yethanel, aceurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve and dilute to volume with methylene chloride, and mix.

Test solution 1 Transfer 5.0 mL of the Test stock solution to a $10-\mathrm{mL}$ volumetric flask and dilute to volume with meth-Hene-chloride, and mix.

Fest solution 22 Transfer 5.0 mL of the Test stock solution to a 10 mL volumetric flask, add $1.0-\mathrm{mL}$ of the Internat standerd solution, dilute to volume with methylene-chleride, and mix.

Standard solution Transfer 1.0 mL of Test solution 1 to a 100 mL volumetric flask, add 10.0 mL of the Internal standetrd solution, and dilute to volume with methylene-chleride.

Chromatographic system (see Chromatography- $\langle 621$ )) The gas chromatograph is equipped with a flame-ienization detector and $-4-\mathrm{mm} \times 1.5 \mathrm{~m}$ columm packed with $3 \%$ liq tid phase-G3 on suppert S1A. The coltumn temperature-is maintained at $130^{\circ}$, and the injection pert and the detector are maintained at $200^{\circ}$. Nitregen is used as the carrier gas at a flow rate of about 30 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the 2 phenoxyethanel peak elutes before the internal standard peak; and the resolution, $R$, between the 2 phenoxyethanel and the internal standard is not less than- 12. Chromatograph Test solution 1, and record the peak respenses as directed for Procedure: no peak appears at the retention time correspending to that of the internal standard; if a peak is observed at that retention time, make any neeessary correction for factors of dilution, and determine the area
due to the interfering compenent that must be-subtracted frem the area of the internal standard peak in the chromatogram of Test solution 2. 2.

Procedure Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the-Standard solution and Test solution 2 into the-gas ehromatograph, record the ehrematograms for a period of time that is not less than five times the retention time of $Z$ phenoxyethanol, and measure the responses for all the peaks. The peak arearatio of the sum of all peaks (exeluding the main peak, the solvent peak, and the internal-standard peak) to the internal standard obtained from Test solution $z$ is not more than the peak area ratio of 2 phenoxyethanel to the internal standard obtained from the Standard soltation: not more than $1.0 \%$ of total impurities is found.

Phenol solution-Prepare a solution of phenol in isopropyl alcohol having a known concentration of about 0.25 mg of phenol per mL.

Standard solution-Dissolve an accurately weighed quantity of USP Phenoxyethanol RS in Phenol solution to obtain a solution having a known concentration of about 5 mg of phenoxyethanol per mL. Accurately transfer $500 \mu \mathrm{~L}$ of this solution to a vial, add $1000 \mu \mathrm{~L}$ of isopropyl alcohol, crimp the vial, and mix on a vortex mixer for about 15 sec onds.

Test solution-Accurately transfer $500 \mu \mathrm{~L}$ of Phenoxyethanol to a tared vial, and determine the weight of Phenoxyethanol taken. Add $1000 \mu \mathrm{~L}$ of isopropyl alcohol, crimp the vial, and mix on a vortex mixer for about 15 sec onds.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and a $0.32-\mathrm{mm} \times 10-\mathrm{m}$ capillary column coated with a $5-\mu \mathrm{m}$ film of stationary phase G27. The carrier gas is helium with a split flow rate of 44 mL per minute. The injector port and the detector are both maintained at $300^{\circ}$.

The column temperature is programmed as follows: the starting column temperature is $80^{\circ}$; after injection, it is increased to $260^{\circ}$ at a rate of $8^{\circ}$ per minute, then held for 10 minutes. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the resolution, $R$, between phenol and phenoxyethanol peaks is not less than 10 ; and the relative standard deviation for replicate injections for the phenoxyethanol peak is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the percentage of total impurities in the portion of Phenoxyethanol taken by the formula:

$$
150(C / W)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of phenoxyethanol in the Standard solution; $W$ is the weight of Phenoxyethanol, in mg, taken to prepare the Test solution; $r_{U}$ is the sum of all additional peak areas in the chromatogram obtained from the Test solution, excluding the main peak, the solvent peak, and the phenol peak; and $r_{S}$ is the peak area of the phenoxyethanol peak in the chromatogram obtained from the Standard solution: not more than $1.0 \%$ of total impurities is found.

## Assay-

Internal standard solution Prepare a-solution of phenol in methanel containing about 0.5 mg per mL .

Standard preparation- Dissolve an aeeurately weighed quantity of USP 2 Phenoxyethanol RS in Internal standerd solution to obtain a solution having a known coneentration of about 1 mg per mL.

Assay preparation Transfer about 100 mg of 2 Phenow yethanol, aceurately weighed, to 100 mL volumetric flask, dissolve in and dilute with Internal standerdsolution to voltme, and mix.

Chromatographic system (see Chromatography (621)) The gas chromatograph is equipped with a flame ionization detectrand a $4 \mathrm{~mm} \times 1.8 \mathrm{~m}$ column packed with $5 \%$ phase $G 16$ on packing S1A. The column is maintained at about $165^{\circ}$, the injection pert at about $200^{\circ}$, and the detector block at about $250^{\circ}$. Nitregen is used as the earrier gas, flowing at rat ofabeut 50 mL per minute. Chremategraph the Standated preparation, and record the peak areas as directed for Procedure: the resolution, $R$, between the internal standard and 2 phenoxyethanel is net less the 2.0 ; the tailing factor is not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Proedure Separately inject equal volumes (about $1 \mu$ L) of the Standerd preparation and the Assay preparation into the gas chrematograph, record the ehrematograms, and measure the areas of the major peaks. Caleulate the quantity, in mg, of $\mathrm{G}_{8} H_{4} \mathrm{O}_{2}$ in the pertion of 2 Phenoxyethanol taken by the formula:

$$
1000 \in\left(R_{L}+R_{s}\right),
$$

in which $C$ is the oneentration, in me per mL, of USP 2 Phenoxyethanol RS in the Standard preparation; and $R_{\psi}$ and $R_{s}$ are the peak area ratio of 2 phenoxyethanol to the internal-standard obtained from the Assay preparation and the-Stadely preparation, respectively.

Phenol solution and Chromatographic system-Prepare as directed under Chromatographic purity.

Standard preparation-Use the Standard solution, prepared as directed under Chromatographic purity.
Assay preparation-Transfer about 500 mg of Phenoxyethanol, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with isopropyl alcohol to volume, and mix. Accurately transfer $500 \mu \mathrm{~L}$ of this solution to a vial, add $1000 \mu \mathrm{~L}$ of isopropyl alcohol, crimp the vial, and mix on a vortex mixer for about 15 seconds.

Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the quantity, in mg, of $\mathrm{C}_{8} \mathrm{H}_{10} \mathrm{O}_{2}$ in the portion of Phenoxyethanol taken by the formula:

$$
150 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Phenoxyethanol RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the responses of the phenoxyethanol peak obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta F F 2 3}^{\text {. }}$

## GENERAL CHAPTERS

## General Tests and Assays

## General Requirements for Tests and Assays

## BRIEFING

〈11〉 Reference Standards, USP 27 page 2111, page 5180 of $P F$ 23(6) [Nov.-Dec. 1997], page 6925 of PF 24(5) [Aug.-Sept. 1998], page 8222 of $P F$ 25(3) [May-June 1999], page 8561 of PF 25(4) [July-Aug. 1999], page 8893 of $P F$ 25(5) [Sept.-Oct. 1999], page 218 of $P F$ 26(1) [Jan.-Feb. 2000], page 471 of $P F$ 26(2) [Mar.-Apr. 2000], page 793 of $P F$ 26(3) [May-June 2000], page 1101 of $P F 26$ (4) [July-Aug. 2000], page 1369 of PF 26(5) [Sept.-Oct. 2000], page 1832 of $P F 27$ (1) [Jan.-Feb. 2001], page 2268 of $P F$ 27(2) [Mar.-Apr. 2001], page 2806 of $P F$ 27(4) [July-Aug. 2001], page 3071 of $P F$ 27(5) [Sept.-Oct. 2001], page 3348 of $P F 27$ (6) [Nov.-Dec. 2001], page 433 of PF 28(2) [Mar.-Apr. 2002], page 839 of PF 28(3) [May-June 2002], page 1224 of $P F 28(4)$ [July-Aug. 2002], page 1468 of PF 28(5) [Sept.-Oct. 2002], page 1913 of PF 28(6) [Nov.-Dec. 2002], page 163 of $P F$ 29(1) [Jan.-Feb. 2003], page 483 of $P F$ 29(2) [Mar.-Apr. 2003], page 710 of PF 29(3) [May-June

2003], page 1137 of $P F$ 29(4) [July-Aug. 2003], page 1601 of $P F 29(5)$ [Sept.-Oct. 2003], and page 2022 of $P F 29(6)$ [Nov.Dec. 2003].
(HDQ) RTS-40672-1; 40494-1; 40268-1; 40538-2; 40020-4; 39836-1; 40596-1; 40234-3; 40592-1; 39775-2

## Add the following:

${ }^{\boldsymbol{\Delta}} \mathbf{U S P}$ Asparagine RS—[To come. $]_{\mathbf{\Delta S S P 2 8}}$
Add the following:
${ }^{\Delta}$ USP Clonidine Related Compound B RS. IUSP28

## Add the following:

${ }^{\Delta}$ USP Fluconazole RS. ${ }_{\mathbf{\Delta} U S P 28}$

## Add the following:

${ }^{\Delta}$ USP Fluconazole Related Compound A RS [2-[2-fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis (1H-1,2,4-triazol-1-yl)-propan-2-ol]. $\mathbf{\Delta}$ USP28

## Add the following:

${ }^{\Delta}$ USP Fluconazole Related Compound B RS [2-(4-fluor-ophenyl)-1,3-bis (1H-1,2,4-triazol-1-yl)-propan-2-ol]. $\mathbf{\Delta S S P 2 8}$

## Add the following:

${ }^{4}$ USP Fluconazole Related Compound C RS [1,1'-(1,3phenylene) ${ }^{\text {di( }}$ ( H -1,2,4-triazole)]. $\mathbf{\Delta U S P 2 8}$

## Add the following:

${ }^{4}$ USP HexafluoroisopropanolRS USP Sevoflurane Related Compound C RS [1,1,1,3,3,3-hexafluoro-2-propa-noll-Do not dry. $\mathbf{\Delta U S P 2 8}$

## Add the following:

${ }^{\mathbf{4}}$ USP Irbesartan RS——Do not dry. $\mathbf{\Delta S P 2 8}$
Add the following:
${ }^{4}$ USP 2-Phenoxyethamol Phenoxyethanol RS—[To come.] $]_{\triangle S P P 28}$
Add the following:
${ }^{4}$ USP Sevomethyl Ether RS USP Sevoflurane Related Compound B RS [1,1,1,3,3,3-hexafluoro-2-methoxy-pro-pane]-Do not dry. $\mathbf{\Delta U S P 2 8}$

## Add the following:

${ }^{\boldsymbol{A}}$ USP Sumatriptan RS—[To come.] $]_{\Delta U S P 28}$

## Add the following:

${ }^{\Delta}$ USP Sumatriptan Succinate RS [1H-indole-5-methanesulfonamide, 3-[2-(dimethylamino)ethyl]- $N$-methyl-, butanedioate (1:1)] $\left(\mathrm{C}_{14} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{4} \diamond 413.49\right)$ - [To come.] $]_{U S P 28}$

## Add the following:

${ }^{\Delta}$ USP Sumatriptan Succinate Related Compound A RS
[[3-[2-(dimethylamino)ethyl]-2-[[3-[2-(dimethylami-no)ethyl]-1 $H$-indol-5-yl]methyl]-1 $H$-indol-5-yl]- $N$-methylmethanesulfonamide succinate salt] $\left(\mathrm{C}_{27} \mathrm{H}_{37} \mathrm{~N}_{5} \mathrm{O}_{2} \mathrm{~S}\right.$. $\mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{4} \diamond 495.68613 .77$ )-[To come. $]_{\Delta U S P 28}$

## Add the following:

${ }^{\Delta}$ USP Sumatriptan Succinate Related Compound C RS
[[3-[2-(dimethylamino)ethyl]-1-(hydroxymethyl)-1H-in-dol-5-yl]- $N$-methylmethanesulfonamide succinate salt] $\left(\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S} \cdot 0.5 \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{4} \triangleleft 325.43384 .47\right)$-[To come.] $]_{\Delta S P 28}$

## Add the following:

${ }^{\text {A }}$ USP Sumatriptan Succinate Related Impurities RS
[Mixture of sumatriptan succinate, [3-[2-(methylami-no)ethyl]-1H-indol-5-yl]- $N$-methylmethanesulfonamide maleate salt, sumatriptan succinate related compound $C$, [3-[2-(dimethylamino- $N$-oxide)ethyl]-1 $H$-indol-5-yl]- $N$ methylmethanesulfonamide, and [3-[2-(aminoethyl)-1H-in-dol-5-yl]- $N$-methylmethanesulfonamide]-[To come.] $]_{\Delta U S P 28}$

## Add the following:

${ }^{\triangle}$ USP Vecuronium Bromide Related Compound F RS
[Name eome- $3 \alpha, 17 \beta$-dihydroxy- $2 \beta$, $16 \beta$-dipiperidinyl$5 \alpha$-androstane, 17-acetate, monomethobromide] $\left(\mathrm{C}_{26} \mathrm{H}_{44} \mathrm{NO}_{3} \triangleleft 415.61\right)\left(\mathrm{C}_{32} \mathrm{H}_{55} \mathrm{BrN}_{2} \mathrm{O}_{3} \diamond 595.69\right)$-[To come.] $]_{U S P 28}$

# Microbiological Tests 

## BRIEFING

$\langle 55\rangle$ Biological Indicators-Resistance Performance Tests, USP 27 page 2150 . It is proposed to revise the sections on Total Viable Spore Count and D-Value Determination to add requirements specified in the proposed new monographs for Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers and Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions, also appearing in this issue of $P F$ (see the briefing for each proposed monograph). Comments regarding this proposal are invited and should be received by February 29, 2004.
(AMB: D. Porter) RTS-40563-1

## Change to read:

## TOTAL VIABLE SPORE COUNT

Remove three specimens of the relevant biologieal indienter
${ }^{\boldsymbol{\Delta}}$ For paper carrier biological indicators, remove three spe-
cimens of the relevant biological indicators ${ }_{\triangle U S P 28}$
from their original individual containers. Disperse the paper into component fibers by placing the test specimens in a sterile 250 mL cup of a suitable blender containing 100 mL of chilled, sterilized Purified Water and blending for 3 to 5 minutes to achieve a homogeneous suspension. Transfer a $10-\mathrm{mL}$ aliquot of the suspension to a sterile, screw-capped 16-×125-mm tube. For Biological Indicator for Steam Sterilization, Paper Carrier, heat the tube containing the suspension in a water bath at $95^{\circ}$ to $100^{\circ}$ for 15 minutes (heat shock), starting the timing when the temperature reaches $95^{\circ}$. For Biological Indicator for Dry-Heat Sterilization, Paper Carrier, and for Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier, heat the tube containing the suspension in a water bath at $80^{\circ}$ to $85^{\circ}$ for 10 minutes, starting the timing when the temperature
$\Delta^{\circ}$ of the spore suspension ${ }_{\triangle U S P 28}$
reaches $80^{\circ}$. Cool rapidly in an ice-water bath at $0^{\circ}$ to $4^{\circ}$. Transfer two $1-\mathrm{mL}$ aliquots to suitable tubes, and make appropriate serial dilutions in sterilized Purified Water, the dilutions being selected as calculated to yield preferably 30 to 300 colonies, but not less than 6 , on each of a pair of plates when treated as described below. Where the biological indicator has a low spore concentration, it may be necessary to modify the dilution series and to use more plates at each dilution. Prepare a separate series of plates for each aliquot. Place 1.0 mL of each selected dilution in each of two 15$\times 100-\mathrm{mm}$ Petri dishes. Within 20 minutes, add to each plate 20 mL of Soybean-Casein Digest Agar Medium (see Microbial Limit Tests $\langle 61\rangle$ ) that has been melted and cooled to $45^{\circ}$ to $50^{\circ}$. Swirl to attain a homogeneous suspension, and allow to solidify. Incubate the plates in an inverted position at $55^{\circ}$ to $60^{\circ}$ for Biological Indicator for Steam Sterilization, Paper Carrier, and at $30^{\circ}$ to $35^{\circ}$ for

Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier and for Biological Indicator for Dry-Heat Sterilization, Paper Carrier or at the optimal recovery temperature specified by the manufacturer, and examine the plates after 24 and 48 hours, recording for each plate the number of colonies, and using the number of colonies after 48 hours to calculate the results. Calculate the average number of spores per specimen from the results, using the appropriate dilution factor. The test is valid if the log number of spores per carrier at 48 hours is equal to or greater than the log number after 24 hours in each case. For Biological Indicator for Steam Sterilization, Self-Contained, aseptically remove the spore strip from the container, and proceed as directed for Biological Indicator for Steam Sterilization, Paper Carrier.
${ }^{\mathbf{\Delta}}$ For Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers, aseptically remove the three metal or plastic carriers from their original packaging or container. Place each carrier in a suitable sterile flask or container containing 100 mL of chilled Purified Water, and sonicate or shake on a reciprocal shaker for 3 to 5 minutes. A previous study should be conducted that ensures the recovery method results in at least $70 \%$ recovery of the labeled spore viable count. Transfer a $10-\mathrm{mL}$ aliquot of the suspension to a sterile, screw-capped $16-\times 125-\mathrm{mm}$ tube. Heat the tubes containing suspensions of Clostridium sporogenes, Bacillus atrophaeus, and Bacillus coagulans at $80^{\circ}$ to $85^{\circ}$ for 10 minutes. Heat the tubes containing a suspension of Geobacillus stearothermophilus at $95^{\circ}$ to $100^{\circ}$ for 15 minutes. Start the timing when the lowest temperature of the stated temperature ranges is reached. Cool rapidly in an ice-water bath at $0^{\circ}$ to $4^{\circ}$. Transfer two 1mL aliquots to suitable tubes, and make appropriate serial dilutions in Purified Water. The selected dilutions should be those that will preferably yield 30 to 300 colonies but not fewer than 6 on each pair of plates when treated as described below. When the biological indicator has a low spore concentration, it may be necessary to modify the dilution series and to use more plates at each dilution. Prepare a separate series of plates for each aliquot. Place 1.0 mL of each selected dilution in each of two $15-\times 100-\mathrm{mm}$ Petri dishes. Within 20 minutes add the aliquot to each plate con-
taining 20 mL of agar that has been melted and cooled to between $45^{\circ}$ and $50^{\circ}$. Swirl to attain a homogeneous suspension.

For C. sporogenes, use Yeast Extract Agar, and incubate anaerobically at $32^{\circ}$ to $37^{\circ}$ for not less than 72 hours. For $G$. stearothermophilus, B. atrophaeus, and B. coagulans, use Soybean-Casein Digest Agar Medium and incubate the plates in an inverted position aerobically at the following respective temperatures for each microorganism: $55^{\circ}$ to $60^{\circ}, 30^{\circ}$ to $35^{\circ}$, and $48^{\circ}$ to $52^{\circ}$, or at the optimum temperature specified by the biological indicator manufacturer. Examine the plates after 48 and 72 hours of incubation for $C$. sporogenes. Examine the plates after 24 and 48 hours for $G$. stearothermophilus, B. atrophaeus, and B. coagulans. Record the number of colonies on each plate using the number of colonies appearing at 48 or 72 hours. Calculate the average number of spores per carrier from the results using the appropriate dilution factor. The test is valid if the log number of spores per carrier at 48 hours is equal to or greater than the log number after 24 hours in each case.
For Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions, prepare a 1:100 dilution of the original spore suspension in chilled Purified Water contained in a sterile, screw-capped $16-\times 125-\mathrm{mm}$ tube, and proceed with the viable spore count procedures specified under Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers. $\mathbf{\triangle U S P 2 8}$

## Change to read:

## D-VALUE DETERMINATION

For all tests described in this section, handle each test specimen with aseptic precautions, using sterilized equipment where applicable.

## Apparatus

For Biological Indicator for Dry-Heat Sterilization, Paper Carrier use an apparatus of known thermodynamic characteristics that has been validated for compliance with the requirements for safety ${ }^{1}$ and performance, ${ }^{2}$ that consists of a sterilizing chamber equipped with a means of heating the contained air, preferably electrically rather than gas fired, and that has adequate movement of the air through forced ventilation (by mechanical devices such as blowers), with sensing and control devices for temperature and timing capable of indicating with an accuracy of not more than $0.5^{\circ}$ and 1 -second intervals, respectively. The geometrical pattern of the heat source(s) is such as to enable the biological indicators under test to be uniformly heated under the specified conditions. The temperature profile in the chamber is known, and cold spots, hot spots, and slow heat zones identified. The chamber has the capability to work within a temperature range of $40^{\circ}$ to $300^{\circ}$, with an accuracy at any particular setting of not less than $\pm 2^{\circ}$. The apparatus is equipped with a suitable additional access door or port so as to enable the entry and insertion (or removal) of specimens within 6 seconds and to enable the temperature to return to the set temperature within 0.5 minute where the specified temperature is $120^{\circ}$ to $190^{\circ}$ and within 1.0 minute where such temperature is $220^{\circ}$ and above.

For Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier use an apparatus that consists of a test chamber, with a means of ensuring adequate mixing of the sterilant gas and a means of heating the sterilant gas to not lower than the preselected operating temperature so that no liquid enters the test chamber, equipped with temperature control and monitoring, pressure control, humidification, and gas concentration monitoring devices. Detailed specifications and operational parameters for suitable apparatus are those published in Standard for a Biological Indica-tor-Evaluator Resistometer for Ethylene Oxide Gas Vessels (BIER/EO) Gas Vessels. ${ }^{3}$

For Biological Indicator for Steam Sterilization, Paper Carrier, and for Biological Indicator for Steam Sterilization, Self-Contained use an apparatus that consists of a chamber equipped with heating, temperature, and steam control and monitoring devices. Detailed specifications and operational parameters for suitable apparatus are those published in Standard for a Biological Indica-tor-Evaluator Resistometer for Saturated Steam (BIER/Steam Vessels). ${ }^{4}$

## Procedure

Carry out the tests for $D$ value at each of the applicable sets of sterilization conditions for which the packaged biological indicator under test is labeled for use. Take a sufficient number of groups of specimens of biological indicators in their original individual containers, each group consisting of 5 to 10 specimens. The number of groups provides a range of observations from not less than one la-

[^13]beled $D$ value below the labeled survival time through not less than one labeled $D$ value above the labeled kill time. Place each group on a separate suitable specimen holder that permits each specimen to be exposed to the prescribed sterilizing condition at a specific location in the sterilizing chamber. Check the apparatus for operating parameters using specimen holders without specimens. Select a series of sterilizing times in increments from the shortest time for the specimens to be tested. The differences in sterilizing times over the series are as constant as feasible, and the difference between adjacent times is no greater than $75 \%$ of the labeled $D$ value.

For Biological Indicator for Dry-Heat Sterilization, Paper Carrier preheat the sterilizing chamber for 30 minutes. Open the access door or port, place one of the holders with a group of specimens in the sterilizing chamber, close the access door or port, and continue to operate the apparatus. Commence timing the heat exposure when the chamber temperature returns to $2^{\circ}$ below the specified temperature. After the contents have been subjected to the sterilizing condition for a predetermined time selected from a series of time increments, remove the holder with the heated specimens, and replace it with another holder with specimens. Repeat the sterilizing procedure similarly, but for another predetermined time, and continue with successive groups until all have been heated appropriately.

For Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier proceed as follows:

1. Evacuate the test chamber to a pressure of not more than 100 $\pm 3 \mathrm{~mm}$ of mercury.
2. Inject sufficient water vapor (e.g., saturated steam) to bring the chamber contents to within $10 \%$ relative humidity of the required humidification condition, and allow the chamber to equilibrate with moisture and to temperature for about 30 minutes.
3. Inject a sufficient quantity of temperature-equilibrated ethylene oxide gas to attain the appropriate concentration $\pm 30 \mathrm{mg}$ of ethylene oxide per L .
4. Subject a group of specimens to the appropriate temperature, humidification, and gas concentration conditions for the required time.
5. Evacuate the test chamber to a pressure of $100 \pm 3 \mathrm{~mm}$ of mercury, and release the vacuum with sterile filtered air. Repeat this until not less than $99 \%$ of the remaining gas has been removed, and remove the holder(s) with the exposed specimens. For exposing further groups of specimens to the sterilization conditions, proceed with steps 6 and 7 .
6. Flush the test chamber five times with filtered air after evacuation each time to a pressure of not more than $100 \pm 3 \mathrm{~mm}$ of mercury.
7. Repeat the entire sterilizing procedure, steps 1 through 6 , for other groups of unexposed specimens, but maintain the specified conditions of step 4 for each of the other required times.

For Biological Indicator for Steam Sterilization, Paper Carrier, exhaust the sterilizing chamber, and within 15 seconds of opening the door, place one of the holders with a group of specimens in the sterilizing chamber, and operate the apparatus to heat up the chamber contents as quickly as possible. After the contents have been subjected to the sterilizing condition for a predetermined time selected from the series of time increments, exhaust the chamber as quickly as possible. Remove the holder with the heated specimens, and replace it with another group of specimens. Repeat the sterilizing procedure similarly, but for another predetermined time, and continue with successive groups until all have been appropriately heated.

For Biological Indicator for Steam Sterilization, Self-Contained follow the procedure indicated for Biological Indicator for Steam Sterilization, Paper Carrier, but handle each self-contained unit as a biological indicator system, with the $D$ value determined for the self-contained system.
${ }^{\text {4 For Biological Indicators for Moist Heat, Dry Heat, and }}$ Gaseous Modes of Sterilization, Metal or Plastic Carriers, follow the same procedures as listed for steam, dry heat, and ethylene oxide biological indicators, paper carriers that are described in this section. The $D$-value exposure conditions for hard surface carriers, such as metal and plastic are the same as the conditions used to determine the $D$ value for paper carriers. If the manufacturer's label permits usage of the biological indicator carrier with all modes of sterilization, then $D$-value, survival-time, and kill-time data will need to be provided by the manufacturer for each mode of sterilization. It is highly likely that metal and plastic biological indicators will be used for gaseous sterilization methods including vapor phase hydrogen peroxide and chlorine dioxide surface sterilization. In those cases the manufacturer will need to define the testing equipment and operational parameters to be used in $D$-value testing. At this time apparatus for conducting $D$-value analyses using vapor phase hydrogen peroxide and chlorine dioxide is not defined in a U.S. standard. The manufacturer, therefore, needs to assure that equipment used for gaseous $D$-val$u e$ determinations is equipped with temperature and relative humidity controls and that the equipment permits adequate mixing of the gaseous sterilant within the chamber environment. Where technology is available, the test chamber should be equipped with monitoring devices for temperature, pressure, humidification, and gas concentration. If gas concentration cannot be accurately measured, the manufacturer must provide the calculation methods used for determining the gaseous phase concentration during the exposure period of the carriers to the gaseous sterilant. The test chamber must also attain an exposure gas concentration in a defined time range and be maintained at a constant gas concentration range for a stated period.

For Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions, conduct $D$-value determinations for each of the microorganisms that are provided as a liquid spore crop suspension. The test is conducted using $0.1-\mathrm{mL}$ aliquots of the original suspension, transferred to 9.9 mL of Purified Water in a sterile tube. Follow $D$-value procedures specified under Biological Indicator for Steam Sterilization, Paper Carrier. Using the Survival Curve method for determination of $D$ values, follow incubation procedures included in Total viable spore count under Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers. The label for $B$. athrophaeus must contain a moist heat, as well as a dry heat, value. The dry heat $D$ value will need to be obtained by inoculating a suitable hard surface carrier, such as metal or glass, with 0.1 mL of the original spore suspension prior to exposing the carrier to conditions stated under Biological Indicator for Steam Sterilization, Paper Carrier. $\mathbf{\Delta U S P 2 8}$

## Recovery

After completion of the sterilizing procedure for Biological Indicator for Dry-Heat Sterilization, Paper Carrier, Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier, or Biological Indicator for Steam Sterilization, Paper Carrier, whichever is applicable, and within a noted time not more than 4 hours, aseptically remove and add each strip to 10 to 30 mL of Soybean-Casein Digest Medium (see Media under Sterility Tests $\langle 71\rangle$ ) to submerge the biological indicator completely in a suitable tube. For each Biological Indicator for Steam Sterilization, Self-Contained specimen, the paper strip is immersed in the self-contained medium according to manufacturers' instructions, within a noted time not more than 4 hours. Incubate each tube at a temperature of $55^{\circ}$ to $60^{\circ}$ for Biological Indicator for Steam Sterilization, Paper Carrier and Biological Indicator for Steam Sterilization, Self-Contained or at $30^{\circ}$ to $35^{\circ}$ for Biological Indicator for Dry-Heat Sterilization, Paper Carrier, and Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier or in any case at the optimal recovery temperature specified by the manufacturer. Observe each inoculated mediumcontaining tube at 24 and 48 hours, and every 1 or 2 days thereafter for a total of 7 days after inoculation. (Where growth is observed at any particular observation time, further incubation of the specimen(s) concerned may be omitted.) Note the number of specimens showing no evidence of growth at any time.
${ }^{4}$ For Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers, recovery of spores from the biological indicator carriers will follow recovery procedures described in the procedures under Total Viable Spore Count. Any one of several described $D$-value determination methods for paper carrier biological indicators may be used to calculate the $D$ value for metal or plastic carriers. Incubation conditions for the four microorganisms that may be used for metal and plastic biological indicators are described in the Total Viable Spore Count section.

For Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions, the method of recovery following sterilization exposure conditions are those methods described in the Total Viable Spore Count section for liquid suspensions, and when a dry heat $D$-value determination is made from $B$. athrophaeus suspensions, the same recovery procedures as described under Biological Indicator for Steam Sterilization, Paper Carrier are followed. $\Delta U S P 28$

## Calculation

This chapter describes the use of the Limited Spearman-Karber Method for determining the $D$ value of biological indicators on spore paper carriers. Use this method in the event of a compendial issue or regulatory referee testing of a biological indicator system. It is recognized that other methods, such as the Survival Curve Method and the Stumbo-Murphy-Cochran procedure, may be routinely used by manufacturers and users of biological indicators to determine $D$ values. The calculation of the $D$ value using the Limited Spearman-Karber Method is based on the use of 10 biological indicators per group. [NOTE-If less than 10 biological indicators are used (i.e., 5), the formula and the various calculation steps will have to be modified, including the Replacement of Missing Values; however, the requirements of the test remain the same.]

Designate the number of specimens taken for each group (i.e., 10) by $n$, and the difference between adjacent times (in minutes) by $\delta$. Designate for each group of the series the number of specimens showing no growth by:

$$
f_{1}, f_{2}, \ldots f_{k}
$$

in which $f_{1}$ is the response of all 10 specimens showing growth $(0 /$ 10 inactivated) in the group held for the shortest time for such result that is adjacent to an intermediate mortality; and $f_{k}$ is the response of all 10 specimens of the group showing no growth (10/ 10 inactivated) in the group held for the longest time for such result that is adjacent to an intermediate mortality. Do not use for the cal-
culations observations for groups beyond the ends of the series, $f_{1}$ and $f_{k}$, giving results that are not adjacent to an intermediate mortality. The test is valid if there is available a result $(0 / 10)$ from a group held for a shorter time than that for the selected shortest time result $\left(f_{1}\right)$, and there is available a result $(10 / 10)$ from a group held for a longer time than that for the selected longest time result $\left(f_{k}\right)$. Calculate the mean heating time, $T$, for achieving complete kill by the equation:

$$
T=T_{k}-\delta / 2-\left(\delta / 10 \times \sum_{l=1}^{k-1} f_{l}\right)
$$

in which $T_{k}$ is the time for achieving the result $f_{k}$. Calculate the $D$ value by the equation:

$$
D=\left(\frac{T}{\log N_{0}+0.2507}\right)
$$

in which $N_{0}$ is the average spore count per carrier determined by Total Viable Spore Count (see above) at the time of making this test. Calculate the variance of $T, V_{T}$, by the equation:

$$
V_{T}=\frac{\delta^{2}}{n^{2}(n-1)} \times \sum_{l=1}^{k-1} f_{l}\left(10-f_{l}\right)
$$

in which $\delta$ represents a constant interval between successive exposures, as defined above.

The standard deviation, $s_{T}$, is the square root of the variance:

$$
s_{T}=\sqrt{V_{T}}
$$

Calculate the lower and upper 95\% confidence limits (approximate CL ) for the $D$ value by the equation:

$$
\text { approximate CL for } D=\left(T \pm 2 s_{T} / \log N_{0}+0.2507\right)
$$

## Replacement of Missing Values

If not more than 1 specimen from a group and not more than 2 specimens from all of the groups giving the results $f_{1}$ through $f_{k}$ are missing, replace each missing value by adding 0 to the number showing no growth, if the number showing no growth in the remaining 9 specimens of that group is 4 or less, and adding 1 if the number showing no growth in the remaining 9 specimens of that group is 5 or more.

## Survival Time and Kill Time

Take two groups, each consisting of 10 specimens of the relevant biological indicator, in their original, individual containers. Place the specimens of a group in suitable specimen holders that permit each specimen to be exposed to the sterilizing conditions at a specific location in the sterilizing chamber. Check the chamber for operating parameters by preheating it to the selected temperature $\pm 2^{\circ}$ in the cases of Biological Indicator for Dry-Heat Sterilization, Paper Carrier and Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier or $\pm 0.5^{\circ}$ in the cases of Biological Indicator for Steam Sterilization, Paper Carrier and Biological Indicator for Steam Sterilization, Self-Contained.

For Biological Indicator for Dry-Heat Sterilization, Paper Carrier, preheat the unit to temperature, and equilibrate the heat chamber. Open the access door or port, and place the holder(s) in the chamber, close the access door or port, and continue to operate the apparatus. Commence timing the heat exposure when the chamber temperature returns to the lower limit of the selected temperature. Expose the specimens for the required survival time, enter the chamber, and remove the holder(s) containing the 10 specimens. Repeat the above procedure immediately, or preheat if a substantial interval has elapsed, so as to subject the second holder(s) containing 10 specimens similarly to the first conditions, but for the required kill time.

For Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier preheat the chamber to equilibrium at the selected temperature $\pm 2^{\circ}$, and initiate and monitor the operating steps 1 through 6 as described for D-Value Determination, appropriate for the combination of gas concentration, temperature, and relative humidity, using a gassing time in step 4 appropriate to the survival time. Repeat the above procedure with two or more groups each consisting of 10 specimens, but using a gassing time in step 4 appropriate to the kill time.

For Biological Indicator for Steam Sterilization, Paper Carrier and Biological Indicator for Steam Sterilization, Self-Contained exhaust the steam chamber, and open the door. Within 15 seconds of opening the door place the loaded holder(s) into the chamber, and operate the apparatus to heat the chamber contents as quickly as possible. Expose the specimens for the required survival time, counting the exposure from the time when the temperature record shows that the chamber has reached the required temperature. Exhaust the chamber as quickly as possible at the end of the exposure period. When the chamber can be safely entered, remove the holder(s) containing the specimens. Repeat the above procedure immediately, or preheat if a substantial interval has elapsed, so as to subject the holder(s) containing 10 specimens similarly to the first exposure. Repeat the above procedure with two more groups each consisting of 10 specimens, but expose the specimens for the required kill time. In each case for the Biological Indicator for Dry-Heat Sterilization, Paper Carrier, Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier, or Biological Indicator for Steam Sterilization, Paper Carrier, whichever is appropriate, after completion of the sterilizing procedure, and within a noted time not more than 4 hours, aseptically remove and add each carrier to 10 to 30 mL of Soybean-Casein Digest Medium (see Media under Sterility Tests $\langle 71\rangle$ ) to submerge the biological indicator completely in a suitable tube. Incubate each tube at a temperature of $55^{\circ}$ to $60^{\circ}$ in the case of Biological Indicator for Steam Sterilization, Paper Carrier, or of $30^{\circ}$ to $35^{\circ}$ in the cases of Biological Indicator for Dry-Heat Sterilization, Paper Carrier,
and Biological Indicator for Ethylene Oxide Sterilization, Paper Carrier, or at the optimal temperature specified by the manufacturer. For Biological Indicator for Steam Sterilization, Self-Contained the paper strip is immersed in self-contained medium according to manufacturers' instructions within a noted time not more than 4 hours and incubated at $55^{\circ}$ to $60^{\circ}$. Observe each inoculated medium-containing tube at 24 and 48 hours, and every 1 or 2 days thereafter for a total of 7 days after inoculation. (Where growth is observed at any particular observation time, further incubation of the specimen(s) concerned may be omitted.) Note the specimens showing no evidence of growth at any time.
${ }^{\boldsymbol{\Delta}}$ For Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers, use the conditions stated for paper strips as described in this section. The method of sterilization selected is dependent on the intended mode of sterilization for the biological indicator.

The Survival time and kill time for Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions is described in the Official Monograph under the same heading. $\triangle U S P 28$

## Chemical Tests and Assays

LIMIT TESTS

BRIEFING
<231〉 Heavy Metals, USP 27 page 2204 and page 1603 of $P F$ 29(5) [Sept.-Oct. 2003]. It is proposed to add a Monitor Preparation to Method III.
(PA4: H. Pappa) RTS-40535-1

## Change to read:

## Method I

pH 3.5 Acetate Buffer-Dissolve 25.0 g of ammonium acetate in 25 mL of water, and add 38.0 mL of 6 N hydrochloric acid. Adjust, if necessary, with 6 N ammonium hydroxide or 6 N hydrochloric acid to a pH of 3.5 , dilute with water to 100 mL , and mix.

Standard Preparation-Into a $50-\mathrm{mL}$ color-comparison tube pipet 2 mL of Standard Lead Solution ( $20 \mu \mathrm{~g}$ of Pb ), and dilute with water to 25 mL . Adjust
${ }^{\mathbf{\Delta}}$ Using a pH meter, adjust $_{\text {UUSP28 }}$
with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0 , using short range pH indientor paper as extemal indieator,
${ }^{4}$ USP28
dilute with water to 40 mL , and mix.
Test Preparation-Into a $50-\mathrm{mL}$ color-comparison tube place 25 mL of the solution prepared for the test as directed in the individual monograph; or, using the designated volume of acid where specified in the individual monograph, dissolve and dilute with water to 25 mL the quantity, in g , of the substance to be tested, as calculated by the formula:

$$
2.0 /(1000 L)
$$

in which $L$ is the Heavy metals limit, in percentage. Adjust
$\Delta_{\text {as a percentage. Using a } \mathrm{pH} \text { meter, adjust }}^{\text {USP28 }}$ with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0 , using short range pH indientor paper as extemal indlentor,
$\triangle$ UUSP28
dilute with water to 40 mL , and mix.
Monitor Preparation-Into a third $50-\mathrm{mL}$ color-comparison tube place 25 mL of a solution prepared as directed for Test Preparation, and add 2.0 mL of Standard Lead Solution. Adjust
${ }^{\mathbf{\Delta}}$ Using a pH meter, adjust ${ }_{\Delta U S P 28}$
with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short range pH indicator paper as external indieator,

## - USP28

dilute with water to 40 mL , and mix.
Procedure-To each of the three tubes containing the Standard Preparation, the Test Preparation, and the Monitor Preparation, add 2 mL of pH 3.5 Acetate Buffer, then add 1.2 mL of thioaceta-mide-glycerin base TS, dilute with water to 50 mL , mix, allow to stand for 2 minutes, and view downward over a white surface ${ }^{*}$ : the color of the solution from the Test Preparation is not darker than that of the solution from the Standard Preparation, and int sity of the color of the
$\Delta_{\text {solution }}$ from the ${ }_{\mathbf{U S P}}$ US
Monitor Preparation is equal to or
$\Delta_{\text {© }}$ darker $_{\Delta U S P 28}$
than that of the
$\mathbf{\Delta}_{\text {solution }}$ from the $\mathbf{\Delta U S P 2 8}$
Standard Preparation. [NOTE-If the color of the Monitor Preparation is lighter than that of the Standard Preparation, use Method $I I$ instead of Method I for the substance being tested.]

* In those countries or jurisdictions where thioacetamide cannot be used, add 10 mL of freshly prepared hydrogen sulfide TS to each of the tubes, mix, allow to stand for 5 minutes, and view downward over a white surface.


## Change to read:

## Method II

pH 3.5 Acetate Buffer-Prepare as directed for Method I. Standard Preparation-Prepare as directed under Meth $I$.
${ }^{\Delta}$ Pipet 4 mL of the Standard Lead Solution into a suitable
test tube, and add 10 mL of 6 N hydrochloric acid. USP28
Test Preparation-Use a quantity, in g, of the substance to be tested as calculated by the formula:

$$
\begin{gathered}
z .0 /(1000 L), \\
4.0 /(1000 L), \mathbf{\Delta U S P 2 8}
\end{gathered}
$$

in which $L$ is the Heavy metals limit, im
$\Delta^{\text {as }} \mathrm{a}_{\Delta U S P 28}$
percentage. Transfer the weighed quantity of the substance to a suitable crucible, add sufficient sulfuric acid to wet the substance, and carefully ignite at a low temperature until thoroughly charred. (The crucible may be loosely covered with a suitable lid during the charring.) Add to the carbonized mass 2 mL of nitric acid and 5 drops of sulfuric acid, and heat cautiously until white fumes no longer are evolved. Ignite, preferably in a muffle furnace, at $500^{\circ}$ to $600^{\circ}$, until the carbon is completely burned off
${ }^{\boldsymbol{\Delta}}$ (no longer than 2 hours). If carbon remains, allow the residue to cool, add a few drops of sulfuric acid, evaporate, and
ignite again. $\mathbf{A S S P 2 8}$
Cool, add 4 mt
${ }^{\Delta} 5 \mathrm{~mL}_{\mathbf{\Delta U S P 2 8}}$
of 6 N hydrochloric acid, cover,
$\Delta_{\text {and }}{ }_{\text {USP } 28}$
digest on a steam bath for 15 minutes, uneover, and slowly evaperate on a steam bath to dryness. Moisten the residue with 1 drop of hydrochloric acid, add 10 mL of hot water, and digest for 2 min utes. Add 6 N ammonium hydroxide drepurise, until the solution is just alkaline to litmus paper, dilute with water 1025 mL , and adjust with 1 Nacetic acid to a pH between 3.0 and 4.0 , using shert range pH indieator paper as external indientor. Filter if necessary, rimse the crucible and the filter with 10 mL of water, combine the filtrate and rinsing in a 50 mL color comparison tube, dilute with water to 40 mL , and mix.
${ }^{\mathbf{4}} 10$ minutes. Cool, and quantitatively transfer the solution to a test tube. Rinse the crucible with a second $5-\mathrm{mL}$ portion of 6 N hydrochloric acid, and transfer the rinsing to the test tube.

Monitor Preparation—Pipet 4 mL of the Standard Lead
Solution into a crucible identical to that used for the Test
Preparation and containing a quantity of the substance under test that is equal to $10 \%$ of the amount required for the

Test Preparation. Evaporate on a steam bath to dryness.

Ignite at the same time, in the same muffle furnace, and under the same conditions used for the Test Preparation. Cool, add 5 mL of 6 N hydrochloric acid, cover, and digest on a steam bath for 10 minutes. Cool, and quantitatively transfer to a test tube. Rinse the crucible with a second $5-\mathrm{mL}$ portion of 6 N hydrochloric acid, and transfer the rinsing to the test
tube. $\triangle$ USP28
Procedure- T
${ }^{\wedge}$ Adjust the solution in UUSP28
each of the tubes containing the Standard Preparation, and
$\Delta$
the Test Preparation,
© and the Monitor Preparation with ammonium hydroxide, added cautiously and dropwise, to a pH of 9 . Cool, and adjust with glacial acetic acid, added dropwise, to a pH of 8 , and then add 0.5 mL in excess. Filter, washing the filter with a few mL of water, into a $50-\mathrm{mL}$ color-comparison tube, and then dilute with water to 40 mL . $\mathbf{A S S P 2 8}$
Add 2 mL of pH 3.5 Acetate Buffer, then add 1.2 mL of thioaceta-mide-glycerin base TS, dilute with water to 50 mL , mix, allow to stand for 2 minutes, and view downward over a white surface ${ }^{*}$ : the color of the solution from the Test Preparation is not darker than that of the solution from the Standard Preparation,
$\Delta$ and the color of the solution from the Monitor Preparation is equal to or darker than that of the solution from the Standard Preparation. [NOTE-If the color of the solution from the Monitor Preparation is lighter than that of the solution from the Standard Preparation, proceed as directed for Method III for the substance being tested. $]_{\text {USP28 }}$

## Change to read:

## Method III

pH 3.5 Acetate Buffer-Prepare as directed for Method I.
Standard Preparation-Transfer a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid to a clean, dry, $100-\mathrm{mL}$ Kjeldahl flask, and add a further volume of nitric acid equal to the incremental volume of nitric acid added to the Test Preparation. Heat the solution to the production of dense, white fumes, cool, cautiously add 10 mL of water and, if hydrogen peroxide was used in treating the Test Preparation, add a volume of 30 percent hydrogen peroxide equal to that used for the substance being tested, and boil gently to the production of dense, white fumes. Again cool, cautiously add 5 mL of water, mix, and boil gently to the production of dense, white fumes and to a volume of 2 to 3 mL . Cool, dilute cautiously with a few mL of water, add 2.0 mL of Standard Lead Solution (20 $\mu \mathrm{g}$ of Pb ), and mix. Transfer to a $50-\mathrm{mL}$ color-comparison tube, rinse the flask with water, adding the rinsing to the tube until the volume is 25 mL , and mix.

## Test Preparation-

${ }^{\Delta}$ Unless otherwise indicated in the individual monograph, use a quantity, in g , of the substance to be tested as calculated by the formula:
2.0/(1000L),
in which $L$ is the Heavy metals limit, as a percentage. $\quad$ USP28 If the substance is a solid-Transfer the
$\Delta_{\text {weighed }}^{\text {USP } 28}$
quantity of the test substance speified in individul mene graph
$\Delta$
$\triangle U S P 28$
to a cle
to a clean, dry, $100-\mathrm{mL}$ Kjeldahl flask. [NOTE-A $300-\mathrm{mL}$ flask may be used if the reaction foams excessively.] Clamp the flask at an angle of $45^{\circ}$, and add a sufficient quantity of a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid to moisten the substance thoroughly. Warm gently until the reaction commences, allow the reaction to subside, and add additional portions of the same acid mixture, heating after each addition, until a total of 18 mL of the acid mixture has been added. Increase the amount of heat, and boil gently until the solution darkens. Cool, add 2 mL of nitric acid, and heat again until the solution darkens. Continue the heating, followed by addition of nitric acid until no further darkening occurs, then heat strongly to the production of dense, white fumes. Cool, cautiously add 5 mL of water, boil gently to the production of dense, white fumes, and continue heating until the volume is reduced to a few mL . Cool, cautiously add 5 mL of water, and examine the color of the solution. If the color is yellow, cautiously add 1 mL of 30 percent hydrogen peroxide, and again evaporate to the production of dense, white fumes and a volume of 2 to 3 mL . If the solution is still yellow in color, repeat the addition of 5 mL of water and the peroxide treatment. Cool, dilute cautiously with a few mL of water, and rinse into a $50-\mathrm{mL}$ color-comparison tube, taking care that the combined volume does not exceed 25 mL .
If the substance is a liquid-Transfer the
$\Delta_{\text {weighed }}{ }_{\text {USP28 }}$
quantity of the test substance specified in the individual mone graph
${ }^{\Delta}{ }_{\Delta U S P 28}$
to a clean, dry, $100-\mathrm{mL}$ Kjeldahl flask. [note-A $300-\mathrm{mL}$ flask may be used if the reaction foams excessively.] Clamp the flask at an angle of $45^{\circ}$, and cautiously add a few mL of a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid. Warm gently until the reaction commences, allow the reaction to subside, and proceed as directed for If the substance is a solid, beginning with "add additional portions of the same acid mixture."
${ }^{\boldsymbol{4}}$ Monitor Preparation-Proceed with the digestion using the same amount of sample and the same procedure as directed in the Test Preparation until the step "Cool, dilute cautiously with a few mL of water." Add 2.0 mL of Lead Standard Solution ( $20 \mu \mathrm{~g}$ of lead), and mix. Transfer to a $50-\mathrm{mL}$ color comparison tube, rinse the flask with water, adding the rinsing to the tube until the volume is 25 mL , and mix. $\mathbf{\Delta U S P 2 8}$

Procedure－Treat the Test Preparation，the Standard Prepara－ tion
$\Delta_{\text {and the Monitor Preparation }}^{\triangle U S P 28}$ as follows：Adjust
${ }^{\boldsymbol{\Delta}}$ Using a pH meter， adjust $_{\mathbf{A}_{\text {USP28 }}}$
the solution to a pH between 3.0 and 4.0 ，using short range pH in dientor paper as external indieator，
$\Delta$
－USP28
with ammonium hydroxide（a dilute ammonia solution may be used，if desired，as the specified range is approached），dilute with water to 40 mL ，and mix．

To each tube add 2 mL of pH 3.5 Acetate Buffer，then add 1.2 mL of thioacetamide－glycerin base TS，dilute with water to 50 mL ， mix，allow to stand for 2 minutes，and view downward over a white surface ${ }^{*}$ ：the color of the Test Preparation is not darker than that of the Standard Preparation，
$\Delta$ and the color of the Monitor Preparation is equal to or
darker than that of the Standard Preparation．$\triangle$ USP28

## Other Tests and Assays

## BRIEFING

$\langle\mathbf{3 8 1}\rangle$ Elastomeric Closures for Injections，USP 27 page 2214 and page 164 of $P F$ 29（1）［Jan．－Feb．2003］．The Expert Committee on Parenteral Products－Industrial is proposing a major revision of this chapter in an effort to move towards harmonization with the European Pharmacopoeia，thus making this chapter amenable to the global pharmaceutical industry．On the basis of comments re－ ceived from industry on the $P F 29(1)$ proposal，appropriate changes were made by the Expert Committee．The revisions to this general test chapter are now scheduled to appear in USP 28，but with an effective implementation date of January 1，2006，pending the receipt of substantial objections or comments that would result in a delay．
（PPI：J．Kelly）RTS—99140－1

## Change to read：

## 〈381〉 ELASTOMERIC CLOSURES FOR INJECTIONS

> An elastemeric clesure may be of synthetic or natural origin. It is generally a complex mixture of many ingredients. These inelude the basic polymer, fillers, aceelerators, vuleanizing agents, and pig ments. The properties of the elastemerie clesure are dependent net enly upen these ingredients, but also on the processing procedure, sueh as mixing, milling, dusting agents used, molding, and euring.
> Factors such as cleansing procedures, contacting media, and eenditions of storage may also affect the suitability of an elaste merie clesure for a specific use．Evaluation of such factors should
be made by appropriate additional specific tests to determine the suitability of an elastomeric closure for its intended use．Criteria for the selection of an elastomeric closure should also－include a eareful review of all the ingredients to assure that no knewn or sus－ peeted careinegens，or other toxic substanees are added．
Befinition－An elastemeric elostre is a packaging compenent that is，or may be，in diree contact with the drug．

## Biologieal Test Procedures

Two stage of testing are indieated．The first stage is the perfor mance of in vitro tests according to the procedures set forth in ehapter－（87），Biological Reactivily Tests，In Iitw．Materials that meet the requirements of the in vitro test are not required to under go further testing．Materials that do not meet the requirements of the in vitro tests are subjected to the second stage of testing which is the performanee of in vivo tests，i．e．，the Systemic Injection Test and Intrent Test，necording to the procedures set forth in ehapter Biological Reactivity Tests，In Viv－〈88）＝：

## Physieochemieal Test Procedures

The following tests are designed to determine pertinent physieo－ ehemical extraction characteristies of elastomeric elosures．Sinee the tests are based on the extraction of the elastomer，it is essentiat that the designated amoun of sufface are of sample be available． meach ease，the specified surface area is available for extraction at the designated temperature．The test methods are devised to detect the majority of expected variations．

Extraction－Solvents－
A：Purified Water．
B：Drug product vehicle（where applieable）．
C：Isoprepyl aleohel．
Apparatus
Autuclave Use an atuclave capable of maintaining a tempera ture of $121 \pm 2^{\circ}$ ，equipped with a thermemeter，a pressure gauge， and a rack adequate to accommodate the test containers above the water level．

Oven Use an oven，preferably a foreed draft model，that will maintain an operating temperature of $105^{\circ} \pm 2^{\circ}$ ．

Reflux Apparattr Use a suitable reflux apparatus having a eapacity of about 500 mL ．

Proeedure－
Preparation of Sample Place in a suitable extraction container a－sufficient number of elastomeric closures to provide $100 \mathrm{~cm}^{2}-0 f$ expesed surface area．Add 300 mL of purified water to ach con fainer，cover with a suitable inverted beaker，and autoclave at 124 $\pm 0.5^{\circ}$ for 30 minuter．［NOTE－Adjust so that the mperature rises rapidly，preferably within 2 to -5 minutes．］Deeant，using a stainless steel sereen to hold the elosures in the containers．Rinse with 100 mL of purified water，gently swinl，and discard the rinsings．Repeat with a second 100 mL pertion of purified water．Treat all blank eontainers in a similar manner．

Extract（with use of Extion Solvent A）Place a properly prepared sample，having an exposed surface area $100 \mathrm{~cm}^{2}$ ，im a suitable container，and add 200 mL of purified water．Cover with a suitable inverted beaker，and extract by heating in an autoclave at $121^{\circ}$ for 2 hours，allowing alequate time for the liquid within the eentainer to reach the extraction temperattre．Allow the attelave to cool rapidly，and cool to room temperature．Treat the blank con－ tainer in a similar manner．

Extracts（with use of Extran Solvent Bor C）Place aprop－ erly prepared sample，having an expesed sufface area of $100 \mathrm{~cm}^{2}$ ； in a suitable Reflux Apparatucentrining 200 mL of Extraction folvent，and reflux for 30 minutes．Treat the blank in a similar man－ ner．

Turbidity [NoTE-Use Extracts prepared with Extraction Sol vent $A, B$, or $C$.$] Agitate the container, and transfer a sufficient$ quantity of Extract, diluted with Extraction Solvent, if necessary, to cell. Measure the turbidity in a suitable ratio turbidimeter (see Spectrophemetry and Light Seattering (854)) against fixed reproducible standards.* The turbidity is the difference between the values obtained for the blank and the sample expressed in Nephelemetric Turbidity Units (NTU), an arbitrafy linear numerieal seale expressing a haze range from absolute clarity to the zone of turbid-势

Redueing Agents-[NOTE-Use Extracts prepared with Extrac tion Solvent A.] Agitate the container, transfer 50 mL of sample extract to a suitable eontainer, and titrate with 0.01 N iodine VS, using 3 mL of stareh TS as the indientor. Treat the blank extract in a similar manner. The difference between the blank and the sample titration is expressed in mL of 0.01 N iodine.

Heary Metals- $\langle\mathbf{z 3 1}\rangle$ - [NOTE-Use Extracts prepared with Ex tan Solvent 4 or $B$.] Transfer 20 mL of the blank and the sant ple ex racts to separate color comparisen tubes. Transfer 2, 6 , and 10 mL of Standed Lead Solution into separate color comparisen tubes, add 2 mL of 1 N acetic acid to each tube, and adjust the vol ume to 25 mL with purified water. Add 10 mL of freshly prepared hydregen sulfide TS to each tube, mix, allow to stand for 5 min utes, and view downward over a white surface. Determine the amount of heary metals in the blank and in the sample. The heary metals content is the difference between the blank and the sample. pH-Change [NOTE-Use Extracts prepared with Extraction Solven $A$ or $B$, adding to extracts obtained with Solvent $A$ suffit eient potassium ehloride to provide a concentration of $0.1 \%$.] Determine the pH of sample extracts $A$ and $B$ potentiometrieally, performing blank determinations with blank extracts $A$ and $B$, and making any necessary corrections. The pH change is the dif ference between the blank and the sample.

Total Extraetables [NOTE-Use Extrets prepared with Ex action Solvent $A, B$, or $C$.] Agitate the containers, and transfer 100 mL aliquets of the blank and the sample to separate, taredeva perating dishes. Evaperate on a steam bath to dryness (Extrats prepared with Extraction Solvent C) or in an oven at $100^{\circ}$, dry at $105^{\circ}$ for 1 hour, cool in a desicentor, and weigh. Caleulate the totat extractables, in me, by the formula:-

$$
z\left(H_{t}-\quad H_{B}\right)
$$

in whieh $H_{y}$ is the weight, in mg, of residue found in the-sample extract aliquet, and $W_{B}$ is the weight, in mg, of residue found in the blank solution aliquet.

## ${ }^{\triangle}$ INTRODUCTION

Elastomeric closures for containers used in the types of preparations defined in the general test chapter Injections $\langle 1\rangle$ are made of materials obtained by vulcanization (cross-linking) polymerization, polyaddition, or polycondensation of macromolecular organic substances (elastomers). Closure formulations contain natural or synthetic elastomers and inorganic and organic additives to aid or control vulcanization, impart physical and chemical proper-

[^14]ties or color, stabilize the closure formulation, or for other purposes. This chapter applies to closures formulated with natural or synthetic elastomeric substances. This chapter does not apply to closures made from silicone elastomer, ła minated closures, or laequered closures, although it does apply to the base elastomer of such eontedestres. however, it does apply to closures treated with silicone (e.g., Dimethicone, $N F$ ). For laminated or coated closures (e.g., PTFE or lacquer coatings), the physicochemical and identification tests apply only to the base elastomer, and not to the laminate coat. However, the functionality tests apply to the entire coated elastomeric closure.

This chapter states test limits for Type I and Type II elastomeric closures: Examples of Type I closures are those used for single-dose containers for aqueous solutions, aqueous suspensions, or solids intended to be reconstituted with an aqueous vehicle. Type II closures are those that, having properties optimized for special uses, may not meet all requirements listed for Type I closures due to physical configuration, material of construction, or both. Examples of Type II closures are those used for multiple-dose containers for injections; single-dose or multiple-dose containers for injections containing vegetable oils, including emulsions and liposomal formulations; er injectable formulations containing other nonaqueous vehicles; Elastomeric seals for injection sites on IV sets, needle shields, or other seals requiring stretchability or resealability may also be ineluded in this and containers of solids intended to be reconstituted with a nonaqueous vehicle.

This chapter is intended as an initial screen to identify elastomeric closures that might be appropriate for use with parenteral preparations on the basis of their biological compatibility, their aqueous extract physicochemical properties, and their functionality. All elastomeric closures suitable for use with parenteral preparations comply with either Type I
or Type II test limits. However, this specification is not intended to serve as the sole evaluation criterion for the selection of such closures. It is the responsibility of the manufacturer of the parenteral preparation to ensure that the closures chosen for use with a partieular preparation enform to the following:-

The components of the preparation in contact with the elestre are not adserbed onte the surface of the clestres and do not migrate into or through the closure to anextent sufficient to affect the preparation adversely. The closure doe not leach substances in quantities suf ficient to affeet product stability assays or tests and the quantity of these substance are harmless in the amounts administered to the patient population for whom the product is intended.

The closures perform all required functions and are eompatible with the preparation for which they are used throughout the product's labeled expiration date.

The following closure evaluation requirements are beyond the scope of this chapter:
-the establishment of closure identification tests and specifications;
-the verification of closure-product physicochemical compatibility;
-the identification and safety determination of closure leachables found in the packaged product; and -the verification of packaged product closure functionality under actual storage and use conditions.

The manufacturer of the preparation must obtain from the supplier an assurance that the composition of the closure does not vary and that it is identical to that of the closure used during compatibility testing. When the supplier informs the manufacturer of the preparation of changes in the composition, compatibility testing must be
repeated, totally or partially, depending on the nature of the changes. Closures must be properly stored, cleaned for removal of environmental contaminants and endotoxins, and sterilized prior to use in packaging parenteral products.

## CHARACTERISTICS

Elastomeric closures are homogeneous and practically free from flash and adventitious materials (e.g., fibers, foreign particles, waste rubber).
Identification of the type of elastomeric material used for the closures is not within the seope of this chapter. The identifieation tests given below distingurisher between elastomeric and monelastomeric closures but does not differentiate the various ypes of material. Identifieation tests ther than these described in this menegraph may be used an routine basis in order to verify that the closures in question are of the same formulation as these previously ap proved for use. Other analytieal methods that may be applied for identification purpes inelude the following:

- determination of relative density
- determination of sulphated ash
- determination of sulphur content
- thin layer chromatography carried out on an extract
- UV absorption spectrophotemetry of an extract
- IR abserption spectrophotometry of a pyrolysate


## IDENTIFICATION TESTS

Identifieation Test A: Streteh a strip of material with a eross section of 1 to $5 \mathrm{~mm}^{2}$ to twice its original length. After holding at wice its length for 1 minute, allow the strip to relax for 30 seconds. The elastomer conforms to the requirements for elasticity if it contracts to less than 1.2 times its eriginal length within 30 -secends.

Identification Test B: Heat 1 to 2 gof material in a heat resistant test tube over an open flame to dry the sample, and eontinue heating until pyrolysate vapers are condensed near the top edge of the test tube. Deposit several drops of the pyrolysate on a potassium bromide dise, and examine by IR abserption spectrephetemetry. The-sample conforms te the test if the IR absorption spectrum matehes that of a ref erence sample of the elastomer.

Identifieation Test C (see Residue on Ignition-(z81));: The residtue is within $\pm 10 \%$ of the result obtained with a reference sample of the elastomer.

Closures are made of a wide variety of elastomeric materials and optional polymeric coatings. For this reason, it is beyond the scope of this chapter to specify identification tests that encompass all possible closure presentations. However, it is the responsibility of the closure supplier and the pharmaceutical manufacturer to verify the identity of the closure elastomeric formulation and any coating or laminate materials used according to suitable, specific identification tests. Examples of some of the analytical test methodologies that may be used include specific gravity determination, sulfated ash determination, sulfur content determination, thin-layer chromatography of an extract, UV spectrophotometry of an extract, or IR absorption spectrophotometry of a pyrolysate.

## TEST PROCEDURES

## Pretest Preparation-of Sample

Whenever pessible, closures should be put into ready tousecondition before being tested, by processing the closures in a manner that will be utilized in normal production con ditions. If clesure-silieonization has been found to-skew physicochemieal analysis results, this process may be elimifated from the proeessing steps. If it is net feasible or practical to utilize normal production conditions, clesures are to
be prepared according to the following procedtre. Place a sufficient number of uncut elastomeric closures to provide $150 \mathrm{~cm}^{2}$-ff expesed surface area in a wide-neeked Type-I glass flack. Add 300 mL of water, cover with an inverted beresilieate-glass beaker, and heat in an autoclave-so that a temperature of $121 \pm 2^{\circ}$ is reached within 20 10-30 min utes, and maintain this temperature for 30 minutes. As quickly as pessible after autoclaving, separate the liquid from the elastomers by decantation. Rinse closures with 100 mL of water, gently swirl, and diseard the rinsings. Repeat the rinsing with a secend 100 mL pertion of water. [NOTE_If clesures undergo normal production conditions ether than autoclaving or steam-sterilization, conditions which are known to affect closure biological reactivity, phy sicochemical characteristies, or functionality (e.g., gamma irradiation), such proeesses must be included in the-sample preparation. $]$

Before performing biological, physicochemical, or functionality tests, it is advisable to pretreat and process closures in a manner simulating actual conditions of use. This is especially important if closures are exposed to processes that may significantly impact the biological, physicochemical, or functionality characteristics of the closure (e.g., gamma irradiation). Elastomeric closures that are normally siliconized prior to use may undergo physicochemical testing without siliconization in order to avoid potential method interference and/or difficulties in interpreting test results. It is appropriate to document the conditions of closure processing, pretreatment, and siliconization when reporting test results.

## Biological Tests

Two stages of testing are indicated. The first stage is the performance of an in vitro test necording to the Agar Diffut sion Test procedure as described in general test chapter Bio-
logical Reactivity Tests, In Vitro $\langle 87\rangle$. Materials that meet the requirements of the in vitro test are not required to undergo further testing.

Materials that do not meet the requirements of the in vitro test are subjected to the second stage of testing, which is the performance of the in vivo tests, Systemic Injection Test and Intracutaneous Test, according to the procedures set forth in the general test chapter Biological Reactivity Tests, In Vivo <88〉.

Type I and Type II closures must both conform to the requirements of either the in vitro or the in vivo biological reactivity tests. [NOTE-Also see the general information chapter The Biocompatibility of Material Used in Drug Containers, Medical Devices, and Implants $\langle 1031\rangle$.]

## Physicochemical Tests

## PREPARATION OF SOLUTION S

Place uncut closures corresponding to a surface area of about $100 \mathrm{~cm}^{2}$ into a suitable glass container, cover with Purified Water or Water for Injection, boil for 5 minutes, and rinse with cold Purified Water or Water for Injection. Place the washed closures into a Type I glass wide-necked flask (see Containers $\langle 661\rangle$ ), add 200 mL of Purified Water or Water for Injection, and weigh. Cover the mouth of the flask with a Type I glass beaker. Heat in an autoclave so that a temperature of $121 \pm 2^{\circ}$ is reached within 20 to 30 minutes, and maintain this temperature for 30 minutes. Cool to room temperature over a period of about 30 minutes. Add Purified Water or Water for Injection to bring it up to the original mass. Shake and immediately decant, and collect the solution. [NOTE-This solution must be shaken before being used in each of the tests.]

## APPEARANCE OF SOLUTION

NOTE-The determination of turbidity may be performed instrumentally using a turbidimeter or by visual comparison.

Opalescence Stock Suspension-Prepare an aqueous solution containing $1 \%$ hydrazine sulfate, and allow to stand for 4 to 6 hours. Prepare an aqueous solution containing $10 \%$ hexamethylenetetramine. Mix equal parts of these solutions, and allow to stand for 24 hours. This Opase Suspension Opalescence Stock Suspension is stable for about 2 months, provided it is stored in a glass container free from surface defects. Mix well before use to ensure nonadherence of material to the container. Discard if the suspension adheres to the glass.

Opalescence Stoek Solution Standard SuspensionPrepare a solution by diluting 15 mL of the Suspansion Opalescence Stock Suspension with water to 1000 mL .

Reference Solution Suspension A-Prepare asolution eontaining 10 mL of freshly prepared Opalese Stock Solution and of water. Prepare a suspension containing 5.0 mL of freshly prepared Opalescence Standard Suspension and 95.0 mL of water.

Reference Solution Suspension B-Prepare alution entrining 30 mL of Opalescence Stock Solution and of Prepare a suspension containing 10.0 mL of Opalescence Standard Suspension and 90.0 mL of water.

Reference Suspension C-Prepare a suspension containing 30.0 mL of Opalescence Standard Suspension and 70.0 mL of water.

Procedure A-Use identical test tubes made of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm . Fill one tube to a depth of 40 mm with Solution S, and three others to the same depth with Reference Suspensions $A, B$, and $C$. Compare the solutions in diffuse daylight 5 minutes after preparation of the reference
suspensions, viewing vertically against a black background. The light conditions shall be such that Reference Suspension $A$ can be readily distinguished from water and that Reference Suspension $B$ can be readily distinguished from Reference Suspension $A$.

Procedure B-Measure the turbidity in a suitable turbidimeter (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) against Reference Suspensions $B$ and $C$.

Requirement-Solution $S$ is not more opalescent than
Referene Solution 4 for Type I closures and not more opalescent than Reference Solution B for Type H-closures. Solution $S$ is not more intensely colored than an equal quantity of examined through identieal, colorless, transparent, and neur tral glass containers, viewed vertically against a white backgreund in diffuse daylight. The difference in Formazine turbidity units (FTU) between Solution $S$ and Reference Suspension $B$ is not greater than 6 FTU for Type I closures and the difference between Solution $S$ and Reference Suspension $C$ is not greater than 18 FTU for Type II closures. For visual inspection Solution $S$ is not more opalescent than Reference Suspension A for Type I closures and not more opalescent than Reference Suspension B for Type II closures. Solution $S$ is not more intensely colored than an equal quantity of a mixture of 6.0 mL of Matching Fluid $O$ (see Color and Achromicity $\langle 631\rangle$ ) and 94.0 mL of diluted hydrochloric acid, examined through identical, colorless, transparent, and neutral glass containers, viewed vertically against a white background in diffuse daylight.

## ACIDITY OR ALKALINITY

Bromothymol Blue Solution-Dissolve 50 mg of bromothymol blue in a mixture of 4 mL of 0.02 M sodium hydroxide and 20 mL of alcohol, and dilute with water to 100 mL .

Procedure-Transfer 20 mL of Solution $S$ to a suitable container, and add 0.1 mL of bromothymol blue TS. Bromothymol Blue Solution. Not more than 0.3 mL of 0.01 N sodium hydroxide produces a blue color. Continue using this same solution to test for alkalinity: not more than 0.8 mL of 0.01 N hydrochloric acid produces a yellow color.

## UV ABSORBANCE

[NOTE-Perform this test within 5 hours of preparing Solution $S$. If dilution of the filtrate is required, the test result must be corrected.] Filter Solution $S$ through a filter, having a $0.45-\mu \mathrm{m}$ porosity discarding the first few mL of the filtrate. Record the UV spectrum between 220 nm 200 nm and 360 nm in a $1-\mathrm{cm}$ cell, with water in a matched cell in the reference beam: the absorbances at these wavelengths do not exceed 0.2 for Type I closures or 4.0 for Type II closures.

## REDUCING SUBSTANCES

[NOTE-Perform this test within 4to 5 hours of Stand prepare preparing Solution S.] Transfer 20.0 mL of Solution $S$ to a $250-\mathrm{mL}$ conical flask, and add 1 mL of diluted sulfuric acid 25 mL of alkaline eupric eitrate TS, and 20 mL of 0.002 N petassium permanganate. and 20 mL of 0.002 M potassium permanganate. Cover the flask, boil for 3 minutes, and cool rapidly to room temperature. Add 1 g of potassium iodide, and titrate with 0.01 N sodium thiosulfate VS, using 0.25 mL of starch solution TS as the endpoint is approached. Perform a blank determination, omitting the specimen, and note the difference in volume of 0.01 N sodium thiosulfate required. The difference between the titration volumes is not greater than 3.0 mL for Type I closures and not greater than 7.0 mL for Type II closures.

## HEAVY METALS

Proceed as directed for Method I under Heavy Metals $\langle 231\rangle$ : not more than $0.0002 \%$ ( 2 ppm ).

## SOLUBLE ZINC CONTENT

Test Solution-Transfer 10.0 mL of Solution $S$ to a 100mL volumetric flask, add 0.5 mL of 0.1 N hydrochloric acid, dilute with 0.1 N hydrochloric acid to volume, and mix.

Zinc Standard Solution-Dissolve an accurately weighed quantity of zinc sulfate in 0.1 N hydrochloric acid, and dilute quantitatively, and stepwise if necessary, with 0.1 N hydrochloric acid to obtain a solution having a known concentration of 5 mg of zinc per mL .

Reference Solution-Transfer 1 mL of Zinc Standard Solution to a $1000-\mathrm{mL}$ volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix. Transfer 10.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, add 0.5 mL of 0.1 N hydrechloric acid, dilute with 0.1 N hydrochloric acid to volume, and mix.

Procedure-Concomitantly determine the absorbances of the Reference Solution and the Test Solution at the zinc emission line at 213.8 nm , with a suitable atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) equipped with a zinc hollow-cathode lamp and an air-acetylene flame, and using 0.1 N hydrochloric acid as the blank. The absorbance of the Test Solution is not greater than that of the Reference Solution.

## AMMONIUM

Take 5 mL of Solution $S$, and if necessary adjust the pH to alkaline using sodium hydroxide TS. Dilute with water to 15 mL , and add 0.3 mL of alkaline mercuric-potassium iodide TS. Prepare a control by dissolving an accurately weighed quantity of ammonium chloride in water and diluting step-
wise to obtain a solution having a known concentration of 1 $\mu \mathrm{g}$ of ammonium ( 1 ppm ) per mL . To 10 mL of this solution add the same amount of sodium hydroxide TS as was added to Solution $S$. Dilute with water to 15 mL , and add 0.3 mL of alkaline mercuric-potassium iodide TS. Any yellow color produced immediaty after 5 minutes is no darker than the color obtained in the control ( 2 ppm ).

## TOTAL SOLIDS

Evaporate 50 mL of Solution $S$ on a water bath to dryness. Dry the residue at $100^{\circ}$ to $105^{\circ}$ for 1 hour, and weigh: not more than 2.0 mg for Type I closures and not more than 4.0 mg for Type II closures is obtained.

## VOLATILE SULFIDES

Place closures, cut if necessary, with a total surface area of $20 \pm 1 \mathrm{~cm}^{2}$ in a $100-\mathrm{mL}$ flask, and add 50 mL of a $2 \%$ citric acid solution. Separately prepare a control solution by placing 0.154 mg of sodium sulfide in a $100-\mathrm{mL}$ flask, and dissolving in 50 mL of a $2 \%$ citric acid solution. Place a piece of lead acetate paper over the mouth of each flask, and maintain the paper in position by placing over it an inverted weighing bottle. Heat the flasks in an autoclave at $121 \pm$ $2^{\circ}$ for 30 minutes. Any black stain on the paper produced by Solution $S$ is not more intense than that produced by the control solution.


## Functionality Tests

NOTE-The following functionality tests of penetrability, fragmentation, and self-sealing, are performed on closures intended to be pierced by a hypodermic needle. The selfsealing test is required only for closures intended for multi-
ple-dose containers. The needle specified for each test is a lubricated long bevel (bevel angle $12 \pm 2^{\circ}$ ) hypodermic needle ${ }^{1}$ with an external diameter of 0.8 mm (21 gauge). However, if needles other than the one specified are required for a specific product package, the manufacturer of the product may consider using these test procedures to verify the closure's functionality under actual conditions of use. In this case, the needle used is described when reporting test results.

## PENETRABILITY

This test is performed on closures intended to be pierced by a hypodermic needle. Fill 10 suitable vials to the nominal volume (or capacity) with water, fit the closures to be examined, and secure with a cap. Using a new tubried leng bevel (bevel angle $12 \pm 2^{\circ}$ ) hypodermic needle, with anew ternal diameter of 0.8 mm , for each sample, hypodermic needle as described above for each sample, pierce the closure with the needle perpendicular to the surface. The force for piercing is not greater than $10 \mathrm{~N}(1 \mathrm{kgf})$ determined with an accuracy of $\pm 0.25 \mathrm{~N}$ ( 25 gf ) for each closure.

## FRAGMENTATION

This test is performed on clesures intended to be piereed

## by a hypodermic needle.

## Aqueous Type I Closures for Liquid Preparations-

Fill 12 clean vials with water to 4 mL less than the nominal capacity. Fit the closures to be examined, secure with a cap, and allow to stand for 16 hours.

Type II Closures for Liquid Preparations-Fill 12 clean vials with sesame oil to 4 mL less than the nominal capacity. Fit the closures to be examined, secure with a cap, and allow to stand for 16 hours.

[^15]Closures for Dry Preparations-Fit closures to be examined into 12 clean vials, Using a hypodermic needle as leseribe above, inject int ach vial 1 mL of water while removing 1 mL of air. Repeat this procedure 4 times for each elestre, piercing each time at different site. Use a new nee dle for each clestre, cheeking that it is not blunted during the test. Filter the liquid in the vials through a filter having a perosity of $0.45 \mu \mathrm{~m}$, and count the rubber fragments vi swally. There are no more than 5 fragments visible ( $\leq-50$ Hm). In ease of doubt or dispute, the particles are to been amined mieroseopieally to determine their nature and size. and secure each with a cap.

Procedure-Using a hypodermic needle as described above, fitted to a clean syringe, inject into each vial 1 mL of water while removing 1 mL of air. [NOTE-For Type II Closures for Liquid Preparations, inject 1 mL of sesame oil while removing 1 mL of air.] Repeat this procedure 4 times for each closure, piercing each time at a different site. Use a new needle for each closure, checking that it is not blunted during the test. Filter the liquid in all the vials through a single filter having a porosity not greater than $0.5 \mu \mathrm{~m}$, and count the rubber fragments visually. There are no more than 5 fragments visible. This limit is based on the assumption that fragments with a diameter $\geq 50 \mu \mathrm{~m}$ are visible to the naked eye. In case of doubt or dispute, the particles are examined microscopically to determine their nature and size.

## SELF-SEALING CAPACITY

This test is performed on closures intended for use with multiple-dose containers. Fill 10 suitable vials with water to the nominal volume. Fit the closures that are to be examined, and cap. Using a hypodermic needle with 0.8 mm diameter, as described above for each closure, pierce each closure 10 times, piercing each time at a different site. Im-
merse the 10 vials in a solution of $0.5 \%$ methylene blue, and reduce the external pressure by 27 kPa for 10 minutes. Restore to atmospheric pressure, and leave the vials immersed for 30 minutes. Rinse the outside of the vials. None of the vials contain any trace of blue solution. $\triangle$ USP28
(Official January 1, 2006)

## Physical Tests and Determinations

## BRIEFING

(621〉Chromatography, USP 27 page 2272, page 170 of $P F$ 29(1) [Jan.-Feb. 2003], and page 2023 of PF 29(6) [Nov.-Dec. 2003]. The revisions proposed to the System Suitability section in this $P F$ are based on comments received regarding the proposals in $P F$ 29(1). Many comments were received concerning the specific numerical values chosen for permitted changes. Several correspondents suggested that these values should harmonize with the EP general chapter 2.2.46 Chromatographic Separation Techniques. On the basis of these comments, the Expert Committee decided that some of the numbers for allowable changes should be revised and that an effort should be made to harmonize with the $E P$. Additional text is added to address concerns regarding the multiple adjustments, the dwell volume, and the particle size for gas chromatography. The packing used in the test for Molecular weight distribution in the Antithrombin III Human monograph, appearing elsewhere in this $P F$, is added to the L packing already designated for Albumin Human under the Chromatographic Reagents section.
(PA4: H. Pappa) RTS—30393-1; 32582-1; 32996-1; 33153-1; 33999-1; 37456-1

## Change to read:

## SYSTEM SUITABILITY

System suitability tests are an integral part of gas and liquid chromatographic methods. They are used to verify that the resolution and reproducibility of the chromatographic system are adequate for the analysis to be done. The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such.

The resolution, $R$, [NOTE-All terms and symbols are defined in the Glossary of Symbols] is a function of column efficiency, $N$, and is specified to ensure that closely eluting compounds are resolved from each other, to establish the general resolving power of the system, and to ensure that internal standards are resolved from the
drug. Column efficiency may be specified also as a system suitability requirement, especially if there is only one peak of interest in the chromatogram; however, it is a less reliable means to ensure resolution than direct measurement. Column efficiency is a measure of peak sharpness, which is important for the detection of trace components.

Replicate injections of a Standard preparation used in the assay or other standard solution are compared to ascertain whether requirements for precision are met. Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation, $S_{R}$, if the requirement is $2.0 \%$ or less; data from six replicate injections are used if the relative standard deviation requirement is more than $2.0 \%$.

The tailing factor, $T$, a measure of peak symmetry, is unity for perfectly symmetrical peaks and its value increases as tailing becomes more pronounced (see Fig. 2). In some cases, values less than unity may be observed. As peak asymmetry increases, integration, and hence precision, becomes less reliable.


Fig. 2. Asymmetrical chromatographic peak.
These tests are performed by collecting data from replicate injections of standard or other solutions as specified in the individual monograph. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions (see Procedures under Tests and Assays in the General Notices). Adjustments of operating enditions to meet system suit ability requirements may be necessary.
${ }^{\boldsymbol{\Delta}}$ If adjustments of operating conditions to meet system suitability requirements are necessary, each of the following is the maximum specification that can be considered, unless otherwise directed in the monograph. Adjustments are permitted only when Reference Standards suitable standards (including Reference Standards) are available for all ant lytes compounds used in the suitability test and are used to show that the adjustments have improved the quality of the chromatography in meeting system suitability requirements. Adjustments to chromatographic systems performed in order to comply with system suitability requirements are not to be made to compensate for column failure or to cir-
cumvent replacing a deteriorated column. Multiple adjustmens that may have a cumulative effect in the performance of the system are to be avoided.
pH of Mobile Phase (HPLC)-The pH of the aqueous buffer used in the preparation of the mobile phase can be adjusted to within $\pm 0.2 \pm 0.5$ units of the value or range specified.

Concentration of Salts in Buffer (HPLC)—The concentration of the salts used in the preparation of the aqueous buffer used in the mobile phase can be adjusted to within $\pm 10 \%$, provided the permitted pH variation (see above) is met.

## Ratio of Components in Mobile Phase (HPLC)-The

 of the miner The following adjustment limits apply to minor components of the mobile phase (specified at $50 \%$ or less). The amount(s) of these component(s) can be adjusted by $\pm 30 \%$ relative or $\pm 2 \%$ absolute (i.e., in relation to the total mobile phase), whichever is larger. However, the change in any component cannot exceed $\pm 10 \%$ absolute, nor can the final concentration of any component be reduced to zero. Adjustment can be made to one minor component in a ternary mixture. Examples of adjustments for binary and ternary mixtures are given below.
## Binary Mixtures-

SPECIFIED RATIO OF $50: 50$ - Thirty percent of 50 is $15 \%$ absolute, but this exceeds the maximum permitted change of $\pm 10 \%$ absolute in either component. Therefore, the mobile phase ratio may be adjusted only within the range of 40:60 to $60: 40$.

SPECIFIED RATIO OF 95:5-Thirty percent of 5 is $1.5 \% \mathrm{ab}-$ solute. However, because adjustments up to $\pm 2 \%$ absolute are allowed, the ratio may be adjusted within the range of 93:7 to 97:3.

SPECIFIED RATIO OF 2:98-Thirty percent of 2 is $0.6 \%$ absolute. In this case an absolute adjustment of $\pm 2 \%$ is not allowed because it would reduce the amount of the first component to zero. Therefore the maximum allowed adjustment is within the range of 1.4:98.6 to 2.6:97.4.

## Ternary Mixtures-

SPECIFIED RATIO OF 60:35:5-For the second component, $30 \%$ of 35 is $10.5 \%$ absolute, which exceeds the maximum permitted change of $\pm 10 \%$ absolute in any component. Therefore the second component may be adjusted only within the range of $25 \%$ to $45 \%$ absolute. For the third component, $30 \%$ of 5 is $1.5 \%$ absolute. Since $\pm 2 \%$ absolute is permitted and provides more flexibility, the third component may be adjusted within the range of $3 \%$ to $7 \%$ absolute. In all cases, a sufficient quantity of the first component is used to give a total of $100 \%$. Therefore, mixture ranges of 50:45:5 to 70:25:5 or 58:35:7 to 62:35:3 would meet the requirement.

## Betectar Wavelength of UV-Visible Detector

 (HPLC)—Deviations from the wavelengths specified in the method are not permitted. The procedure specified by the detector manufacturer, or another validated procedure, is to be used to verify that error in the detector wavelength is, at most, $\pm 3 \mathrm{~nm}$.Column Length (GC, HPLC): can be adjusted by as much as $\pm 70 \% .-50 \%$ to $+100 \%$.

Column Inner Diameter (GC, HPLC): can be adjusted by as much as $\pm 25 \% 50 \% . \pm 25 \%$ for HPLC and $\pm 50 \%$ for GC.

Film Thickness (Capillary GC): can be adjusted by as much as $-50 \%$ to $+100 \%$.

Particle Size (HPLC): can be reduced by as much as 50\%.

Particle Size (GC): going from a larger to a smaller/a smaller to a larger (if it is the same "Range Ratio", which is the diameter of the largest particle divided by the diameter
of the smallest particle) particle size GC mesh support is acceptable, provided the chromatography meets the requirements of the system suitability.

Flow Rate (GC, HPLC): can be adjusted by as much as $\pm 50 \%$.

Injection Volume (GC, HPLC): can be reduced as far as is consistent with accepted precision and detection limits. It may be increased to as much as twice the volume speciffed, provided there are no adverse effects-on factors-sueh as baseline, peak shapes, resolution, linearity, and retention times.

Column Temperature (HPLC): can be adjusted by as much as $\pm 20^{\circ} . \pm 10^{\circ}$. Column thermostating is recommended to improve control and reproducibility of retention time.

Column Temperature (GC): can be adjusted by as much
as $\pm 2 \%$, in terms of absolute temperature $\pm 10 \%$.
Oven Temperature Program (GC)—Adjustment of
temperatures is permitted as stated above. For the times specified for the temperature to be maintained or for the temperature to be changed from one to another, an adjustment of up to $\pm 20 \%$ is permitted.

Gradient Elution (HPLC)—The configuration of the equipment employed may significantly alter the resolution, retention time, and relative retentions described in the method. Should this occur, it may be due to excess dwell time, which is the volume between the point at which the two eluants meet and the top of the column. $\triangle$ USP28

Unless otherwise directed in the monograph, system suitability parameters are determined from the analyte peak.To ascertain the effectiveness of the final operating system, it should be subjected to suitability testing. Replicate injections of the standard preparation required to demonstrate adequate system precision may be made before the injection of samples or may be interspersed among sample injections. System suitability must be demonstrated throughout the run by injection of an appropriate control preparation at appropriate intervals.
The control preparation can be a standard preparation or a solution containing a known amount of analyte and any additional materials useful in the control of the analytical system, such as excipients or impurities. Whenever there is a significant change in equipment or in a critical reagent, suitability testing should be
performed before the injection of samples. No sample analysis is acceptable unless the requirements of system suitability have been met. Sample analyses obtained while the system fails
$\Delta_{\text {system suitability }}^{\mathbf{\Delta U S P 2 8}}$
requirements are unacceptable.

## Change to read:

## CHROMATOGRAPHIC REAGENTS

The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer. [NOTE-Particle sizes given in this listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category of packings or phases listed below, there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

## Packings

L1-Octadecyl silane chemically bonded to porous silica or ceramic micro-particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L2-Octadecyl silane chemically bonded to silica gel of a controlled surface porosity that has been bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L3-Porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.
L4-Silica gel of controlled surface porosity bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.
L5-Alumina of controlled surface porosity bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L6-Strong cation-exchange packing-sulfonated fluorocarbon polymer coated on a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L7-Octylsilane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L8-An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support, $10 \mu \mathrm{~m}$ in diameter.

L9- $10-\mu \mathrm{m}$ irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating.

L10-Nitrile groups chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L11-Phenyl groups chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L12-A strong anion-exchange packing made by chemically bonding a quaternary amine to a solid silica spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L13-Trimethylsilane chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L14-Silica gel $10 \mu \mathrm{~m}$ in diameter having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating.
L15-Hexylsilane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L16-Dimethylsilane chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L17-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form, 7 to $11 \mu \mathrm{~m}$ in diameter.

L18-Amino and cyano groups chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L19-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the calcium form, about $9 \mu \mathrm{~m}$ in diameter.

L20-Dihydroxypropane groups chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L21-A rigid, spherical styrene-divinylbenzene copolymer, 5 to $10 \mu \mathrm{~m}$ in diameter.

L22-A cation-exchange resin made of porous polystyrene gel with sulfonic acid groups, about $10 \mu \mathrm{~m}$ in size.

L23-An anion-exchange resin made of porous polymethacrylate or polyacrylate gel with quaternary ammonium groups, about $10 \mu \mathrm{~m}$ in size.

L24-A semi-rigid hydrophilic gel consisting of vinyl polymers with numerous hydroxyl groups on the matrix surface, 32 to $63 \mu \mathrm{~m}$ in diameter. ${ }^{5}$

L25-Packing having the capacity to separate compounds with a molecular weight range from 100-5000 (as determined by polyethylene oxide), applied to neutral, anionic, and cationic water-soluble polymers. A polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contained some residual carboxyl functional groups) was found suitable.

L26-Butyl silane chemically bonded to totally porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L27-Porous silica particles, 30 to $50 \mu \mathrm{~m}$ in diameter.
L28-A multifunctional support, which consists of a high purity, $100 \AA$, spherical silica substrate that has been bonded with anionic exchanger, amine functionality in addition to a conventional reversed phase C 8 functionality.

L29-Gamma alumina, reverse-phase, low carbon percentage by weight, alumina-based polybutadiene spherical particles, 5 $\mu \mathrm{m}$ in diameter with a pore volume of $80 \AA$.

L30-Ethyl silane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L31-A strong anion-exchange resin-quaternary amine bonded on latex particles attached to a core of $8.5-\mu \mathrm{m}$ macroporous particles having a pore size of $2000 \AA$ and consisting of ethylvinylbenzene cross-linked with $55 \%$ divinylbenzene.

L32-A chiral ligand-exchange packing-L-proline copper complex covalently bonded to irregularly shaped silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L33-Packing having the capacity to separate dextrans by molecular size over a range of 4000 to $500,000 \mathrm{Da}$. It is spherical, silica-based, and processed to provide pH stability. ${ }^{6}$

L34-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the lead form, about $9 \mu \mathrm{~m}$ in diameter.

L35-A zirconium-stabilized spherical silica packing with a hydrophilic (diol-type) molecular monolayer bonded phase having a pore size of $150 \AA$.

L36-A 3,5-dinitrobenzoyl derivative of L-phenylglycine covalently bonded to $5-\mu \mathrm{m}$ aminopropyl silica.

L37-Packing having the capacity to separate proteins by molecular size over a range of 2,000 to $40,000 \mathrm{Da}$. It is a polymethacrylate gel.

L38-A methacrylate-based size-exclusion packing for watersoluble samples.

L39-A hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin.

L40-Cellulose tris-3,5-dimethylphenylcarbamate coated porous silica particles, 5 to $20 \mu \mathrm{~m}$ in diameter.

L41-Immobilized $\alpha_{1}$-acid glycoprotein on spherical silica particles, $5 \mu \mathrm{~m}$ in diameter.

L42-Octylsilane and octadecylsilane groups chemically bonded to porous silica particles, $5 \mu \mathrm{~m}$ in diameter.

L43-Pentafluorophenyl groups chemically bonded to silica particles
$\square$ by a propyl spacer, $\boldsymbol{m}_{1 S}$ (USP27)
5 to $10 \mu \mathrm{~m}$ in diameter.

[^16]■YMC-Pack PVA-SIL manufactured by YMC Co., Ltd.■1S (USP27)
${ }^{6}$ Available as TSKgel G4000 SWXL from TosoHaas (www.tosohaas.com).

L44-A multifunctional support, which consists of a high purity, $60 \AA$, spherical silica substrate that has been bonded with a cationic exchanger, sulfonic acid functionality in addition to a conventional reversed phase C 8 functionality.

L45-Beta cyclodextrin bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.
L46-Polystyrene/divinylbenzene substrate agglomerated with quaternary amine functionalized latex beads, $10 \mu \mathrm{~m}$ in diameter.

L47-High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, $8 \mu \mathrm{~m}$ in diameter. ${ }^{7}$

L48-Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion-exchange microbeads, $15 \mu \mathrm{~m}$ in diameter.

L49-A reversed-phase packing made by coating a thin layer of polybutadiene onto spherical porous zirconia particles, 3 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{8}$

L50-Multifunction resin with reversed-phase retention and strong anion-exchange functionalities. The resin consists of ethylvinylbenzene, $55 \%$ cross-linked with divinylbenzene copolymer, 3 to $15 \mu \mathrm{~m}$ in diameter, and a surface area not less than $350 \mathrm{~m}^{2}$ per g. Substrate is coated with quaternary ammonium functionalized latex particles consisting of styrene cross-linked with divinylbenzene. ${ }^{9}$

L51—Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{10}$

L52-A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{11}$

L53-Weak cation-exchange resin consisting of ethylvinylbenzene, $55 \%$ cross-linked with divinylbenzene copolymer, 3 to 15 $\mu \mathrm{m}$ diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than $500 \mu \mathrm{Eq} /$ column. ${ }^{12}$

L54-A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 $\mu \mathrm{m}$ in diameter. ${ }^{13}$
${ }^{\boldsymbol{\Delta}}$ L55-A strong cation-exchange resin made of porous silica coated with polybutadiene-maleic acid copolymer, about $5 \mu \mathrm{~m}$ in diameter. ${ }^{14}$
${ }^{\mathbf{\Delta}}$ L56-Propyl silane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{15}{ }_{\Delta U S P 27}$
-L53 \#\# (Alendronic Acid Tablets, PRP-X100)—An an-ion-exchange resin consisting of a rigid, spherical styrenedivinylbenzene copolymer with trimethylammonium groups at a loading of about 2 mEq per g, 3 to $20 \mu \mathrm{~m}$ in diameter. ${ }^{\text {is }}$ (USP27)

[^17]-L54 \#\# (Maltose, Aminex HPX-87N)—Strong cationexchange resin consisting of sulfonated cross-linked styr-ene-divinylbenzene copolymer in the sodium form, about 7 to $11 \mu \mathrm{~m}$ in diameter. ${ }^{\mathrm{b}}$ (1S (USP27)
-L57 \#\# (Nevirapine, Supelcosil ABZ)—Spherical, porous silica gel, 3 or $5 \mu \mathrm{~m}$ in diameter, the surface of which has been covalently modified with palmitamidopropyl groups and endcapped with acetamidopropyl groups to a ligand density of about $6 \mu$ moles per $\mathrm{m}^{2}$. ${ }^{\mathrm{c}}$ (IS (USP27)
-L58 \#\# (Albumin Human, Antithrombin III Human, TSKgel G3000 SW)—Packing having the capacity to separate proteins by molecular weight over the range of 10 to 500 kDa . It is spherical $(10 \mu \mathrm{~m})$, silica-based, and processed to provide hydrophilic characteristics and pH stability. ${ }^{\text {d }}{ }_{1 S}$ (USP27)
-L59 \#\# (Clonidine, Zorbax SB-C3)—Propyl silane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{21}{ }^{1 S}$ (USP27)
-L60 \#\# Bethanecol Chloride, Bethanecol Chloride Tablets, IC-Pak C M/D)—A strong cation exchange resin made of porous silica coated with polybutadiene-maleic acid copolymer, about $5 \mu \mathrm{~m}$ in diameter. ${ }^{23}$ 1S (USP27)
-L64 \#\# (Lycopene, Lycopene Preparation, YMC 30)-
C30 silane bonded phase on a fully porous spherical silica, 3 to $15 \mu \mathrm{~m}$ in diameter. $\quad 1 \mathrm{~S}$ (USP27)

[^18]-L\#\# (Clopidogrel Bisulfate, Ultron ES-OVM)—A chir-al-recognition protein, ovomucoid, chemically bonded to silica particles, about $5 \mu \mathrm{~m}$ in diameter, with a pore size of $120 \AA$. $\quad$ 2S (USP27)
-L\#\# (Enoxaparin Sodium Injection, IonPac AG11)—[To
come.] ${ }_{\text {2S (USP27) }}$
-L\#\# (Enoxaparin Sodium Injection, IonPac AS11)—[To
come.] $]_{\text {2S (USP27) }}$
■ L\#\# (Enoxaparin Sodium, Dowex 1X8)-[To come.] $]_{\text {2S (USP27) }}$
-L\#\# (Enoxaparin Sodium, Dowex 50WX2)—[To
come.] $]_{\text {2S (USP27) }}$

## Phases

G1-Dimethylpolysiloxane oil.
G2-Dimethylpolysiloxane gum.
G3-50\% Phenyl-50\% methylpolysiloxane.
G4-Diethylene glycol succinate polyester.
G5-3-Cyanopropylpolysiloxane.
G6-Trifluoropropylmethylpolysiloxane.
G7-50\% 3-Cyanopropyl-50\% phenylmethylsilicone.
G8-80\% Bis(3-cyanopropyl)-20\% 3-cyanopropylphenylpolysiloxane (percentages refer to molar substitution).

G9-Methylvinylpolysiloxane.
G10-Polyamide formed by reacting a $\mathrm{C}_{36}$ dicarboxylic acid with 1,3-di-4-piperidylpropane and piperidine in the respective mole ratios of 1.00:0.90:0.20.

G11-Bis(2-ethylhexyl) sebacate polyester.
G12-Phenyldiethanolamine succinate polyester.
G13-Sorbitol.
G14-Polyethylene glycol (av. mol. wt. of 950 to 1050).
G15-Polyethylene glycol (av. mol. wt. of 3000 to 3700 ).
G16-Polyethylene glycol compound (av. mol. wt. about 15,000 ). A high molecular weight compound of polyethylene glycol with a diepoxide linker. Available commercially as Polyethylene Glycol Compound 20M, or as Carbowax 20M, from suppliers of chromatographic reagents.

G17-75\% Phenyl-25\% methylpolysiloxane.
G18-Polyalkylene glycol.
G19-25\% Phenyl-25\% cyanopropyl-50\% methylsilicone.
G20-Polyethylene glycol (av. mol. wt. of 380 to 420).
G21-Neopentyl glycol succinate.
G22-Bis(2-ethylhexyl) phthalate.
G23-Polyethylene glycol adipate.
G24-Diisodecyl phthalate.
G25-Polyethylene glycol compound TPA. A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with terephthalic acid. Available commercially as Carbowax $20 \mathrm{M}-\mathrm{TPA}$ from suppliers of chromatographic reagents.

G26-25\% 2-Cyanoethyl-75\% methylpolysiloxane.
G27-5\% Phenyl-95\% methylpolysiloxane.
G28-25\% Phenyl-75\% methylpolysiloxane.
G29-3, 3'-Thiodipropionitrile.
G30--Tetraethylene glycol dimethyl ether.
G31-Nonylphenoxypoly(ethyleneoxy)ethanol (av. ethyleneoxy chain length is 30 ); Nonoxynol 30 .

G32-20\% Phenylmethyl-80\% dimethylpolysiloxane.
G33-20\% Carborane-80\% methylsilicone.
G34-Diethylene glycol succinate polyester stabilized with phosphoric acid.

G35-A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with nitroterephthalic acid.
G36-1\% Vinyl-5\% phenylmethylpolysiloxane.
G37-Polyimide.
G38-Phase G1 containing a small percentage of a tailing inhibitor. ${ }^{16}$

G39—Polyethylene glycol (av. mol. wt. about 1500).
G40-Ethylene glycol adipate.
G41-Phenylmethyldimethylsilicone ( $10 \%$ phenyl-substituted).
G42-35\% phenyl-65\% dimethylpolysiloxane (percentages refer to molar substitution).

G43-6\% cyanopropylphenyl-94\% dimethylpolysiloxane (percentages refer to molar substitution).

G44-2\% low molecular weight petrolatum hydrocarbon grease and $1 \%$ solution of potassium hydroxide.

G45-Divinylbenzene-ethylene glycol-dimethylacrylate.
G46-14\% Cyanopropylphenyl-86\% methylpolysiloxane.
G47-Polyethylene glycol (av. mol. wt. of about 8000).
G48-Highly polar, partially cross-linked cyanopolysiloxane.
G49_Proprietary derivatized phenyl groups on a polysiloxane backbene. ${ }^{17}$
-G50 \#\# (Docosahexaenoic Acid)—Polyethylene glycol, cross-linked (av. mol. wt. of more than 20,000). ${ }^{\mathrm{e}}{ }^{1 S}{ }_{\text {(USP27) }}$

## Supports

NOTE--Unless otherwise specified, mesh sizes of 80 to 100 or, alternatively, 100 to 120 are intended.

S1A-Siliceous earth for gas chromatography has been flux-calcined by mixing diatomite with $\mathrm{Na}_{2} \mathrm{CO}_{3}$ flux and calcining above $900^{\circ}$. The siliceous earth is acid-washed, then water-washed until neutral, but not base-washed. The siliceous earth may be silanized by treating with an agent such as dimethyldichlorosilane ${ }^{18}$ to mask surface silanol groups.

S1AB-The siliceous earth as described above is both acid- and base-washed. ${ }^{18}$

S1C-A support prepared from crushed firebrick and calcined or burned with a clay binder above $900^{\circ}$ with subsequent acidwash. It may be silanized.

S1NS-The siliceous earth is untreated.
S2-Styrene-divinylbenzene copolymer having a nominal surface area of less than $50 \mathrm{~m}^{2}$ per g and an average pore diameter of 0.3 to $0.4 \mu \mathrm{~m}$.

S3-Copolymer of ethylvinylbenzene and divinylbenzene having a nominal surface area of 500 to $600 \mathrm{~m}^{2}$ per $g$ and an average pore diameter of $0.0075 \mu \mathrm{~m}$.

S4-Styrene-divinylbenzene copolymer with aromatic - O and N groups, having a nominal surface area of 400 to $600 \mathrm{~m}^{2}$ per $g$ and an average pore diameter of $0.0076 \mu \mathrm{~m}$.

S5-40- to 60-mesh, high-molecular weight tetrafluorethylene polymer.

[^19]S6-Styrene-divinylbenzene copolymer having a nominal surface area of 250 to $350 \mathrm{~m}^{2}$ per g and an average pore diameter of $0.0091 \mu \mathrm{~m}$.

S7-Graphitized carbon having a nominal surface area of $12 \mathrm{~m}^{2}$ per $g$.

S8-Copolymer of 4-vinyl-pyridine and styrene-divinylbenzene.

S9-A porous polymer based on 2,6-diphenyl-p-phenylene oxide.

S10-A highly polar cross-linked copolymer of acrylonitrite and divinylbenzene.

S11-Graphitized carbon having a nominal surface area of 100 $\mathrm{m}^{2}$ per g modified with small amounts of petrolatum and polyethylene glycol compound. ${ }^{19}$

S12-Graphitized carbon having a nominal surface area of 100 $\mathrm{m}^{2}$ per g .

## Briefing

$\langle 645\rangle$ Water Conductivity, USP 27 page 2286. It is proposed to clarify the language in Stage 1 under Procedure to emphasize that it is a step function, not interpolation. The intention of the Pharmaceutical Waters Expert Committee is to use the more conservative conductivity values.
(PW: F. Barletta) RTS-40694-1

## Change to read:

## PROCEDURE

## Stage 1

1. Determine the temperature of the water and the conductivity of the water using a nontemperature-compensated conductivity reading. The measurement may be performed in a suitable container or as an on-line measurement.
2. Using the Stage 1-Temperature and Conductivity Requirements table, find the temperature value that is not greater than the measured temperature,
${ }^{\Delta}$ i.e., the next lower temperature. $\mathbf{u U S P}^{\text {US }}$.
The corresponding conductivity value is the limit that ture.
On this table is the limit. [NOTE-Do not interpolate.]
3. If the measured conductivity is not greater than the table val3. If the measured conductivity is not greater than the table value, the water meets the requirements of the test for conductivity. If
the conductivity is higher than the table value, proceed with Stage 2.
[^20]| Stage 1——Temperature and Conductivity Requirements <br> (for nontemperature-compensated conductivity <br> measurements only) |  |
| :---: | :---: |
| Temperature | Conductivity Requirement $(\mu \mathrm{S} / \mathrm{cm})$ |
| 0 | 0.6 |
| 5 | 0.8 |
| 10 | 0.9 |
| 15 | 1.0 |
| 20 | 1.1 |
| 25 | 1.3 |
| 30 | 1.4 |
| 35 | 1.5 |
| 40 | 1.7 |
| 45 | 1.8 |
| 50 | 1.9 |
| 55 | 2.1 |
| 60 | 2.2 |
| 65 | 2.4 |
| 70 | 2.5 |
| 75 | 2.7 |
| 80 | 2.7 |
| 85 | 2.7 |
| 90 | 2.7 |
| 95 | 2.9 |
| 100 | 3.1 |

## Stage 2

4. Transfer a sufficient amount of water ( 100 mL or more) to a suitable container, and stir the test specimen. Adjust the temperature, if necessary, and, while maintaining it at $25 \pm 1^{\circ}$, begin vigorously agitating the test specimen while periodically observing the conductivity. When the change in conductivity (due to uptake of atmospheric carbon dioxide) is less than a net of $0.1 \mu \mathrm{~S} / \mathrm{cm}$ per 5 minutes, note the conductivity.
5. If the conductivity is not greater than $2.1 \mu \mathrm{~S} / \mathrm{cm}$, the water meets the requirements of the test for conductivity. If the conductivity is greater than $2.1 \mu \mathrm{~S} / \mathrm{cm}$, proceed with Stage 3.

## Stage 3

6. Perform this test within approximately 5 minutes of the conductivity determination in Step 5, while maintaining the sample temperature at $25 \pm 1^{\circ}$. Add a saturated potassium chloride solution to the same water sample ( 0.3 mL per 100 mL of the test specimen), and determine the pH to the nearest 0.1 pH unit, as directed under $p H\langle 791\rangle$.
7. Referring to the Stage 3-pH and Conductivity Requirements table, determine the conductivity limit at the measured pH value. If the measured conductivity in Step 4 is not greater than the conductivity requirements for the pH determined in Step 6, the water meets the requirements of the test for conductivity. If either the measured conductivity is greater than this value or the pH is outside the range of 5.0 to 7.0 , the water does not meet the requirements of the test for conductivity.

Stage 3-pH and Conductivity Requirements (for atmosphere and temperature equilibrated samples only)

|  | Conductivity Requirement $(\mu \mathrm{S} / \mathrm{cm})$ |
| :---: | :---: |
| 5.0 | 4.7 |
| 5.1 | 4.1 |
| 5.2 | 3.6 |
| 5.3 | 3.3 |
| 5.4 | 3.0 |
| 5.5 | 2.8 |
| 5.6 | 2.6 |
| 5.7 | 2.5 |
| 5.8 | 2.4 |
| 5.9 | 2.4 |
| 6.0 | 2.4 |
| 6.1 | 2.4 |
| 6.2 | 2.5 |
| 6.3 | 2.4 |
| 6.4 | 2.3 |
| 6.5 | 2.2 |
| 6.6 | 2.1 |
| 6.7 | 2.6 |
| 6.8 | 3.1 |
| 6.9 | 3.8 |
| 7.0 | 4.6 |

## BRIEFING

〈711〉 Dissolution, USP 27 page 2303. The USP Expert Committee on Biopharmaceutics has decided that it will no longer encourage the inclusion of new dissolution procedures based on pooled sampling as found in the general chapter $\langle 711\rangle$. The Committee finds that the procedure for pooled sampling prevents the observation of intertablet variability otherwise possible with unit sampling. As a result of the Committee decision, it is proposed to delete the Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets and the Interpretation for a Pooled Sample from the general chapter text. The procedure and interpretation text removed from the general chapter will be incorporated into the tests for Dissolution in the individual monographs where pooled sampling is currently employed.
(BPC: W. Brown) RTS-40597-1

## Delete the following:

${ }^{\wedge}$ Procedure-for a Pooled Sample for Capsules, Uneoated Tablets, and-Plain-Coated Tablets Use this procedure where Proedure for a Porled Sample is specified in the individualmenograph. Proeed as directed under Procedure for Gapsules, Uneoated Tablets, and Plain-Coated Tablets. Combine-equat velume of the filtered solutions of the six or twelve individual speeimens withdrawn, and use the pooled sample as the test solution. Determine the average amount of the active ingredient dissolved in the pooled sample. $\triangle$ USP28

## Change to read: <br> Interpretation-

Unit Sample-Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to the accompanying Acceptance Table. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content; the $5 \%, 15 \%$, and $25 \%$ values in the Acceptance Table are percentages of the labeled content so that these values and $Q$ are in the same terms.

Acceptance Table

|  | Number <br> Tested | Acceptance Criteria |
| :---: | :---: | :--- | | Stage | 6 | Each unit is not less than $Q+5 \%$. <br> Average of 12 units $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or <br> greater than $Q$, and no unit is less than $Q-$ <br> $\mathrm{S}_{1}$ |
| :---: | :---: | :--- |
| $\mathrm{~S}_{2}$ | 6 | $15 \%$. |
| $\mathrm{S}_{3}$ | 12 | Average of 24 units $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\mathrm{S}_{3}\right)$ is equal <br> to or greater than $Q$, not more than 2 units <br> are less than $Q-15 \%$, and no unit is less <br> than $Q-25 \%$. |

Pooled Sample Unless otherwise specified in the individuat monegraph, the requirements are met if the quantities of active in gredient dissolved from the pooled sample conform to the acempanying Aceeptane Table for a Pooled Sample. Continue testing through the three stage unless the results conform at either $S_{+}$or $S_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient specified in the individual menograph, expressed as a percentage of the labeled content.

| Aceeptanee Table for a Pooled Sample |  |  |
| :---: | :---: | :---: |
|  | Number |  |
| Stage | Fested | Acceptane Criteria |
| $\mathrm{S}_{+}$ | $\checkmark$ | Average ameunt dissolved is not less than $Q+10 \%$. |
| $S_{3}$ | $\dagger$ | Averag ann dis $\left(\mathrm{S}_{+}+\mathrm{S}_{2}\right)$ is equal to ryeater than $0+5 \%$ |
| $\mathrm{S}_{3}$ | 12 | Average mount dissolved ( $\mathrm{S}_{4}+\mathrm{S}_{2}+\mathrm{S}_{3}$ )is equal to or greater than $Q$. |

# GENERAL CHAPTERS 

## General Information

## BRIEFING

$\langle 1010\rangle$ Analytical Data-Interpretation and Treatment, page 187 of $P F$ 29(1) [Jan.-Feb. 2003]. This proposed new general information chapter is again presented with changes reflecting comments received. In addition, the Expert Committee on Biostatistics has rewritten Appendices $D$ and $E$ to clarify the examples given for evaluation of analytical methods. This general informational chapter addresses the needs of the nonstatistician scientist who may be called upon to employ the basic statistical methods given. The Expert Committee recommends that the information contained in this proposal not be viewed as defining acceptable statistical practice for compendial purposes. The scope of this chapter does not allow a complete disquisition on statistical methods available for such purposes. Thus the content should be viewed as a basic primer with practical applications. To allow further exploration of the statistical principles given, a list of references is given as Appendix $F$.

Comments regarding this proposal are invited and should be submitted by May 15, 2004.
(BST: W. Brown) RTS—39970-1; 39990-1; 40041-1; 400441; 40045-1; 40061-3

## Add the following:

## © $\langle 1010\rangle$ ANALYTICAL DATAINTERPRETATION AND TREATMENT

## INTRODUCTION

This chapter provides information regarding acceptable practices for the analysis and consistent interpretation of data obtained from chemical and other analyses. Basic statistical approaches for evaluating data are described, and the treatment of outliers and comparison of analytical methods are discussed in some detail. It she inferred, however, that the analysis tools mentioned in this
ehapter form an exhaustive list. Other, equally valid, statistieal methods may be used at the discretion of the manufactarer.
[NOTE-It should not be inferred that the analysis tools mentioned in this chapter form an exhaustive list. Other, equally valid, statistical methods may be used at the discretion of the manufacturer.]

Assurance of the quality of pharmaceuticals is accomplished by combining a number of practices, including robust formulation design, validation, testing of starting materials, in-process testing, and final-product testing. Each of these practices is dependent on reliable test methods. In the development process, test procedures are developed and validated to ensure that the manufactured products are thoroughly characterized. Final-product testing provides further assurance that the products are consistently safe, efficacious, and in compliance with their specifications.

Measurements are inherently variable. The variability of biological tests has long been recognized by the USP. For example, the need to consider this variability when analyzing biological test data is addressed under Design and Analysis of Biological Assays $\langle 111\rangle$. The chemical analysis measurements commonly used to analyze pharmaceuticals are also inherently variable, although less so than those of the biological tests. However, in many instances the acceptance criteria are proportionally tighter, and thus, this smaller allowable variability has to be considered when analyzing data generated using analytical procedures. If the variability of a measurement is not characterized and stated along with the result of the measurement, then the data can only be interpreted in the most limited sense. For example, stating that the difference between the averages from two laboratories when testing a common set of samples is
$10 \%$ has limited interpretation, in terms of how important such a difference is, without knowledge of the intralaboratory variability.

This chapter provides gridance direction for scientifically acceptable treatment and interpretation of data. Statistical tools that may be helpful in the interpretation of analytical data are described. Many descriptive statistics, such as the mean and standard deviation, are in common use. Other statistical tools, such as outlier tests, can be performed using several different, scientifically valid approaches, and examples of these tools and their applications are also included. The framework within which the results from a compendial test are interpreted is clearly outlined in Test Results, Statistics, and Standards under General Notices and Requirements. Selected references that might be helpful in obtaining additional information on the statistical tools discussed in this chapter are listed in Appendix $F$ at the end of the chapter. USP does not endorse these citations, and they do not represent an exhaustive list. Further information about many of the methods cited in this chapter may also be found in most statistical textbooks.

## PREREQUISITE LABORATORY PRACTICES AND PRINCIPLES

The sound application of statistical principles to laboratory data requires the assumption that such data have been collected in a traceable (i.e., documented) and unbiased manner. To ensure this, the following practices are beneficial.

## Sound Record Keeping

Laboratory records are maintained with sufficient detail, so that other equally qualified analysts can reconstruct the experimental conditions and review the results obtained.

When collecting data, the data should generally be obtained with more decimal places than the specification requires and rounded only after final calculations are completed.

## Sampling Considerations

Effective sampling is an important step in the assessment of a quality attribute of an article. The purpose of sampling is to provide representative data (the sample) for estimating the properties of the population (the article). How to attain such a sample depends entirely on the question that is to be answered by the sample data. In general, use of a random process is considered the most appropriate way of selecting a sample. Indeed, a random and independent sample is necessary to ensure that the resulting data produce valid estimates of the properties of the population. Generating a nonrandom or "convenience" sample risks the possibility that the estimates will be biased. The most straightforward type of random sampling is called simple random sampling, a process in which every unit of the population has an equal chance of appearing in the sample. However, sometimes this method of selecting a random sample is not optimal because it cannot guarantee equal representation among factors (i.e., time, location, machine) that may influence the critical properties of the article. For example, if it requires 12 hours to manufacture all of the units in a lot and it is vital that the sample be representative of the entire production process, then taking a simple random sample after the production has been completed may not be appropriate because there can be no guarantee that such a sample will contain a similar number of units made from every time period within the 12hour process. Instead, it is better to take a systematic random sample whereby a unit is randomly selected from the production process at systematically selected times or locations (e.g., sampling every 30 minutes from the units produced at
that time) to ensure that units taken throughout the entire manufacturing process are included in the sample. Another type of random sampling procedure is needed if, for example, a product is filled into vials using four different filling machines. In this case it would be important to capture a random sample of vials from each of the filling machines. A stratified random sample, which randomly samples an equal number of vials from each of the four filling machines, would satisfy this requirement. Regardless of the reason for taking a sample (e.g., batch-release testing), a sampling pron should be established to provide details on how the sample is to be obtained to ensure that the sample is representative of the entirety of the article and that the resulting data have the required sensitivity. The sample should be che representive. The optimal sampling strategy will depend on knowledge of the manufacturing and analytical measurement processes. Once the sampling scheme has been defined, it is likely that the sampling will include some element of random selection. Finally, there must be sufficient sample collected for the original analysis, subsequent verification analyses, and other analyses.

Tests discussed in the remainder of this chapter assume that simple random sampling has been performed.

## Use of Reference Standards

Where the use of the USP Reference Standard is specified, the USP Reference Standard, or a secondary standard traceable to the USP Reference Standard, is used. Because the assignment of a value to a standard is one of the most important factors that influences the accuracy of an assy, analysis, it is critical that this be done correctly. The procedures outlined belaw may be useful in this regard.

## System Performance Verification <br> The performanee of an analytieal system should be evaltuted at specified time intervals to ensure that the appropriate level of performance has been maintained. In addition, an ongoing routine assessment may be performed at appropriate intervals by analyzing a control sample, whese analy tieal properties have been carefully determined, or using

 ether means, such as, variation ameng the standards, back ground signal-to noise ratios, ete. If a change in the operating properties of the analytical procedtre is observed, proper performanee needs to be re-established, and all results obtained between the last acceptable performance ver iffien to berifying an acceptable level of performance for an analytical system in routine or continuous use can be a valuable practice. This may be accomplished by analyzing a control sample at appropriate intervals, or using other means, such as, variation among the standards, background signal-to-noise ratios, etc. Attention to the measured parameter, such as charting the results obtained by analysis of a control sample, can signal a change in performance that requires adjustment of the analytical system.
## Method Validation

All methods are appropriately validated as specified under Validation of Compendial Methods $\langle 1225\rangle$. The USP NF methods are assumed to be valid and to comply with the GFR. An already validated method should be applied to a new sample formulation only after confliming that the new matrix doe not interfere with the aecuracy, linearity, or precision of the method. Methods published in the $U S P-N F$ have been validated and meet the Current Good

Manufacturing Practices regulatory requirement for validation as established in the Code of Federal Regulations. A validated method may be used to test a new formulation only after confirming that the new formulation does not interfere with the accuracy, linearity, or precision of the method. It may not be assumed that a validated method could correctly measure the active ingredient in a formulation that is different from that used in establishing the original validity of the method.

## MEASUREMENT PRINCIPLES AND VARIATION

All measurements are, at best, estimates of the actual ("true" or "accepted") value for they contain random variability (also referred to as random error) and may also contain systematic variation (bias). Thus, the measured value differs from the actual value because of variability inherent in the measurement. If an array of measurements consists of individual results that are representative of the whole, statistical methods can be used to estimate informative properties of the entirety, and statistical tests are available to investigate whether it is likely that these properties comply with given requirements. The resulting statistical analyses should address the variability associated with the measurement process as well as that of the entity being measured. Statistical measures used to assess the direction and magnitude of these errors include the mean, standard deviation, and expressions derived therefrom, such as the coefficient of variation (CV, also called the relative standard deviation, RSD). The estimated variability can be used to calculate confidence intervals for the mean, or measures of variability, and tolerance intervals capturing a specified proportion of the individual measurements.

The use of statistical measures must be tempered with good judgment, especially with regard to representative sampling. Most of the statistical measures and tests cited in this chapter rely on the assumptions that the distribution of the entire population is represented by a normal distribution and that the analyzed sample is a representative subset of this population. The normal (or Gaussian) distribution is bell-shaped and symmetric about its center and has certain ether characteristics that are required for these tests to be valid. If the assumption of a normal distribution for the population is not warranted, then normality can often be achieved (at least approximately) through an appropriate transformation of the measurement values. For example, many variables have distributions with longer right tails than left. Such distributions can often be made approximately normal through a log transformation. An alternative approach would be to use "distribution-free" or "nonparametric" statistical procedures that do not require that the shape of the population be that of a normal distribution. When the objective is to construct a confidence interval for the mean or for the difference between two means, for example, then the normality assumption is not as important because of the central limit theorem. However, one must verify normality of data to construct valid confidence intervals for standard deviations and ratios of standard deviations, perform some outlier tests, and construct valid statistical tolerance limits. In the latter case, normality is a critical assumption. Simple graphical methods, such as dot plots, histograms, and normal probability plots, are useful aids for investigating this assumption.

A single analytical measurement may be useful in quality assessment if the sample is from a whole that has been prepared using a well-validated, documented process and if the analytical errors are well known. The obtained analytical result may be qualified by including an estimate of the associated errors. There may be instances when one might consider the use of averaging because the variability associated with an average value is always reduced as compared to the variability in the individual measurements. The choice of whether to use individual measurements or averages will depend upon the use of the measure and its variability. For example, when multiple measurements are obtained on the same sample aliquot, such as from multiple injections of the sample in an HPLC method, it is generally advisable to average the resulting data for the reason discussed above. Howere, if the datare obtained from independent samples taken from the lot, then averaging would enly be advisable if lot uniformity had already been cen firmed.

Variability is associated with the dispersion of observations around the center of a distribution. The most commonly used statistic to measure the center is the sample mean ( $\bar{x}$ ):

Method variability can be estimated in various ways. The most common and useful assessment of a method's variability is the determination of the standard deviation based on repeated independent ${ }^{1}$, tmeorrelate measurements of a control sample. The standard deviation, $s$, is calculated by the formula:

$$
s=\sqrt{\sum_{i=1}^{n}\left(x_{i}-\bar{x}\right)^{2} /(n-1)}
$$

in which $x_{i}$ is the individual measurement in a set of $n$ measurements; and $\bar{x}$ is the mean of all the measurements. The relative standard deviation (RSD) is then calculated as:

$$
R S D=\frac{s}{x} \cdot 100 \%
$$

and expressed as a percentage. For biologieal assays, the data often need to be log transformed to achieve nermality. An alternative form for the RSD that is appropriate when the data have been log (base e) transformed is:


[^21]where in this ease $s$ would be the standard deviation of the log (base ) transformed data. ${ }^{2}$ If the data requires $\log$ tranformation to achieve normality (e.g., for biological assays), then alternative methods are available. ${ }^{3}$

A control sample is defined as a homogeneous and stable sample that is tested at specific intervals sufficient to monitor the performance of the method for which it was established. Test data from a control sample can be used to monitor the method variability or be used as part of ther for reperting systatability requirements. ${ }^{4}$ The control sample should be essentially the same as the test sample and should be treated similarly whenever possible. A control chart can be constructed and used to monitor the method performance on a continuing basis as shown under Appendix $A$.

A precision study should be conducted to provide a better estimate of method variability. The precision study may be designed to determine intermediate precision (atinat ity - "between run" + "within run" variability) (which includes the components of both "between run" and "within-
z-An alternative formula for caleulating RSD-for biolegieal assays is

${ }^{3}$ When data has been $\log$ (base $e$ ) transformed to achieve normality, alternative forms for the RSD are:

$$
R S D=100 \% \cdot\left(e^{s}-1\right)
$$

and

$$
R S D=100 \% \cdot \sqrt{e^{s^{2}}-1}
$$

where, in this case, $s$ is the standard deviation of the $\log$ (base $e$ ) transformed data.
${ }^{4}$ See System Suitability under Chromatography $\langle 621\rangle$.
run" variability) and repeatability ("within-run" variability). The intermediate precision studies should allow for changes in the experimental conditions that might be expected, such as different analysts, different preparations of reagents, different days, and different instruments. To perform a precision study, the test is repeated several times. Each run must be completely independent of the others to provide accurate estimates of the various components of variability. In addition, within each run, replicates are made in order to estimate repeatability. See an example of a precision study under Appendix B.
A confidence interval for the mean may be considered in the interpretation of data. Such intervals are calculated from several data points using the sample mean $(\bar{x})$ and sample standard deviation $(s)$ according to the formula:

$$
\left(\bar{x}-t_{\alpha / 2, n-1} \frac{s}{\sqrt{n}}, \bar{x}+t_{\alpha / 2, n-1} \frac{s}{\sqrt{n}}\right),
$$

in which $t_{\alpha 2, n-1}$ is a statistical number dependent upon the sample size $(n)$, the number of degrees of freedom $(n-1)$, and the desired confidence level $(1-\alpha)$. Its values are obtained from published tables of the Student $t$-distribution. The confidence interval provides an estimate of the range within which the "true" population mean ( $\mu$ ) falls, and it also evaluates the reliability of the sample mean as an estimate of the true mean. If the same experimental set-up were to be replicated over and over and a $95 \%$ (for example) confidence interval for the true mean is calculated each time, then $95 \%$ of such intervals would be expected to contain the true mean, $\mu$. One cannot say with certainty whether or not the confidence interval derived from a specific set of data actually collected contains $\mu$. However, it can be said that, assuming the data are normally distributed and the
standard deviation was correctly estimated, the procedure used to construct the confidence interval guarantees that $95 \%$ of such confidence intervals contain $\mu$.

## OUTLYING RESULTS

Occasionally, observed analytical results are very different from those expected. Aberrant, anomalous, contaminated, discordant, spurious, suspicious or wild observations; and flyers, rogues, and mavericks are properly called outlying results. Like all laboratory results, these outliers must be documented, interpreted, and managed. Such results may be accurate measurements of the entity being measured, but are very different from what is expected. Alternatively, due to an error in the analytical system, the results may not be typical, even though the entity being measured is typical. When an outlying result is obtained, systematic laboratory and process investigations of the result are conducted to determine if an assignable cause for the result can be established. Factors to be considered when investigating an outlying result include-but are not limited to-human error, instrumentation error, calculation error, and product or component deficiency. If an assignable cause that is not related to a product or component deficiency can be identified, then retesting may be performed on the same sample, if possible, or on a new sample. Resampling should be a rare event. The precision and accuracy of the method, the Reference Standard, process trends, and the specification limits should all be examined. Data may be invalidated, based on this documented investigation, and eliminated from subsequent calculations.

If no documentable, assignable cause for the outlying laboratory result is found, the result may be tested, as part of the overall investigation, to determine whether it is an outlier.

However, careful consideration is warranted when using these tests. Two types of errors may occur with outlier tests: (a) labeling observations as outliers when they really are not; and (b) failing to identify outliers when they truly exist.

Clearly, the first type of error could have a mere significant impact on pharmaceutical laberatory results in particular. This type of error is minimized when potential outliers are further awy frem the other observations. Any judgment about the acceptability of data in which outliers are observed requires careful interpretation.
"Outlier labeling" is informal recognition of suspicious laboratory values that should be further investigated with more formal methods. The selection of the correct outlier identification technique often depends on the initial recognition of the number and location of the values. Outlier labeling is most often done visually with graphical techniques. "Outlier identification" is the use of statistical significance tests to confirm that the values are inconsistent with the known or assumed statistical model.

When used appropriately, outlier tests are valuable tools for pharmaceutical laboratories. Several tests exist for detecting outliers. Examples illustrating three of these procedures, the Extreme Studentized Deviate (ESD) Test, Dixon's Q Test, and Hampel's Rule, are presented in Appendix C.

Choosing the appropriate outlier test will depend on the sample size and distributional assumptions. Many of these tests (e.g., the Generalized Extreme Studentized Deviate ESD Test) require the assumption that the data generated by the laboratory on the test samples can be thought of as a random sample from a population that is normally distributed, possibly after transformation. If a transformation is made to the data, the outlier test is applied to the transformed data. Common transformations include taking the logarithm or square root of the data. Other approaches to handling single and multiple outliers are available and can
also be used. These include tests that use robust measures of central tendency and spread, such as the median and median absolute deviation and exploratory data analysis (EDA) methods. "Outlier accommodation" is the use of robust techniques, such as tests based on the order or rank of each data value in the data set instead of the actual data value, to produce results that are not adversely influenced by the presence of outliers. The use of such methods reduces the risks associated with both types of error in the identification of outliers.
"Outlier rejection" is the actual removal of the identified outlier from the data set. However, an outlier test cannot be the sole means for removing an outlying result from the laboratory data. An outlier test may be useful as part of the evaluation of the significance of that result, along with other data. Outlier tests have no applicability in cases where the variability in the product is what is being assessed, such as content uniformity, dissolution, or release-rate determination. In these applications, a value determined to be an outlier may in fact be an accurate result of a nonuniform product. All data, especially outliers, should be kept for future review. Unusual data, when seen in the context of other historical data, are often not unusual after all but reflect the influences of additional sources of variation.

In summary, the rejection or retention of an apparent outlier can be a serious source of bias. The nature of the testing as well as scientific understanding of the manufacturing process and analytical method have to be considered to determine the source of the apparent outlier. An outlier test can never take the place of a thorough laboratory investigation. Rather, it is performed only when the investigation is inconclusive and no deviations in the manufacture or testing of the product were noted. Even if sueh statistientests indiente a value to be an outlier, it should be retained in the record
and given full consideration in the assessment of conformance to aceeptance criteria. It is good practice to perform the ealeulations with and without the outlier to assess its im
pact. Even if such statistical tests indicate that one or more values are outliers, they should still be retained in the record. Including or excluding outliers in calculations to assess conformance to acceptance criteria should be based on scientific judgment and the internal policies of the manufacturer. It is often useful to perform the calculations with and without the outliers to evaluate their impact.

Outliers that are attributed to measurement process errors should be reported (i.e., footnoted), but not included in further statistical calculations. When assessing conformance to a particular acceptance criterion, it is important to define whether the reportable result (the result that is compared to the limits) is an average value, an individual measurement, or something else. If, for example, the acceptance criterion was derived for an average, then it would not be statistically appropriate to require individual measurements to also satisfy the criterion because the variability associated with the average of a series of measurements is smaller than that of any individual measurement.

## COMPARISON OF ANALYTICAL METHODS

It is often necessary to compare two methods to determine if their average results or their variabilities differ by an amount that is deemed important. The goal of a method comparison experiment is to generate adequate data to evaluate the equivalency of the two methods over a range of concentrations. Some of the considerations to be made when performing such comparisons are discussed in this section.

## Precision

Precision is the degree of agreement among individual test results when the analytical method is applied repeatedly to a homogeneous sample. For an alternative method to be considered to have "comparable" precision to that of a current method, its precision (see Analytical Performance Characteristics under Validation of Compendial Methods $\langle 1225\rangle$ ) must not be worse than that of the current method by an amount deemed important. A decrease in precision (or increase in variability) can lead to an increase in the number of results expected to fail required specifications. On the other hand, an alternative method providing improved precision is acceptable.

One way of comparing the precision of two methods is by estimating the variance for each method (the sample variance, $s^{2}$, is the square of the sample standard deviation) and calculating a confidence interval for the ratio of (true) variances, where the ratio is defined as the variance of the alternative method to that of the current method. Thise done in terms of standard deviations well. An example is outlined under Appendix $D$. The upper limit of the confidence interval should be compared to an upper limit deemed acceptable, a priori, by the analytical laboratory. If the upper limit of the confidence interval is less than this upper acceptable limit, then the precision of the alternative method is considered acceptable in the sense that the use of the alternative method will not lead to an important loss in precision. Note that if the upper limit of the confidence interval is less than one, then the alternative method has been shown to have improved precision relative to the current method.

The confidence interval method just described is preferred to applying the two-sample $F$-test to test the statistical significance of the ratio of variances. To perform the two-sample $F$-test, the calculated ratio of sample variances would be
compared to a critical value based on tabulated values of the $F$ distribution for the desired level of confidence and the number of degrees of freedom for each variance. Tables providing $F$-values are available in most standard statistical textbooks. If the calculated ratio exceeds this critical value, a statistically significant difference in precision is said to exist between the two methods. However, if the calculated ratio is less than the critical value, this does not prove that the methods have the same or equivalent level of precision; but rather that there was not enough evidence to prove that a statistically significant difference did, in fact, exist.

## Accuracy

Comparison of the accuracy (see Analytical Performance Characteristics under Validation of Compendial Methods $\langle 1225\rangle$ ) of methods provides information useful in determining if the new method is equivalent, on the average, to the current method. A simple method for making this comparison is by calculating a confidence interval for the difference in true means, where the difference is defined as the sample mean of the alternative method minus that of the current method.

The confidence interval should be compared to a lower and upper range deemed acceptable, a priori, by the laboratory. If the confidence interval falls entirely within this acceptable range, then the two methods can be considered equivalent, in the sense that the average difference between them is not of practical concern. The lower and upper limits of the confidence interval only show how large the true difference between the two methods may be, not whether this difference is considered tolerable. Such an assessment can only be made within the appropriate scientific context.

The confidence interval method just described is preferred to the practice of applying a two-sample $t$ test to test the statistical significance of the difference in averages. One way to perform the two-sample $t$-test is to calculate the confidence interval and to examine whether or not it contains the value zero. The two methods have a statistically significant difference in averages if the confidence interval excludes zero. A statistically significant difference may not be large enough to have practical importance to the laboratory because it may have arisen as a result of highly precise data or a larger sample size. On the other hand, it is possible that no statistically significant difference is found, which happens when the confidence interval includes zero, and yet an important practical difference cannot be ruled out. This might occur, for example, if the data are highly variable or the sample size is too small. Thus, while the outcome of the two-sample $t$-test indicates whether or not a statistically significant difference has been observed, it is not informative with regard to the presence or absence of a difference of practical importance.

## Determination of Sample Size

The geal of a methed comparison experiment is to gener-
ate adequate data to evaluate the equivalency of two methods over a range of concentrations. Samplesize determination is similar to that for testing hypetheses abeut averages differenees, Sample size determination is based on the comparison of the accuracy and precision of the two methods ${ }^{5}$ and is similar to that for testing hypotheses about average differences in the former case and variance ratios in
the latter case, but the meaning of some of the input is different. The first component to be specified is $\delta$, the largest acceptable difference between the two methods that, if achieved, still leads to the conclusion of equivalence. That is, if the two methods differ by no more than $\delta$, they are considered acceptably similar. The comparison can be twosided as just expressed, considering a difference of $\delta$ in either direction, as would be used when comparing means. Alternatively, it can be one-sided as in the case of comparing variances where a decrease in variability is acceptable and equivalency is concluded if the variability of the more variable method is not more than $\delta \%$ greater than that of the less variable method. A researcher will need to state $\delta$ based on knowledge of the current method and/or its use, or it may be calculated. One consideration, when there are specifications to satisfy, is that the new method should not differ by so much from the current method as to risk generating out-of-specification results. One then chooses $\delta$ to have a low likelihood of this happening by, for example, comparing the distribution of data for the current method to the specification limits. This could be done graphically or by using a tolerance interval, an example of which is given in Appendix $E$. In general, the choice for $\delta$ must depend on the scientific requirements of the laboratory, not just on the desire to test only a small number of samples.
The next two components relate to the likelihood of error. The data could lead to a conclusion of similarity when the methods are unacceptably different (as defined by $\delta$ ). This is

[^22]called a false positive or Type I error. The error could also be in the other direction; that is, the methods could be similar, but the data do not permit that conclusion. This is a false negative or Type II error. With statistical methods, it is not possible to completely eliminate the possibility of either error. However, by choosing the sample size appropriately, the probability of each of these errors can be made acceptably small. The acceptable maximum probability of a Type I error is commonly denoted as $\alpha$ and is commonly taken as $5 \%$, but may be chosen differently. The desired maximum probability of a Type II error is commonly denoted by $\beta$. Often, $\beta$ is specified by indirectly by choosing a desired level of $1-$ $\beta$, which is called the "power" of the test. In the context of equivalency testing, power is the probability of correctly concluding that two identieal methods are equivalent. Power is commonly taken to be $80 \%$ or $90 \%$ (corresponding to a $\beta$ of $20 \%$ or $10 \%$ ), though other values may be chosen. The protocol for the experiment should specify $\delta, \alpha$, and power. The sample size will depend on all of these components. An example is given in $F$ Appendix E. Although ApF Appendix $E$ determines only a single value, it is often useful to determine a table of sample sizes corresponding to different choices of $\delta, \alpha$, and power. Such a table often allows for a more informed choice of sample size to better balance the competing priorities of resources and risks (false negative and false positive conclusions).

APPENDIX A: CONTROL CHARTS


Fig. 1. Individtul $X$ or individual measurements control ehat for control samples. In this particular example, the mean for all the samples ( $x$ ) is 100 , the upper control limit is 104.5 , and the lower control limit is 95.5 .


Fig. 1. Individual $X$ or individual measurements control chart for control samples. In this particular example, the mean for all the samples $(\bar{x})$ is 102.0 , the UCL is 106.5 , and the LCL is 97.5 .

Figure 1 illustrates a control chart for individual values. There are several different methods for calculating the upper control limit (UCL) and lower control limit (LCL). One of the more commonly used methods involves the moving range, which is defined as the absolute difference between two consecutive measurements $\left(\left|x_{\mathrm{i}}-x_{\mathrm{i}-1}\right|\right)$. These moving ranges are averaged ( $\overline{M R}$ ) and used in the following formulae:

$$
\begin{aligned}
& U C L=\bar{x}+3 \frac{\overline{M R}}{d_{2}} \\
& L C L=\bar{x}-3 \frac{\overline{M R}}{d_{2}}
\end{aligned}
$$

where $\bar{x}$ is the sample mean, and $d_{2}$ is based on the number of observations associated with the moving range calculation. Where $n=2$ (two consecutive measurements), as here, $d_{2}=1.128$. For the example in Figure 1, the $\overline{M R}$ was 1.7:


$$
U C L=102.0+3 \frac{1.7}{1.128}=106.5
$$

$$
L C L=102.0-3 \frac{1.7}{1.128}=97.5
$$

## APPENDIX B: PRECISION STUDY

Table 1 displays data collected from a precision study. This study consisted of five independent runs and, within each run, results from three replicates were collected.

Performing an analysis of variance (ANOVA) on the data in Table 1 leads to the ANOVA table (Table 1A). Because there were an equal number of replicates per run in the precision study, values for Variance Run and Variance Rep can be derived from the ANOVA table in a straightforward manner. The equations below calculate the variability associated with both the runs and the replicates where the $M S_{\text {within }}$ represents the "error" or "within-run" mean square, and $M S_{\text {between }}$ represents the "between-run" mean square.

$$
\text { Variance }_{\text {Rep }}=M S_{\text {within }}=0.102
$$

$$
\text { Variance }_{\text {Run }}=\frac{M S_{\text {between }}-M S_{\text {within }}}{\# \text { of reps per run }}=\frac{3.550-0.102}{3}=1.149
$$

Estimates can still be obtained with unequal replication, but the formulae are more complex. Studying the relative magnitude of the two variance components is important when designing and interpreting a precision study. For example, for these data the between-run component of variability is
much larger than the within-run component. This suggests that performing additional runs would be more beneficial to reducing variability than performing more replication per run (see Table 2 below).

Table 2 shows the computed variance and RSD of the mean (i.e., of the reportable value) for different combinations of number of runs and number of replicates per run using the formulae:


Standard deviation of the mean $=\sqrt{\text { Variance of the mean }}$

$$
R S D=\frac{\text { Standard deviation of the mean }}{\text { Average of all results }} \times 100 \%
$$

For example, the Variance of the mean, Standard deviation of the mean, and RSD of a test involving two runs and three replicates per each run are $0.592,0.769$, and $0.76 \%$ respectively, as shown below.

Variance of the mean $=\frac{1.149}{2}+\frac{0.102}{(2 \cdot 3)}=0.592$

$$
\text { Standard deviation of the mean }=\sqrt{0.592}=0.769
$$

$$
R S D=\frac{0.769}{100.96} \times 100 \%=0.76 \%
$$

Where 100.96 is the mean for all the data points in Table 1. As illustrated in Table 2, increasing the number of runs from one to two provides a more dramatic reduction in the variability of the reportable value than does increasing the number of replicates per run.

No distributional assumptions were made on the data in Table 1 as the purpose of this Appendix is to illustrate the calculations involved in a precision study. In general, if the datare nermally distributed in the precision stady, then the standard deviation of the mean should be reported. How ever, if the log transformed data are nermally distributed, then the RSD should be reperted.

## APPENDIX C: EXAMPLES OF OUTLIER TESTS FOR ANALYTICAL DATA

Given the following set of 10 measurements: 100.0, $100.1,100.3,100.0,99.7,99.9,100.2,99.5,100.0$, and $95.7($ mean $=99.5$, standard deviation $=1.369)$ are there any outliers?

## Generalized Extreme Studentized Deviate (ESD) Test

This is a modified version of the ESD Test that allows for testing up to a previously specified number, $r$, of outliers from a normally distributed population. Let $r$ equal 2 , and $n$ equal 10 .

Stage $1(\mathrm{n}=10)-$ Normalize each result by subtracting the mean from each value and dividing this difference by the standard deviation (see Table 3). ${ }^{6}$

Take the absolute value of these results, select the maximum value $\left(\left|\mathrm{R}_{1}\right|=2.805\right)$, and compare it to a previously specified tabled critical value $\lambda_{1}(2.290)$ based on the selected significance level (for example, 5\%). The maximum value is larger than the tabled value and is identified as being inconsistent with the assumed model of normality. Sources for $\lambda$ values are included in many statistical textbooks. remaining data. Sources for $\lambda$-values are included in many statistical textbooks. Caution should be exercised when using any statistical table to ensure that the correct notations (i.e., level of acceptable error) are used when extracting table values.

Stage $2(\mathrm{n}=9)$-Remove the observation corresponding to the maximum absolute normalized result from the original data set, so that $n$ is now 9. Again, find the mean and standard deviation (Table 3, right two columns), normalize each value, and take the absolute value of these results. Find the maximum of the absolute values of the 9 normalized results $\left(\left|R_{2}\right|=1.905\right)$, and compare it to $\lambda_{2}(2.215)$. The maximum value is not larger than the tabled value.

Conclusion-The result from the first stage, 95.7 , is declared to be an outlier, but the result from the second stage, 99.5, is not an outlier.

## Dixon-Type Tests

Similar to the ESD test, the two smallest values will be tested as outliers; again assuming the data come from a single normal population.
${ }^{6}$ The difference between each value and the mean is termed the residual. Other Studentized residual outlier tests exist where the residual, instead of being divided by the standard deviation, can be divided by the standard deviation times the square root of $n-1$ divided by $n$.

Stage $1(\mathrm{n}=10)$-The results are ordered on the basis of their magnitude (i.e., $X_{n}$ is the largest observation, $X_{n-1}$ is the second largest, etc., and $X_{1}$ is the smallest observation). Dixon's Test has different ratios based on the sample size (in this example, with $n=10$ ), to declare $X_{1}$ an outlier, the following ratio, $Q_{4}$, is caleulated by the formula:-

$r_{11}$, is calculated by the formula:

$$
r_{11}=\frac{X_{2}-X_{1}}{X_{n-1}-X_{1}}
$$

A different ratio would be employed if the largest data peint was tested as an outlier. The $Q_{4}$ result is compared to a $\pi_{4}$ value in a table of critieal values. If $Q_{4+}$ is grenter than $\pi_{H+}$, then it is declared an outlier. For the above set of data, $Q_{H}=$ $(99.5-95.7) /(100.2 \quad 95.7)=0.80$. This ratio is greater that \# $_{4}$, which is 0.477 at the $5 \%$ significance level. Sources for $Q$ values are ineluded in many statistieal textbooks. A different ratio would be employed if the largest data point was tested as an outlier. The $r_{11}$ result is compared to an $r_{11,0.05}$ value in a table of critical values. If $r_{11}$ is greater than $r_{11,0.05}$, then it is declared an outlier. For the above set of data, $r_{11}=$ $(99.5-95.7) /(100.2-95.7)=0.84$. This ratio is greater than $r_{11,0.05}$, which is 0.477 at the $5 \%$ significance level. Sources for $r_{11,0.05}$-values are included in many statistical textbooks.

Stage 2 Remove the smallest observation frem the ori ginal data set, so that $n$ is now -9 . The same $Q_{H}$ - equation is used, but a new critical $\pi 11$ value for $n=9$ is needed ( $\pi_{1+}=$ 0.512). Now $\mathrm{Q}_{4}=(99.7-99.5) /(100.2-99.5)-0.29$, which is less than $\pi_{H}$ and not signiffeant at the $5 \%$ level.

Stage 2-Remove the smallest observation from the original data set, so that $n$ is now 9 . The same $r_{11}$ equation is used, but a new critical $r_{11,0.05}$ value for $n=9$ is needed ( $r_{11}$, $0.05=0.512)$. Now $r_{11}=(99.7-99.5) /(100.2-99.5)=0.29$, which is less than $r_{11,0.05}$ and not significant at the $5 \%$ level.

Conclusion-Therefore, 95.7 is declared to be an outlier. This stepwise procedure is not an exact procedure for testing for the second outlier as the result of the second test is conditional upon the first. Because the sample size is also reduced in the second stage, the end result is a procedure that usually lacks the sensitivity of the exact procedures that Dixon provides for testing for two outliers simultaneously; however, these procedures are beyond the scope of this Appendix.

Both tests previously illustrated in this Appendix as sumed that the samples-were taken from a normally distributed population. Other tests are also available, including these based on rebust measures, such as the median and median abselute deviation (MAD). One-such method is ealled Hampel's Rule and is deseribed below.

## Hampel's Rule

Step 1-The first step in applying Hampel's Rule is to normalize the data. However, instead of subtracting the mean from the data each data point and dividing the difference by the standard deviation, the median is subtracted from each data value and the resulting differences are divided by the MAD MAD (see below). The calculation of MAD is done in three stages. First, the median is subtracted from each data point. Next, the absolute values of the differences are obtained. These are called the absolute deviations. Finally, the median of the absolute deviations is calculated and multiplied by the constant 1.483 to obtain MAD.

Step 2-The second step is to take the absolute value of the normalized data. Any such result that is greater than 3.5 is declared to be an outlier. Table 4 summarizes the calculations.

The value of 95.7 is again identified as an outlier. This value can then be removed from the data set and Hampel's Rule re-applied to the remaining data. The resulting table is displayed as Table 5. Similar to the previous examples, 99.5 is not considered an outlier.

## APPENDIX D: COMPARISON OF METHODS— PRECISION

The following example illustrates the calculation of a $90 \%$ confidence interval for the ratio of (true) variances for the purpose of comparing the precision of two methods. It is assumed that the data distribution for both methods is approximately normal. The laberabelie that the preeision of the alternative method is acceptable if its standard deviation is not more than fold greater than that of the eurrent method. $\Lambda$ A $90 \%$ (tw-sided) confidence interval is used when a $5 \%$ one-sided test is sought. Here, the test is ene sided, since only the increased standard deviation of the alternative methed is of concem. Some care must beekercised in using two sided intervals in this way, as they must have the property of equal tails-mest common intervals have this property. For this example, assume the laboratory will accept the alternative method if its precision (as measured by the variance) is no more than four-fold greater than that of the current method.

To determine the appropriate sample size for precision, one possible method involves a trial and error approach using the following formula:

Power $=\operatorname{Pr}\left[F>\frac{1}{4} F_{\alpha, n-1, n-1}\right]$
where $n$ is the smallest sample size required to give the desired power, which is the likelihood of correctly claiming the alternative method has acceptable precision when in fact the two methods have equal precision; $\alpha$ is the risk of wrongly claiming the alternative method has acceptable precision; and the 4 is the allowed upper limit for an increase in variance. F-values are found in commonly available tables of critical values of the $F$-distribution. $F_{\alpha, n-l, n-1}$ is the upper $\alpha$ percentile of an $F$-distribution with $n-1$ numerator and $n-$ 1 denominator degrees of freedom; that is, the value exceeded with probability $\alpha$. Suppose initially the laboratory guessed a sample size of 11 per method was necessary (10 numerator and denominator degrees of freedom); the power calculation would be as follows: ${ }^{7}$

$$
\begin{array}{r}
\operatorname{Pr}\left[F>\frac{1}{4} F_{\alpha, n-1, n-1}\right]=\operatorname{Pr}\left[F>\frac{1}{4} F_{.05,10,10}\right]= \\
\operatorname{Pr}\left[F>\frac{2.978}{4}\right]=0.6311
\end{array}
$$

In this case the power was only $63 \%$; that is, even if the two methods had exactly equal variances, with only 11 samples per method, there is only a $63 \%$ chance that the experiment will lead to data that permit a conclusion of no more than a four-fold increase in variance. Most commonly, sample size is chosen to have at least $80 \%$ power, with choices of $90 \%$ power or higher also used. To determine the appropriate sample size, various numbers can be tested until a probability is found that exceeds the acceptable limit (e.g., power > 0.90 ). For example, the power determination for sample sizes of 12-20 are displayed in Table 6. In this case, the in-

[^23]itial guess at a sample size of 11 was not adequate for comparing precision, but 15 samples per method would provide a large enough sample size if $80 \%$ power were desired, or 20 per method for $90 \%$ power.

Typically the sample size for precision comparisons will be larger than for accuracy comparisons. If the sample size for precision is so large as to be impractical for the laboratory to conduct the study, there are some options. The first is to reconsider the choice of an allowable increase in variance. For larger allowable increases in variance, the required sample size for a fixed power will be smaller. Another alternative is to plan an interim analysis at a smaller sample size, with the possibility of proceeding to a larger sample size if needed. In this case, it is strongly advisable to seek professional help from a statistician.

Now, suppose the laboratory opts for $90 \%$ power and obtains the results presented in Table 7 based on the data generated from 20 independent runs per method.

Ratio $=$ Alternative Method Variance/Current Method Variance $=45.0 / 25.0=1.8$
Lower Limit of Confidene Interval-Ratiol $/ F_{95}=1.84$ 2.85-0.63 Lower Limit of Confidence Interval = Ratio/ $F_{\text {.05 }}=1.8 / 2.168=0.83$
Upper Limit of Confidence Interval-Ratio $/ F_{05}=1.81$ 0.39-4.62 Upper Limit of Confidence Interval = Ratio/ $F_{.95}=1.8 / 0.461=3.90$

NOTE- $F_{\text {.05 and }} F_{95}$-are tabulated 5 th and 95 th percentiles from an $F$ distribution, in this example with 15 and 10 degree of freedom.

Discussion The experiment cannot prove that the preeision of the alternative method is aceeptable because the upper limit of the confidene interval (4.6) is greater than the upper aceeptable limit $\left(2^{2}=4\right)$. Because the lower limit of the confidence interval was less than 1 , there is not a statistieally signiffeant difference (at the 10\% level) between
the precision of the alternative method and the precision of the current method. Nevertheless, based on the scientifie requirement of the laboratory, there is not sufficient informat tion to allow for the use of the alternative methed. In such a ease, a second experiment with a larger sample-size-should be performed. How much additional testing should oeeur ean be derived by assuming the true ratio of variances (alternative/current) is 1.8 and increasing the sample sizes until the upper limit of the confidence interval beeomes less than 4. For example, if sample-size for the alternative methed is increased to 41 and the sample size for the current method increased to 31, then the upper limit of the confidence inter wal would be 3.6, which is less than-4.

For this application, a 90\% (two-sided) confidence interval is used when a $5 \%$ one-sided test is sought. The test is one-sided, because only an increase in standard deviation of the alternative method is of concern. Some care must be exercised in using two-sided intervals in this way, as they must have the property of equal tails-most common intervals have this property. Because the upper limit of the confidence interval, 3.90 , is less than the allowed limit, 4.0 , the study has demonstrated that the alternative method has acceptable precision. If the same results had been obtained from a study with a sample size of 15 -as if $80 \%$ power had been cho-sen-the laboratory would not be able to conclude that the alternative method had acceptable precision (upper confidence limit of 4.47).

## APPENDIX E: COMPARISON OF METHODSDETERMINING THE LARGEST ACCEPTABLE DIFFERENCE, $\delta$, BETWEEN TWO METHODS

This Appendix describes one approach to determining the difference, $\delta$, between two methods (alternative-current), a difference that, if achieved, still leads to the conclusion of equivalence between the two methods. Without any other
prior information to guide the laboratory in the choice of $\delta$, it is a reasonable way to proceed. Sample size calculations under various scenarios are discussed in this Appendix.

## Tolerance Interval Determination

Suppose the sample mean and the standard deviation for the current method are 99.5 and 2.0 , respectively. Ther tes were caleulated using the last 50 results generated by this particular method. These values were calculated using the last 50 results generated by this specific method for a particular (control) sample. Given this information, the tolerance limits can be calculated by the following formula:

$$
\bar{x} \pm K s
$$

in which $\bar{x}$ is the mean; $s$ is the standard deviation; and $K$ is based on the level of confidence, the proportion of results to be captured in the interval, and the sample size, $n$. Tables providing $K$ values are available. In this example, the value of $K$ required to enclose $95 \%$ of the population with $95 \%$ confidence for 50 samples is $\mathcal{Z . 3 7 9}-2.382$. The tolerance limits are calculated as follows:

$$
99.5 \pm 2.379 \times 2.0
$$

$$
99.5 \pm 2.382 \times 2.0
$$

hence, the tolerance interval is $(94.7,104.3)$.

## Comparison of the Tolerance Limits to the

## Specification Limits

Assume the specification interval for this method is (90.0, 110.0). The following quantities can be defined: the lower specification limit (LSL) is 90.0, the upper specification limit (USL) is 110.0, the lower tolerance limit (LTL) is 94.7, and the upper tolerance limit (UTL) is 104.3. Calculate the acceptable difference, $(\delta)$, in the following manner:

$$
\begin{aligned}
& A=\mathrm{LTL}-\mathrm{LSL} \text { for } \mathrm{LTL} \geq \mathrm{LSL} \\
& (A=94.7-90.0=4.7) \\
& B=\mathrm{USL}-\mathrm{UTL} \text { for } \mathrm{USL} \geq \mathrm{UTL} \\
& (B=110.0-104.3=5.7) ; \text { and } \\
& \delta=\text { minimum }(A, B)=4.7
\end{aligned}
$$



Fig. 2. A graph of the quantities calculated above.
With this choice of $\delta$, and assuming the two methods have comparable precision, the confidence interval for the difference in means between the two methods (alternative-current) should fall within -4.7 and +4.7 to claim that no important difference exists between the two methods.

Quality control analytical laboratories eftemetimes deal with $99 \%$ tolerance limits, in which cases the interval will widen. Using the previous example, the value of $K$ required to enclose $99 \%$ of the population with $99 \%$ confidence for 50 samples is 3.390 . The tolerance limits are calculated as follows:

$$
99.5 \pm 3.390 \times 2.0
$$

the resultant wider tolerance interval is $(92.7,106.3)$. Similarly, the new LTL of 92.7 and UTL of 106.3 would produce a smaller $\delta$ :

$$
\begin{aligned}
& A=\mathrm{LTL}-\mathrm{LSL} \text { for } \mathrm{LTL} \geq \mathrm{LSL} \\
& (A=92.7-90.0=2.7) \\
& B=\mathrm{USL}-\mathrm{UTL} \text { for } \mathrm{USL} \geq \mathrm{UTL} \\
& (B=110.0-106.3=3.7) ; \text { and } \\
& \delta=\text { minimum }(A, B)=2.7
\end{aligned}
$$

Choosing a larger $\delta$ leads to a smaller $n$ but at the cost of increasing the risk of making the wrong conclusion.

## Sample Size

Formulae are available that can be used for a specified $\delta$, under the assumption that the population variances are known and equal, to calculate the number of samples required to be tested per method, $n$. The level of confidence and power must also be specified. [NOTE-Power refers to the probability of correctly concluding that two identical methods are equivalent.] For example, if $\delta=4.7$, and the two population variances are assumed to equal 4.0, then, for a $5 \%$ level ef confidence test ${ }^{8}$ and $80 \%$ power (with associated $z$-values of 1.645 and 1.282 , repectively), the sample size is approximated by the following formula:

$$
n \geq \frac{2 \sigma^{2}}{\delta^{2}}\left(z_{\alpha}+z_{\beta / 2}\right)^{2}
$$

$$
n \geq \frac{2(4)}{(4.7)^{2}}(1.645+1.282)^{2}=3.10
$$

Thus, assuming each method has a population variance, $\sigma^{2}$, of 4.0 , the number of samples, $n$, required to conclude with $80 \%$ probability that the two methods are equivalent $(90 \%$ confidence interval for the difference in the true means falls between -4.7 and +4.7 ) when in fact they are identical (the true mean difference is zero) is 4 . Because the normal distribution was used in the above formula, 4 is actually a lower bound on the needed sample size. If feasible, one might want to use a larger sample size. Values for $z$ for common confidence levels are presented in Table 8. The formula above makes three assumptions: 1) the variance used in the sample size calculation is based on a sufficiently large

[^24]amount of prior data to be treated as known; 2) the prior known variance will be used in the analysis of the new experiment, or the sample size for the new experiment is sufficiently large so that the normal distribution is a good approximation to the $t$ distribution; and 3) the laboratory is confident that there is no actual difference in the means, the most optimistic case. It is not common for all three of these assumptions to hold. The formula above should be treated most often as an initial approximation. Deviations from the three assumptions will lead to a larger required sample size. In general, we recommend seeking assistance from someone familiar with the necessary methods.

When a $\log$ transformation is required to achieve normality, the sample size formula needs to be slightly adjusted as shown below. Instead of formulating the problem in terms of the population variance and the largest acceptable difference, $\delta$, between the two methods, it now is formulated in terms of the population RSD and the largest acceptable proportional difference between the two methods.

$$
n \geq \frac{2 \sigma_{L}^{2}}{\delta_{L}^{2}}\left(z_{\alpha}+z_{\beta / 2}\right)^{2}
$$

where
and $\rho$ represents the largest acceptable proportional difference between the two methods ((alternative-current)/current) and the population RSDs are assumed known and equal.

## APPENDIX F: COMPARHSON OF METHODSCALCULATION OF SAMPLE SIZE

Formulae are available that ean be used for a specified $\delta$, under the assumption that the pepulation variances are known and equal, to calculate the number of samples required to be tested per method, $n$. The level of confidence and power must also be specified. [NOTE Power refers to the probability of correctly concluding that identient methods arequivalent.] For example, if $\delta=4.7$, and the two population rarianees are assumed to equal-4.0, then, for a-95\% level of confidene and $80 \%$ power (with assoeiated $z$ values of 1.64 and 1.28 , repectively), the sample size is approximated by the following formula:-

$n \geq \frac{2(4)}{(47)^{2}}(1.64+1.28)^{2}-(0.36)(8.53)=3.07$

Thus, assuming each method has a pepulation variance, $\sigma^{2}$, Of 4.0 , the number of samples, $n$, required to conclude with $80 \%$ probability that the methods are equivalent $(90 \%$ eonfidence interval for the difference in the true means falls between -4.7 and +4.7 ) when in fact they are identical (the true mean difference is zere) is 3. Because the normal dis tribution was used in the above formula, 3 is actually a low
er bound on the needed sample-size. If feasible, one might want to use a larger sample-size. Values of $z$ for commen eenfidence-levels are given in the fellowing table.

A more conservative but exact approach is to use the pooled sample variance as an estimate of the commen popufation variance and to use the correspending student twat ues, adjusting them for different sample sizes. Tables providing $t$ values are available in statistical textbooks. Using the same-information, the caleulations would be as follows:


$$
n \geq \frac{2(4)}{(4.7)^{2}}(2.02+1.47)^{2}-(0.36)(12.18)=4.38
$$

In this case, using the pooled sample variance of 4.0 , the number of samples required is 5 . Note that this was the smallest $n$ that satisffed the above inequality.

In many cases, information is provided in terms of a lar gest acceptable percent difference, $p$, and the pepulation RSDs are assumed to be known and equal. This neeessarily implies that the pepulation variances are unequal. The sample size formula then becomes-

or, alternatively,

where $R S D_{\text {est }}$ is the pooled sample $R S D$. Note that in the above formulae, $\rho$ - is interpreted as the propertional change in average respense frem the current method to the alternative method as a function of the geometric mean of the twe methods.

## APPENDIX G: F: ADDITIONAL SOURCES OF INFORMATION

There may be a variety of statistical tests that can be used to evaluate any given set of data. This chapter presents several tests for interpreting and managing analytical data, but many other similar tests could also be employed. The chapter simply highlighted illustrates the analysis of data and some of the more commen upproaches. using statistically acceptable methods. As mentioned in the Introduction, specific tests are presented for illustrative purposes, and USP does not endorse any of these tests as the sole approach for handling analytical data. Additional information and alternative tests can be found in the references listed below or in many statistical textbooks.

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## TABLES

Table 1. Data from a Precision Study

| Replicate | Run Number |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Number | 1 | 2 | 3 | 4 | 5 |
| 1 | 100.70 | 99.46 | 99.96 | 101.80 | 101.91 |
| 2 | 101.05 | 99.37 | 100.17 | 102.16 | 102.00 |
| 3 | 101.15 | 99.59 | 101.01 | 102.44 | 101.67 |
| Mean | 100.97 | 99.47 | 100.38 | 102.13 | 101.86 |
| Standard Deviation | 0.236 | 0.111 | 0.556 | 0.321 | 0.171 |
| RSD $^{1}$ | $0.234 \%$ | $0.111 \%$ | $0.554 \%$ | $0.314 \%$ | $0.167 \%$ |
| 1 RSD (relative standard deviation) $=100 \% \times$ (standard deviation/mean) |  |  |  |  |  |

Table 1A. Analysis Variance Table for Data Presented in Table 1

| Source of <br> Variation | Degrees of Freedom <br> $(\mathrm{df})$ | Sum of Squares <br> $(\mathrm{SS})$ | Mean Squares ${ }^{1}$ <br> $(\mathrm{MS})$ | $\mathrm{F}=M S_{B} / M S_{W}$ |
| :--- | :---: | :---: | :---: | :---: |
| Between Runs | 4 | 14.200 | 3.550 | 34.88634 .80 |
| Within Runs | 10 | 1.0171 .018 | 0.102 |  |
| Total | 14 | 15.217 |  |  |
| ${ }^{1}$ The Mean Squares Between $\left(\mathrm{MS}_{\mathrm{B}}\right)=\mathrm{SS}_{\text {Between }} / \mathrm{df}_{\text {Between }}$ and the Mean Squares Within $\left(\mathrm{MS}_{\mathrm{w}}\right)=\mathrm{SS}_{\text {Within }} / \mathrm{df}_{\text {Within }}$ |  |  |  |  |

Table 2. Computed Variance and RSD of the Mean

| No. of Runs | No. of <br> Replicates | Precision of the Mean Corresponding to Various Test Plans (\# of Runs, \# of Reps per Run) |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  |  | Variance of the Mean | SD of the <br> Mean | Mean ${ }^{1}$ | RSD (\%) |
| 1 | 1 | 1.251 | 1.118 | 100.96 | 1.11 |
| 1 | 2 | 1.200 | 1.095 | 100.96 | 1.09 |
| 1 | 3 | 1.183 | 1.088 | 100.96 | 1.08 |
| 2 | 1 | 0.625 | 0.791 | 100.96 | 0.78 |
| 2 | 2 | 0.600 | 0.775 | 100.96 | 0.77 |
| 2 | 3 | 0.592 | 0.769 | 100.96 | 0.76 |

[^25]Table 3. Generalized ESD Test Results

| $n=10$ |  |  |  |
| :---: | :---: | :---: | :---: |
| Data | Normalized | Data | Normalized |
| 100.3 | +0.555 | 100.3 | +1.361 |
| 100.2 | +0.482 | 100.2 | +0.953 |
| 100.1 | +0.409 | 100.1 | +0.544 |
| 100.0 | +0.336 | 100.0 | +0.136 |
| 100.0 | +0.336 | 100.0 | +0.136 |
| 100.0 | +0.336 | 100.0 | +0.136 |
| 99.9 | +0.263 | 99.9 | -0.272 |
| 99.7 | +0.117 | 99.7 | -1.089 |
| 99.5 | -0.029 | 99.5 | $\mathbf{- 1 . 9 0 5}$ |
| 95.7 | $\mathbf{2 . 8 0 5}$ |  |  |
| 99.54 |  | 99.95 |  |
| SD $=$ |  |  | 0.245 |

Table 4. Test Results Using Hampel's Rule


Table 5. Test Results of Re-Applied Hampel's Rule

| $n=9$ |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: |
|  | Data | Deviations from the Median | Absolute <br> Deviations | Absolute <br> Normalized |
|  | 100.3 | 0.3 | 0.3 | 2.02 |
|  | 100.2 | 0.2 | 0.2 | 1.35 |
|  | 100.1 | 0.1 | 0.1 | 0.67 |
|  | 100 | 0 | 0 | 0 |
|  | 100 | 0 | 0 | 0 |
|  | 100 | 0 | 0 | 0 |
|  | 99.9 | -0.1 | 0.1 | 0.67 |
|  | 99.7 | $-0.3$ | 0.3 | 2.02 |
|  | 99.5 | $-0.5$ | 0.5 | 3.37 |
| Median $=$ | 100 |  | 0.1 |  |
| MAD $=$ |  |  | 0.148300 .14 |  |

Table 6. Power Determinations for Various Sample Sizes (Specific to the Example in Appendix D)

| Sample Size | $\operatorname{Pr}\left[F>1 / 4 F_{0.05, n-L n-1}\right]$ |
| :---: | :---: |
| 12 | 0.7145 |
| 13 | 0.7495 |
| 14 | 0.7807 |
| 15 | 0.8083 |
| 16 | 0.8327 |
| 17 | 0.8543 |
| 18 | 0.8732 |
| 19 | 0.8899 |
| 20 | 0.9044 |

Table 7. Example of Measures of Variance for Independent Runs (Specific to the Example in Appendix D)
\(\left.$$
\begin{array}{lccc}\hline & \begin{array}{c}\text { Variance } \\
\text { (standard deviation) }\end{array} & \begin{array}{c}\text { Sample } \\
\text { Size }\end{array} & \begin{array}{c}\text { Degrees of } \\
\text { Method }\end{array}
$$ <br>

\hline Freedom\end{array}\right]\)| Alternative | $45.0(6.71)$ | 1620 | 1519 |
| :--- | :--- | :--- | :--- |
| Current | $25.0(5.00)$ | +20 | 1019 |

Table 8. Common Values for a Standard Normal (9) Distribution

|  | $z$ values <br> One-tailed ( $\alpha)$ | Fwotailed ( $\alpha / 2)$ |
| :--- | :---: | :---: |
| Genfidence levet | 2.33 | 2.58 |
| $99 \%$ | 1.64 | 1.96 |
| $95 \%$ | 1.28 | 1.64 |
| $90 \%$ | 0.84 | 1.28 |
| $80 \%$ |  |  |


|  | $z$-values |  |  |
| :---: | :---: | :---: | :---: |
| Confidence level | One-tailed $(\alpha)$ | Two-tailed $(\alpha / 2)$ |  |
| $99 \%$ | 2.326 | 2.576 |  |
| $95 \%$ | 1.645 | 1.960 |  |
| $90 \%$ | 1.282 | 1.645 |  |
| $80 \%$ | 0.842 | 1.282 |  |

BRIEFING
〈1051〉Cleaning Glass Apparatus, USP 27 page 2493.The proposed revisions further clarify the glassware cleaning recommendations provided in this chapter. In addition, minor editorial style changes have been made.
(PW: F. Barletta) RTS-39550-1

## Change to read:

Success in conducting many Pharmacopeial assays and tests depends upon the utmost cleanliness of the glassware apparatus used. Specifieally,
${ }^{\Delta}$ For example,
the accuracy of the assays of heparin sodium and vitamin $\mathrm{B}_{12}$ activity, as well as the pyrogen and total organic carbon tests, are particularly dependent upon scrupulously clean glassware.

One effective method used in the past for cleaning glassware is the application of hot nitric acid. A second traditional method for removing organic matter that does not require heat is the use of a chromic acid-sulfuric acid mixture. However, the chromic acid wash is not recommended because of the hazardous and toxic nature of the material.
Several safer alternatives including the use of cleansing agents, such as trisodium phosphate and synthetic detergents, have proven highly useful, but require prolonged rinsing.
${ }^{\Delta}$ It may be useful to rinse with diluted nitric or sulfuric acid prior to rinsing with water. This operation will facilitate re-
moval of residual alkaline material. $\triangle U S P 28$
For optical measurements, special care is required for cleaning containers, but the use of both chromic acid and highly alkaline solutions should be avoided.
Effective removal of organic matter is very important for testing pharmaceutical waters in accordance with the general test chapter Total Organic Carbon $\langle 643\rangle$. It has been demonstrated that an alkaline detergent comprised of potassium hydroxide as the primary ingredient ${ }^{*}$ leaves the least amount of organic matter residuals. Heating in a muffle furnace produces comparable results and is the least labor-intensive procedure; however, it requires specialized equipment.

In all cases, it is important to verify that the cleaning procedure is appropriate for the particular test or assay being undertaken. This can be accomplished via blank runs, scientific judgments, residuals data from cleansing agent and detergent manufacturers, or other controls. Specifically, special care is required for cleaning containers for optical measurement applications; the use of highly alkaline and the no longer recommended chromic acid solutions should be avoided.
${ }^{\Delta}$ Finally, a statement should be included in the cleaning protocol describing how the success of the cleaning procedure will be assessed. $\Delta U S P 28$

## Briefing

$\langle\mathbf{1 0 8 2}\rangle$ Genotoxicity Testing. This new proposed general information chapter presents a number of test procedures that may be used to test for genotoxicity of compendial articles as indicated in the general information chapter The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants $\langle 1031\rangle$. The methods included in this new chapter are capable of detecting mutations, chemical changes to DNA, and alterations in chromosomal structure, and are divided into in vitro and in vivo methods. In vitro methods include Salmonella typhimurium Reverse Mutation Assay, Escherichia coli Reverse Mutation Assay, Saccharomyces cerevisiae Gene Mutation Assay, Mammalian Cell Gene Mutation Tests, Tests for Detection of Chemical Damage to DNA: DNA Damage and Repair/Unscheduled DNA Synthesis in Mammalian Cells, Saccharomyces cerevisiae Mitotic Recombination Assay, Mammalian Cytogenetic Test, and Sister Chromatid Exchange Assay in Mammalian Cells. In vivo methods include Micronucleus Test, Mammalian Bone Marrow Cytogenetic TestChromosomal Analysis, Rodent Dominant Lethal Test, Mammalian Germ-Cell Cytogenetic Assay, Mouse Spot Test, and Mouse Heritable Translocation Assay.

Comments should be sent to USP headquarters for consideration by the Expert Committee on General Toxicology and Biocompatibility no later than March 1, 2004.
(GTB: D. Porter) RTS-40476-1

## Add the following:

## - <1082 $\rangle$ GENOTOXICITY TESTING

Testing for genotoxicity seeks to determine whether the material under test causes some form of damage to DNA, to one or more genes, or to one or more chromosomes of an organism. The damage could include one or more of the following:

1. Mutation, such as that caused by an insertion, deletion, translocation, or substitution of one or more nucleotides into DNA.
2. A chemical change to the DNA, such as the intercalation of acridine into DNA, or abnormal base parings.
3. Alterations in the structure of one or more chromosomes, or a change in the number of chromosomes.
[^26]A single nucleotide deletion, addition, or translocation can lead to far-reaching effects on a cell (and potentially the organism as well). The deletion can cause a frame-shift mutation in which the codons beyond the point of the deletion/addition are no longer correct. This can result in the production of a messenger RNA that is subsequently translated into a protein with an incorrect amino acid sequence. Most often, such a protein will no longer perform its intended role as well, if at all. Even worse is the possibility that the mutant protein will have deleterious effects. If the deletion/addition/translocation occurs in a regulatory portion of the DNA, normal gene expression can be disrupted, resulting in interrupted DNA or RNA synthesis, or unscheduled DNA or RNA synthesis. A single nucleotide substitution can lead to inherited diseases such as sickle cell disease or phenylketonuria. Somatic effects include the possible activation of ras oncogenes and epithelial cancers. A deletion and/or translocation can cause inherited diseases such as hemophilia and Duchenne's muscular dystrophy. Somatic effects can include the activation of myc and abl oncogenes, and the appearance of cancers such as lymphomas and leukemias.

The interaction between nucleotide bases from one DNA strand to another, or between the template DNA strand and the nascent messenger RNA strand, is due to hydrogen bonding. Upon binding of a chemical, such as acridine, to a portion of a DNA strand, it is possible that subsequent hydrogen bonding in that region of nucleotides intended for new DNA or messenger RNA synthesis would be disrupted. This disruption can result in miscoded strands.

In some circumstances where a gross change in chromosome structure or number has occurred, it is possible to observe this microscopically. Alterations in chromosomal structure include breaks, deletions, and rearrangements. The loss or gain of an entire chromosome can lead to inherited diseases, such as Down's or Turner's syndrome, and somatic effects, such as the loss of tumor suppressor genes and the appearance of various cancers.

Changes to one or a few nucleotides require observations for changes in a potentially wide array of physiological activities. Many agents can cause damage to DNA at high concentrations. Of particular interest in genotoxicity testing is determining whether an article under test can induce DNA damage at concentrations that are not overtly toxic at the level of the organism (subtoxic levels). The purpose of this chapter is to provide guidance on evaluating the potential for genotoxicity caused by medical devices and implants. The need for testing medical devices and implants for genotoxicity may be determined by the flowcharts and tables provided in the general information chapter The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants $\langle 1031\rangle$.

A multi-step process, delineated in general information chapter $\langle 1031\rangle$, is followed in determining which, if any, toxicological tests need to be performed on a given article. In some cases, sufficient evidence may be available from previously marketed articles to satisfy toxicology requirements (see Fig. 1 in general information chapter $\langle 1031\rangle$ ). Important factors addressed in Fig. 1 (general information chapter $\langle 1031\rangle$ ) include the type and extent of contact with the body, the chemical composition, the manufacturing process, and the sterilization process, along with the aforementioned similarity to previously marketed articles.

If it is determined that further toxicological testing is necessary, the classification of medical devices provided in Table 2 of general information chapter $\langle 1031\rangle$ is important, because the degree and extent of toxicological testing is strongly influenced by the nature of the bodily contact of the article. The classification derived from Table 2 (general information chapter $\langle 1031\rangle$ ), coupled with the length of expo-
sure to the article used as stated in Tables 3-5 (general information chapter $\langle 1031\rangle$ ), is used to determine which toxicological tests need to be performed. Table 1 below presents information extracted from Tables 3-5 of general information chapter $\langle 1031\rangle$ indicating those circumstances for which genotoxicity testing is required.

Table 1. Articles Requiring Genotoxicity Testing Based on Article Category and Length of Exposure

| Device Category | Body Contact | Contact <br> Duration ${ }^{\mathrm{a}}$ |
| :--- | :--- | :---: |
| Surface devices | Mucosal membrane | C |
| External communicating devices | Breached or compromised surfaces | Blood path, indirect |
|  | Tissue, bone, or dentin communicating | C |
| Implant devices | Circulating blood | $\mathrm{B}, \mathrm{C}$ |
|  | Tissue or bone | $\mathrm{A}^{\mathrm{b}}, \mathrm{B}, \mathrm{C}$ |
| Blood | $\mathrm{B}, \mathrm{C}$ |  |

a Legend: A-Limited (less than 24 hours); B—Prolonged (24 hours to 30 days); C—Permanent (more than 30 days). ${ }^{\mathrm{b}}$ Test that may be applicable.

## TEST PROCEDURES

## General

In most circumstances, more than one type of test should
dependent upon the in vitro results. If the results from the in vitro testing clearly indicate that the article under test has genotoxic properties, in vivo testing need not be performed.

There are many instances where not all of the in vitro tests within a battery indicate that an article may be genotoxic. Because there are numerous mechanisms by which DNA and/or chromosomes may be damaged, and because a test battery should include methods examining different mechanisms, the lack of perfect correlation is to be expected. If the results of the test battery suggest that an article may be genotoxic, then subsequent in vivo tests may be appropriate.

## Sample Preparation ${ }^{1}$

This section provides general guidance on preparing samples for genotoxicity testing. The article should be in its final form before testing (i.e., the final product). If the configuration of the final product is such that testing it in its final form is impractical, then representative portions of it should be evaluated. An important point is that should the article be composed of several types of material, a representative portion of each part of the article that can contact bodily surfaces should be evaluated. This includes portions of the device with surface coatings, seams, adhesives, etc. If a portion of the article is composed of a chemical or chemicals thought to have increased potential for genotoxicity, it may be appropriate to test the material to a disproportionate degree relative to its abundance in the article. If the article cures in situ, it should be evaluated following the minimum time of curing that may occur in the clinical setting.

In all cases, the test article, any associated reference standards, and positive and negative controls should be handled in a manner preventing either chemical or microbial contamination. If the test article is normally supplied nonsterile, but is then sterilized prior to use, the article should be sterilized according to the manufacturer's instructions prior to use. Likewise, when designing the genotoxicity study, it is important to bear in mind whether there is a potential for the article to undergo repeated sterilization cycles.

In many cases, an article to be tested needs to be cut into smaller pieces prior to testing/extraction. These cut surfaces have the potential to expose different chemical entities to the test system. This may be particularly important to consider if an article might undergo such cutting prior to actual clinical use. Conversely, it may not be necessary to include portions of the article that are not exposed to body fluids during

[^27]clinical use. These determinations are critical to ensuring the appropriateness of the extraction/processing procedures, and in turn, the relevance and accuracy of the test results.

## Sample Extraction

For the many tests to be performed in assessing genotoxicity, it will be necessary to prepare an extract of the article to be tested. In performing extractions of articles to be evaluated, it is important to consider a number of points. In vitro test systems require that the solvents used in the extraction procedures be compatible with cell-based methods and should be chosen for their similarity to body fluids that will contact the article during clinical use. Harsh solvents are not useful in such cases. Extraction media should be evaluated for their cytotoxic potential. Media that may be useful for extraction include physiological saline, liquid culture media (minus serum), various vegetable oils, low concentration of dimethyl sulfoxide (DMSO), various low concentration mixtures of alcohol with other liquids, polyethylene glycol made iso-osmotic, etc. The general chapter Biological Reactivity Tests, In Vitro $\langle 87\rangle$ lists Sodium Chloride Injection as another extraction medium.

It is important that extractions are done in suitable containers that will not alter the chemical nature of the product being extracted. General chapter $\langle 87\rangle$ indicates that glass containers made of Type I glass be used. If the container is to be sealed, then the exposed surface of the elastomeric liner should be completely protected with an inert solid disk 50 to $75 \mu \mathrm{~m}$ in thickness.

The extraction conditions should be such that the potential for altering the chemical nature (hence genotoxic potential) of the article is minimized. Given the generally longterm exposure of organisms to the test articles being examined for genotoxicity, the most appropriate extraction conditions may be at $37^{\circ}$ for 24-72 hours. The extraction period
may be shortened by the use of higher temperatures, but it should be demonstrated that such elevated temperatures do not alter the chemical nature of the article. In cases where an article may be exposed to higher temperatures prior to clinical use, extraction at a higher temperature would be appropriate.
The quantity of article to be extracted is related to the thickness of the article and the type of material of which it is composed. For natural elastomers $\leq 1.0 \mathrm{~mm}$ thick, the ratio of article to extractant should be $3 \mathrm{~cm}^{2}$ per mL of extractant. If the natural elastomer is $>1.0 \mathrm{~mm}$ thick, the ratio should be $1.25 \mathrm{~cm}^{2}$ per mL . For other materials with readily measured surface areas $\leq 0.5 \mathrm{~mm}$ thick, the ratio should be 6 $\mathrm{cm}^{2}$ per mL , with thicker materials extracted at $3 \mathrm{~cm}^{2}$ per mL . For those articles for which a surface area cannot be readily determined, a ratio of 0.1 to 0.2 g per mL should be used.

## Test Battery Selection

There are a number of approaches that may be taken when designing the test battery for use with a particular article. When the chemistry of the article and its likely breakdown products are well established, the in vitro tests might be selected because of their known sensitivity to the classes of compounds pertinent to the article. In some cases, cells from a variety of species/phyla may be employed. At times, the use of a base test possessing a wealth of historical data might be coupled with one or more tests selected for their sensitivity to those aspects of the base test that provide weak results. Finally, selecting in vitro tests that can reflect the potential forms of damage discussed above (changes to the nucleotide sequence of DNA, chemical changes to DNA, chromosomal alterations) is often an effective approach given that no assumptions need to be made about chemical classes or the mode of genotoxicity.

## IN VITRO TESTS

There are many in vitro tests available for use in genotoxicity testing. Following the general approach suggested in this chapter, three or more tests should be selected based upon their ability to reflect the three separate mechanisms of genotoxicity described above. The tests in this section are divided into those that detect mutation (e.g., changes to the nucleotide sequence of DNA), those that detect chemical changes to the DNA, and those that detect chromosomal damage.

## Tests for Detection of Mutation

## Salmonella typhimurium REVERSE MUTATION ASSAY

This test is based upon measuring an increase in the number of histidine-independent colonies of Salmonella typhimurium beyond the number of naturally occurring revertants as a result of exposure to the test article. The reversion to histidine independence could be due to base changes or frame shift mutations. The test is performed by exposing bacteria to the test article, with or without the presence of a metabolic activation system, on minimal medium (lacking histidine). The article can be a solid or an extract made from a solid.

Bacteria-There should be at least 4 strains of Salmonella typhimurium used in this method, including TA 1535, TA 1537, TA 98, and TA 100. Other strains may be used, when appropriate. It is best to employ seed lot techniques of culturing to ensure that no microorganisms in the test are more than 5 passages removed from the original culture as provided by an appropriate cell repository. The bacteria should be grown in a suitable broth medium (such as fluid lactose medium) to the late exponential to early stationary phase $\left(10^{8}-10^{9}\right.$ cfu per mL ). Incubation should be at a temperature of $32.5 \pm 2.5^{\circ}$.

The bacteria should be examined to ensure that the appropriate phenotype is present. The requirement for histidine in the culture medium should be demonstrated. The rate of spontaneous reversion to histidine independence should also be established by culturing on minimal medium. Bacteria displaying a higher rate of reversion relative to earlier rates for that lot should not be used. Expected antibiotic resistance, such as to ampicillin, should also be demonstrated.

Metabolic Activation System—A suitable metabolic activation system may be prepared from the livers of rodents. The system contains a postmitochondrial fraction supplemented with various cofactors. Such systems can be made within the laboratory, or purchased from various commercial suppliers. A number of agents may be used to induce activation of liver enzymes.

Medium-An appropriate medium for conducting the test should be histidine free, and may include ampicillin. Such media may be obtained commercially.

Test Article-Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo $\langle 88\rangle$. Concentrations of test article that are not overtly cytotoxic should be used. A cytotoxic effect on the bacteria may be demonstrated by a reduction in the density of the bacterial lawn for cultures plated on growth medium plus the test article, by a reduction in the number of spontaneous revertants, or by the degree of survival of cultures treated and then plated on growth media. The maximum noncytotoxic concentration, plus at least four lower concentrations, should be tested.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). Positive chemical controls are strain-specific. Sodium azide is effective with TA 1535
and TA 100, 2-nitrofluorene is effective with TA 98, and 2-aminoanthracene is effective with TA 1537. 2-Aminoanthracene is an effective positive control when metabolic activation systems are included. Other positive and negative controls may be appropriate as well.

Test Performance-Culture plates ( 10 cm may be used) containing solidified histidine-free medium may be used. The test article should be mixed with 0.1 mL of the bacterial culture as described in Bacteria and 2 mL of molten (overlay) agar. [NOTE-The agar should be cooled to approximately $42^{\circ}$ to $45^{\circ}$ before adding the bacteria.] If a metabolic activation system is to be included, it should be added after the addition of the bacteria and test article. Negative controls should include the same components minus the test article. The contents in the overlay agar tube should be poured over the surface of a plate of solidified agar and the agar overlay should be allowed to cool and solidify. Plates should be incubated at $32.5 \pm 2.5^{\circ}$ for $48-72$ hours, after which the number of colonies should be counted.

Observations and Interpretation-The number of revertant colonies (those that can grow on medium without histidine) should be recorded for all plates. Statistical comparisons between test and control plates should be made to determine if a statistically significant difference in the number of revertants exists. An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the number of revertants is seen. Also, a statistically significant difference between test and controls for at least 1 test article concentration is indicative of a genotoxic effect. If neither a significant dose-response difference, or single test point difference between test and controls is found, the article is not genotoxic in this test system.

## Escherichia coli REVERSE MUTATION ASSAY

This test, similar to the Salmonella typhimurium Reverse Mutation Assay, measures the reversion of specific strains of bacteria from a particular amino acid dependence to an independent state. In this case, the reversion is from a trypto-phan-dependent to independent state. Also, as in the Salmonella typhimurium Reverse Mutation Assay, bacteria should be exposed to the test article with and without a metabolic activation system.

Bacteria-Culturing of bacteria should be done in the same manner and under the same conditions as described for Bacteria in the Salmonella typhimurium Reverse Mutation Assay. The strains that should be used are Escherichia coli WP2, WP2 uvrA, and WP2 uvrA pKM 101. If appropriate, other strains may be used.

The bacteria should be examined to ensure that the appropriate phenotype is present. The requirement for tryptophan in the culture medium should be demonstrated. The rate of spontaneous reversion to tryptophan independence should also be established by culturing on minimal medium. Bacteria displaying a higher rate of reversion relative to earlier rates for that lot should not be used. Expected antibiotic resistance, such as to ampicillin, and sensitivity to mitomycin C, should also be demonstrated.

Metabolic Activation System—A suitable metabolic activation system may be the same as that described for the Metabolic Activation System in the Salmonella typhimurium Reverse Mutation Assay.

Medium-An appropriate medium for conducting the test should be tryptophan-free, and may include ampicillin. Such media may be obtained commercially.
Test Article-See Test Article in the Salmonella typhimurium Reverse Mutation Assay.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). Methyl methane sulfonate, 4-nitroquinoline oxide or $N$-ethyl $N$-nitro nitrosoguanidine are effective positive controls when metabolic activation systems are not included. 2-Aminoanthracene may be used as a positive control when a metabolic activation system is included. Other positive and negative controls may be appropriate as well.

Test Performance-Perform the test using the same procedure as that described for Test Performance in the Salmonella typhimurium Reverse Mutation Assay.

Observations and Interpretation-Perform as described for Observations and Interpretation in the Salmonella typhimurium Reverse Mutation Assay. The criteria for the determination of potential genotoxicity for a test article are also the same as those in the Salmonella typhimurium Reverse Mutation Assay.

## Saccharomyces cerevisiae GENE MUTATION ASSAY

This is another assay designed to identify mutations due to base substitutions or frame shifts in DNA. In this case, the test microorganism is a eukaryotic cell type (a species of yeast). There are a variety of mutations present in the most commonly used haploid strain of Saccharomyces cerevisiae that may be reversed, resulting in a number of different outcomes. In some cases, resistance to antibiotics such as canavanine and cycloheximide has developed as result of a reverse mutation. In other cases, red mutants requiring adenine become white mutants, still requiring adenine. Other mutations in the most commonly used strain include lys $1-1, \operatorname{trp} 5-48$, his $1-7$, and hom 3-10. The most commonly used diploid strain is homozygous for ilv 1-92.

Yeast—Although a number of strains of Saccharomyces cerevisiae may be used, the most commonly used yeast haploid strain is XV 185-14C, and the most commonly used diploid strain is $\mathrm{D}_{7}$. Typical incubation temperatures for yeast are $22.5 \pm 2.5^{\circ}$.

The yeast should be examined to ensure that the appropriate phenotype is present. The requirement for particular amino acids, or sensitivity to specific antibiotics, or particular color phenotypes, etc., should be demonstrated as appropriate to the test system. The rate of spontaneous reversion should also be established by culturing on a medium appropriate to a given test system. Yeast displaying a higher rate of reversion relative to earlier rates for that lot should not be used.

Metabolic Activation System-A suitable metabolic activation system may be the same as that described for Metabolic Activation System in the Salmonella typhimurium Reverse Mutation Assay.

Medium-Since there are a variety of potential reversions that may be tested for, there are a variety of media that may be suitable. A growth medium should be used in order to enrich the cells to the point where 1 mL of culture would contain $1-5 \times 10^{7}$ cells per mL . Other media should be used to select for revertants. For example, if the appearance of cycloheximide-resistant mutations is to be examined, the selective media should include a concentration of cycloheximide inhibitory to nonrevertants.

Test Article-Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo $\langle 88\rangle$. It is necessary to use concentrations of test article that are not overtly cytotoxic. A
cytotoxic effect on the bacteria may be demonstrated by a reduction in cell viability and growth. The maximum noncytotoxic concentration, plus at least 4 other lower concentrations, should be used.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). Positive controls should include those that act without the presence of a metabolic activation system, and those that do require a metabolic activation system. Examples of those that act without the metabolic activation system include methylmethanesulfonate, ethylmethanesulfonate, and 4-nitroquinoline- N -oxide. N Nitrosodimethylamine and cyclophosphamide are examples of positive controls requiring the presence of a metabolic activation system. Other positive and negative controls may be appropriate as well.
Test Performance-Typically, $1-5 \times 10^{7}$ cells per mL in the growth phase should be exposed to the test article in liquid culture for up to 18 hours at $22.5 \pm 2.5^{\circ}$ using a shaking incubator. Metabolic activation systems would be added to this preparation. After incubation, the cells should be pelleted in a centrifuge in a nondestructive manner. The pellet should be washed and resuspended for placement on the surface of the appropriate selective medium. The plates are then incubated for $4-7$ days at $22.5 \pm 2.5^{\circ}$. Negative controls undergo the same treatment, except that no exposure to the test article occurs. Repeat the study using cells in the stationary phase if the results of the first study are negative.

Observations and Interpretation-The number of revertants found on the test plates, and spontaneous revertants on the control plates, should be determined. The number of colonies plated should be determined through the use of
plates containing growth medium for the yeast. The frequency of mutants on both the control and the test plates should then be calculated.

Statistical comparisons between test and control plates should be made to determine if a statistically significant difference in the number of revertants exists. An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the number of revertants is seen. Also, a statistically significant difference between test and controls of at least 1 test article concentration is indicative of a genotoxic effect. If neither a significant doseresponse difference nor a single, test-point difference between test and controls is found, the article is not genotoxic in this test system.

## IN VITRO MAMMALIAN CELL GENE MUTATION TESTS

This is another test designed to show mutations involving frame shifts or base pair changes resulting in a mutation from a cell sensitive to pyrimidine analogs such as bromodeoxyuridine ( BrdU ) to an insensitive form. Of the commonly used cell lines for this procedure, the cells normally contain functional thymidine kinase (TK), hypox-anthine-guanine phophoribosyl transferase (HPRT) and $\mathrm{Na}^{+} / \mathrm{K}^{+}$ATPase enzymes. When functional TK is present, the presence of a pyrimidine analog such as BrdU results in the incorporation of the analog into nucleotides, a mutation that leads to disruption of normal cell activities. A mutant cell with a deficient TK will not incorporate the analog, thus the cell survives. A similar situation exists for cells with normal HPRT, where the presence of a compound like 8azaguanine leads to disruption of cellular function, whereas the mutant cell with a dysfunctional HPRT will not incorpo-
rate the analog. When the presence of an inactivated $\mathrm{Na}^{+} / \mathrm{K}^{+}$ ATPase is under investigation, ouabain may be used as the selective agent.
Mammalian Cells-The most commonly used cell lines are L5178Y mouse lymphoma cells, and V-79 and L5178Y Chinese hamster cells. Required conditions for culturing are provided by the suppliers. Cell lines should not be passaged indefinitely; the karyotypes should be examined periodically; and the cells should also be examined to ensure that they are not undergoing an increased rate of spontaneous mutation leading to insensitivity to the selective agents.

Culture conditions should be appropriate to the cells. Commercial suppliers of mammalian cell lines will generally provide information on culture conditions, including appropriate media, supplements, etc. Mammalian cells are often incubated at $37^{\circ}$ in $5 \%$ carbon dioxide at saturated relative humidity.

Metabolic Activation System—A suitable metabolic activation system may be the same as that described for Metabolic Activation System in the Salmonella typhimurium Reverse Mutation Assay.

Test Article-Extracts of solid test articles should be prepared as that described for Preparation of Extracts in the Biological Reactivity Tests, In Vivo $\langle 88\rangle$. It is necessary to use concentrations of test article that are not overtly cytotoxic. At least 4 other lower concentrations should be used as well.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). Positive controls should include those that act without the presence of a metabolic activation
system, and those that do require a metabolic activation system. A search of numerous toxicological databases on the Internet can provide examples of suitable positive controls.

Table 2 lists the names of several toxicological databases available on the Internet and gives their URLs (Uniform Resource Locators).

Table 2. Toxicological Databases Available on the Internet
Name of Database $U^{\text {U }}$

| Agency for Toxic Substances and Disease Registry | http://www.atsdr.cdc.gov/ |
| :---: | :---: |
| Office of Environmental Health Hazard Assessment | http://www.oehha.org/risk/chemicalDB/index. asp |
| ${ }^{\mathrm{b}}$ Status Report: No Significant Risk Levels for Carcinogens and Acceptable Intake Levels for Reproductive Toxicants | http://www.oehha.org/prop65/pdf/tb0194r2.pdf |
| The Carconogenic Potency Project | http://potency.berkeley.edu/cpdb.html |
| Chemical Toxicology Database | http://wwwdb.mhlw.go.jp/ginc/html/db1.html |
| U.S. Environmental Protection Agency | http://www.epa.gov/ |
| National Environmental Publications Internet Site (EPA) | http://www.epa.gov/ncepihom/nepishom/ srch.htm |
| Integrated Risk Information System | http://www.epa.gov/iris/ |
| Summary of Evaluations Performed by the Joint FAO/WHO | http://jecfa.ilsi.org/search.cfm |
| Expert Committee on Food Additives (JECFA 1956-2001) |  |
| IPCS INCHEM (JECFA - Monographs \& Evaluations) | http://www.inchem.org/jecfa.html |
| IPCS INCHEM (Chemical Safety Information from | http://www.inchem.org/ |
| Intergovernmental Organizations) |  |
| National Toxicology Program | http://ntp-server.niehs.nih.gov/ |
| Risk Assessment Information System | http://risk.lsd.ornl.gov/rap_hp.shtml |
| Toxicology Excellence for Risk Assessment | http://www.tera.org/ |
| TOXNET | http://toxnet.nlm.nih.gov/ |

${ }_{\mathrm{b}} \mathrm{a}$ URLS are subject to change.
${ }^{\mathrm{b}}$ This is a specific document published by the California Environmental Protection Agency.

Test Performance-Monolayer cultures or cell suspensions may be used. They should be exposed to the test article in full growth medium with or without a metabolic activation system for a length of time sufficient to allow development of the mutant phenotype under investigation. After that time, the cultures should be subdivided such that half
of the cells are seeded into full growth medium and the other half into medium containing the selective agent. A cell count of the suspension prior to seeding should be made in order to permit calculating normal plating efficiency and the rate of mutation.

Observations and Interpretation-Using the cell counts for negative controls and for test articles, the rate of mutation formation should be calculated as a percentage of the controls. The results should be examined for the presence of statistically significant differences between test and controls.

An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the number of mutants is seen. Also, a statistically significant difference between test and controls for at least 1 test article concentration is indicative of a genotoxic effect. If neither a significant dose-response difference or single test point difference between test and controls is found, the article is not genotoxic in this test system.

## Tests for Detection of Chemical Damage to DNA: DNA Damage and Repair/Unscheduled DNA Synthesis in Mammalian Cells In Vitro

Mammalian cells possess enzymatic machinery with which damaged portions of DNA can be excised, then replaced via new synthesis of DNA. Such synthesis of DNA can be considered to be unscheduled in the sense that it does not occur as part of mitosis. The synthesis of DNA may be monitored by the uptake of radiolabeled thymidine $\left({ }^{3} \mathrm{H}-\right.$ TdR). Various means may be employed by which scheduled DNA synthesis (due to mitotic activity) may be inhibited, thereby facilitating the determination of unscheduled DNA synthesis.

Mammalian Cells-A wide range of mammalian cells may be used in this test. These include established lines, short-term rat hepatocyte cultures, and human lymphocyte cultures. Various methods may be used in culturing hepatocytes and lymphocytes.

For established cell lines, required conditions for culturing are provided by the suppliers. Cell lines should not be passaged indefinitely, the karyotypes should be examined
periodically, and the cells should also be examined to ensure that they are not undergoing an increased rate of spontaneous mutation leading to insensitivity to the selective agents.

Culture conditions should be appropriate to the cells in use. Commercial suppliers of mammalian cell lines will generally provide information on culture conditions, including appropriate media, supplements, etc. Mammalian cells are often incubated at $37^{\circ}$ in $5 \%$ carbon dioxide at saturated relative humidity.

Metabolic Activation System—A suitable metabolic activation system may be the same as described for Metabolic Activation System in the Salmonella typhimurium Reverse Mutation Assay. This system would not be used if rat hepatocytes are chosen for the test.

Test Article-Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo $\langle 88\rangle$. The highest concentration of test article should cause some mild cytotoxic effects. At least four other lower concentrations should be used as well.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). Positive controls should include those that act without the presence of a metabolic activation system and those that do require a metabolic activation system (a metabolic activation system should not be used with rat hepatocyte cultures). A search of numerous toxicological databases on the Internet can provide examples of suitable positive controls. Table 1 lists the names of several toxicological databases available on the Internet, and gives their URLs. Positive controls for use with rat hepatocyte cultures include 7,12-dimethylbenzanthracene and 2-acetylaminofluorene. For established cell lines, positive controls include

4-nitroquinoline- $N$-oxide (without a metabolic activation system) and $N$-dimethylnitrosoamine (with metabolic activation).

Test Performance-Regardless of the cell type used, the test procedure involves exposing cell cultures to the test article, with labeled thymidine (approximately $10 \mu \mathrm{Ci}$ per mL ) added simultaneously or shortly after the period of exposure to the test article. Two methods of determining the amount of unscheduled DNA synthesis are indicated below.

Autoradiographic Method-After exposure to the test article and labeled thymidine, the cells (in suspension) should be placed on microscope slides and air-dried. Nuclei may be swollen by exposing the microscope slides with attached cells to $1 \%$ sodium citrate for 10 minutes. Cells should then be fixed using a mixture of alcohol and acetic acid (3:1) (three changes). The slides should then be air-dried for at least 24 hours, dipped into a suitable autoradiographic emulsion (in a darkroom), air-dried again, placed in a lightproof container, and stored at $4^{\circ}$ for $7-10$ days. No moisture should be allowed to enter the containers during storage. Next, the exposed emulsion should be developed in D19, then fixed. A suitable counter stain (such as one containing hematoxylin and eosin) should be applied.
Liquid Scintillation Counting Method-Because there is no microscopic examination with this method, it is important to block normal mitotic synthesis of DNA. Such blockage may be accomplished by the use of arginine-deficient medium, low serum, hydroxyurea in the culture medium, or by other appropriate means. The cells may then be exposed to the test article with labeled thymidine as described above. After the exposure, DNA should be extracted from the cells [NOTE-Numerous techniques are available, and commercial kits are also available for DNA extraction]. The total DNA should be calculated and the extent of labeled thymidine uptake determined.

## Observations and Interpretation-

Autoradiographic Method-Grains overlying at least 50 nuclei per slide should be determined microscopically. Because some background grain formation may occur, the average number of grains overlying 3 cytoplasmic areas should be subtracted from the number of grains overlying the nucleus. This value is the net nuclear gain count. Average the net nuclear gain counts as appropriate to obtain mean nuclear gain counts. Only nuclei with normal appearances should be counted. Cells with mitotic figures should not be counted. These counts should be done for both test article-treated cultures and for controls.

The test article is considered to cause increased unscheduled DNA synthesis if the following applies:
a. there is at least, on average, an increase of 5 or more for the mean nuclear grain count per test article-treated nucleus versus associated controls, or
b. the percentage of nuclei with 6 or more grains is $10 \%$ or above that of the population examined, relative to associated controls.

Liquid Scintillation Counting Method-The total DNA should be calculated and the extent of labeled thymidine uptake determined. This should be done for both test articletreated cultures and for controls. The incorporation of labeled thymidine should be reported in terms of dpm per $\mu \mathrm{g}$ of DNA. Differences between test and controls should be evaluated statistically.

An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the extent of unscheduled DNA synthesis is found. Also, a statistically significant difference between test and controls for at least 1 test article concentration is indicative of a genotoxic effect. If neither a significant dose-response difference nor single test point difference between test and controls is found, the article is not genotoxic in this test system.

## Tests for Detection of Chromosomal Damage

## Saccharomyces cerevisiae MITOTIC RECOMBINATION ASSAY

This test is designed to identify changes to the structure of DNA caused by exposure to a test article. The structural change might involve crossing over during mitosis or a translocation of a portion of DNA from one location on a single strand to another location on the same strand. Specific diploid strains of the yeast, Saccharomyces cerevisiae, are used.
Crossing over may manifest itself in the form of homozygous recessive colonies arising from a previously heterozygous strain of yeast. Translocation of a portion of DNA from one location to another on the same strand (also known as mitotic gene conversion) may cause the development of revertants from auxotrophic states (mutants requiring particular nutritional additives not required by normal, or prototrophic yeast). Such translocations may occur upon exposure of yeast containing two differing defective alleles for the same gene.

Yeast—Although a number of strains of Saccharomyces cerevisiae may be used, the most commonly used strains for detection of mitotic crossing over are $\mathrm{D}_{5}$ or $\mathrm{D}_{7}$. The $\mathrm{D}_{7}$ strain is XV $185-14 \mathrm{C}$, and the most commonly used strains for detection of translocation are $\mathrm{D}_{4}, \mathrm{D}_{7}$, and $\mathrm{JD}_{1}$. Typical incubation temperatures for yeast are $22.5 \pm 2.5^{\circ}$.

The yeast should be examined to ensure that the appropriate phenotype is present. The requirement for particular amino acids, or sensitivity to specific antibiotics, or particular color phenotypes, etc., should be demonstrated as appropriate to the test system. The rate of spontaneous reversion should also be established by culturing on a medium appropriate to a given test system. Yeast displaying a higher rate of reversion relative to earlier rates for that lot should not be used.

Metabolic Activation System—A suitable metabolic activation system may be the same as that described for Metabolic Activation System in the Salmonella typhimurium Reverse Mutation Assay.

Media-Because there are a variety of potential reversions/mutations that may be tested for, there are a variety of media that may be suitable. A growth medium should be used in order to enrich the cells to the point where 1 mL of culture would contain $1-5 \times 10^{7}$ cells per mL . Other media should be used to select for revertants. For example, if the appearance of prototrophic revertants is to be detected, the selective media should not include the substance needed by the auxotrophs.

Test Article-Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo $\langle 88\rangle$. Concentrations of test article that are not overtly cytotoxic should be used. A cytotoxic effect on the bacteria may be demonstrated by a reduction in cell viability and growth. The maximum noncytotoxic concentration, plus at least four other lower concentrations, should be used.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). Positive controls should include those that act without the presence of a metabolic activation system and those that do require a metabolic activation system. Examples of those that act without the metabolic activation system include methylmethanesulfonate, ethylmethanesulfonate, and 4-nitroquinoline- N -oxide. Cy clophosphamide is an example of a positive control requiring the presence of a metabolic activation system. Other positive and negative controls may be appropriate as well.

Test Performance-Typically, $1-5 \times 10^{7}$ cells per mL in the growth phase should be exposed to the test article extract in liquid culture for up to 18 hours at $22.5 \pm 2.5^{\circ}$ using a shaking incubator. Metabolic activation systems should be added to this preparation. After incubation, the cells should be pelleted in a centrifuge in a nondestructive manner. The pellet should be washed and resuspended for placement on the surface of the appropriate selective medium. The plates are then incubated for $4-7$ days at $22.5 \pm 2.5^{\circ}$. Negative controls undergo the same treatment, except that no exposure to the test article extract occurs. If plates are being used to detect the presence of red and pink homozygous colonies due to mitotic crossing over, incubate the plates in a refrigerator ( $2^{\circ}$ to $8^{\circ}$ ) for 24-48 hours to permit development of the pigmentation. Repeat the study using cells in the stationary phase if the results of the first study are negative.

Observations and Interpretation-The number of revertants/recombinations found on the test plates and the number of spontaneous revertants/recombinations on the control plates should be determined. The number of colonies plated should be determined by using plates containing growth medium for the yeast. The frequency of mutants on both the control and the test plates should then be calculated.

Statistical comparisons between the test and control plates should be made to determine if a statistically significant difference in the number of revertants/recombinants exists. An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the number of revertants is observed. Also, a statistically significant difference between the test and controls for at least 1 test article concentration is indicative of a genotoxic effect. If neither a significant dose-response difference nor a single test-point difference between test and controls is found, the article is not genotoxic in this test system.

## IN VITRO MAMMALIAN CYTOGENETIC TEST

In this procedure, any of a number of mammalian cell types are exposed in culture to a test article. Shortly before harvesting of the cells, they are exposed to agents that stop mitotic activity. Any cells that had reached the metaphase stage of mitosis will be stopped at the point where the chromosomes (paired chromatids at this stage) are lined up along the midline of the cell undergoing mitosis. This greatly facilitates the subsequent microscopic examination for structural alterations to the chromosomes/chromatids.

The alterations to structure may involve the chromosome prior to mitosis, in which case both sister chromatids will be altered, or the alteration may involve only one of the sister chromatids. In the latter case, the effect of the test article was not at the level of the chromosome prior to mitosis.
Mammalian Cells-A wide range of mammalian primary cell cultures or established cell lines may be used. The advantages to using primary cultures include a greater likelihood that the chromosomal structure is normal. Disadvantages include the considerable increase in labor and technical skill required to obtain the cells from the tissue source, and the limited number of passages to be expected from a primary, nontransformed culture of the cells. Many appropriate established lines are available from commercial suppliers. Required conditions for culturing are provided by the suppliers. While these advantages are important, and include the ability of many of these cell lines to be passaged many times, such lines also have the disadvantage of an increased likelihood of abnormal karyotypes. Therefore, cell lines should not be passaged indefinitely, and the karyotypes should be examined on a routine basis to ensure that the cells undergoing exposure to test articles are not demonstrating an increased rate of spontaneous abnormal karyotype development.

Culture conditions should be as appropriate to the cells in use. Commercial suppliers of mammalian cell lines will generally provide information on culture conditions, including appropriate media, supplements, etc. Mammalian cells are often incubated at $37^{\circ}$ in $5 \%$ carbon dioxide at saturated relative humidity.

Metabolic Activation System-A suitable metabolic activation system may be the same as that described for Metabolic Activation System in the Salmonella typhimurium Reverse Mutation Assay.

Test Article-Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo $\langle 88\rangle$. It is necessary to use concentrations of test article that are not overtly cytotoxic. A cytotoxic effect on the cells may be demonstrated by a reduction in cell viability and growth. The maximum concentration should be that which causes approximately a $50 \%$ reduction in mitoses. This will be manifested by a reduction in cell doublings. At least four other lower concentrations should be used as well.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). Positive controls should include those that act without the presence of a metabolic activation system and those that do require a metabolic activation system. A search of numerous toxicological databases on the Internet can provide examples of suitable positive controls. For example, ethylmethanesulfonate can be identified by such a search.

Test Performance-The specifics of the culturing will depend upon the cell type used. Established cell lines should be generated from stock cultures, possibly originating from cells stored frozen in liquid nitrogen (or in the vapor phase above liquid nitrogen). The cells should be seeded at an ap-
propriate density that is also dependent upon the type of cell used. Commercial suppliers will generally indicate details pertinent to subculturing for each established cell type. If human lymphocytes are to be used, whole, heparinized blood should be placed in the culture medium. A mitogen should be added to induce mitotic activity. An example of a suitable mitogen is phytohemagglutinin.

If established cell lines are used, exposure to the test article should occur while the cells are in the exponential growth phase. This means that the cells should be exposed prior to reaching confluence, or when evidence of slowing of growth is observed. Human lymphocytes (mitogen stimulated) should be treated in the same manner. Cells should be exposed to a test article both in the presence and absence of a metabolic activation system.
The length of time over which the cells should be exposed to the test article is dependent in part on the specific cell type and its normal rate of mitotic division, and in part upon whether the test article alters the normal mitotic rate. Therefore, cells should be examined at several times postadministration of the test article. Human lymphocyte cultures, which grow in suspension, can have the test article added at different times, allowing for a single harvest time with cells having undergone exposure for different lengths of time.

Regardless of the cell type used, an agent that inhibits mitotic activity, such as colchicine, should be added to the cultures approximately 2 hours before the cells are harvested for examination. Colchicine acts by disrupting microtubule formation. Normal functioning of the microtubules is required for ongoing mitotic activity.

For cells grown as monolayers, harvesting would require disruption of the monolayers in a manner that does not disrupt the cells. There are a number of methods for loosening monolayers and preparations of suspensions, including the
use of trypsin/EDTA. Portions of the cell suspension (derived from monolayers or from suspension cultures) should be applied to microscope slides, then fixed and stained such that the chromosomes may be examined. A number of stains are suitable.

Observations and Interpretation-Chromosomal aberrations seen in cells in metaphase should be determined. Table 3 lists some of the aberrations that may be checked. For established cell lines, cells with the modal chromosome number $\pm 2$ centromeres may be counted. If human lymphocytes are used, only cells with 46 centromeres should be examined. The number of cells examined should be based on knowledge of the spontaneous (negative control) appearance of altered chromosomes and on the statistical power desired. A statistical power calculation requires (1) knowledge of the typical variance for the test system, (2) a prior determination of the Type I and Type II errors that are acceptable, and (3) the minimum detectable difference required. It is best that statistical power calculations be performed a priori, although after-the-fact power calculations may be done to determine the realized sensitivity of the test.

Table 3. Some Examples of Chromosomal

## Aberrations

| Chromosomal breakage (micronuclei) |
| :--- |
| Chromosomal bridges |
| Chromosomal fragments |
| Chromosomal gaps |
| Dicentric chromosomes |
| Polyploidy |
| Hyperdiploidy |
| Chromatid deletion |
| Chromatid gaps |
| Chromatid breakage (fragments) |
| Sister chromatid exchanges |

Chromosomal bridges
Chromosomal fragments
Chromosomal gaps
Dicentric chromosomes
Polyploidy
Hyperdiploidy
Chromatid deletion
Chromatid gaps
Chromatid breakage (fragments)
Sister chromatid exchanges

The number of cells in the test samples showing chromosomal aberrations and the spontaneously occurring chromosomal aberrations on the control plates should be determined. The number of metaphase cells counted for both article-treated test cells and controls should be recorded. The frequency of mutants for both control and test cell cultures should then be calculated.

Statistical comparisons between test and control cultures should be made to determine if a statistically significant difference in the number of mutants exists. An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the number of mutants is observed. Also, a statistically significant difference between test and controls for at least 1 test article concentration is indicative of a genotoxic effect. If neither a significant dose-response difference nor a single test-point difference between test and controls is found, the article is not genotoxic in this test system.

## IN VITRO SISTER CHROMATID EXCHANGE ASSAY IN MAMMALIAN CELLS

During the process of mitosis, each chromosome replicates, forming two sister chromatids. One possible outcome of exposure of a test article to a genotoxic agent is an increase in the rate of sister chromatid exchange. In such exchanges, the DNA strand of each chromatid breaks, presumably at homologous loci, then the strands recombine with the opposite sister chromatid. In order to evaluate such recombination events, it is necessary that one be able to distinguish between the two sister chromatids. In this method, cells are cultured in the presence of BrdU after the period of incubation with the test article for two cell cycles. Then the cells are exposed to an agent that blocks microtubule function (such as colchicine), and the cells are stained in one of several possible ways such that sister chromatid exchanges can be quantified.

Mammalian Cells-A variety of mammalian cell lines may be appropriate for this method, both established cell lines such as Chinese hamster ovary or lung cells, or human lymphocytes. Many such appropriate established lines are available from commercial suppliers. Required conditions for culturing are provided by the suppliers. Cell lines should not be passaged indefinitely, and the karyotypes should be examined on a routine basis to ensure that the cells undergoing exposure to test articles are not demonstrating an increased rate of spontaneous sister chromatid exchange.

Culture conditions should be as appropriate to the cells in use. Commercial suppliers of mammalian cell lines will generally provide information on culture conditions, including appropriate media, supplements, etc. Mammalian cells are often incubated at $37^{\circ}$ in $5 \%$ carbon dioxide at saturated relative humidity.

Metabolic Activation System—A suitable metabolic activation system may be the same as that described for Metabolic Activation System in the Salmonella typhimurium Reverse Mutation Assay.
Test Article-Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo $\langle 88\rangle$. The highest concentration of test article that should be used should give rise to a significant but not lethal toxic effect. At least two other lower concentrations should be used as well.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). Positive controls should include those that act without the presence of a metabolic activation system and those that do require a metabolic activation system. A search of numerous toxicological databases on the Internet can provide examples of suitable positive controls. For example, ethylmethanesulfonate can be identified by
such a search as a suitable positive control in the absence of a metabolic activation system. Dimethylnitrosamine is a suitable positive control when a metabolic activation system is present.

Test Performance-Cells derived from established cell lines should be used while they are in the exponential growth phase. Human lymphocytes should be used in a semisynchronous condition. The cells (approximately $10^{6}$ ) should be exposed to the test article ranging from 1-2 hours up through 2 complete cell cycles. The exposure to a test article should include cultures both with and without a metabolic activation system. At the end of the exposure period, the cells should be centrifuged and washed clear of the test article. Next, the cells should be cultured in the presence of $\operatorname{BrdU}(10 \mu \mathrm{M}$ final concentration) for 2 cell cycles ( 2 doublings). The length of time required for the 2 cycles should be determined empirically. It is possible that the time needed for a cell doubling prior to exposure to the test article may have changed as a result of the exposure.

At the end of the exposure period to BrdU, the cells should be treated with an inhibitor of microtubule function (e.g., colchicine or colcemid). This will cause cells that are in metaphase to retain that distribution of the sister chromatids. Any of a variety of cytological techniques could be used to make chromosome preparations. For example, the cells can be treated with 0.75 M KCl to cause swelling, then washed at least 3 times in a mixture of methanol and acetic acid (3:1) for fixation. The cells can then be placed on microscope slides, and air dried.
The slides can then be stained for approximately 10 min utes in Hoechst 33258 (about $5 \mu \mathrm{~g}$ per mL ) in $\mathrm{M} / 15$ Sorensen's buffer. Then the cells may be mounted in the same buffer and exposed to UV light for a period of time long enough to permit identification of the sister chromatids. After

UV exposure, the cells should be stained with $10 \%$ Giemsa for 10 minutes, then washed and mounted in a commercially available mounting medium.

Observations and Interpretation-At a minimum, 25 metaphase cells should be examined for both control and test article-treated cultures to establish the rates of spontaneously occurring and test article-induced sister chromatid exchange. For established cell lines, cells with the modal chromosome number $\pm 2$ centromeres may be counted. If human lymphocytes are used, only cells with 46 centromeres should be examined.

The number of sister chromatid exchanges, the number of chromosomes, and the mean number of sister chromatid exchanges per chromosome should be determined. Statistical comparisons between test and control cultures should be made to determine if a statistically significant difference in the number of sister chromatid exchanges exists. An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the number of sister chromatid exchanges is observed. Also, a statistically significant difference between test and controls for at least 1 test article concentration is indicative of a genotoxic effect. If neither a significant dose-response difference nor a single test-point difference between test and controls is found, the article is not genotoxic in this test system.

## IN VIVO TESTS

## MICRONUCLEUS TEST

This test is designed to detect damage to chromosomes and/or the mitotic spindle as a consequence of exposure to test articles. New erythrocytes are being continuously produced as a consequence of mitotic divisions of stem cells in the bone marrow. Because of the high rate of mitotic activity of these cells, test articles that have toxic effects on chromosomes and/or the mitotic spindle can be easily identified
through the use of hematopoietic stem cells. Moreover, as a mature erythrocyte is formed, its principal nucleus is expelled. However, should a micronuclei form as a result of damage caused to the stem cell (chromosomal damage and/or mitotic spindle damage can cause this), the micronuclei are not expelled, and are easily visualized.

Animals-Adult male and/or female mice may be used. [NOTE-Other species may also be used.] A suitable strain is CD-1, although others are acceptable. Prior to use, it is essential to acclimatize the animals to the laboratory conditions for at least 5 days. All animals should be handled in accordance with the guidelines in the appropriate regulatory requirements established for the humane treatment of animals. At least 5 test animals and 5 control animals should be used per group (dose level). Animals may be grouphoused, and provided food and water ad libitum.

Test Article—Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo $\langle 88\rangle$. When $\mathrm{LD}_{50}$ data are available for the test article, the highest concentration tested may be set at $50 \%$ of the $\mathrm{LD}_{50}$. Two other doses, a low of $10 \%$ of the $\mathrm{LD}_{50}$ and an intermediate dose, should be used. In some cases it may not be possible to obtain an $\mathrm{LD}_{50}$ for the test article. In that case, the highest concentration should be chosen to emulate the maximum exposure (proportionately) that a human might experience for the test article.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). Trimethylenemelamine may be used as a positive control.

Test Performance-Most often, the test article is administered once via oral gavage. In some cases the test article may be given more than once, but there should be no cytotoxicity evident in the bone marrow cells should this be
done. Bone marrow samples should typically be taken at 12, 48 and 72 hours after the last dose was administered. To collect the samples, the animals are euthanized and the marrow from the femurs should be aspirated and collected in 5 mL of fetal calf serum. After centrifugation, the cells should be smeared onto microscope slides and stained appropriately. One such stain is May-Gruenwald solution and Giemsa, followed by clearing in water.

Observations and Interpretation-At least 1000 polychromatic erythrocytes should be evaluated for the presence of micronuclei. The percentage of polychromatic erythrocytes with micronuclei should be determined. Other cell types should be counted as well, because some test articles may cause toxic effects on hematopoiesis other than that evidenced by increased numbers of micronuclei. The percentage of polychromatic erythrocytes versus normochromatic erythrocytes should also be determined.
The results should be analyzed statistically for the presence of significant differences between test and control animals. A significant increase in the number of polychromatic erythrocytes with micronuclei in test animals versus controls, occurring in a dose-related manner, is indicative of a toxic effect. Likewise, if such a significant difference is found for at least one dose, a toxic effect for the test article is again indicated. If no significant differences are found between test and control articles, the article would not be considered genotoxic in this test system.

IN VIVO MAMMALIAN BONE MARROW CYTOGENETIC TESTCHROMOSOMAL ANALYSIS

This in vivo test is designed to test for the presence of damage to chromosomes/chromatids as a result of exposure to test articles. After exposure of the animals to the test article, bone marrow cells are removed and chromosomal preparations are made. The cells examined are in the metaphase stage of mitosis.

Animals-Healthy young adult male and/or female rodents of a variety of species may be used. Prior to use, it essential to acclimatize the animals to the laboratory conditions for at least 5 days. All animals should be handled in accordance with the guidelines in the appropriate regulatory requirements established for the humane treatment of animals. At least 5 test animals and 5 control animals should be used per group (dose level). Animals may be grouphoused (by sex), and provided food and water ad libitum.

Test Article-Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo $\langle 88\rangle$. The maximum dose can be the maximal amount that is tolerated or that which produces some cytotoxic effects (such as reduction in the normal rate of mitoses). If desired, lower doses can also be evaluated.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). A search of numerous toxicological databases on the Internet (Table 2) can provide examples of suitable positive controls. The positive control selected should be known to cause chromosomal damage in vivo.

Test Performance-The test article extract should be administered via oral gavage or by intraperitoneal injection. If desired, other routes of administration may be used. Most often, the test article should be administered only once, although repeated dosing is permissible depending upon toxicological information. Animals should receive intraperitoneal injections of an agent known to block microtubule function (such as colchicine) at least 3 hours prior to the collection of marrow samples. The treatment with the microtubule inhibitor may have to occur earlier in order to accumulate enough cells in metaphase. Bone marrow samples should typically be taken at 6,24 , and 48 hours after the
last dose was administered. To collect the samples, the animals are euthanized and the marrow from the femurs should be aspirated and collected in 5 mL of fetal calf serum. After centrifugation, the cells should be smeared onto microscope slides and stained appropriately. One such stain is MayGruenwald solution and Giemsa, followed by clearing in water.

Observations and Interpretation-Chromosomal aberrations seen in cells in metaphase should be determined. Table 3 lists some of the aberrations that may be checked for. The number of cells examined should be based on knowledge of the spontaneous (negative control) appearance of altered chromosomes and the statistical power desired. A statistical power calculation requires (1) knowledge of the typical variance for the test system, (2) a prior determination of the Type I and Type II errors that are acceptable, and (3) the minimum detectable difference required. It is best that statistical power calculations be performed a priori, although after-the-fact power calculations may be done to determine the realized sensitivity of the test.

The number of cells in the test animals showing chromosomal aberrations and the spontaneously occurring chromosomal aberrations in control animals should be determined. The number of metaphase cells counted for both test articletreated animals and controls should be recorded. The frequency of mutants for both control and test animals should then be calculated.

Statistical comparisons between test and control animals should be made to determine if a statistically significant difference in the number of mutants exists. An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the number of mutants is seen. Also, a statistically significant difference between test and controls for at least 1 test article concentration (in studies where more than 1 dose is used) is indicative of a gen-
otoxic effect. If neither a significant dose-response difference nor a single test-point difference between test and controls is found, the article is not genotoxic in this test system.

## RODENT DOMINANT LETHAL TEST

This in vivo test is used to detect damage to germ cells resulting from exposure to test articles. In particular, this test detects dominant lethal mutations. Such mutations do not cause dysfunction of the gametes, but result in lethality to the fertilized egg or developing embryos. Most such dominant lethal mutations are thought to be the result of chromosomal damage, although the possibility of gene mutations such as a frame shift cannot be ruled out.

Animals-Most often, healthy, sexually mature male and/or female rats or mice are used. Prior to use, it is essential to acclimatize the animals to the laboratory conditions for at least 5 days. All animals should be handled in accordance with the guidelines established for the humane treatment of animals in the appropriate regulatory requirements. Animals may be group-housed (by sex), and provided food and water ad libitum. The number of animals to use should be based on a statistical power calculation factoring in desired error rates, variability, and sensitivity. In a typical experiment, $30-50$ animals would be used per mating interval, with enough mating intervals used to span the stages of germ cell development in male animals.
Test Article-Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo 〈88〉. The maximum dose should cause some signs of toxicity, for example, a slight reduction in fertility. Nontoxic substances may be tested at 5 g per kg if practical, otherwise at the highest dose possible.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). A search of numerous toxicological databases on the Internet (Table 2) can provide examples of suitable positive controls. Examples of suitable positive controls include triethylenemelamine, cyclophosphamide, and ethyl methanesulfonate.

Test Performance-The test article extract should be administered to males via oral gavage or by intraperitoneal injection. If desired, other routes of administration may be used. Most often, the test article extract should be administered only once, although repeated dosing is permissible depending on toxicological information. Treated males should be mated to untreated females at a sufficient number of intervals to span the range of gamete development in the males. Females should be euthanized in the second half of pregnancy, and the uteri and ovaries removed for examination.

Observations and Interpretation-The number of corpora lutea should be determined from the ovaries. The number of live and dead implantations in the uteri should be determined. Using these values, the postimplantation loss may be calculated by taking the ratio of dead versus total implants. The pre-implantation loss may be calculated by taking the ratio of corpora lutea versus implantations. Determining the ratio of implantations in the test versus control animals may be another means of calculating the pre-implantation loss.

Statistical comparisons between test and control animals should be made to determine if a statistically significant difference in pre- or post-implantation losses exists. An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the number of losses is observed. Also, a statistically significant difference
between test and controls for at least 1 test article concentration (in studies where more than 1 dose is used) is indicative of a genotoxic effect. If neither a significant dose-response difference nor a single test-point difference between test and controls is found, the article is not genotoxic in this test system.

## MAMMALIAN GERM-CELL CYTOGENETIC ASSAY

This test is similar to the Rodent Dominant Lethal Test in that male rodents are exposed to test articles, as a result of which damage to the germ cells may occur. In this test, chromosomal damage is assessed using chromosomal preparations derived from testes. As with previous tests, the cells examined are in metaphase, and the accumulation of cells in that stage is facilitated by the use of an agent inhibitory to microtubule function.

Animals-Most often, healthy, sexually mature male mice or Chinese hamsters are used, although other species may also be used. Prior to use, it is essential to acclimatize the animals to the laboratory conditions for at least 5 days. All animals should be handled in accordance with the guidelines in the appropriate regulatory requirements established for the humane treatment of animals. Animals may be group-housed and provided food and water ad libitum. There should be at least 5 animals used per experimental and control group.
Test Article-Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo $\langle 88\rangle$. The maximum dose should cause some signs of cytotoxicity. Nontoxic substances may be tested at 5 g per kg if practical, otherwise at the highest dose possible. At least two other concentrations should be used to establish a dose-response relationship.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). A search of numerous toxicological databases on the Internet (Table 2) can provide examples of suitable positive controls. A suitable positive control should be one known to cause chromosomal abberations in vivo visible in metaphase spermatocytes.
Test Performance-The test article extract should be administered to males via oral gavage or by intraperitoneal injection. If desired, other routes of administration may be used. Most often, the test article should be administered only once, although repeated dosing is permissible depending on toxicological information. At appropriate times prior to euthanization of the animals and testes collection, an agent inhibitory to microtubule function (such as colchicine) should be administered. For mice, the agent may be administered 3-5 hours prior to euthanasia. More time may be required for Chinese hamsters. Typically, testes should be collected at 6,24 , and 48 hours.

A variety of techniques may be used to obtain cells undergoing spermatogenesis from the testes. These cells may be treated with 0.75 M KCl to cause swelling, then washed at least 3 times in a mixture of methanol and acetic acid (3:1) for fixation. The cells can then be placed on microscope slides and air dried. The cells can then be stained with $10 \%$ Giemsa for 10 minutes to facilitate observation of chromosomal/chromatidal damage.

Observations and Interpretation-At least 100 metaphase cells (with the full complement of centromeres) should be scored. Chromosome/chromatid damage (see Table 3) should be tabulated. Also, the ratio of spermatogonial mitoses to first and second meiotic metaphases can serve as an index of cytotoxicity.

The number of cells showing chromosomal aberrations found in the test samples, and spontaneously occurring chromosomal aberrations in controls, should be determined. The number of metaphase cells counted for both test articletreated cells and controls should be recorded. The frequency of mutants for both control and test cell samples should then be calculated.

Statistical comparisons between test and control animals should be made to determine if a statistically significant difference in the number of mutants exists. An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the number of mutants is observed. Also, a statistically significant difference between test and controls for at least 1 test article concentration is indicative of a genotoxic effect. If neither a significant dose-response difference nor a single test-point difference between test and controls is found, the article is not genotoxic in this test system.

## MOUSE SPOT TEST

Pregnant females heterozygous for a number of genes affecting coat pigmentation as caused by the action of melanoblasts are used in this method. The principle is that a mutation of the dominant allele while the embryo is developing would permit phenotypic expression of the recessive allele, resulting in a change in coat pigmentation. An increase in the frequency of these spots in test animals versus controls is indicative of a genotoxic effect.

Animals-For this method, it is necessary to use pregnant animals from specific mating pairs in order to obtain the required heterozygotic embryos. Appropriate matings would be between T strain mice and HT strain mice, or between T strain mice and C57/B1. Other matings may also be appropriate. Prior to use, it essential to acclimatize the animals to the laboratory conditions for at least 5 days. All animals
should be handled in accordance with the guidelines in the appropriate regulatory requirements established for the humane treatment of animals. Animals may be group-housed and provided food and water ad libitum. There should be a sufficient number of pregnant females to generate enough offspring for a statistical analysis of the data. The specific test system will govern the numbers required.

Test Article-Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo $\langle 88\rangle$. The maximum dose should cause some signs of toxicity such as reduced liter size. Nontoxic substances may be tested at 1 g per kg if practical, otherwise at the highest dose possible. At least one other concentration should be used.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (ex-
tracted as appropriate). A search of numerous toxicological databases on the Internet (Table 2) can provide examples of suitable positive controls. A suitable positive control should be one known to cause increases in spots due to somatic mutations.

Test Performance-The test article extract should be administered to males via oral gavage or by intraperitoneal injection. If desired, other routes of administration may be used. Most often, the test article should be administered only once on days 8,9 , or 10 of pregnancy, although repeated dosing over these days is permissible.

The offspring should be evaluated for the presence of spots between 3-4 weeks following birth. There are 3 types of spots to be distinguished, as indicated in Table 4.

Table 4. Types of Spots to be Evaluated in the Mouse Spot Test

| Spot Type | Description | Presumed Cause |
| :--- | :--- | :--- |
| WMVS | White spots within 5 mm of mid-ventral line | Cell killing |
| MDS | Yellow, agouti-like spots associated with <br> mammae, genitalia, throat, axillary and <br> inguinal areas, mid-forehead | Misdifferentiation |
| RS | Pigmented and white spots randomly <br> distributed | Somatic mutation |

Observations and Interpretation-The number of spots of the three types described in Table 4 should be determined. The spots of greatest importance in this test are the RS spots, as they are presumed to be due to somatic mutations.

Statistical comparisons between test and control animals should be made to determine if a statistically significant difference in the number of RS spots exists. An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the number of RS spots
is observed. Also, a statistically significant difference between test and controls for at least 1 test article concentration is indicative of a genotoxic effect. If neither a significant dose-response difference nor a single test-point difference between test and controls is found, the article is not genotoxic in this test system.

## MOUSE HERITABLE TRANSLOCATION ASSAY

This test is designed to detect structural and numerical changes to chromosomes and to germ cells in the progeny of the test animals. There are a number of approaches that may be used in this method. In some cases, only male progeny are examined. In others, progeny of both sexes are examined. When females are used, they are examined, in part, for X-chromosome loss. Some carriers of translocations, and females missing one X -chromosome, show reduced fertility. In some cases, translocations cause complete sterility. Cytogenetic examination is also performed in this method using germ cells in metaphase from $F_{1}$ males or the male offspring derived from $F_{1}$ females.

Animals-For this method, mice are most often used. No specific strain is required, although the litter size should average more than 8 , and be relatively constant. Prior to use, it is essential to acclimatize the animals to the laboratory conditions for at least 5 days. All animals should be handled in accordance with the guidelines in the appropriate regulatory requirements established for the humane treatment of animals. Animals may be group-housed and provided food and water ad libitum. There should be a sufficient number of pregnant females to generate enough
offspring for a statistical analysis of the data. The most common mode of testing with this method involves an analysis of $F_{1}$ males, and typically at least $500 F_{1}$ males should be used. The number of P animals should be determined accordingly.
Test Article—Extracts of solid test articles should be prepared as described in Preparation of Extracts under Biological Reactivity Tests, In Vivo $\langle 88\rangle$. The maximum dose should cause some signs of toxicity, but not such that reproductive behavior or animal survival is affected. Nontoxic substances may be tested at 1 g per kg if practical, otherwise at the highest dose possible. At least two other concentrations should be used.

Controls-Both positive and negative controls should be used to check system performance. USP High-Density Polyethylene RS may be used as a negative control (extracted as appropriate). A search of numerous toxicological databases on the Internet (see Table 2) can provide examples of suitable positive controls. A suitable positive control should be one known to cause increased heritable translocations.

Test Performance-The test article extract should be administered to males via oral intubation or by intraperitoneal injection. If desired, other routes of administration may be used. Most often, the test article should be administered only once, although repeated dosing is permissible. Both males and females should be treated. Subsequent matings after treatment should be timed such that every stage of gametogenic development is covered. After mating, the females should be housed individually. After birth, the number and the sexes of the progeny should be recorded. The females may be discarded if no longer needed for the test.

Most frequently, the $\mathrm{F}_{1}$ males would be examined by cytogenetic analysis. Testes preparation should be made as described in the Mammalian Germ-Cell Cytogenetic Assay. Carriers of translocations will have multivalent configurations at diakinesis-metaphase I in at least two primary spermatocytes. Mitotic metaphases from spermatogonia or bone marrow should be examined in males with small testes and meiotic breakdown prior to diakinesis. Evidence for a c/t type translocation in males is evidenced by the presence of an unusually long and/or short chromosome in each of 10 cells. Some translocations that lead to male sterility can be identified only by banding analysis of mitotic chromosomes.

In some cases, the $F_{1}$ animals undergo fertility testing with subsequent evaluation of $\mathrm{F}_{2}$ progeny. The reduction of fertility of the $F_{1}$ animals may result in reduced litter sizes, or in differences observed during an analysis of uterine content of the females, such as was performed in the Rodent Dominant Lethal Test. The $\mathrm{F}_{2}$ animals may be the result of matings between $F_{1}$ males and females, or between $F_{1}$ males with other females from the same colony, but not $F_{1}$ females. Regardless of the pairings, the size and sexes from the $F_{2}$ progeny are recorded. $F_{2}$ progeny of small litters are kept for further testing if $F_{1}$ females were used in the pairings. Female carriers of translocations are identified by the cytogenetic analysis of their male offspring, the results of
which demonstrate the presence of translocations. $\mathrm{F}_{1}$ females that had lost an X-chromosome will have altered sex ratios in their litters (from 1:1 to 1:2 males to females). If the $\mathrm{F}_{2}$ litter meets pre-established criteria for normalcy, further testing of the $\mathrm{F}_{1}$ animal(s) would not be required, as the animal(s) would be classified as normal. If the first $\mathrm{F}_{2}$ litter does not serve to identify a carrier in the $\mathrm{F}_{1}$ cross, one or more subsequent $\mathrm{F}_{2}$ litters can be analyzed. If a clear determination of the $\mathrm{F}_{1}$ animal(s) status still can't be made, cytogenetic and uterine analyses may be performed. Uterine content may be performed as described in the Rodent Dominant Lethal Test.

Observations and Interpretation-Table 5 lists the observations to be made depending upon the type of assessment. Statistical comparisons between test and control animals should be made to determine if a statistically significant difference in the number of translocations exists. An indication of potential genotoxicity may be found if a statistically significant dose-response relationship to the number of translocations is seen. Also, a statistically significant difference between test and controls for at least 1 test article concentration is indicative of a genotoxic effect. If neither a significant dose-response difference, nor single test-point difference between test and controls is found, the article is not genotoxic in this test system.

Table 5. Observations to be Made Based on Type of Assessment for Mouse Heritable Translocation Assay

| Type of <br> Assessment |  |
| :--- | :--- |
| Fertility of $\mathrm{F}_{1}$ animals | Mean litter size of normal matings, individual litter sizes of translocation carriers. |
|  | Mean number of live and dead uterine implants for each mating of $\mathrm{F}_{1}$ |
|  | translocation carriers. |
| Cytogenetic analyses of cells | Number and types of multivalent configurations and the total number of cells per |
| in diakinesis-metaphase I | translocation carrier. |
| Sterile $\mathrm{F}_{1}$ carriers | Total number of matings, duration of mating period. Testes weights and cyto- |
|  | genetic analysis results. |
| XO females | Mean litter size, sex ratio of $\mathrm{F}_{2}$ progeny, cytogenetic analysis results. |

## REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals, S2A (1995).
2. ICH Harmonized Tripartite Guideline: Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals, S2B. $\mathbf{\Delta U S P 2 8}$

## BRIEFING

$\langle\mathbf{1 1 8 4}\rangle$ Sensitization Testing. This new proposed general information chapter presents a number of test procedures that may be used to test for the sensitization potential of compendial articles as indicated in general information chapter The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants $\langle 1031\rangle$.

There are six methods presented using guinea pigs, and three methods that use mice. The guinea pig methods include the Magnusson \& Kligman Maximization, Standard Buehler, Open Epicutaneous, Freund's Complete Adjuvant, Optimization, and Split Adjuvant tests. The mouse tests include the Local Lymph Node Assay, Mouse Ear Swelling, and Vitamin A Enhancement tests.

Comments should be sent to USP Headquarters for consideration by the Expert Committee on General Toxicology and Biocompatibility no later than March 1, 2004.
(GTB: D. Porter) RTS-40475-1

## Add the following:

## ^ <1184〉 SENSITIZATION TESTING

## INTRODUCTION

This chapter considers sensitization and hypersensitization in the context of medical devices and implants, and describes methodologies for testing such articles for their potential to cause sensitization.

There are four types of hypersensitization reactions according to the Gell and Coombs classification system. Type I reactions involve the fixation of IgE to mast cells that subsequently release pharmacologically active substances, such as histamine. Type II reactions are the result of IgG and/or IgM binding to target cells, followed by complement fixation and cell lysis. Type III reactions are caused by the presence of antigen-antibody complexes that cause physical damage such as kidney damage due to glomerular blockage.

Type IV reactions are cell-mediated (involve the action of T cells and their interaction with the human lymphocyte antigens). Type IV reactions are also called delayed-type hyper-
sensitivity reactions. Table 1 below summarizes the types of reactions, the mediators of the reactions, and examples of representative diseases.

Table 1. The Four Types of Hypersensitization Reactions*, Mediators, and Disease Examples

| Reaction |  |  |
| :---: | :---: | :---: |
| Class | Mediators | Disease Examples |
| Type I | IgE molecules bound to mast cells interact with antigen to release pharmacologically active substances | Hay fever, bronchial asthma, other atopic reactions |
| Type II | IgM and/or IgM molecules interact with target cells, fix complement, cell lysis | Various drug allergies, erythroblastosis fetalis, hemolytic anemia, thrombocytopenia |
| Type III | Antigen-antibody complexes, complement | Arthus reaction, serum sickness, allergic glomerulonephritis |
| Type IV | T lymphocytes, antigen, monocytes, macrophages | Contact dermatitis |

If further toxicological testing is necessary, the classification of medical devices provided in Table 2 from general information chapter $\langle 1031\rangle$ is important, as the degree and extent of toxicological testing that is required is strongly influenced by the nature and duration of the bodily contact with the article. The classification derived from Table 2 (chapter $\langle 1031\rangle$ ), coupled with the length of exposure to the article, is used in Tables 3-5 (chapter $\langle 1031\rangle$ ) to determine which toxicological tests need to be performed. Table 2 below presents information extracted from Tables 3-5 of chapter $\langle 1031\rangle$ indicating those circumstances for which sensitization testing should be considered.

Table 2. Articles For Which Sensitization Testing Should Be Considered Based on Article Category and Length of Exposure

| Device Category | Body Contact | Contact Duration |
| :--- | :--- | :--- |
| Surface devices | Skin | $\mathrm{A}^{\mathrm{a}}, \mathrm{B}^{\mathrm{b}}, \mathrm{C}^{\mathrm{c}}$ |
|  | Mucosal membrane | $\mathrm{A}, \mathrm{B}, \mathrm{C}$ |
|  | Breached or compromised surfaces | $\mathrm{A}, \mathrm{B}, \mathrm{C}$ |
| External communicating devices | Blood path, indirect | $\mathrm{A}, \mathrm{B}, \mathrm{C}$ |
|  | Tissue, bone, or dentin communicating | $\mathrm{A}, \mathrm{B}, \mathrm{C}$ |
|  | Circulating blood | $\mathrm{A}, \mathrm{B}, \mathrm{C}$ |
| Implant devices | Tissue or bone | $\mathrm{A}, \mathrm{B}, \mathrm{C}$ |
|  | Blood | $\mathrm{A}, \mathrm{B}, \mathrm{C}$ |

${ }^{a}$ A: limited (less than 24 hours);
${ }^{\mathrm{b}}$ B: prolonged ( 24 hours to 30 days);
${ }^{\text {c }} \mathrm{C}$ : permanent (more than 30 days)

There are 9 test methodologies reviewed in this chapter. Table 3 lists the methods and the species with which they are performed.

Table 3. Test Methodologies That May Be Used in Sensitization Testing, and Species Required for Test

| Test | Species Used in <br> Test |
| :--- | :--- |
| Magnusson \& Kligman <br> Maximization | Guinea pig |
| Standard Buehler |  |
| Open Epicutaneous | Guinea pig |
| Freund's Complete Adjuvant | Guinea pig |
| Optimization | Guinea pig pig |
| Split Adjuvant | Guinea pig |
| Local Lymph Node Assay | Mouse |
| Mouse Ear Swelling | Mouse |
| Vitamin A Enhancement | Mouse |

Given the preponderance of testing performed with either the Magnusson \& Kligman Guinea Pig Maximization Test (GPMT) or Buehler Tests (BT), those tests will be reviewed in detail in this chapter. A brief summary of the remaining tests is provided as alternatives to the more frequently used procedures.

Each test should be periodically validated in the performing laboratory using positive controls such as hexyl cinnamic aldehyde, mercaptobenzothiazole, or benzocaine (positive controls recommended by the Organization for Economic Cooperation and Development [OECD]).

## MAGNUSSON \& KLIGMAN GUINEA PIG MAXIMIZATION TEST (GPMT)

## Animals

Either male and female albino guinea pigs or both may be used. All animals should be in good health and weigh between 300 g and 500 g at the start of the experiment. The females should not be pregnant, nor should they have borne young previously. Prior to use, it is essential to acclimatize
the animals to the laboratory conditions for at least 5 days. All animals should be handled in accordance with the guidelines in the appropriate regulatory requirements established for the humane treatment of animals. At least 10 test animals and 5 control animals should be used. To obtain sufficient analytical power (i.e., to detect weak sensitizers) it may be necessary to use 20 test animals and 10 control animals. Additional animals may be required to establish the proper doses to administer (see Determination of Test Article Concentration).

## Housing and Feeding

The animal room should be held at $20 \pm 3^{\circ}$, at $30 \%$ to $70 \%$ relative humidity, with 12 hours of light and dark. Animals may be housed individually or in group housing. Standard laboratory diets may be used (those satisfactory for guinea pigs ensure an adequate amount of ascorbic acid). Drinking water should be available ad libitum.

## Animal Pretest Preparation

Animals should be randomized via a validated randomization method. For example, such methods may utilize random number tables or computer-generated random numbers. Sites on the animals intended for test article application (intrascapular region) should have the hair removed in a manner that does not abrade the skin. This may be accomplished via clipping, shaving, or with chemical depilatories. The chemical depilatory must not elicit irritation of its own. General observations of the animals prior to use in the test should be recorded, including any indication of ill health (do not use such animals in tests), and body weights.

## Test Article Preparation ${ }^{1}$

The use of this test requires that the test article can be injected intradermally. When the test article is not suitable for direct administration, extracts should be prepared according to the procedure provided in general chapter Biological Reactivity Tests, In Vivo 〈88〉.

## Determination of Test Article Concentration

The purpose of this preliminary study is to determine the concentrations of Test Article Preparation to be used during the initial induction phase and the second challenge phase of a GPMT study. Two or three animals may be used for the concentration determination.

A range of concentrations of the test article, or extracts of the article, should be injected intradermally ( 0.1 mL per site), using the solvent that will be employed in the Test Procedure. The concentration that causes only mild to moderate irritation (no extensive skin destruction, with no evidence of overt systemic toxicity to the animals) should be used in the Intradermal Injection Induction Phase of the Test Procedure.

Using two or more animals, apply via occlusive dressings and patches, a range of concentrations of test article or extracts of the article. Remove the dressings/patches after 24 hours, and examine the sites for erythema. Choose the concentration that causes only slight erythema for the Topical Application Induction Phase of the Test Procedure. Use the highest concentration of test article or extract that does not cause erythema for the Challenge Phase of the Test Procedure. If the irritation threshold is not reached, then select the highest possible concentration for the Topical Application Induction Phase and Challenge Phase of the Test Procedure.

[^28]
## Test Procedure

## INTRADERMAL INJECTION INDUCTION PHASE

This phase requires three pairs of injections administered intradermally, with the test and control injection of each pair on opposite sides intrascapularly. Each injection should contain 0.1 mL , with injection pairs 1 and 2 administered nearer to the head, and injection pair 3 administered slightly farther towards the tail. The pairs are nominally within an area of 8 $\mathrm{cm}^{2}$. The pairs of injections consist of the following:

Injection pair 1: A 1:1 (v/v) mixture of Freund's Complete Adjuvant (FCA), an oil-water emulsion containing mycobacteria, and the appropriate solvent/vehicle (see Biological Reactivity Tests, In Vivo $\langle 88\rangle$ ). Control animals receive a mixture of FCA and physiological saline (1:1).

Injection pair 2: The Test Article Preparation in the concentration as specified in

Determination of Test Article Concentration, using the appropriate solvent/vehicle. Control animals receive only the solvent/vehicle.

Injection pair 3: The Test Article Preparation in the concentration as specified in Determination of Test Article Concentration in a 1:1 (v/v) mixture with FCA. Control animals receive an injection of a $1: 1(\mathrm{v} / \mathrm{v})$ mixture of FCA and solvent/vehicle.

## TOPICAL APPLICATION INDUCTION PHASE

Seven days ( $\pm 1$ day) after completion of the Intradermal Injection Induction Phase, administer the test sample by topical application to the intrascapular region of each animal. For both test and control animals, if the Test Article Preparation does not cause skin irritation, apply $10 \%$ sodium lauryl sulfate in petrolatum approximately 24 hours before the start of the Topical Application Induction Phase to induce a local irritation.

Test animals should have $2-\times 4-\mathrm{cm}$ pieces of filter paper or absorbent gauze fully loaded with the Test Article Preparation (prepared within 24 hours of use) using the concentration selected in Determination of Test Article Concentration applied to each injection site. The filter paper or absorbent gauze should be secured to the animals using occlusive dressings. Control animals receive the same treatment, except that the appropriate solvent/vehicle is used instead of the test article.

Remove the dressings and patches approximately 48 hours after application.

## CHALLENGE PHASE

This phase should occur $14 \pm 1$ days after the Topical Application Induction Phase. Hair should be removed from the test application sites. Filter paper patches or chambers are soaked with a freshly prepared Test Article Preparation in the concentration specified in Determination of Test Article Concentration. This is done for all test and control animals. The patches or chambers are secured with an occlusive dressing and removed after $24 \pm 2$ hours.

## Observations

At approximately 24, 48, and 72 hours after removal of the challenge patches, the application sites should be examined for signs of reactions. Of particular importance are in-
stances where the reaction of the test animals exceeds that of the control animals. All signs of reactivity should be recorded, with particular attention paid to signs of erythema and edema. A true edematous reaction will blanch under gentle pressure. The longer the period of blanching, the greater the severity of edema.

## Interpretation

There is more than one way of evaluating and grading the results from GPMT. Tables 4, 5 and 6 list details for three such grading systems. Grades of 1 or higher in the test animals, with grades of less than 1 in control animals, are indicative of sensitization. If control animals display grade 1 reactivity, and if the test animals display reactivity above the greatest reactivity seen in the control animals, sensitization due to the test article is again suspected. The percentages in Table 4 need to be revised if there are only 10 test animals (i.e., the caegories would be $0,<10 \%, 10 \%-30 \%, 31 \%-$ $60 \%, 61 \%-80 \%$, and $81 \%-100 \%$.) If there are 20 test animals, then multiples of $5 \%$ are appropriate.

## Table 4. Classification Based on Percent of

## Responsive Test Animals

| \% of Positives |
| :---: |
| in |

Test Group $\quad$ Assigned Grade Class

Table 5. Classification Based on Erythema and Edema Formation

| Erythema and Eschar | Grade |
| :--- | :---: |
| No erythema | 0 |
| Slight or equivocal erythema | $<1$ |
| Well-defined erythema | 2 |
| Moderate erythema | 3 |
| Severe erythema to slight eschar formation | 4 |


| Edema |  |
| :--- | :---: |
| No edema | 0 |
| Slight or equivocal edema | $<1$ |
| Well-defined edema | 2 |
| Moderate edema | 3 |
| Severe edema | 4 |

The results should be submitted for statistical analysis (e.g., chi-square contingency table) to determine if the differences in scores between treated and control animals are significant. The response of the test group versus the control group should be compared statistically. (The Mann-Whitney U test can be used for the comparison.)

Table 6. Classification Based on Erythema

> Formation Alone

| Erythema formation | Grade |
| :--- | :---: |
| No erythema | 0 |
| Discrete or patchy erythema | 1 |
| Moderate and confluent erythema | 2 |
| Intense erythema and swelling | 3 |

## Rechallenge

The extent of any response in the negative control group, under experimental conditions, shows the irritation potential of the Test Article Preparation. In this case, test and control animals should be rechallenged 1 week later on the un-
treated side of the animal, with a reduced concentration of the Test Article Preparation. A sensitized guinea pig will react to some degree to both challenges. A weak reaction occurring at a single time point in only one challenge should cast strong doubt as to whether that guinea pig is truly sensitized. ${ }^{2}$

## STANDARD BUEHLER TESTS (SBT)

Animals<br>See Animals in the Magnusson \& Kligman Guinea Pig Maximization Test (GPMT).

## Housing and Feeding

See Housing and Feeding in the Magnusson \& Kligman Guinea Pig Maximization Test (GPMT).

## Animal Pretest Preparation

See Animal Pretest Preparation under Magnusson \& Kligman Guinea Pig Maximization Test (GPMT). The fur of the guinea pig may be removed from one flank by clipping.

## Test Article Preparation

See Test Article Preparation in the Magnusson \& Kligman Guinea Pig Maximization Test (GPMT).

[^29]
## Determination of Test Article Concentration

The purpose of this preliminary study is to determine the concentrations of Test Article Preparation to be used during the initial induction phase and the second challenge phase of an SBT study. Two or three animals may be used for the concentration determination.

A range of concentrations of the test article, or extracts of the article, should be applied using patches (for example, four $4 \mathrm{~cm}^{2}$ absorbant pads) or chambers. The patches should be held in place using tape (if necessary) and occlusive dressings. The patches should be removed after approximately 6 hours, and any residues of the test chemical are removed from the test site. Observations are made at that time, and at 24 and 48 hours.

The concentration that causes only mild to moderate irritation (slight erythema, with no evidence of overt toxicity to the animals) and can be applied repeatedly to the same site should be used in the Induction Phase of the Test Procedure. Use the highest concentration of test article or extract that does not cause erythema for the Challenge Phase of the Test Procedure.

## Test Procedure

## INDUCTION PHASE

Apply 0.4 mL of the Test Article Preparation in an appropriate solvent/vehicle at the dose identified in Determination of Test Article Concentration. Use patches similar to those used in Determination of Test Article Concentration. The patches should be applied to one flank (hair clipped off) and held in place occlusively for 6 hours. The animals may need to be restrained to ensure occlusion. Patches and any visible residues should be removed after 6 hours. Control animals also receive patches, but these contain only the appropriate solvent/vehicle. This process should be repeated
three times a week for both test and control animals on the same site for three consecutive weeks (weekly intervals are used in the modified Buehler Test).

## CHALLENGE PHASE

This phase should be carried out 14 days after the last application of the Induction Phase. Clip the hair off the previously untested flank of each animal 24 hours before the challenge application. As in the Induction Phase, apply patches containing the test article (concentration specified in Determination of Test Article Concentration) or solvent/vehicle alone to the untested areas of the test and control animals. To obtain well-defined edges at the application sites, commercial chambers with a lipped edge are preferred. Secure the patches with occlusive dressings, and keep them in place for 6 hours. Remove all patches after 6 hours.

## Observations

At $22 \pm 2$ hours after removal of the patches, the application sites should have the animal's fur removed via clipping or depilation. After approximately 2 more hours, grade the sites (Tables 4, 5 or 6 may be employed). All signs of reactivity should be recorded, with particular attention paid to signs of erythema and edema. Repeat the grading once again after 24 to 48 hours more have elapsed. The response of the test group versus the control group can be compared statistically. (The Mann-Whitney U test can be used for the comparison.)

## Interpretation

The results should be submitted for a statistical analysis (e.g., chi-square contingency table) to determine if the differences in scores between treated and control animals are significant.

See Interpretation in the Magnusson \& Kligman Guinea Pig Maximization Test (GPMT).

## Rechallenge

See Rechallenge in the Magnusson \& Kligman Guinea Pig Maximization Test (GPMT).

## OTHER SENSITIZATION TEST PROCEDURES

The Magnusson \& Kligman Guinea Pig Maximization Test and the Standard Buehler Tests are the most frequently performed sensitization tests. However, there are a number of other methods that may be useful in the assessment of the potential for sensitization. Some may be applicable to both solid test articles and extracts, some only to extracts.
Where the use of guinea pigs is called for in the following tests, the animals and their housing should meet the requirements as specified for Animals in the Magnusson \& Kligman Guinea Pig Maximization Test. The fur of the guinea pig should be removed from test sites as indicated for Animal Pretest Preparation in the Magnusson \& Kligman Guinea Pig Maximization Test.

## Draize Test

This was the first predictive test accepted by the regulatory agencies, and is still in use. The test uses guinea pigs and the test article is administered via intradermal injections.

## TEST ARTICLE PREPARATION

This test requires that the test article be in the form of a solution that may be directly applied to the animal's skin. Therefore, extracts of the material would need to be made. See Biological Reactivity Tests, In Vivo $\langle 88\rangle$ for information on the preparation procedure.

## INDUCTION PHASE

One flank of each of 20 guinea pigs is shaved, then 0.05 mL of a $0.1 \%$ solution of test article is injected into the anterior flank. The next day, and then every other day thereafter up to day $20,0.1 \mathrm{~mL}$ of the test article is injected into a new site on the same flank.

## CHALLENGE PHASE

This phase begins 2 weeks after the final injection of the Induction Phase. The untreated flank is shaved, then 0.05 mL of test article is injected into each of the 20 guinea pigs. Twenty previously untreated animals serve as the controls, and receive injections of the test article as well.

## OBSERVATIONS

The test sites of all control and test animals are evaluated for erythema at 24 and 48 hours after the challenge injections. The degree of reaction in test animals is compared to the reaction in control animals. A larger and/or more intense response by the test animals versus the control animals is indicative of sensitization.

## Open Epicutaneous Test

This test uses guinea pigs. The goal is to determine the dose required to induce sensitization by simulating human usage via topical application of the test article.

## TEST MATERIAL PREPARATION

This test requires that the test article be in the form of a solution that may be directly applied to the animal's skin. Therefore, extracts of the material need to be made. See Biological Reactivity Tests, In Vivo $\langle 88\rangle$ for information on the preparation procedure.

## PRELIMINARY TESTING

A series of concentrations of test article is applied to $2 \mathrm{~cm}^{2}$ areas of skin on the anterior flank of 6 to 8 guinea pigs ( 0.025 mL per application). The test sites should be examined for erythema 24 hours after test article administration. The highest concentration that does not cause irritation (maximum nonirritant concentration) and the lowest concentration causing erythema in approximately $25 \%$ of the animals (minimum irritant concentration) are determined.

## INDUCTION PHASE

The test article (or control vehicle) is applied to $8 \mathrm{~cm}^{2}$ areas of the flank skin of 6 to 8 guinea pigs daily for 3 weeks, or five times a week for 4 weeks. The amount per application is 0.01 mL . A set of increasing concentrations is again employed, ranging from the minimum irritant concentration using a stepwise progression. The test article should be applied to the same sites each time, unless irritation develops, in which case a new site on the same flank should be used. Control animals receive the same series of treatments using the vehicle instead of the test article.

## CHALLENGE PHASE

Each animal is challenged on the untreated flank 24 to 72 hours after the last Induction Phase treatment using 0.025 mL applied to $2 \mathrm{~cm}^{2}$ areas. A set of increasing concentrations is used, from minimum irritant concentration to the maximum nonirritant concentration, and five lower concentrations are also used.

## OBSERVATIONS

The test sites are evaluated at 24,48 , and 72 hours posttreatment. The maximum concentration that does not cause irritation in the control group is determined. Animals from
the test groups that develop inflammatory responses at concentrations lower than the maximum nonirritating concentration in the controls should be considered to be sensitized.

## Freund's Complete Adjuvant Test

This test is based upon the use of intradermal injections using the test article in a mixture of Freund's complete adjuvant and distilled water (50:50).

## TEST MATERIAL PREPARATION

Because this test uses intradermal injections, extracts of the test material need to be made in order to use this procedure. See Biological Reactivity Tests, In Vivo $\langle 88\rangle$ for information on the extraction procedure.

## PRELIMINARY TESTING

The minimum irritating and the maximum nonirritating concentrations are determined in the same manner as for Preliminary Testing in the Open Epicutaneous Test.

## INDUCTION PHASE

The test area consists of six $2 \mathrm{~cm}^{2}$ areas across the shoulders of the guinea pigs. Two groups of 10 to 20 guinea pigs each should be used. The test group animals are injected intradermally with 0.1 mL of a $5 \%$ solution of the test article extract in FCA/water. Control animals receive injections with FCA/water without the test article. These injections are repeated every 4 days until a total of three injections have been given.

## CHALLENGE PHASE

This phase should begin 2 weeks after the last injection of the Induction Phase. Topical applications of 0.025 mL of test article at the minimum irritating and the maximum non-
irritating concentrations, plus two lower concentrations, are administered to $2 \mathrm{~cm}^{2}$ areas of the shaved flank. The test sites should remain uncovered.

## OBSERVATIONS

The test sites are examined for the presence of erythema 24,48 and 72 hours after the topical applications. The minimum nonirritating concentration in the control animals should be determined. Those test animals that display erythema at concentrations lower than the minimum nonirritating concentration in the control animals should be considered to be sensitized.

## Optimization Test

This test has some similarities to the older Draize Test. Unlike the Draize Test, however, this test uses both intradermal and topical treatments, and includes adjuvant for some induction injections.

## TEST MATERIAL PREPARATION

As with other test procedures that incorporate intradermal injections, the test article needs to be in a form suitable for injection. See Biological Reactivity Tests, In Vivo $\langle 88\rangle$ for information on the extraction procedure.

## INDUCTION PHASE

Twenty test and 20 control guinea pigs are used. A total of 10 intradermal injections should be given to each animal. Test animals receive 0.1 mL of a mixture of $0.1 \%$ test article and $0.9 \%$ saline ( $50: 50$ ) on day 1 , with one injection into a shaved flank, and another into a portion of shaved dorsal skin. Two and 4 days later, one intradermal injection of the test article in saline is given to eight new dorsal sites. Every other day during weeks 2 and 3, the test article is injected intradermally into 10 sites over the shoulders in a

50:50 mixture of saline and FCA. The same sequence of injections is given to the 20 control animals, except that no test article is included with the saline or saline/FCA injections.

## CHALLENGE PHASE

Thirty-five days after the first injection, the animals are challenged topically with 0.1 mL of the $0.1 \%$ solution of test article in saline (for test animals). The control animals receive saline injections only. At 45 days after the first injection, a second topical challenge is given. A nonirritating concentration of test article ( 0.05 mL ) is applied topically to a $1 \mathrm{~cm}^{2}$ area of untreated skin. This site should then be covered with a $2 \mathrm{~cm}^{2}$ piece of filter paper, after which an occlusive dressing should be applied. The patch should be removed after 24 hours.

## OBSERVATIONS

Twenty-four hours after each injection during week 1, the thickness of a fold of skin over the injection sites for each animal should be measured using a caliper ( mm ), and the two largest cross-diameters of each erythematous reactions should be recorded (mm). The reaction volumes are calculated by multiplying the fold thickness by the products of the two cross-diameters (expressed as $\mu \mathrm{L}$ ). The mean reaction ( +1 SD ) volume during week 1 should be calculated for each animal.

Challenge reaction volumes are calculated for each animal following the injections at day 35 . If an animal develops a challenge reaction volume greater than its mean reaction volume +1 SD , it should be considered sensitized.

Following the patch testing challenge, the test sites are evaluated for erythema and edema. Evaluations should be made using Table 5.

The number of positive animals should be compared statistically with the pseudopositive control animals. This should be done for both intradermal injection results and patch testing results. The Fisher exact test may be used.

The results from the intradermal injections and the patch testing, following separate statistical analysis, may be combined and evaluated using Table 7 in order to classify a test article as a strong, moderate, or weak sensitizer; or not a sensitizer.

Table 7. Classification Scheme for Test Articles Based on the Optimization Test

| Intradermal | Patch Test |  |
| :--- | :--- | :--- |
| $\%$ of Positive | \% of Positive |  |
| Animals | animals | Classification |
| $\mathrm{S}^{*},>75$ | and/or S, $>50$ | Strong sensitizer |
| $\mathrm{S}, 50-75$ | and/or S, 30-50 | Moderate sensitizer |
| $\mathrm{S}, 30-50$ | N.S. ${ }^{*}, 0-30$ | Weak sensitizer |
| N.S., 0-30 | N.S., 0 | Not a sensitizer |
| ${ }^{\text {N }} \mathrm{S}=$ significant, N.S. $=$ not significant |  |  |

## Split Adjuvant Test

This test makes use of both FCA and skin damage. The test article is applied topically.

## TEST MATERIAL PREPARATION

Because this test employs topical test article applications, the article can be either in solid or liquid form. If extracts are to be made, see chapter Biological Reactivity Tests, In Vivo $\langle 88\rangle$ for extraction procedures.

## INDUCTION PHASE

Ten to 20 guinea pigs are used for both test and control groups. An area of back skin immediately behind the scapulas should be shaved to the extent that the skin becomes glis-
tening. The shaved areas should then be treated with dry ice for 5 to 10 seconds. A dressing made of loose mesh gauze with stretch adhesive and a $2-\times 2-\mathrm{cm}$ opening should be placed over the treated area, then secured with adhesive tape. The test article ( 0.2 mL of viscous materials, 0.1 mL of liquids, or solid material) is placed within the opening in the dressing on top of the treated skin. Two layers of \#2 filter paper should be placed over the test article, then backed by occlusive tape. Then the filter paper/occlusive backed material should be secured to the surrounding dressing with adhesive tape. After 2 days have passed, the filter paper should be lifted from the test sites, and the test article reapplied on the same site. The filter paper and backing should be secured once again. After 2 more days, the filter paper should be lifted and two injections of 0.075 mL of FCA should be administered into the edges of the test site. Then the test material is once again applied, and the filter paper/backing resecured. The test article should be reapplied once more on day 7 and the filter paper/backing resealed. On day 9 , the filter paper and all associated dressing material should be removed.

## CHALLENGE PHASE

On day 22 following the induction treatment, 0.5 mL of test material (or the solid article) should be applied to a $2-\times$ $2-\mathrm{cm}$ area of shaved midback. The test sites should be covered by filter paper and backed by adhesive tape. This should be held in place with an elastic bandage secured with adhesive tape. Control animals receive the same challenge phase treatment. The preparation should be removed after 24 hours.

## OBSERVATIONS

Twenty-four, 48 , and 72 hours after the removal of the challenge phase preparation, the test sites should be evaluated for erythema and edema. The grading scheme of Table 5 could be employed.

## Mouse Ear Swelling Test

There are a number of potential advantages in using mice versus guinea pigs for sensitization methods. The classic guinea pig tests tend to be costly and require a long time to complete. Moreover, with the dependence upon relatively subjective scoring based on edema and erythema, methodological robustness, and ruggedness may be questionable. This test uses mice and employs both topical exposures and injections.

## ANIMALS

Female, 6 to 8 -week old CF-1, Balb/c, or Swiss mice should be used. They may be group housed in direct bedding cages. Acclimatization should be for at least 5 to 7 days. Food (appropriate mouse feed) and water should be available ad libitum. No animals with damaged pinnae should be used in the study. The thickness of both ears of each animal should be measured and recorded at this time.

## TEST MATERIAL PREPARATION

As with other test procedures that incorporate intradermal injections, the test article needs to be in a form suitable for injection. See Biological Reactivity Tests, In Vivo $\langle 88\rangle$ for information on the extraction procedure.

## PRELIMINARY TESTING

The minimally irritating and maximally nonirritating concentrations of test article for this procedure should be determined. This is done by using four groups of two mice and examining the effects of at least four concentrations of test article.

## INDUCTION PHASE

The abdomens of the animals should be shaved, then tapestripped using a surgical adhesive tape until the test area is glistening. A single injection of 0.05 mL of FCA is subdivided into two injection sites administered intradermally within the shaved/stripped area, but along the borders. After the adjuvant injections, $100 \mu \mathrm{~L}$ of test article (using the minimally irritating concentration) or vehicle (controls) is applied to the center of the shaved test areas. After the test areas dry, the mice should be returned to their cages. The tape stripping and application of test article (but not FCA) is repeated each day for the next 3 days.

## CHALLENGE PHASE

This phase should occur 7 days after the final topical induction application. The test article (highest nonirritating concentration) should be applied topically ( $20 \mu \mathrm{~L}$ ) to one ear, while the opposite ear receives $10 \mu \mathrm{~L}$ of vehicle alone. This should be done for both test and control animals.

## OBSERVATIONS

The thickness of both ears of each animal should be recorded after 24 and 48 hours postchallenge. The measurements should be made with a caliper (a spring-loaded caliper is preferable). A sensitized animal is one in which the test article-treated ear is at least $20 \%$ thicker than its opposite ear. For the test to be valid, the test article-treated ears of control animals should not be more than $10 \%$ thicker than
the opposite ears. If the control animal ears do not meet the requirements, the test should be repeated using lower concentrations.

## Local Lymph Node Test

This test is based on the observation that exposure of the mice to sensitizers can cause hyperplasia of T cells within the auricular lymph nodes of mice. The method combines both in vivo and in vitro phases, and requires the use of radioisotopes. An unusual aspect of this test is that no challenge phase is required.

## ANIMALS

Four groups of four mice at least, male or female CBA/ca mice (only one sex in a given test) between the ages of 8 to 12 weeks should be used.

## TEST MATERIAL PREPARATION

Although in theory one could apply a solid test article to the dorsal surface of the ear of a mouse, in practice an extract of such an article should be used. See Biological Reactivity Tests, In Vivo $\langle 88\rangle$ for information on the extraction procedure.

## PRELIMINARY TESTING

A nontoxic concentration of test article should be used. If not already established, a preliminary test for overt toxicity may be required to establish a suitable dose.

## INDUCTION PHASE

Twenty-five $\mu \mathrm{L}$ of the appropriate test article concentration, or vehicle (controls), should be applied to the dorsal surface of each pinna for 3 consecutive days. Five days after the first treatment, the animals should be injected, via the tail vein, with 2.5 mL of phosphate buffered saline containing
$20 \mu \mathrm{ci}$ of ${ }^{3} \mathrm{H}$-methyl thymidine. Five hours after the isotopic injection, the animals should be euthanized. The draining auricular lymph nodes should be removed from each animal of each test and control group. The nodes from all animals within a given group should be combined, such that a single cell suspension can be made from each group of animals. The cell suspension can be made by passing the nodes through a 200 -mesh stainless steel gauze using a syringe plunger. The cells should then be centrifuged at $190 \times g$ for 10 minutes, resuspended in 3 mL of $5 \%$ trichloroacetic acid (TCA), and held overnight at $4^{\circ}$.

The resulting precipitate should be recovered by centrifugation, and the pelleted precipitate should be resuspended in 1 mL of $5 \%$ TCA. The suspension should then be placed in scintillation vials with 10 mL of scintillation fluid, and the disintegrations/minute ( dpm ) counted with a $\beta$-counter.

## OBSERVATIONS

The ratio of dpm for each test group should be compared to the dpm for the control group. If the ratio equals or exceeds 3 for any test group, the concentration of test article used with that group may be considered to be sensitizing.

## Vitamin A Enhancement Test

This test is similar to the Mouse Ear Swelling Test in that test articles are applied topically to the abdomen, with a challenge application to the ears, followed by measurements of ear thickness. A principal difference is the use of mouse feed supplemented with vitamin A acetate. The purpose of the supplementation is to increase the reactivity of the immune system, thereby increasing the potential sensitization reaction.

ANIMALS
Male, 3 to 4-week old Balb/c mice should be maintained on a diet supplemented with vitamin A acetate. The diet may be prepared by mixing each kg of feed with 0.477 g of gelatinized vitamin A acetate. The feed mixture should be used within 3 weeks of preparation. Mice intended for use in sensitization studies should have been on the supplemented diet for at least 4 weeks. The mice at the time of the sensitization study should therefore be between 7 and 10 weeks old. The thickness of both ears of each animal should be measured and recorded at this time.

## TEST MATERIAL PREPARATION

Although, in theory, one could apply a solid test article to the dorsal surface of the ear of a mouse, in practice an extract of such an article should be used. See Biological Reactivity Tests, In Vivo $\langle 88\rangle$ for information on the extraction.

## PRELIMINARY TESTING

The maximally nonirritating dose and minimally irritating concentrations should be determined using separate groups of animals. This could be done as described for Preliminary Testing in the Mouse Ear Swelling Test.

## INDUCTION PHASE

The fur of the abdomen and thorax of 10 mice per group should be shaved. Then $100 \mu \mathrm{~L}$ of test article (at the minimally irritating concentration) should be applied to the test areas on days $0,2,4,7$, and 11 . Control animals receive 100 $\mu \mathrm{L}$ of vehicle alone on the same schedule.

## CHALLENGE PHASE

This phase should occur 4 days after the final application of the Induction Phase. Twenty-five $\mu \mathrm{L}$ of test article (at the maximally nonirritating concentration) should be applied to each ear of each animal in the test and control groups.

## OBSERVATIONS

Ear thickness for both ears of each animal should be recorded after 24 and 48 hours postchallenge. The measurements should be made with a caliper (a spring-loaded caliper is preferable). The percent increase in ear thickness should be calculated for each ear by subtracting the pretreatment measurement from the post-treatment measurement, dividing the result by the pretreatment measurement, then multiplying by 100 . The response of the test group versus the control group should be compared statistically. (The Mann-Whitney $U$ test could be used for the comparison.)

The results of individual animals should also be calculated. If an increase in ear thickness for an animal from the test group is at least $50 \%$ greater than the largest increase of a control animal, that is indicative of sensitization. As an overall evaluation, should the results of the study provide a significant result of the statistical test at $\mathrm{p}<0.01$ for the control versus test group comparisons, or if at least two test animals have ear thickness increases in excess of $50 \%$ of the maximum control thickness changes and the group comparison showed a $p<0.05$, sensitization is indicated for the test article. $\Delta U S P 28$

## Briefing

$\langle 1232\rangle$ Instrumentation for Analysis of High Purity Pharmaceutical Waters. This proposed new chapter is meant to complement Water for Pharmaceutical Purposes $\langle 1231\rangle$ and to serve as a resource for those involved in the production and analysis of the USP waters. On the basis of inquiries and comments received since the major water monograph revisions of 1996, the Pharmaceutical Water Expert Committee has decided that additional compendial information is necessary. This general information chapter is an attempt to meet this need. The Committee encourages public comments. Address comments to Frank Barletta in the Information Standards Division.
(PW: F. Barletta) RTS-40499-1

## Add the following:

## - $\langle 1232\rangle$ INSTRUMENTATION FOR ANALYSIS OF HIGH PURITY PHARMACEUTICAL WATERS

## INTRODUCTION

In the production of Purified Water and Water for Injection (WFI) the term "quality of water" is not rigorously defined, but it is generally accepted to mean "the concentration and type of impurities" found in the water. Advances in the science of water treatment have resulted in technologies that produce more water at lower cost and of higher quality. Consequently, the amount of impurities found in Purified Water and Water for Injection has decreased. The analytical methods have also improved to keep up with the improving water quality.

It would be impractical to describe all of the possible impurities because of the number of organic, inorganic, and ionic species that could enter a water system from the outside environment. The number of known chemicals is in the hundreds of thousands, and, theoretically, many could be found at a very low concentration in a water system. The nature of water treatment systems is such that very few unit operations are designed to selectively remove specific con-
taminants. There are notable exceptions such as water softeners that are effective at displacing calcium and magnesium with sodium to protect systems from scale. It becomes expensive and very impractical to identify all impurity species in a pharmaceutical water system. The analytical instrumentation required to measure alkaline metal and heavy metal impurities (by atomic absorption or ion chromatography) is expensive, and the technology is not commercially available for measurement of specific organics in the $\mu \mathrm{g} / \mathrm{L}(\mathrm{ppb})$ range.

The more practical approach is to categorize impurities according to various attributes such as chemical properties, physical properties, organic/inorganic, oxidizability, toxicity, etc. One practical method of categorizing the impurity species is a determination of the degree of ionic behavior of the chemical moiety. For example, $\mathrm{H}^{+}, \mathrm{OH}^{-}, \mathrm{Na}^{+}, \mathrm{Ca}^{2+}$, $\mathrm{Mg}^{2+}, \mathrm{HCO}_{3}^{-}, \mathrm{Cl}^{-}, \mathrm{HSO}_{4}^{-}$, and other ionic species are commonly found in pharmaceutical water systems. All of these ions have a physical property in common: namely, that they are charged species and, therefore, detectable by conductivity. The majority of species that would be nonionic are organic. These consist of low molecular weight alcohols, ketones, and organic acids that are not completely removed by water systems because of their size or polarity. A valuable method for detecting these organic species is the use of a test for total organic carbon (TOC).
Both conductivity and TOC have the advantage of quantifying these types of impurities in the aggregate with great sensitivity. The advantage is also a disadvantage as neither measurement can distinguish or measure individual impurities, only the aggregate.

Not all types of impurities fall into the ionic/non-ionic (conductive or TOC) category. Another class of impurity can be described as inorganic and nonionic (and therefore nonconductive). They include some dissolved metals, metal
oxides, other metal forms, and semimetals such as those that are silica-based. These species may be very weakly ionized and, therefore, would not be detectable by any conventional conductivity or TOC method. Particles also represent another class of impurity. These could be carbonaceous or sil-ica-based, but they are not normally detectable by conductivity or TOC because they are typically nonionic and exist at undetectable concentrations for TOC analysis. However, the presence of substantive concentrations of these types of impurities is unlikely if the water treatment system is effective.
The final significant category of impurities consists of microorganisms. Although microorganisms are carbonaceous material, the detectability by conductivity or TOC is not practical because their molecular concentrations are too low to be detected by these methods. Microorganisms deserve special note because they can grow and interfere with drug chemistry and cause harm to the patient if they are not controlled (see Water for Pharmaceutical Purposes $\langle 1231\rangle)$.
Until USP 23, Supplement 5 , the primary methods for ensuring the quality of bulk Purified Water and Water for Injection were a series of wet chemistry tests that were sensitive to ammonia, calcium, chloride, carbon dioxide, sulfate, and oxidizable substances. The tests for these six species were subjective, unreliable, and not predictive of the true quality of water. The quality of water is better described by its conductivity and TOC and the primary methods for verifying water quality have shifted to these measurements.

Neither conductivity nor TOC are specific to any of the ions or species listed above. TOC is considered a one-forone replacement for the Oxidizable Substances (potassium permanganate) test, while conductivity is a sensitive test for all ionic (i.e., conductive) species. Both methods have
the advantages of being quantitative, numerical, robust, available for use on-line or off-line, and useful for quality control.

## TOTAL ORGANIC CARBON (TOC)

Organic chemistry is the study of carbon-containing compounds. The fully oxidized form of carbon, carbon dioxide $\left(\mathrm{CO}_{2}\right)$, is inorganic. $\mathrm{CO}_{2}$ is mildly reactive with water, and it is usually detected by its concomitant compounds and ions: carbonic acid $\left(\mathrm{H}_{2} \mathrm{CO}_{3}\right)$, bicarbonate $\left(\mathrm{HCO}_{3}{ }^{-}\right)$, and carbonate $\left(\mathrm{CO}_{3}{ }^{2-}\right)$. These three species are the result of the dissolution of $\mathrm{CO}_{2}$ in water and subsequent acid dissociation; they are not included in the TOC definition. Our concern is the remaining carbonaceous species that are not completely oxidized. These are the organic compounds that provide a fuel source for microorganisms, sustain biofilm, and may adversely impact drug chemistry.

Organic carbon enters the water system from several locations. The usual source of TOC is from the municipal water supply or from private wells. In January, 2002, the Environmental Protection Agency began regulating TOC levels in municipalities serving a population of 10,000 or more. Source water TOC can vary anywhere from 1 to 10 mg of carbon per L. The primary source of this TOC is from the decomposition of plants and animals and subsequent runoff or leaching into the municipal feed water sources. The composition of these TOC products range from low molecular weight species such as urea to high molecular weight humic acids that give water an "iced tea" coloring. Other organic compounds found in water can be the direct result of industrial pollutants, pesticides, herbicides, and other man-made contaminants.

Other sources of TOC are the accidental introduction of TOC into the pharmaceutical water system and the degradation of water system components. The former is the result of
error, such as opening a wrong valve. The latter could be the breakdown of a plastic component in the water system or the presence of holes in the reverse osmosis (RO) membrane system. Regardless of the source, any of these TOC contaminants can be detrimental to the control of the water system.

Treatment methods to reduce TOC are discussed in Water for Pharmaceutical Purposes $\langle 1231\rangle$. In brief, various methods such as RO and filtration can reduce TOC concentration. Also, oxidizing agents such as chlorine and ozone can break up organic molecules. They are not, however, very selective and will attack nearly all organic molecules. The cleavage of large molecules creates smaller organic molecules that are easily digested and assimilated by microorganisms. Dead bacteria can also produce decomposition products called endotoxins that may produce a fever when injected into the body. The quantity of total organic carbon in pharmaceutical waters is of primary concern because it can enhance microorganism growth.

Volatile organic compounds are not a major contaminant in pharmaceutical water systems. Most contaminants are nonvolatile and are naturally occurring or anthropogenic organics. TOC measurements provide a single nonspecific measurement, detecting a broad spectrum of compounds without performing tests for individual contaminants.

## Laboratory TOC Technologies

TOC analysis was developed initially for the measurement of relatively high levels of TOC in water and waste water. Technological advances, however, have produced instruments that measure low levels of TOC in water down to sub-ppb levels, thus allowing for its application in the pharmaceutical industry. The principal TOC technologies are
based on the oxidation of organic carbon to $\mathrm{CO}_{2}$ and subsequent detection of the $\mathrm{CO}_{2}$ by either conductometric or photometric means.
Some water samples contain dissolved $\mathrm{CO}_{2}$ (and $\mathrm{HCO}_{3}{ }^{-}$ and $\mathrm{CO}_{3}{ }^{2-}$ ) at the outset of the analysis, so the inorganic carbon (IC) must be removed or measured as part of the analysis. For any oxidation technology, depending on the TOC and IC levels, removal of the dissolved $\mathrm{CO}_{2}$ is always an option. In order to achieve accurate measurement of TOC in some samples, it is necessary to minimize the contribution of IC to the total signal. If it is determined that IC background is detrimental to the sample measurement, then the IC can be purged from the water sample by vacuum, nitrogen sparging, or acid addition, depending on the technology. This should not be necessary unless the TOC is very low and the IC very high. In pharmaceutical bulk water supplies, IC concentrations are typically low, and removal is not required for accurate TOC results. The basic oxidation and detection techniques used in TOC equipment are described below; however, other combinations of technologies that are not described may also be in use.

Combustion Oxidation/Nondispersive Infrared Detection (NDIR)—This technology combination is most often configured for laboratory use. Combustion oxidation uses oxygen and high temperatures ( $>600^{\circ}$ ) and a catalyst such as platinum ( Pt ) to facilitate the oxidation and convert the organic compounds to $\mathrm{CO}_{2}$. This technique has demonstrated high oxidation efficiency for both dissolved and particulate organics. The catalyst, however, can become poisoned and cause low recovery. NDIR is very selective for $\mathrm{CO}_{2}$ in the presence of water vapor. After oxidation of the sample, the $\mathrm{CO}_{2}$ is delivered to the detection chamber by a carrier gas. The concentration of $\mathrm{CO}_{2}$ is directly proportional to the absorption response according to Beer's Law. As with any absorption spectrophotometric method, NDIR
is most sensitive at higher concentrations. Compared to other detectors, NDIR detectors can exhibit extended warm-up times at start-up. NDIR detectors typically require a comparatively higher calibration frequency.

Heated Persulfate Oxidation/NDIR Detection-Heated persulfate oxidation instruments generate hydroxyl radicals ( $\cdot \mathrm{OH}$ ) by heating the persulfate to $>95^{\circ}$. The hydroxyl radicals act as powerful oxidizing agents. The cation form of the persulfate and its concentration vary, with concentrations ranging from $2 \%$ to $15 \%$. Heated persulfate is typically combined with the previously described NDIR detection method to measure $\mathrm{CO}_{2}$. This technology combination is typically applied in laboratory instrument configurations. Heated persulfate is a very efficient oxidation method. Its main disadvantages are the volume of reagent required.

UV Oxidation/NDIR Detection—UV oxidation uses UV light to generate hydroxyl radicals from the photolysis of water. In some instruments, persulfate is added, which is activated by UV to increase the oxidative capacity. This technology combination is most commonly found in laboratory configurations. The natural spectral output of a low pressure Hg lamp generates light of wavelength 253.7 and 184.9 nm . The shorter wavelength generates the oxidizing radicals, while both wavelengths are efficient at cleaving bonds in large and small organic molecules. This combination provides an efficient oxidation and measurement system. UV oxidation methods are particularly well suited for lower TOC concentrations found in pharmaceutical waters. The main advantage is the oxidation efficiency at lower TOC concentrations. The disadvantages are that the UV Hg lamps must be periodically replaced and that, as previously described, the NDIR detector systems are complex.

UV/Persulfate Oxidation/Membrane Conductometric Detection-In this technology, $\mathrm{CO}_{2}$ is generated by UV radiation (as described above), and the dissolved $\mathrm{CO}_{2}$ passes
through a gas-permeable membrane to an on-board source of low conductivity water. The resulting increase in conductivity in this water is directly proportional to the $\mathrm{CO}_{2}$ produced from the UV oxidation. Persulfate is typically added to enhance oxidation at TOC concentrations greater than 1 ppm. This technology combination makes use of the high sensitivity that conductivity measurements have at low concentrations of $\mathrm{CO}_{2}$, and the membrane separation helps to eliminate the typical chemical interferences that can disrupt conductivity measurements.

## Sampling Techniques for Laboratory Analysis-Be-

cause compendial pharmaceutical waters have very low TOC (the USP limit is about $500 \mu \mathrm{~g}$ of carbon/L, but $<50$ $\mu \mathrm{g}$ of carbon/L, and lower, is more likely), pharmaceutical waters require the following special handling to have valid TOC measurements.

1. The water should be delivered from a hose or delivery receptacle in the same manner in which it is used in production.
2. The storage container may be any type that does not shed or leach TOC, and it must be scrupulously clean. Many plastic or polymeric containers are either unacceptable because of extractable TOC or they are too difficult to clean. Limited types of materials such as PTFE, PFA, and PVDF have found acceptance because of their low leach rates. Glass is an excellent material due to its negligible TOC leach rate and its cleanability. Cleaning of the glass according to Cleaning Glass Apparatus $\langle 1051\rangle$ is advised.
3. The container should be completely filled with the sample to keep the trapped air to a minimum. The container should be closed immediately to prevent atmospheric contamination.
4. The time between sampling and analysis should be kept to a minimum. If the samples are analyzed by an offsite laboratory, they should be refrigerated to minimize microbial growth.
5. The setting of the flow control valve should not be changed, and the sample bottle should not touch the port while taking the sample.
6. For compendial purposes, the water should be tested at a point that is equivalent to the quality of water used in production. This may require testing at several points, or at a location after the last-use point before the return to the tank in a recirculating system.

## On-Line TOC Technologies

The most common on-line TOC methods used in pharmaceutical applications employ UV oxidation and conductivity detection. These technologies are designed for exclusive use with low conductivity water supplies and with the device connected directly to the sample to eliminate exposure to the atmosphere. The low sample conductivity ensures an IC concentration so low that its removal is not necessary. No reagents are required because at TOC concentrations of 500 ppb or less, UV oxidation alone is usually sufficient for complete recovery.

UV oxidation can be applied on a fixed volume of sample or by irradiating a continuous stream to the UV source. Conductivity measurements are made during or immediately following the oxidation step. In one configuration, a gaspermeable membrane is used after the UV oxidation to separate $\mathrm{CO}_{2}$ from other potentially conductive oxidation by products.

The main advantages of on-line technologies are the benefit of continuous unattended measurement of TOC, the availability of continuous trending of the water system,
the ability to respond to a disturbance immediately, and the elimination of sample collection, handling, and transportation errors.

## Sampling Techniques for On-Line TOC Analysis-

On-line TOC analysis has the advantage of being able to provide data continuously and without the difficulties in sample handling that accompany off-line TOC measurements. Typically, clean tubing is attached to the water system and water flow is directed to the inlet of the TOC instrument. Appropriate care should be taken to eliminate dead-legs and subsequent backflow of the sample line when the instrument is not in use.

## Technology Summary

Some of the oxidation and detection techniques work in tandem and are ideally suited for Purified Water and Water for Injection. These methods have the necessary resolution and sensitivity to perform the basic TOC measurement functions. The main differences between the technologies are the capital costs, consumables (UV lamps, gases, reagents), and maintenance and labor (preparing reagents, replacing catalysts, installing gas generators), and suitability for laboratory or on-line analysis.

Detection limits will vary by technology, and the analysis method must be able to meet the System Suitability requirements and detect the levels of TOC prescribed in Total Organic Carbon $\langle 643\rangle$. IR-based detection methods involve a well-established technique that requires a large sample size, a purge gas, long warm-up times, and frequent calibration. These detection methods are well suited to high TOC concentrations and are not susceptible to interferences that may be found in water. UV/conductivity methods are best suited
for on-line process use in pharmaceutical waters, where the sensitivity of conductivity measurements is ideally suited to measuring the conductivity of $\mathrm{CO}_{2}$-containing solutions; the conductivity-based techniques are capable of a much lower limit of detection. The analysis time for each technology can vary from 0.5 to 30 minutes. Calibration requirements will also differ, varying from daily or weekly to annually. Calibration may be done by the user in-place or may require special attention by factory or trained personnel. Gases, chemicals, lamps, and other supplies will impact operating costs.

## CONDUCTIVITY

A conductivity measurement system is similar in concept to a TOC measurement system. A TOC analyzer cannot quantify individual organic species, only the aggregate carbon in the form of $\mathrm{CO}_{2}$. Likewise, a conductivity measurement does not distinguish between ions. It measures the total conductivity of charged ionic species.

A conductivity measurement is performed by measuring the AC resistance (conductance $=1 /$ resistance) between two electrodes of a known geometrical construction. The resistance of the fluid between the two electrodes will increase with electrode distance, $d$, and decrease with electrode area, $A$. To correct for this geometrical factor, the cell constant, $\phi$, of the sensor is equivalent to the distance between the electrodes divided by the area of the electrodes.

$$
\begin{equation*}
\varphi\left(\mathrm{cm}^{-1}\right)=\frac{\mathrm{d}}{\mathrm{~A}} \tag{1}
\end{equation*}
$$

The cell constant normalizes the resistance, $\Omega$, (or conductance, $S$, to eliminate the impact of the sensor geometry, thereby resulting in the familiar water quality measurement of resistivity, $\rho$ (or conductivity, $\kappa$ ). The equations that relate these measurements are the following:

$$
\begin{equation*}
\varphi(\Omega-\mathrm{cm})=\frac{\operatorname{resistance}(\Omega)}{\varphi\left(\mathrm{cm}^{-1}\right)} \tag{2}
\end{equation*}
$$

$$
\begin{gather*}
\kappa(\mathrm{S} / \mathrm{cm})=\text { conductance }(\mathrm{S}) \times \varphi\left(\mathrm{cm}^{-1}\right) \\
\kappa(\mathrm{S} / \mathrm{cm})=\frac{1}{\varphi(\Omega-\mathrm{cm})} \tag{4}
\end{gather*}
$$

A temperature device, such as a resistance temperature device (RTD) or thermistor, will be embedded in most conductivity sensors. The meter will measure the resistance of that device and convert it to a temperature according to its known temperature-resistance relationship.

The fundamental operation of conductivity measurement systems consists of measurement of the resistance between the electrodes, correction for the cell constant to get a conductivity or resistivity measurement, and then compensation for the raw measurement for temperature using an algorithm in the meter. In order to meet the requirements of Water Conductivity $\langle 645\rangle$, the temperature compensation feature is disabled, and the uncompensated measurement is used to determine water quality acceptance.

## Impact of Water Chemistry on Conductivity

Electrical conductivity of water is a measure of the ionfacilitated flow of current between two electrodes through the water. The fundamental equation to describe the conductivity is the following:

$$
\begin{equation*}
\kappa=10^{-3} \sum_{i}^{\substack{\text { all } \\ \text { ions }}} \Lambda_{i}^{\circ} \mathrm{C}_{\mathrm{i}} \tag{5}
\end{equation*}
$$

where $\kappa$ is the conductivity (Siemens $/ \mathrm{cm}$ ), $\Lambda_{\mathrm{i}}$ is the limiting molar conductivity of ion $i$ (Siemens- $\mathrm{cm}^{2} /$ mole) and $C_{i}$ is the concentration of ion $i$ (mole/L). The equation is summed over all ions present in the water. If the concentrations are expressed in molality (moles $/ \mathrm{kg}$ of water), then the equation is adjusted for the water density.

Water molecules dissociate into $\mathrm{H}^{+}$and $\mathrm{OH}^{-}$according to the equation:

$$
\begin{equation*}
\mathrm{H}_{2} \mathrm{O} \rightleftharpoons\left[\mathrm{H}^{+}\right]+\left[\mathrm{OH}^{-}\right] \tag{6}
\end{equation*}
$$

and the extent of the reaction is determined by the dissociation constant, $K_{w}$.

$$
\begin{equation*}
K_{w}=\left[\mathrm{H}^{+}\right]\left[\mathrm{OH}^{-}\right]=1.00 \times 10^{-14} \text { at } 25^{\circ} \tag{7}
\end{equation*}
$$

$$
\begin{equation*}
p K_{w}=-\log \left(K_{w}\right)=14 \text { at } 25^{\circ} \tag{8}
\end{equation*}
$$

In the absence of any other chemical species, electroneutrality and Equation 7 require that

$$
\begin{equation*}
\left[\mathrm{H}^{+}\right]=\left[\mathrm{OH}^{-}\right]=1 \times 10^{-7} \mathrm{~mole} / \mathrm{L} \tag{9}
\end{equation*}
$$

The limiting molar conductivity at $25^{\circ}$ of $\mathrm{H}^{+}$and $\mathrm{OH}^{-}$are 349.8 and $198.6 \mathrm{~S}-\mathrm{cm}^{2} / \mathrm{mol}$, respectively. The resulting conductivity of pure water is $5.48 \times 10^{-8} \mathrm{~S} / \mathrm{cm}(0.0548 \mu \mathrm{~S} / \mathrm{cm})$. The resistivity is the multiplicative inverse (Equation 4) of the conductivity, or 18.2 M Megohm- $\mathrm{cm}(\mathrm{M} \Omega-\mathrm{cm})$.
At temperatures other than $25^{\circ}$ - the commonly used reference temperature-two phenomena directly impact the conductivity of pure water. First, the dissociation constant of water varies significantly over the range of $0^{\circ}$ to $100^{\circ}$. The value of $K_{w}$ changes by a factor of 400 , as the $p K_{w}$ is 14.9 at $0^{\circ}$ and 12.2 at $100^{\circ}$. The resulting change in $K_{w}$ causes a true increase in the ion concentrations as the temperature increases. The second effect is the temperature dependence of the ion mobility. The ion mobility is a measure of the ability of ions to conduct, which is directly related to each ion's limiting molar conductivity. The mobility of both ions increases by a factor of $\sim 3$ over the range of $0^{\circ}$ to $100^{\circ}$. The combination of these two effects causes the conductivity of pure water to increase from $0.0116 \mu \mathrm{~S} / \mathrm{cm}$ at $0^{\circ}$ to $0.777 \mu \mathrm{~S} / \mathrm{cm}$ at $100^{\circ}(86.1 \mathrm{M} \Omega-\mathrm{cm}$ to $1.29 \mathrm{M} \Omega-\mathrm{cm})$.

Though it is not unusual for some compendial water systems to produce pure water, most water treatment systems that produce Purified Water and Water for Injection have small amounts of impurities that pass through the water system. The impurities are usually simple alkali metal ions, possibly some lighter transition metal ions, and common counter ions such as $\mathrm{Cl}^{-}, \mathrm{SO}_{4}{ }^{2-}$, and $\mathrm{HCO}_{3}{ }^{-}$. In addition, some gases, most notably $\mathrm{CO}_{2}$, readily dissolve in water and react to form $\mathrm{H}^{+}$and $\mathrm{HCO}_{3}{ }^{-}$, predictably affecting conductivity and pH . Regardless of the ionic impurity, each has its own characteristic limiting molar conductivity. Thus the measured conductivity of the water in a pharmaceutical system is determined from Equation 5, after consideration of all ions present at their respective concentrations.

## Temperature Compensation

Temperature compensation is the adjustment of a chemical or physical measurement at any temperature to its value at a reference temperature, $25^{\circ}$ in this case. The purpose of the compensation is to provide a universal reference point so that measurements taken at different temperatures can be properly compared. For example, if the conductivity of the water system is $0.11 \mu \mathrm{~S} / \mathrm{cm}$ at $37^{\circ}$, but later in the day it is $0.13 \mu \mathrm{~S} / \mathrm{cm}$ at $40^{\circ}$, the increase can be the result of the natural increase in ion mobility due to temperature, or it could be the result of more impurities in the water. The benefit of temperature compensation is that it can distinguish natural changes from water quality changes.

Prior to the application of microprocessors, temperature compensation was performed either by "correcting the signal" with the addition of analog circuitry or by numerically adjusting postmeasurement. Temperature compensation is currently performed automatically by the chemically-based numerical algorithms in the instrumentation.

Temperature compensation for conductivity measurements of pure water is difficult to perform accurately. For almost all types of fluids except pure water, the dependence of the conductivity on temperature is, on the average, about $\sim 1.9 \%$ to $2.2 \%$ per degree over the entire $0^{\circ}$ to $100^{\circ}$ range. This linear compensation factor applies for most process fluids and drinking waters, because the conductivity is dominated by the ions that are not related to water dissociation. However, because of the low impurity levels found in Purified Water or Water for Injection systems, the chemical composition of the ions in water is primarily due to $\mathrm{H}^{+}$and $\mathrm{OH}^{-}$, with smaller (or similar) amounts of other ions. The temperature dependence of the conductivity, therefore, becomes less predictable because of the temperature dependence of the water chemistry. For example, at $0^{\circ}$ the conductivity of pure water changes at a rate of $>7 \%$ per degree, while at $100^{\circ}$ the temperature dependence is $<2.5 \%$
per degree. As the impurity levels increase, the temperature dependence moderates until it reaches $\sim 2 \%$ per degree. The appropriate correction for temperature compensation varies and must be accounted for correctly, depending on the temperature and the impurity level. On-line process instrumentation performs this correction automatically, but the algorithms remain trade secrets.

As the chapter Water Conductivity $\langle 645\rangle$ was being developed in the early 1990s, it was established that the measurements would be made in a nontemperature-compensated mode to eliminate the variability that is found from one instrument manufacturer to another. This resulted in the table, Stage 1-Temperature and Conductivity Requirements in the chapter Water Conductivity $\langle 645\rangle$ that set conductivity limits that are temperature dependent. The table takes into account the natural increase in conductivity as a function of temperature, while ensuring that certain impurity levels are not exceeded.

## Conductivity Technologies

Conductivity Sensors-A conductivity sensor used in pharmaceutical water measurements typically consists of two concentric electrodes, separated by an inert electrical insulator, with a cell constant that is usually anywhere from 0.01 to $0.1 \mathrm{~cm}^{-1}$. For on-line measurements, the sensor should be inserted into the tee of a piping system. Sidestream measurements are possible, but direct immersion into the piping are less costly (i.e., no water loss with no risk to the water system). The electrode material should be compatible with the water system to prevent galvanic action between the water piping and the sensor. The insulator should be resistant to the water and to the processing conditions that may be present. The sensor design and geometry should be invariant to the high temperatures (up to steam sterilizable conditions at $131^{\circ}$ and 40 psia or higher), sanitization che-
micals, UV, pressure, and flow rates that the sensor might be exposed to. Any change in the geometric construction of the sensor will cause a change in the apparent measurement of the conductivity.

Stainless steel electrodes should be passivated, at a minimum, to reduce the possibility of corrosion or rouging. Passivation materials such as nitric acid, phosphoric acid, and citric acid are commonly used. Surface finishes having exposed surfaces with Roughness Average $\left(R_{a}\right)<10 \mu$ in (better than standard machine finishes) are readily attainable. The process connection to the water system can be any suitable connection type; however, a sanitary tri-clamp flange and gasket to provide a clean, tight seal between the sensor flange and water system are recommended. Welding of the electrodes to the flange should be clean and of pharmaceutical grade. Threaded process connections should be averted to eliminate deadlegs; however, this parameter has no impact on the conductivity measurement.

The electrode material and insulator for off-line measurements are not critical, provided they give accurate measurements. Environmental factors are not present. To make accurate measurements, platinum electrodes should be avoided because a process called platinization is required periodically to recondition the surface of the electrode. However, this process is not robust, and it is difficult to determine when platinization is necessary, except by alternative verification measurements. An adverse impact to measurement accuracy is also greatest at low conductivity. Common electrode materials include stainless steel, titanium, hastelloy, and graphite to a lesser extent. Titanium is widely used in the microelectronics industry because of its naturally passive surface and resistance to pure water. All of these electrode materials require low maintenance, if prop-
erly sanitized and cleaned. Repassivation of stainless steel electrodes may be needed if the material rouges or becomes scratched.

The concentric electrode design is not required, but it does result in mechanically rugged sensor construction that can withstand the pressures and flow changes in a water system. Also, the grounded shield design protects the sensor from any nearby surfaces that will impact the electric field and cause altered measurement in unshielded electrodes. Other subtle factors impacting sensor design and system accuracy are the electrode's macroscopic and microscopic properties. Large cell areas are preferable because this reduces the metal-water impedance that is formed at the electrode surface. Smaller cell areas can cause an undesirable increase in the measured cell resistance.

The two principal types of temperature devices are negative temperature coefficient (NTC) thermistors and 100 or 1000 platinum resistance temperature devices (RTDs). Both device types operate on the principle that their resistance changes in known and precise ways as a function of temperature. Both types are low in cost and have desirable electrical response characteristics. NTC thermistors have a very high, nonlinear sensitivity over a narrow temperature range, and their sensitivity drops markedly as the temperature increases. Platinum RTDs have a more linear response over a very wide dynamic range, and they are mechanically more robust than NTC thermistors. Repeatability of the resis-tance-temperature response for RTDs tends to be better than NTC thermistors.

Conductivity Instrumentation-The primary function of the conductivity meter is to make the AC resistance measurement, make the temperature measurement, and display the conductivity. The frequency of the AC measurement is critical to the accuracy of the measurement. At lower conductivity, lower measurement frequencies $(<200 \mathrm{~Hz}$ ) are uti-
lized to provide enough time to charge up the sensor to make an accurate measurement. At higher conductivity (nonpharmaceutical water), the AC measurement is made at a much higher frequency (up to $10,000 \mathrm{~Hz}$ ). High frequencies are required to reduce polarization (collection of ions) at the electrodes. If the AC frequency is too low and the ion concentration is too high, ions will collect at each electrode and disrupt the flow of current and subsequently disrupt the measurement. Cable capacitance and fluid capacitance also greatly impact the measurement accuracy, especially at the lowest conductivity; therefore, unique analog measurement systems are applied to make accurate measurements.

Most conductivity meters have multiple circuits to operate at multiple frequencies over a wide dynamic range. This operating frequency and range of the meter are executed internally and automatically by the meter. Older instruments and some hand-held meters may require manual adjustment of the operating range.

A meter may be placed as far as 100 meters away from the sensor, so the capability of transferring analog or digital signals over these distances necessitates the use of appropriate cable shielding. Also, the use of 3- and 4 -wire measurements is commonly applied to reduce the negative impact of leadwire resistance, especially for long cables.

Although temperature compensation is not intended in Water Conductivity $\langle 645\rangle$, temperature compensation is used by a pharmaceutical facility to monitor and control the water system, in which case accurate temperature measurement is critical. At $20^{\circ}$, a $1^{\circ}$ measurement error will result in a $5 \%$ error in the calculated compensated conductivity. At $80^{\circ}$, the same error will result in a $10 \%$ error in the calculated compensated conductivity. Accurate temperature calibration is necessary to ensure accurate measurements.

Other features found in on-line conductivity analyzers are multiple channel inputs, setpoint alarms, relay control, $0 / 4-20 \mathrm{~mA}$ output, digital output, and multiple types of measurements (conductivity, resistivity), multiple compensation options, and several units of expression (the common set of units is $\mathrm{S} / \mathrm{cm}$ or $\mu \mathrm{S} / \mathrm{cm}$, but there is a small growing trend toward displaying measurements in $\mathrm{S} / \mathrm{m}$ which is an SI unit). Another requirement in Water Conductivity $\langle 645\rangle$ is a display resolution of $0.1 \mu \mathrm{~S} / \mathrm{cm}$, though more resolution is typical.

## Conductivity System Calibration

When a complete conductivity system calibration is required, it should be performed in the following sequence. Calibrate the meter first, then the sensor afterwards. The sensor may be calibrated on the same meter or a different, calibrated meter.

Conductivity Meter Calibration-The purpose of this calibration is to verify and adjust, if necessary, the temperature measurement circuit and AC conductivity measurement circuit of the meter. There is no requirement for accuracy of the temperature circuit in general chapter Water Conductivity $\langle 645\rangle$, but an accuracy of $\pm 0.25^{\circ}$ is typical. Calibration is performed by removing the sensor from the meter and replacing the sensor with a precision resistor of known value. The resistor is a simulator of a specific temperature. Comparison of the simulated and measured temperature will result in an adjustment of the temperature measurement circuit. There should be a provision within the meter to adjust the circuit calibration for temperature.

The same procedure is done for the AC conductivity measurement circuit. Replace the sensor with another precision resistor. Compare the simulated and measured conductivity and adjust, if necessary. Due to the multiple AC measurement circuits in these meters, calibrate either all of the cir-
cuits or the circuit that is in use during normal operation. Specific details for selecting the resistor values and calibrating the meter are supplied by instrument manufacturers. The accuracy required in general chapter $\langle 645\rangle$ is $\pm 0.1 \mu \mathrm{~S} / \mathrm{cm}$. There should be a provision within the meter to adjust the circuit calibration for conductivity.

Conductivity Sensor Calibration-Calibration of the sensor is performed by accurately measuring the cell constant. Standard manufacturing practices can generate sensors with repeatable nominal cell constants, but typical tolerances can lead to variations up to $\pm 10 \%$. Calibration of the sensor in solutions of known, traceable conductivity is the only acceptable method.

The sources of primary standard solutions for cell constant calibration include the following:

- The preparation of ASTM solutions according to D1125 or D5391


## - NIST standard solutions

- Pure water with no impurities

Most commercial sensors are not calibrated in primary standard solutions, but they are calibrated in a solution whose conductivity is known by a secondary transfer conductivity standard. The secondary standard is determined by calibration in the primary standard solutions, usually in an ASTM standard solution(s), and this secondary sensor is used to calibrate commercial sensors.

This presents a dilemma for the pharmaceutical user because the primary standard solutions are all $>100 \mu \mathrm{~S} / \mathrm{cm}$, while the user is operating at $<5 \mu \mathrm{~S} / \mathrm{cm}$, and commonly at $<0.2 \mu \mathrm{~S} / \mathrm{cm}$. This problem is solved in one of two ways. First, if the conductivity measurement system (sensor and meter) has sufficient dynamic range and it is demonstrably accurate over the applicable range-from the calibration solution to the normal operating condition-then the sensor can be calibrated in the higher conductivity solution and
then used in the low conductivity pharmaceutical water. Another method is calibration of the sensor in a recirculating pure water system generated by a mixed-bed de-ionization loop. The conductivity of pure water as a function of temperature is well documented. With an accurate temperature measurement, the conductivity is accurately known and can be used as a primary reference in the normal operating range of the sensor and meter. This technique results in a sensor that is calibrated very accurately, but it is impractical for most end-users to execute themselves.

Calibration of sensors in standard solutions that are $<10$ $\mu \mathrm{S} / \mathrm{cm}$ is possible but has several nuances. Solutions in this conductivity range may be unstable, because of the intrusion of $\mathrm{CO}_{2}$ (from the air) into the solutions. Once the containers are opened, the $\mathrm{CO}_{2}$ reacts immediately with water to form carbonic acid, $\mathrm{H}_{2} \mathrm{CO}_{3}$. Carbonic acid weakly dissociates into $\mathrm{H}^{+}$and $\mathrm{HCO}_{3}^{-}$, and this will impact the conductivity by up to $1 \mu \mathrm{~S} / \mathrm{cm}$ unless preventive measures are taken. Another difficulty is the increased level of cleanliness that is needed to perform the calibration. If there is any residue on the sensor before immersion into the standard solution, the cleanliness and accuracy of the solution is compromised. The advantage of the high conductivity primary standard is that it can better tolerate trace impurities. The advantage of the pure water standard is that it never has impurities. In general chapter $\langle 695\rangle$, calibration accuracy of the cell constant is required to be $\pm 2 \%$, and this is readily achieved.

Frequency of Calibration-Water Conductivity $\langle 645\rangle$ makes no recommendation on the frequency of calibrating conductivity meters or sensors. The frequency should be based on historical data, system performance, and the manufacturer's recommendations. For conductivity meters, a 6month calibration cycle, or longer, is typical. For sensors, the materials, type of construction, and operating conditions can influence the calibration cycle. A sensor calibration cer-
tificate with a 6 -month to 1 -year expiration is typical. Ultimately, it is the amount of risk the user is willing to take that is the deciding factor. Documentation of all calibrations is vital for regulatory purposes.

During normal operation, calibration of robust conductivity sensors should not be required more than every 6 months to 1 year. Only mechanical or chemical disturbances of the sensor should impact the cell constant. For example, $0.1 \mathrm{~cm}^{-}$ ${ }^{1}$ sensors tend to be more robust than $0.01 \mathrm{~cm}^{-1}$ sensors because the higher cell constant sensors have greater spacing (d) between the electrodes than the lower cell constant sensors. As a result, minor mechanical disturbances have a greater impact on the lower cell constant sensors.

## Off-Line Conductivity Measurements

Care should be taken when conductivity measurements of Purified Water or Water for Injection are taken off-line, e.g., in a laboratory. If the water conductivity (measured on-line) is $<1 \mu \mathrm{~S} / \mathrm{cm}$, then virtually any measurement of that same water made in the laboratory will result in a higher conductivity. The immediate reaction of $\mathrm{CO}_{2}$ with the water will cause the formation of $\mathrm{H}_{2} \mathrm{CO}_{3}$ as described above, and cause the conductivity to rapidly and immediately increase. As a result, it is very difficult to correlate on-line measurements to laboratory measurements.

For example, a water system with filtration, reverse osmosis, and mixed-bed de-ionization may be producing Purified Water with a nominal quality of $0.055 \mu \mathrm{~S} / \mathrm{cm}(18 \mathrm{M} \Omega-\mathrm{cm})$ water consistently. When this water conductivity is measured in-line, the measurement may vary from 0.054 to $0.057 \mu \mathrm{~S} / \mathrm{cm}$. When the same water is transported into the laboratory, the conductivity may vary from 0.8 to $1.5 \mu \mathrm{~S} /$ cm . The conductivity increase will be due solely to the $\mathrm{CO}_{2}$. The increase in the variability in this off-line measurement will also be significant (almost $100 \%$ ), while the on-
line measurement varies about $5 \%$. The increased fluctuation is due to the variations in concentration of $\mathrm{CO}_{2}$ in the ambient area at the time. Pristine air will have a concentration of about $375 \mathrm{ppm} \mathrm{CO}_{2}$, but normal industrial conditions would have the $\mathrm{CO}_{2}$ concentration vary from 500 to 1200 ppm . The variability in the $\mathrm{CO}_{2}$ concentration is completely beyond the control of the analyst, but it grossly impacts the measurement and completely obscures any possible correlation of off-line with on-line measurements. $\Delta$ USP28

## REAGENTS, INDICATORS, AND SOLUTIONS

## Reagent Specifications

## BriEfing

1,5-Dimethyl-1,5-diazaundecamethylene polymethobromide (Polybrene). This new reagent is used in dissolving the chromogenic substrate for the amidolytic test in the Assay under the Antithrombin III Human monograph, appearing elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-37456-2

## Add the following:

© $\mathbf{1 , 5}$-Dimethyl-1,5-diazaundecamethylene polymethobromide (Polybrene), [28728-55-4]—This is a positively charged polymer. It is available as an off-white, crystalline solid or powder and is extremely hygroscopic. Use a suitable reagent grade. ${ }^{112}$ ©USP28

## Briefing

Sodium 1-Heptanesulfonate, USP 27 page 2710. It is proposed to clarify the name of this reagent by adding the synonym " 1 -Hexanesulfonic acid."
(HDQ: M. Marques) RTS-40477-1

## Change to read:

Sodium 1-Heptanesulfonate
© (1-Hexanesulfonic acid), $\triangle U S P 28$
$\mathrm{C}_{7} \mathrm{H}_{15} \mathrm{NaO}_{3} \mathrm{~S}$ - $\mathbf{2 0 2 . 2 5}$-Use a suitable grade.

## BRIEFING

Sodium 1-Hexanesulfonate, USP 27 page 2710. It is proposed to clarify the name of this reagent by adding the synonym " 1 -Pentanesulfonic acid."
(HDQ: M. Marques) RTS-40489-1

## Change to read:

Sodium 1-Hexanesulfonate,
© (1-Pentanesulfonic acid), $\triangle U S P 28$
$\mathrm{C}_{6} \mathrm{H}_{13} \mathrm{NaO}_{3} \mathrm{~S}-\mathbf{1 8 8 . 2 2}$-Use a suitable grade.

## BriEfing

Thyroglobulin. This new reagent is used for determining the void volume of the sizing column in the test for Molecular weight distribution in the proposed monograph for Antithrombin III Human appearing elsewhere in this $P F$.
(BBP: R. Tirumalai) RTS-37456-3

## Add the following:

${ }^{\Delta}$ Thyroglobulin, [9010-34-8]-Available as a slightly beige, freeze-dried powder made from bovine or porcine thyroid gland having a molecular weight of approximately 670 kDa . Use a suitable grade. $\quad$ USP28

## BRIEFING

Wright's Stain. This new reagent is used for staining platelets in the Identification test in the proposed Platelets monograph, appearing elsewhere in this number of $P F$.
(BBP: R. Tirumalai) RTS-40379-1

## Add the following:

${ }^{\mathbf{\Delta}}$ Wright's Stain-A mixture of methylene blue, methylene azure, and the eosinates of both, available as a solid and as a solution in methanol. Use a suitable grade. [NOTE-If a solid is used, dissolve 6.0 g of Wright's stain powder (CAS\# 68988-92-1, dark green powder) and 0.6 g of Giemsa stain powder (CAS\# 51811-82-6, dark green to black powder or crystals) in 1000 mL of methanol. Stir overnight, and filter before use.] ${ }_{\mathbf{\Delta S P 2 8}}$

## Test Solutions

## BRIEFING

Test Solutions (TS), USP 27 page 2725, page 1905 of $P F 27(1)$ [Jan.-Feb. 2001], page 3117 of $P F$ 27(5) [Sept.-Oct. 2001], and page 1682 of PF 29(5) [Sept.-Oct. 2003]. For Folin-Ciocalteu Phenol TS, it is proposed to add instructions on how to prepare this test solution when it is used for Method 2 in the Total Protein Assay for protein determination (see Biotechnology-Derived ArticlesTests $\langle 1047\rangle$ ). In the absence of any adverse comments, this proposed revision will be implemented via the Second Interim Revision Announcement pertaining to USP 27-NF 22, with an official date of April 1, 2004. For Hydroxylamine Hydrochloride TS, it is proposed to specify the solvent used in the preparation of the bromophenol blue solution.
(BPC: M. Marques) RTS-40655-1; 40479-1

## Add the following:

-Cupric Citrate TS—Dissolve 25 g of cupric sulfate, 50 g of citric acid, and 144 g of anhydrous sodium carbonate in water, and dilute with water to 1000 mL . $\quad$ IS (USP27)

## Add the following:

-Ferroin TS—Dissolve 0.7 g of ferrous sulfate and 1.76 g of $o$-phenanthroline monohydrochloride monohydrate in water, and dilute with water to 100 mL . 1 (USP27)

## Change to read:

Folin-Ciocalteu Phenol TS-Into a $1500-\mathrm{mL}$ flask introduce 100 g of sodium tungstate, 25 g of sodium molybdate, 700 mL of water, 50 mL of phosphoric acid, and 100 mL of hydrochloric acid. Reflux the mixture gently for about 10 hours, and add 150 g of lithium sulfate, 50 mL of water, and a few drops of bromine. Boil the mixture, without the condenser, for about 15 minutes, or until the excess bromine is expelled. Cool, dilute with water to 1 liter, and filter: the filtrate has no greenish tint. Before use, dilute 1 part of the filtrate with 1 part of water.

- When used for protein determination (i.e., Lowry assay), this reagent must be further diluted (1:5) with water. See Method 2 in Total Protein Assay under Biotechnology-Derived Articles—Tests $\langle 1047\rangle$ ••2


## Change to read:

Hydroxylamine Hydrochloride TS-Dissolve 3.5 g of hydroxylamine hydrochloride in 95 mL of 60 percent alcohol, and add 0.5 mL of bromophenol blue solution ( 1 in 1000 )
${ }^{\Delta}(1 \text { in } 1000 \text { of alcohol })_{\Delta U S P 28}$
and 0.5 N alcoholic potassium hydroxide until a greenish tint develops in the solution. Then add 60 percent alcohol to make 100 mL .

## Change to read:

Methyl Yellow TS-Dilute with aleohol a-commereially avait able stock solutionof methyl yellow in aleohel ${ }^{86}$ to obtain selution having a concentration of 0.10 mg per mL .

- Prepare a solution containing 0.10 mg per mL in alcohol.■2S (USP27)


## Add the following:

■Nickel Standard Solution TS——Dissole 4.78 g of nickel
(II) sulfate heptahydrate in water, and dilute with water to

1000 mL . Immediately prior to use, dilute 10.0 mL of the solution so obtained with water to 1000 mL . Suitable nickel standard solutions are also available commercially.■1S (USP27)

## Add the following:

■Perchloric Acid TS——Dilute 8.5 mL of perchloric acid with water to $100 \mathrm{~mL} . \mathbf{m 1 S}_{\text {(USP27) }}$

## BRIEFING

Reagent Footnotes, USP 27 page 2738, page 1133 of $P F$ 26(4) [July-Aug. 2000], page 3373 of $P F 27(6)$ [Nov.-Dec. 2001], page 266 of PF 29(1) [Jan.-Feb. 2003], page 508 of PF 29(2) [Mar.Apr. 2003], and page 1257 of $P F 29(4)$ [July-Aug. 2003]. Footnote 112 is added to identify the name under which $1,5-\mathrm{Di}-$ methyl-1,5-Diazaundecamethylene Polymethobromide is commercially available.
(HDQ: M. Marques) RTS-RTS—37456-2

## Add the following:

-112 Commercially available as Polybrene.』USP28

## REFERENCE TABLES

## Briefing

Description and Relative Solubility of USP and NF Articles, USP 27 page 2747 , page 5310 of $P F 23(6)$ [Nov.-Dec. 1997], page 7017 of $P F$ 24(5) [Sept.-Oct. 1998], page 8282 of $P F 25(3)$ [MayJune 1999], page 8589 of $P F$ 25(4) [July-Aug. 1999], page 8917 of $P F$ 25(5) [Sept.-Oct. 1999], page 9254 of $P F 25(6)$ [Nov.-Dec. 1999], page 504 of $P F$ 26(2) [Mar.-Apr. 2000], page 837 of $P F$ 26(3) [May-June 2000], page 1135 of $P F$ 26(4) [July-Aug. 2000], page 1385 of $P F$ 26(5) [Sept.-Oct. 2000], page 1907 of $P F$ 27(1) [Jan.-Feb. 2001], page 2281 of $P F 27$ (2) [Mar.-Apr. 2001], page 2839 of $P F$ 27(4) [July-Aug. 2001], page 3374 of PF 27(6) [Nov.-Dec. 2001], page 554 of $P F$ 28(2) [Mar.-Apr. 2002], page 1236 of $P F$ 28(4) [July-Aug. 2002], page 1542 of $P F$ 28(5) [Sept.-Oct. 2002], page 1953 of $P F$ 28(6) [Nov.-Dec. 2002], page 266 of $P F$ 29(1) [Jan.-Feb. 2003], page 509 of $P F$ 29(2) [Mar.-Apr. 2003], page 812 of $P F 29(3)$ [May-June 2003], page 1262 of $P F$ 29(4) [July-Aug. 2003], page 1684 of PF 29(5) [Sept.-Oct. 2003], and page 2057 of $P F$ 29(6) [Nov.Dec. 2003].
(HDQ) RTS—39836-1; 40020-4; 40234-4; 40268-1; 404211; 40478-1; 40596-1; 40672-1

## Add the following:

${ }^{4}$ E-Asparagine: Asparagine: White crystals or a crystalline powder. Soluble in water; practically insoluble in alcohol and in ether. Its solutions are acid to litmus. It melts at about $234^{\circ} \cdot \mathbf{\Delta U S P 2 8}$

## Change to read:

Clemastine Fumarate: Colerless to faintly yellow, odorless, erystalline pow der.
${ }^{\Delta}$ White to off-white, odorless powder. $\Delta U S P 28$
Its solutions are acid to litmus. Very slightly soluble in water; slightly soluble in methanol; very slightly soluble in chloroform.

## Add the following:

${ }^{4}$ Fluconazole: White or almost white, crystalline powder. Freely soluble in methanol; soluble in alcohol and in acetone; sparingly soluble in isopropanol and in chloroform; slightly soluble in water; very slightly soluble in toluene. $\mathbf{\Delta U S P 2 8}$

## Add the following:

${ }^{\mathbf{4}}$ Losartan Potassium: White to off-white powder. Freely soluble in water; soluble in isopropyl alcohol; slightly soluble in acetonitrile. $\triangle$ USP28

## Add the following:

$\mathbf{\Delta Z}_{\mathbf{Z}}$-Phenoxyethanol: Phenoxyethanol: A colorless, slightly viscous liquid. Slightly soluble in water; miscible with acetone, with alcohol, and with glycerol; slightly soluble in peanut oil and in olive oil. NF category: Antimicrobial preservative. $\triangle$ USP28

## Add the following:

${ }^{4}$ Sumatriptan: White to yellowish white pale yellow powder. Freely soluble Very slightly soluble in water. IUSP28 $^{\text {I }}$

Items from Earlier Numbers of PF that Have Not Yet Appeared in a Supplement, and are Therefore Candidates for Subsequent Supplements.

## GENERAL NOTICES AND REQUIREMENTS

"Official" and "Official Articles"-See PF Vol. 29 No. 6, page 1823.

Significant Figures and Tolerances-See PF Vol. 29 No. 6, page 1824.

General Chapters-See PF Vol. 29 No. 6, page 1825.
Ingredients and Processes-See PF Vol. 29 No. 6, page 1825.
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Acetaminophen and Aspirin Tablets-See PF Vol. 27 No. 3, page 2495.

Acetaminophen, Aspirin, and Caffeine Tablets-See PF Vol. 27 No. 3, page 2495.
Capsules Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 27 No. 3, page 2496.

Oral Powder Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 27 No. 3, page 2496.

Oral Solution Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 27 No. 6, page 3241.

Tablets Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 27 No. 3, page 2496.

Acetaminophen and Codeine Phosphate Capsules-See PF Vol. 29 No. 3, page 601.
Acetaminophen and Codeine Phosphate Oral Solution-See PF Vol. 29 No. 3, page 601.
Acetaminophen and Codeine Phosphate Oral Suspension-See PF Vol. 29 No. 3, page 601.
Acetaminophen and Codeine Phosphate Tablets-See PF Vol. 29 No. 3, page 602.
Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solu-tion-See PF Vol. 27 No. 3, page 2499.
Acetaminophen and Diphenhydramine Citrate Tablets-See PF Vol. 27 No. 3, page 2499.
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets-See PF Vol. 27 No. 3, page 2499.
Acetaminophen and Pseudoephedrine Hydrochloride TabletsSee PF Vol. 27 No. 3, page 2500.

Acetazolamide-See PF Vol. 27 No. 3, page 2500.
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Glacial Acetic Acid-See PF Vol. 27 No. 3, page 2501.
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Acetohexamide Tablets-See PF Vol. 27 No. 3, page 2501.
Acetohydroxamic Acid Tablets-See PF Vol. 27 No. 3, page 2503.
Acetylcholine Chloride-See PF Vol. 27 No. 3, page 2502.
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Dehydrated Alcohol Injection-See PF Vol. 27 No. 3, page 2507.
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| $\dagger\langle 1175$ Preformulation Guidelines-Preview | 26 | 6 | 1672 |
| $\dagger\langle 1191\rangle$ Stability Considerations in Dispensing Practice- | 26 | 5 | 1378 |
| Introduction, Stability Studies in Manufacturing, <br> Responsibility of the Pharmacist, Labile Preparations |  |  |  |
| Reagents, Indicators, and Solutions |  |  |  |
| $\dagger$ Bromobimane (added) | 25 | 2 | 7804 |
| $\dagger$ Potassium Permanganate, Tenth-Normal (0.1 N)-Erratum | 29 | 1 | 266 |
| Reference Tables |  |  |  |
| Container Specifications |  |  |  |
| $\dagger$ Kava Capsules | $26$ | 3 | $836$ |
| $\dagger$ Kava Tablets | 26 | 3 | 836 |
| Description and Relative Solubility |  |  |  |
| $\dagger$ Indinavir | 27 | 2 | 2281 |
| $\dagger$ Starch (Preview) | 21 | 5 | 1243 |

$\dagger$ New cancellations in 30(1).

$$
1
$$

## HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps (Stages).

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In $P F$, this stage appears as OFFICIAL INQUIRY STAGE 4 in the Harmonization section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

## Stage 5: Consensus

## A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

## B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.
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## MONOGRAPHS (NF)

## BRIEFING

Hydroxypropyl Cellulose, $N F 22$ page 2877. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Hydroxypropyl Cellulose monograph. This is part of the process of international harmonization of monographs and general analytical methods of the European (EP), Japanese (JP), and United States (USP) pharmacopeias. The following draft monograph, which represents the USP-style Stage 4 draft, is based on an IPEC consensus prepared by the three International Pharmaceutical Excipients Councils (IPEC-America, IPEC-Japan, and IPEC-Europe).

Changes from existing $U S P-N F, E P$, and $J P$ monographs are justified by the following:
(1) Definition-A modification to the definition has been proposed. The second sentence should read, "It contains not less than 53.4 percent and not more than 80.5 percent of the hydroxypropoxy groups, calculated on the dried basis." The modification has been proposed to ensure solubility performance and to distinguish Hydroxypropyl Cellulose from Low-Substituted Hydroxypropyl Cellulose. A lower limit of hydroxypropoxy content is appropriate. The Japanese Pharmacopoeia, current lower limit of 53.4 was recommended.
(2) Packaging and storage - No change. This requirement is in the NF 19, the European Pharmacopoeia, and the Japanese Pharmacopoeia monographs.
(3) Labeling-A revision to the Labeling section has been proposed to delete the following statement: "The indicated viscosity may be in the form of a range encompassing $50 \%$ to $150 \%$ of the average value." The recommended statement, "Label it to indicate the nominal viscosity in an aqueous solution of stated concentration and temperature." is contained in both the European Pharmacopoeia and the NF 19 monographs. No requirement is found in the Japanese Pharmacopoeia.
(4) Identification-In order to make the Identification test more reliable, two new tests ( $C$ and $D$ ) have been proposed. Test $C$ is proposed because neither Methylcellulose nor Hydroxypropyl Methylcellulose are soluble in alcohol. Test $D$ (infrared spectroscopy) is listed as an alternative because it can also distinguish between Hydroxypropyl Cellulose, Low-Substituted Hydroxypropyl Cellulose, Methylcellulose, and Hydroxypropyl Methylcellulose.
(5) Viscosity-The proposed change is to specify an LV-type rotational viscometer with spindle and speed combinations for materials with labeled viscosity of 75 cP or higher. This viscosity measurement method is common to all manufacturers of Hydroxypropyl Cellulose at this time. However, different manufacturers currently use different measuring conditions, therefore the limit should be based on label claims that specify the conditions used for the measurements.
(6) pH - No change. The actual range in $N F 19$ is $5.0-8.0$, and in the European Pharmacopoeia it is $5.0-8.5$. In practice, no commercial material exists above a pH of 8.0.
(7) Loss on drying - The proposed recommendation is to change the drying time from 3 hours to 4 hours. Equilibrium Loss on drying is not reached in 3 hours, according to studies the IPEC have performed. According to the studies, there is no significant increase in weight after 4 hours.
(8) Residue on ignition-For harmonization, a total Residue on ignition limit of $0.8 \%$ is recommended, representing total ash ( $0.2 \%$ limit) and the total silica ( $0.6 \%$ limit). The corresponding European Pharmacopoeia Sulfated ash test limit is $1.6 \%$. The European Pharmacopoeia monograph also contains a separate Silica test, with a limit of $0.6 \%$. The limit for Residue on ignition is $0.5 \%$. The Japanese Pharmacopoeia monograph does not contain a separate test and limit for silica. The limit of $0.8 \%$ is appropriate to allow the addition of silica as a flow aid at current commercial levels, yet ensures that the material is of the appropriate quality. At a level of $0.8 \%$, porcelain or suitable glass crucibles should be satisfactory without going to the expense of platinum crucibles.
(9) Limit of silica-For harmonization, the Limit of silica test has been recommended for deletion. The three IPEC groups felt that a separate test is not necessary to determine the silica level. The total Residue on ignition limit is adequate to provide appropriate control, and the specific amount of silica allowed does not have to be limited beyond what would be detected by this method. However, any added anti-caking agents (such as silica) that are used should be identified on the label, and the label should show the target amount added.
(10) Heavy metals-The test is common to the NF 19 and European Pharmacopoeia monographs. The lower limit of $0.002 \%$ is recommended, thereby removing the need for a lead test. Another proposed revision is to perform Method III (Wet Digestion) from the general chapter 231 instead of Method II. Ignition of samples as done in Methods I and II has been shown to result in a loss of up to $50 \%$ (the studies were performed by IPEC) of the actual heavy metals content.
(11) Lead and Chloride-With the proposed revised Heavy metals limit of $0.002 \%$, it is recommended that the NF 19 Lead test not be included. The current European Pharmacopoeia and Japanese Pharmacopoeia monographs do not contain a Lead test. It is recommended that the Chloride test from the European Pharmacopoeia and the Japanese Pharmacopoeia not be included, based on the wide variation between the European Pharmacopoeia ( $0.5 \%$ ) and Japanese Pharmacopoeia ( $0.142 \%$ ) limits.
(12) Assay for hydroxypropoxy groups-No change. The chromic acid oxidation method from the $N F 19$ is preferred because of that method's accuracy. The gas chromatographic method (Ziessel GC method) described in the Japanese Pharmacopoeia is reported to have better reproducibility than the titration method, but gives consistently low results. The results obtained by the chromic acid oxidation method appear to be closer to the actual value than the results from the Ziessel GC method, and, therefore, this method is preferred by $U S P$ and $E P$. The $J P$ is reluctant to incorporate this method in their monograph because they currently do not use chromic acid in any of their monographs, and they want to avoid the use of hazardous materials such as chromic acid. Certainly the $U S P$ and $E P$ also agree with minimizing the use of hazardous reagents, whenever possible. However, in this case there are no other suitable methods available at this time that can give accurate results. Therefore, the use of chromic acid is justified and necessary.
(13) Glyoxal-Although there has been discussion concerning the need for a glyoxal requirement with certain other cellulose derivatives such as Hydroxyethylcellulose and Hydroxypropyl Methylcellulose due to multi-use equipment, the IPEC do not believe that there is any need for this requirement for Hy droxypropyl Cellulose. None of the commercial suppliers of Hydroxypropyl Cellulose currently use glyoxal in their manufacturing equipment. Therefore, there is no chance of residual glyoxal being present in Hydroxypropyl Cellulose.
(EMC: J. Lane) RTS-40440-1

## Add the following:

## Hydroxypropyl Cellulose

Cellulose, 2-hydroxypropyl ether [9004-64-2].
» Hydroxypropyl Cellulose is a partially substituted poly(hydroxypropyl) ether of cellulose. It contains not less than 53.4 percent and not more than 80.5 percent of hydroxypropoxy groups, calculated on the dried basis. It may contain suitable anticaking agents.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle$ —USP Hydroxypropyl Cellulose RS.

Labeling-Label it to indicate the nominal viscosity in an aqueous solution of stated concentration and temperature.

## Identification-

A: Dissolve 1 g of Hydroxypropyl Cellulose in 100 mL of water. Transfer 10 mL of this solution to a suitable container. Heat the solution to $45^{\circ}$ : the solution becomes cloudy or a flocculent precipitate is formed, and the turbidity or precipitate disappears on cooling.
B: Transfer 1 mL of the solution from Identification test $A$ to a glass plate, and allow the water to evaporate: a thin, self-sustaining film is formed.

C: To 1 g of Hydroxypropyl Cellulose, add 100 mL of $95 \%$ denatured alcohol, and dissolve. Allow to stand after stirring: a homogenous and viscous liquid is produced.

D: As an alternative to Identification test $C$, the infrared spectrum compares to that of USP Hydroxypropyl Cellulose RS.

Viscosity $\langle 911\rangle$ : not less than $50 \%$ and not more than $150 \%$ of the labeled claim; use an LV-type rotational viscometer with the spindle and speed combination for materials with labeled viscosity of 75 cP or higher.
$\mathbf{p H}\langle 791\rangle$ : between 5.0 and 8.0 for a $1 \%$ solution.
Loss on drying $\langle 731\rangle$-Dry it at $105^{\circ}$ for 4 hours: it loses not more than $5.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.8 \%$ of the weight of test specimen taken for the ignition.

Heavy metals, Method III $\langle 231\rangle$ : 0.002\%.

## Assay for hydroxypropoxy groups-

Apparatus-The apparatus for hydroxypropoxy group determinations is shown diagrammatically in Figure 1. Figure 2 shows the boiling or reaction flask, consisting of a $125-\mathrm{mL}$ conical-bottom boiling flask modified to provide a thermocouple (or thermometer) well and an inlet with a $1.0-\mathrm{mm}$ capillary tip for nitrogen and water. It is fitted with a distillation head that leads to a condenser. The reaction flask shown in Figure 1 is immersed in an oil bath equipped with an electric heater capable of heating the bath at the desired rate and maintaining the temperature at $155^{\circ}$. The distillate is collected in a flask. [NOTE-The tube from the condenser to the flask must be below the surface of the liquid in the flask to ensure the capture of all of the acetic acid formed. See Figure 1.]


Fig. 1. Apparatus for hydroxypropoxy determination.


Fig. 2. Boiling flask.

Procedure-Transfer about 65 mg of Hydroxypropyl Cellulose, previously dried at $105^{\circ}$ for 1 hour and accurately weighed, into the reaction flask. Add 5 mL of water and swirl gently for 5 minutes. Add 10 mL of chromium trioxide solution ( 30 g in 70 mL ). Assemble the apparatus as shown in Figure 1 and Figure 2, and immerse the reaction flask in the oil bath, slightly above the level of the chromium trioxide solution. Start the condenser cooling water, and pass nitrogen gas through the flask at a rate of about 70 to 75 mL per minute. Raise the temperature of the oil bath to $155^{\circ}$ during a 30 -minute period, and maintain it at this temperature throughout the determination. [NOTE-Too rapid an initial rise in temperature results in high blank determinations.] Monitor the temperature of the reaction mixture in the reaction flask using a thermocouple or thermometer in a well, as shown in Figure 1 and Figure 2. When a reaction mixture temperature of $102 \pm 1^{\circ}$ is reached, add water through the water inlet until the reaction mixture temperature drops to $97 \pm 1^{\circ}$. Continue this $97^{\circ}$ to $102^{\circ}$ temperature cycle until 100 mL of distillate has been collected. Detach the condenser from the distillation head and wash with water, collecting the washings in the flask containing the distillate. Titrate the solution with 0.02 N sodium hydroxide VS to a pH of $7.0 \pm 0.1$, using an expanded-scale pH meter equipped with glass and calomel electrodes. Record the volume, $V$, of the 0.02 N sodium hydroxide used, then add 500 mg of sodium bicarbonate and 10 mL of 2 N sulfuric acid. After evolution of carbon dioxide has ceased, add 1 g of potassium iodide; insert the stopper in the flask; shake the mixture; and allow the solution to stand in the dark for 5 minutes. Titrate the liberated iodine with 0.02 N sodium thiosulfate VS to the sharp disappearance of the yellow iodine color, adding a few drops of starch TS to confirm the endpoint. Record the volume, $Y$, required. This titration, $Y \mathrm{~mL}$, multiplied by the empirical factor, $K$, appropriate to the particular ap-
paratus and reagents in use (see calculation below), gives the acid equivalent not caused by acetic acid. The acetic acid equivalent is $(V-K Y) \mathrm{mL}$ of 0.02 N sodium hydroxide.

Obtain the empirical factor, $K$, for the apparatus by performing a blank determination in which the Hydroxypropyl Cellulose is omitted. The acidity of the blank for a given apparatus and given reagents is in a fixed ratio to the oxidizing equivalent of the distillate in terms of sodium thiosulfate:

$$
K \text { factor }=\left(V_{B} \times N_{1}\right) /\left(Y_{B} \times N_{2}\right),
$$

in which $V_{B}$ is the volume, in mL , of 0.02 N sodium hydroxide required in the blank run; $N_{1}$ is the normality of the 0.02 N sodium hydroxide; $Y_{B}$ is the volume, in mL , of 0.02 N sodium thiosulfate required in the blank run; and $N_{2}$ is equal to the normality of the 0.02 N sodium thiosulfate.

Calculate the percentage of hydroxypropoxy groups $\left(-\mathrm{OCH}_{2} \mathrm{CHOHCH}_{3}\right)$ by the formula:

$$
100\left(V_{A} N_{1}-K Y_{A} N_{2}\right)(0.079 / W)
$$

in which $V_{A}$ is the volume, in mL , of 0.02 N sodium hydroxide required for titration of the sample; $N_{1}$ is the normality of the 0.02 N sodium hydroxide; $K$ is the empirical factor; $Y_{A}$ is the volume, in mL , of 0.02 N sodium thiosulfate required for titration of the sample; $N_{2}$ is the normality of the 0.02 N sodium thiosulfate; and $W$ is the quantity, in g, of sample used. Each mL of 0.02 N sodium hydroxide is equivalent to 1.502 mg of hydroxypropoxy groups $\left(-\mathrm{OCH}_{2} \mathrm{CHOHCH}_{3}\right)$.

The results obtained as a percentage of hydroxypropoxy content may be converted to terms of average molecular substitution of glucose units by means of the accompanying graph (see Figure 3).


Fig. 3. Graph for converting percentage of substitution, by weight, of hydroxypropoxy groups to molecular substitution per glucose unit.

## BRIEFING

Low-Substituted Hydroxypropyl Cellulose, NF 22 page 2879. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Low-Substituted Hydroxypropyl Cellulose monograph, as part of the process of international harmonization of monographs and general analytical methods of the European (EP), Japanese (JP), and United States (USP) pharmacopeias. The following draft monograph, which represents the USP-style Stage 4 draft, is based on a IPEC consensus comments prepared by the three International Pharmaceutical Excipients Councils (IPEC-America, IPEC-Japan, and IPEC-Europe).

Changes from existing $U S P-N F, E P$, and $J P$ monographs are justified.
(1) In the opening paragraph (the definition)-No change. The content range is common to both the Japanese Pharmacopoeia and the NF 22 monographs. The European Pharmacopoeia does not contain a monograph for Low-Substituted Hydroxypropyl Cellulose.
(2) Packaging and storage - No change. This requirement is common to the NF 22 and the Japanese Pharmacopoeia monographs.
(3) Identification-The proposed change is to replace tests $A$ and $B$ with an IR test while retaining test $C$. The IR test is useful for discriminating Low-Substituted Hydroxypropyl Cellulose from Hydroxypropyl Cellulose which is identical in the chemical composition, but is different only in the substituent content.
(4) pH -It is recommended to include this test in the harmonized monograph. This test is in the Japanese Pharmacopoeia monograph and is provided in the Description and Solubility section of NF 22.
(5) Loss on drying - No change. The test and drying time are common to the NF 22 and the Japanese Pharmacopoeia monographs. The $N F$ limit is $5.0 \%$. The Japanese Pharmacopoeia limit is $6.0 \%$. The limit from NF 22 is recommended.
(6) Residue on ignition-For harmonization, a total Residue on ignition limit of $0.8 \%$ is recommended. Current limits in the $N F$ and Japanese Pharmacopoeia are $0.5 \%$ and $1.0 \%$, respectively. Actual products distributed in Japan sometimes have higher residue on ignition value than $0.5 \%$ (this is based on the process capability). It is proposed to define the ignition temperature as $800^{\circ} \pm 25^{\circ}$ of the USP condition so that the pertinent monographs in other pharmacopeias would specify it independent of their general test so as to avoid possible confusion.
(7) Heavy metals-No change. The test and limit are common to the NF 22 and Japanese Pharmacopoeia monographs. The NF 22 test and limit are recommended.
(8) Chloride-It is recommended to delete the Chloride test. Residue on ignition value of the raw material cellulose is very small (usually less than $0.1 \%$ ). It is considered that most of chloride in a product is composed of sodium chloride and that it is a major inorganic impurity. Then content of sodium chloride would reflect the Residue on ignition value. Therefore, IPEC thinks that it is not meaningful to provide an overlapping test of Chloride.
(9) Assay-No change. This test procedure is common to USP and JP.
(10) Glyoxal-Although there has been discussion concerning the need for a glyoxal requirement with certain other cellulose derivatives such as Hydroxyethylcellulose and Hydroxypropyl Methylcellulose due to multi-use equipment, we do not believe that there is any need for this requirement for Low-Substituted Hydroxypropyl Cellulose. No glyoxal is used in the manufacturing equipment used by any of the commercial suppliers of Low-Substituted Hydroxypropyl Cellulose at this time. Therefore, there is no chance of residual glyoxal being present in Low-Substituted Hydroxypropyl Cellulose.
(EMC: J. Lane) RTS-40439-1

## Add the following:

## Low-Substituted Hydroxypropyl Cellulose

» Low-Substituted Hydroxypropyl Cellulose is a low-substituted poly(hydroxypropyl) ether of cellulose. It contains not less than 5.0 percent and not more than 16.0 percent of hydroxypropoxy groups, calculated on the dried basis.

Packaging and storage-Preserve in tight containers.
USP Reference standard $\langle 11\rangle$ - USP Low-Substituted Hydroxypropyl Cellulose RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Shake thoroughly 0.1 g with 10 mL of water. Add 1 g of sodium hydroxide, and shake until it becomes homogeneous. Transfer 5 mL to a suitable container, add 10 mL of a mixture of acetone and methanol (4:1), and shake: a white, flocculent precipitate is formed.
$\mathbf{p H}\langle 791\rangle$ : between 5.0 and 7.5 , in a suspension obtained by shaking 1.0 g with 100 mL of water.

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 1 hour: it loses not more than $5.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.8 \%$.
Heavy metals, Method III $\langle 231\rangle: 0.001 \%$.
Assay-[Caution-Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps of the Assay preparation and the standard preparation in a properly functioning hood. Specific safety practices to be followed are to be identified to the analyst performing this test.]
Hydriodic acid-Use a reagent having a specific gravity of at least 1.69 , equivalent to $55 \% \mathrm{HI}$.

Internal standard solution-Transfer about 2.5 g of toluene, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask containing 10 mL of $o$-xylene, dilute with $o$-xylene to volume, and mix.

Standard preparation-Into a suitable serum vial weigh about 135 mg of adipic acid and 4.0 mL of Hydriodic acid, pipet 4 mL of Internal standard solution into the vial, and close the vial securely with a suitable septum stopper. Weigh the vial and contents accurately, add $30 \mu \mathrm{~L}$ of isopropyl iodide through the septum with a syringe, again weigh, and calculate the weight of isopropyl isopropyl iodide added, by difference. Shake, and allow the layers to separate.

Assay preparation-Transfer about 0.065 g of dried Low Substituted Hydroxypropyl Cellulose, accurately weighed, to a $5-\mathrm{mL}$ thick-walled reaction vial equipped with a pres-
sure-tight septum-type closure, add an amount of adipic acid equal to the weight of the test specimen, and pipet 2 mL of Internal standard solution into the vial. Cautiously pipet 2 mL of Hydriodic acid into the mixture, immediately cap the vial tightly, and weigh accurately. Continuously mix the contents of the vial while heating at $150^{\circ}$ for 60 minutes. Allow the vial to cool for about 45 minutes, and again weigh. If the weight loss is greater than 10 mg , discard the mixture, and prepare another Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The gas chromatograph is equipped with a thermal conductivity detector and a $4-\mathrm{mm} \times 1.8-\mathrm{m}$ glass column packed with $20 \%$ liquid phase G28 on 100 - to 120 -mesh support S1C that is not silanized. Helium is used as the carrier gas and the temperature of the column is maintained at $130^{\circ}$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 1.0, 1.6, and 3.6 for isopropyl iodide, toluene, and $o$-xylene, respectively; and the resolution, $R$, between toluene and isopropyl iodide is not less than 2.0.

Calibration-Inject about $2 \mu \mathrm{~L}$ of the upper layer of the Standard preparation into the gas chromatograph, and record the chromatogram. Calculate the relative response factor, $F_{l}$, of equal weights of toluene and isopropyl iodide taken by the formula:

$$
Q_{I} / R_{S I},
$$

in which $Q_{I}$ is the quantity ratio of isopropyl iodide to toluene in the Standard preparation; and $R_{S I}$ is the peak area ratio of isopropyl iodide to toluene obtained from the

## Standard preparation.

Procedure-Inject about $2 \mu \mathrm{~L}$ of the upper layer of the Assay preparation into the gas chromatograph, and record the chromatogram. Calculate the percentage of hydroxypro-
poxy $\left(-\mathrm{OCH}_{2} \mathrm{CHOHCH}_{3}\right)$ in the Low Substituted Hydroxypropyl Cellulose taken by the formula:

$$
2(75 / 170) F_{I} R_{U I}\left(W_{T} / W_{U}\right)
$$

in which 75/170 is the ratio of the formula weights of hydroxypropoxy and isopropyl iodide; $F_{I}$ is defined under Ca libration; $R_{U I}$ is the ratio of the area of the isopropyl iodide peak to that of the toluene peak obtained from the Assay preparation; $W_{T}$ is the weight, in g , of toluene in the Internal standard solution; and $W_{U}$ is the weight, in g , of Low Substituted Hydroxypropyl Cellulose taken for the Assay.

## BRIEFING

Magnesium Stearate, $N F 22$ page 2889. The United States Pharmacopeia, a member of the Pharmacopoeial Discussion Group, is the coordinating pharmacopeia for the international harmonization of the compendial standards for Magnesium Stearate. The text presented below represents the OFFICIAL INQUIRY STAGE 4 draft in the harmonization process, based in part on comments received in response to the CONSENSUS STAGE 5B draft. Because of significant changes in the tests for the Limit of cadmium, Limit of lead, and Limit of nickel, the draft has reverted to the OFFICIAL INQUIRY STAGE 4. It is proposed to correct erroneous matrix modifier solution preparations within the tests for the Limit of cadmium, Limit of lead, and Limit of nickel. Readers are therefore urged to review these late-stage proposals carefully and to respond to USP no later than February 29, 2004.

The differences between the revised STAGE 4 Harmonization draft for Magnesium Stearate and the previous STAGE 5A document include the following:

1. The revised OFFICIAL INQUIRY STAGE 4 draft represents a document in global format with no references to specific general chapters. Those references will be introduced at a later stage in the process.
2. Definition-The reference to edible sources has been removed and will be considered a specific local attribute for USP. USP will retain this section from the current $N F$ monograph.
3. Labeling-EP and JP request that this attribute be non-harmonized. USP agrees, and the revised STAGE 4R draft reflects this change. USP will retain this section from the current $N F$ monograph.
4. Packaging and storage-No change.
5. USP Reference standards-No change.
6. Identification-No change.
7. Acidity of alkalinity-No change.
8. Loss on drying - No change.
9. Limit of chloride-No change.
10. Limit of sulfate-No change.
11. Heavy metals-This test will be added as a specific local attribute for JP.
12. Limit of cadmium, Limit of lead, and Limit of nickel-The matrix modifiers were corrected and a statement was added to allow for different modifiers, depending on equipment manufacturers. Clarification was made to the test solution preparations to include milliliters as the measurement volume. JP will not stipulate these attributes.
13. Stearic acid and palmitic acid-No change.
14. Assay-No change.
15. Microbial limits - EP and JP request that this attribute be nonharmonized. USP agrees, and the STAGE 4 draft reflects this change. USP will retain this section from the current $N F$ monograph.
16. Specific surface area-EP requests that this attribute be nonharmonized. USP agrees, and the STAGE 4 draft reflects this change. USP will retain this section from the current $N F$ monograph.
17. Organic volatile impurities-This attribute will be considered a specific local attribute for USP. USP will retain this section from the current $N F$ monograph.
18. Characters-This attribute will be considered a specific local attribute for EP.
(EMC: J. Lane) RTS-40528-1

## Add the following:

## Magnesium Stearate

Octadecanoic acid, magnesium salt.
Magnesium stearate [557-04-0].
» Magnesium Stearate is a compound of magnesium with a mixture of solid organic acids and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. It contains not less than 4.0 percent and not more than 5.0 percent of Mg , calculated on the dried basis.

Packaging and storage-Preserve in tight containers.
USP Reference standards $\langle 11\rangle-U S P$ Palmitic Acid $R S$. USP Stearic Acid RS.

## Identification-

A: Mix 5.0 g with 50 mL of peroxide-free ether, 20 mL of diluted nitric acid, and 20 mL of water in a round-bottom flask. Connect the flask to a reflux condenser and reflux until dissolution is complete. Allow to cool, then transfer the con-
tents of the flask to a separator. Shake, allow the layers to separate, and transfer the aqueous layer to a flask. Extract the ether layer with two $4-\mathrm{mL}$ portions of water, and add these aqueous extracts to the main aqueous extract. Wash the aqueous extract with 15 mL of peroxide-free ether, transfer the aqueous extract to a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Retain this solution for the Limit of chloride and Limit of sulfate tests. A portion of this solution, in the presence of ammonium chloride yields no more than a slightly hazy precipitate when neutralized with ammonium carbonate TS, but on the subsequent addition of dibasic sodium phosphate TS, a white, crystalline precipitate, which is insoluable in 6 N ammonium hydroxide is formed.

B: The retention times of the peaks corresponding to stearic acid and palmitic acid in the chromatogram of the Test solution correspond to those in the chromatogram of the System suitability solution, as obtained in the test for Relative content of stearic acid and palmitic acid.

Acidity or alkalinity-Transfer 1.0 g to a $100-\mathrm{mL}$ beaker, add 20 mL of carbon dioxide-free water, boil on a steam bath for 1 minute with continuous shaking, cool, and filter. Add 0.05 mL of bromothymol blue TS to 10 mL of the filtrate: not more than 0.05 mL of 0.1 N hydrochloric acid or 0.1 N sodium hydroxide is required to change the color of the indicator.

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ to constant weight: it loses not more than $6.0 \%$ of its weight.

Limit of chloride $\langle 221\rangle$ —A $10.0-\mathrm{mL}$ portion of the aqueous solution obtained in Identification test $A$ shows no more chloride than corresponds to 1.4 mL of 0.020 N hydrochloric acid (0.1\%).

Limit of sulfate $\langle 221\rangle$-To a 6.0 mL portion of the aqueous solution obtained in Identification test $A$, add water to make a total volume of 30 to 40 mL , and if necessary, neutralize
the solution with hydrochloric acid to litmus. Add 1 mL of 3 N hydrochloric acid, 3 mL of barium chloride TS, and sufficient water to make 50 mL . Mix and allow to stand for 10 minutes. Compare the turbidity, if any, with that produced in a solution containing 3.0 mL of 0.020 N sulfuric acid (1.0\%).

Limit of cadmium $\langle 231\rangle$ - [NOTE-For the preparation of all aqueous solutions and for the rinsing of glassware before use, employ water that has been passed through a strongacid, strong-base, mixed-bed ion-exchange resin before use. Select all reagents to have as low a content of cadmium, lead, and nickel as practicable, and store all reagent solutions in containers of borosilicate glass. Cleanse glassware before use by soaking in warm 8 N nitric acid for 30 minutes and rinse with deionized water.]
Matrix modifier solution-Prepare a solution in water containing 20 g of monobasic ammonium phosphate and 1 g of magnesium nitrate per 100 mL of solution. Alternatively, use an appropriate matrix modifier as recommended by the manufacturer of the graphite furnace atomic absorption (GFAA) spectrometer.
Standard solution-Transfer 82.5 mg of cadmium nitrate tetrahydrate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in water and dilute with water to volume, and mix. Pipet 1.0 mL of the resulting solution into a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Pipet 1.0 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, add 25 mL of nitric acid, dilute with water to volume, and mix to obtain a solution having a known concentration of $0.0030 \mu \mathrm{~g}$ of Cd per mL .

Test stock solution-Transfer about 100 mg of Magnesium Stearate, accurately weighed, to a suitable polytetrafluoroethylene (PTFE)-lined acid-digestion bomb, and add 2.5 mL of nitric acid. Close and seal the bomb according
to the manufacturer's operating instructions. [Caution: When using an acid-digestion bomb, be thoroughly familiar with the safety and operating instructions. Carefully follow the bomb manufacturer's instructions regarding care and maintenance of these acid-digestion bombs. Do not use metal jacketed bombs or liners that have been used with hydrochloric acid because of contamination from corrosion of the metal jacket by hydrochloric acid.] Heat the bomb in an oven at $170^{\circ}$ for 3 hours. Air cool the bomb slowly to room temperature as per the bomb manufacturer's instructions. Place the bomb in a hood, and open carefully as corrosive gases may be expelled. Dilute the residue with water to 10.0 mL in a volumetric flask.

Reagent blank-Transfer 25 mL nitric acid to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Test solutions-Pipet 1.0 mL of the Test stock solution into a $10-\mathrm{mL}$ volumetric flask, dilute with Reagent blank to volume, and mix. Prepare mixtures of this solution, the Standard solution, and the Reagent blank with the following proportional compositions, by volume (mL): 1.0/0/1.0, 1.0/ $0.5 / 0.5$, and $1.0 / 1.0 / 0$. Add $50 \mu \mathrm{~L}$ of Matrix modifier solution to each mixture, and mix. These Test solutions contain, respectively, $0,0.00075 \mu \mathrm{~g}$ per mL , and $0.0015 \mu \mathrm{~g}$ per mL of cadmium from the Standard solution. [NOTE-Retain the remaining Test stock solution for use in the tests for Limit of lead and Limit of nickel.]

Procedure-Concomitantly determine the absorbances of the Test solutions at the cadmium emission line at 228.8 nm with a suitable GFAA spectrophotometer equipped with a pyrolytic tube with platform and a cadmium hollow-cathode lamp. Use the Reagent blank to set the instrument to zero, and use the temperature programming recommended for Cd
by the GFAA manufacturer. Examples of temperature parameters for GFAA analysis of Cd are shown below:

|  |  |  | Atomiza- <br> tion |
| :--- | :--- | :--- | :--- |
|  | Drying | Ashing | Stage |
|  | Stage | Stage |  |
| Temperature | $110^{\circ}$ | $600^{\circ}$ | $1800^{\circ}$ |
| Ramp Time | 10 seconds | 10 seconds | 0 seconds |
| Hold Time | 20 seconds | 30 seconds | 5 seconds |

Plot the absorbances of the Test solutions versus their contents of cadmium, in $\mu \mathrm{g}$ per mL , as furnished by the Standard solution, draw the straight line best fitting the three points, using a linear least-squares fit, and extrapolate the line until it intercepts the concentration axis on the negative side. From the intercept determine the concentration, $C$, in $\mu \mathrm{g}$ per mL , of cadmium in the Test solution containing 0 mL of the Standard solution. Calculate the content, in ppm, of Cd in the specimen taken by the formula:

$$
200,000(C / W)
$$

in which $W$ is the weight, in mg, of Magnesium Stearate taken to prepare the Test stock solution. Alternatively, the GFAA software can be used to calculate the Cd content of the sample. For either calculation, the correlation coefficient $(r)$ of the standard additions plot must be at least 0.995 , and the limit is 3 ppm .

Limit of lead-[NOTE-For the preparation of all aqueous solutions and for the rinsing of glassware before use, employ water that has been passed through a strong-acid, strong-base, mixed-bed ion-exchange resin before use. Select all reagents to have as low a content of cadmium, lead,
and nickel as practicable, and store all reagent solutions in containers of borosilicate glass. Cleanse glassware before use by soaking in warm 8 N nitric acid for 30 minutes, and rinse with deionized water.]

Matrix modifier solution -Prepare as directed for Matrix modifier solution under Limit of cadmium.

Standard solution-Dissolve 159.8 mg of lead nitrate in 100 mL of water to which 1 mL of nitric acid has been added, then dilute with water to 1000 mL . Prepare and store this solution in glass containers free from soluble lead salts. Transfer 10.0 mL to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a second $100-\mathrm{mL}$ volumetric flask, add 25 mL of nitric acid, dilute with water to volume, and mix. This solution contains $0.100 \mu \mathrm{~g}$ of lead per mL .

Test stock solution-Use a portion of the Test stock solution retained from the test for Limit of cadmium.
Reagent blank-Prepare as directed for Reagent blank under Limit of cadmium.

Test solutions-Prepare mixtures of the Test stock solution, the Standard solution and the Reagent Blank with the following proportional compositions, by volume (mL): $1.0 / 0 / 1.0,1.0 / 0.5 / 0.5$, and $1.0 / 1.0 / 0$. Add $50 \mu \mathrm{~L}$ of the Ma trix modifier solution to each mixture, and mix. These Test solutions contain, respectively, $0,0.025 \mu \mathrm{~g}$ per mL , and 0.05 $\mu \mathrm{g}$ per mL of lead from the Standard solution.
Procedure-Concomitantly determine the absorbances of the Test solutions at the lead emission line at 283.3 nm , with a suitable GFAA spectrophotometer equipped with a pyrolytic tube with platform and a lead hollow-cathode lamp. Use the Reagent blank to set the instrument to zero, and
use the temperature programming recommended for Pb by the GFAA manufacturer. Examples of temperature parameters for GFAA analysis of Pb are shown below:

|  |  |  | Atomiza- |
| :--- | :--- | :--- | :--- |
|  | Drying | Ashing | tion |
| Stage | Stage | Stage |  |
| Temperature | $110^{\circ}$ | $600^{\circ}$ | $1800^{\circ}$ |
| Ramp Time | 10 seconds | 10 seconds | 0 seconds |
| Hold Time | 20 seconds | 30 seconds | 5 seconds |

Plot the absorbances of the Test solutions versus their contents of lead, in $\mu \mathrm{g}$ per mL , as furnished by the Standard solution, draw the straight line best fitting the three points, using a linear least-squares fit, and extrapolate the line until it intercepts the concentration axis on the negative side. From the intercept determine the concentration, $C$, in $\mu \mathrm{g}$ per mL , of lead in the Test solution containing 0 mL of the Standard solution. Calculate the content, in ppm, of Pb in the specimen taken by the formula:

$$
20,000(C / W)
$$

in which $W$ is the weight, in mg, of Magnesium Stearate taken to prepare the Test stock solution. Alternatively, the GFAA software can be used to calculate the Pb content of the sample. For either calculation, the correlation coefficient $(r)$ of the standard additions plot must be at least 0.995 , and the limit is 10 ppm .

Limit of nickel-[NOTE-For the preparation of all aqueous solutions and for the rinsing of glassware before use, employ water that has been passed through a strong-acid, strong-base, mixed-bed ion-exchange resin before use. Select all reagents to have as low a content of cadmium, lead,
and nickel as practicable, and store all reagent solutions in containers of borosilicate glass. Cleanse glassware before use by soaking in warm 8 N nitric acid for 30 minutes, and rinse with deionized water.]

Matrix modifier solution-Prepare as directed for Matrix modifier solution under Limit of cadmium.

Standard solution-Transfer 247.7 mg of nickel nitrate hexahydrate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in water and dilute with water to volume, and mix. Pipet 1.0 mL of the resulting solution into a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Pipet 1.0 mL of this solution into a $10-\mathrm{mL}$ volumetric flask, add 2.5 mL of nitric acid, dilute with water to volume, and mix to obtain a solution having a known concentration of $0.050 \mu \mathrm{~g}$ of Ni per mL .

Test stock solution-Use a portion of the Test stock solution retained from the test for Limit of cadmium.
Reagent blank-Prepare as directed for Reagent blank under Limit of cadmium.

Test solutions-Prepare mixtures of the Test stock solution, the Standard solution and the Reagent Blank with the following proportional compositions, by volume (mL): $1.0 / 0 / 1.0,1.0 / 0.5 / 0.5$, and $1.0 / 1.0 / 0$. Add $50 \mu \mathrm{~L}$ of the Ma trix modifier solution to each mixture, and mix. These Test solutions contain, respectively, $0,0.0125 \mu \mathrm{~g}$ per mL , and $0.25 \mu \mathrm{~g}$ per mL of nickel from the Standard solution.
Procedure-Concomitantly determine the absorbances of the Test solutions at the nickel emission line at 232.0 nm , with a suitable GFAA spectrophotometer equipped with a pyrolytic tube with platform and a lead hollow-cathode lamp. Use the Reagent blank to set the instrument to zero, and use the temperature programming recommended for Ni
by the GFAA manufacturer. Examples of temperature parameters for GFAA analysis of Ni are shown below:

|  | Drying |  |  |
| :--- | :--- | :--- | :--- |
| Stage | Ashing |  |  |
| Stage | Stage |  |  |
| Temperature | $110^{\circ}$ | $600^{\circ}$ | $1800^{\circ}$ |
| Ramp Time | 10 seconds | 10 seconds | 0 seconds |
| Hold Time | 20 seconds | 30 seconds | 5 seconds |

Plot the absorbances of the Test solutions versus their contents of nickel, in $\mu \mathrm{g}$ per mL , as furnished by the Standard solution, draw the straight line best fitting the three points, using a linear least-squares fit, and extrapolate the line until it intercepts the concentration axis on the negative side. From the intercept determine the concentration, $C$, in $g$ per mL , of nickel in the Test solution containing 0 mL of the Standard solution. Calculate the content, in ppm, of Ni in the specimen taken by the formula:

$$
20,000(C / W)
$$

in which $W$ is the weight, in mg , of Magnesium Stearate taken to prepare the Test stock solution. Alternatively, the GFAA software can be used to calculate the Ni content of the sample. For either calculation, the correlation coefficient $(r)$ of the standard additions plot must be at least 0.995 , and the limit is 5 ppm .

## Relative content of stearic acid and palmitic acid-

System suitability solution-Transfer about 50 mg each of USP Stearic Acid RS and USP Palmitic Acid RS to a small conical flask fitted with a suitable reflux condenser. Add 5.0 mL of a solution prepared by dissolving 14 g of boron trifluoride in methanol to make 100 mL , swirl to mix, and reflux for 10 minutes until the solids have dissolved. Add 4 mL of chromatographic $n$-heptane through the condenser,
and reflux for 10 minutes. Cool, add 20 mL of saturated sodium chloride solution, shake, and allow the layers to separate. Pass the $n$-heptane layer through 0.1 g of anhydrous sodium sulfate (previously washed with chromatographic $n$-heptane) into a suitable flask. Transfer 1.0 mL of this solution to a $10-\mathrm{mL}$ volumetric flask, dilute with chromatographic $n$-heptane to volume, and mix.

Test solution-Transfer about 100 mg of Magnesium Stearate, accurately weighed, to a small conical flask fitted with a suitable reflux condenser, and proceed as directed for System suitability solution, beginning with "Add 5.0 mL of solution prepared by dissolving..."

Chromatographic system-(see Chromatography $\langle 621\rangle$ )-The gas chromatograph is equipped with a flameionization detector, maintained at about $260^{\circ}$, a splitless injection system, and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ fused silica capillary column bonded with a $0.5-\mu \mathrm{m}$ layer of phase G16. The column temperature is maintained at $70^{\circ}$ for about 2 minutes after injection, then programmed to increase at the rate of $5^{\circ}$ per minute to $240^{\circ}$, and maintained at this temperature for 5 minutes. The injection port temperature is maintained at about $220^{\circ}$. The carrier gas is helium with a flow rate of about 2.4 mL per minute.
Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.86 for methyl palmitate and 1.0 for methyl stearate; the resolution, $R$, between the methyl palmitate and methyl stearate peaks is not less than 5.0; and the relative standard deviation of the peak area responses for the palmitate and stearate peaks for replicate injections is not greater than $6.0 \%$. The relative standard deviation of the peak area response ratio of the palmitate to stearate peaks from these replicate injections is not more than 1.0\%.

Procedure- Inject about $1 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure the peak area responses for all of the fatty acid ester peaks in the chromatogram. Calculate the percentage of stearic acid in the fatty acid fraction of Magnesium Stearate taken by the formula:

$$
100 A / B
$$

in which $A$ is the area due to the methyl stearate peak, and $B$ is the sum of the areas of all of the fatty acid ester peaks in the chromatogram. Similarly, calculate the percentage of palmitic acid in the portion of Magnesium Stearate taken. The stearate peak comprises not less than $40 \%$, and the sum of the stearate and palmitate peaks is not less than $90 \%$ of the total area of all fatty acid ester peaks in the chromatogram.

## Assay-

Ammonium chloride pH 10 buffer solution-Dissolve 5.4 g of ammonium chloride in water, add 20 mL of ammonium hydroxide, and dilute with water to 100 mL .

Procedure-Transfer about 500 mg of Magnesium Stearate, accurately weighed, to a $250-\mathrm{mL}$ conical flask. Add 50 mL of a mixture of butyl alcohol and dehydrated alcohol (1:1), 5 mL of ammonium hydroxide, 3 mL of Ammonium chloride pH 10 buffer solution, 30.0 mL of 0.1 M edetate disodium VS, and 1 or 2 drops of eriochrome black TS, and mix. Heat at $45^{\circ}$ to $50^{\circ}$ until the solution is clear. Cool, and titrate the excess edetate disodium with 0.1 M zinc sulfate VS until the solution color changes from blue to violet. Perform a blank determination, and make any necessary correction. Each mL of 0.1 M edetate disodium is equivalent to 2.431 mg of Mg .

## PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the Staff Directory to find the contact information).

Briefings Each Preview is preceded by a Briefing in the following format:

## Briefing

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being used, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see How To Use $P F$ ), the name of the scientific staff liaison who handled this item, and the USP tracking correspondence number, as shown in the example below:
(PA5: K. Russo) RTS—55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.
PHARMACOPEIAL PREVIEWS ..... 347
MONOGRAPHS (USP) ..... 349
Pepsin [new] ..... 349
GENERAL INFORMATION CHAPTERS ..... 351
〈1092〉 The Dissolution Procedure: Development and Validation ..... 351

## MONOGRAPHS (USP)

## BRIEFING

Pepsin. Because there is no existing USP monograph for this article, a new monograph is being previewed. The Definition is based in part on the 1965 NF 12 monograph. The Identification test is based on the ability of Pepsin to cleave the chromophore from an insoluble protein-dye complex. The Assay is based on a standard method for the quantitation of pepsin activity. Interested parties are encouraged to submit comments to USP headquaters for consideration by the Expert Committee on Biotechnology and Natural Therapeutics.
(BNT: I. DeVeau) RTS-40249-1

## Add the following:

## Pepsin

» Pepsin is prepared from the gastric mucosa of the domestic hog (Sus scrofa L.); animals used are suitable for human consumption. It contains gastric proteinases active in acid medium ( pH 1 to 5). It has an activity not less than 0.5 USP Pep$\sin$ Units per mg, calculated on the dried basis. One USP Unit of Pepsin activity is the activity that releases the equivalent of $1 \mu$ mole of tyrosine per minute under the conditions of the Assay.

Packaging and storage-Preserve in tight containers, protected from light, and store between $2^{\circ}$ and $8^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Pepsin RS. USP Hemoglobin Protease Substrate RS.

## Identification-

Dilute hydrochloric acid solution-Prepare as directed in the Assay.

Fibrin blue suspension-Suspend 30 mg of fibrin blue in 20 mL of Dilute hydrochloric acid solution. Shake before use.

Test solution-Dissolve a sufficient quantity of Pepsin, accurately weighed, in Dilute hydrochloric acid solution, to obtain a solution containing 10 USP Pepsin Units per mL . Adjust to $\mathrm{pH} 1.6 \pm 0.1$, if necessary.

Procedure-Add 1 mL of Test solution to 4 mL of the Fi brin blue suspension, mix and place in a water bath at $25^{\circ}$ with gentle shaking. Prepare a blank solution at the same time and in the same manner using 1 mL of water instead of the Test solution. Filter the suspensions after 15 minutes of incubation: the filtrate of the blank is colorless and the filtrate of the Test solution is blue.

Microbial limits $\langle 61\rangle$-Total viable aerobic count not more than 1000 CFU per g, the total combined molds and yeast count not more than 100 CFU per g , and it meets the requirements of the tests for absence of Escherichia coli and Salmonella species.

Loss on drying $\langle 731\rangle$-Dry at $60^{\circ}$ at 5 mm of mercury over phosphorus pentoxide for 4 hours: it loses not more than $5.0 \%$ of its weight.

## Assay-

Dilute hydrochloric acid solution-Dilute 30 mL of 1.0 M hydrochloric acid with water to 1000 mL , and adjust to a pH of $1.6 \pm 0.1$.

Hemoglobin solution-Dissolve 2 g of USP Hemoglobin Protease Substrate RS, accurately weighed, in 75 mL of Di lute hydrochloric acid solution. Adjust to a pH of $1.6 \pm 0.1$, bring to 100 mL with Dilute hydrochloric acid solution and dissolve 25 mg of thimerosal.
$4 \%$ Trichloroacetic acid solution-Prepare a $4.0 \%(\mathrm{w} / \mathrm{v})$ solution in water.

5\% Trichloroacetic acid solution-Prepare a $5.0 \%$ (w/v)
solution in water.

Sodium hydroxide solution-Prepare a solution containing $20 \%$ (w/v) sodium hydroxide.

TCA-washed filters-Wash a sufficient quantity of suitable, individual filters with $5 \%$ Trichloroacetic acid solution. Determine the suitability of the filter by washing with an additional 5 mL of $5 \%$ Trichloroacetic acid solution and collecting the filtrate. The UV absorbance of the filtrate, measured at 275 nm using unfiltered 5\% Trichloroacetic acid solution as the blank, is less than 0.04 . Rinse the filters with water, and air dry.

Standard preparation-Dissolve a sufficient quantity of USP Pepsin RS, accurately weighed, in Dilute hydrochloric acid solution to obtain a solution containing 0.5 USP Pepsin Units per mL . Before dilution to final volume, adjust to a pH of $1.6 \pm 0.1$, if necessary, using 1 M hydrochloric acid. [NOTE--Prepare not more than 15 minutes before use.]

Assay preparation-Dissolve a sufficient quantity of Pepsin, accurately weighed, in Dilute hydrochloric acid solution to obtain a solution containing 0.5 USP Pepsin Units per mL . Before dilution to final volume, adjust to a pH of $1.6 \pm 0.1$, if necessary, using 1 M hydrochloric acid. [NOTES-Use immediately. Avoid shaking and foaming during preparation of the Standard and Assay preparations.]

Procedure-Designate test tubes in duplicate $T, T_{\mathrm{b}}, S_{1}$, $S_{1 \mathrm{~b}}, S_{2}, S_{2 \mathrm{~b}}, S_{3}$, and $S_{3 \mathrm{~b}}$. Prepare a single blank test tube. Add 0.25 mL of Dilute hydrochloric acid solution to tubes $S_{2}, S_{2 \mathrm{~b}}, T$, and $T_{\mathrm{b}}$; add 0.5 mL of Dilute hydrochloric acid solution to tubes $S_{1}$ and $S_{1 \mathrm{~b}}$. Add 1.0 mL of Dilute hydrochloric acid solution to the blank test tube. To tubes $S_{1}$ and $S_{1 \mathrm{~b}}, S_{2}$ and $S_{2 \mathrm{~b}}$, and $S_{3}$ and $S_{3 \mathrm{~b}}$ add $0.5 \mathrm{~mL}, 0.75 \mathrm{~mL}$, and 1.0 mL , respectively, of the Standard preparation. Add 0.75 mL of the Assay preparation to tubes $T$ and $T_{\mathrm{b}}$. Add 10.0 mL of $4 \%$ Trichloroacetic acid solution to tubes $S_{1 \mathrm{~b}}, S_{2 \mathrm{~b}}, S_{3 \mathrm{~b}}, T_{\mathrm{b}}$, and the blank and mix by shaking. Heat the tubes and Hemoglobin solution in a $25^{\circ} \pm 0.1^{\circ}$ water bath
until temperature equilibrium. Mix 5.0 mL of Hemoglobin solution to the blank tube and tubes $S_{\mathrm{lb}}, S_{2 \mathrm{~b}}, S_{3 \mathrm{~b}}$, and $T_{\mathrm{b}}$. Add 5.0 mL of Hemoglobin solution successively and at intervals of 30 seconds to tubes $S_{1}, S_{2}, S_{3}$, and $T$. Mix immediately after each addition. Exactly 10 minutes after adding the Hemoglobin solution, stop the reaction by quickly mixing, at intervals of 30 seconds, 10.0 mL of $4 \%$ Trichloroacetic acid solution to tubes $S_{1}, S_{2}, S_{3}$, and $T$. Wait about 15 minutes and filter the contents of each tube twice through individual $T C A$-washed filters, discarding the first 5 mL . Place 3.0 mL of each filtrate into individual tubes and mix 20 mL of water. Add to each tube 1.0 mL of Sodium hydroxide solution and 1.0 mL of Folin-Ciocalteu phenol TS. After 15 minutes, and using the blank, measure the absorbance of solutions $S_{1}, S_{2}, S_{3}, S_{1 \mathrm{~b}}, S_{2 \mathrm{~b}}, S_{3 \mathrm{~b}}$, and $T$ at 540 nm . Correct the average absorbance values for the filtrates obtained from tubes $S_{1}, S_{2}$ and $S_{3}$ by subtracting the average values obtained for the filtrates from tubes $S_{1 \mathrm{~b}}, S_{2 \mathrm{~b}}$, and $S_{3 \mathrm{~b}}$, respectively. Calculate a calibration curve of the corrected absorbance values against volume of Standard preparation used. Determine the activity of Pepsin using the corrected absorbance for the Assay preparation together with the calibration curve and taking into account dilution factors.

## 〈11〉 USP Reference Standards

## Add the following:

USP Hemoglobin Protease Substrate RS. [To come.]

## Add the following:

USP Pepsin RS. [To come.]

## Description and Solubility

## Add the following:

Pepsin: A white or slightly yellow, crystalline or amorphous powder, hygroscopic. Soluble in water; practically insoluble in alcohol. The solution in water ( 1 in 50 ) is slightly acidic.

## GENERAL CHAPTERS

## General Information

## BRIEFING

<1092 $\rangle$ The Dissolution Procedure: Development and Validation. This new general information chapter previewed here is intended to address several issues. Aspects of method development are mentioned only superficially in the current general information chapter In Vitro and In Vivo Evaluation of Dosage Forms $\langle 1088\rangle$. This previewed chapter goes into greater detail and gives guidance to the analyst on developing meaningful dissolution methods. Similarly, the general information chapter Validation of Compendial Methods $\langle 1225\rangle$ only touches on the special considerations for validation of dissolution testing, whereas this previewed new chapter provides a typical detailed step-by-step approach for designing and validating a dissolution test. Lastly, the previewed chapter gives guidance to the analyst on validation and the use of new technologies and equipment in dissolution testing. This new informational chapter is loosely based on a stimuli article, "A New General Information Chapter on Dissolution" by Gray VA, Brown CK, Dressman JB, and Leeson LJ that appeared in PF 27(6) [Nov.Dec. 2001]. This article was revised on the basis of comments from industry, the FDA and other regulatory bodies, and the USP Expert Council and its Committees. Readers are encouraged to send their comments concerning the format and the contents of this previewed information chapter to William Brown.
(BPC: W. Brown) RTS—39647-1; 40232-2; 40485-1; 40486-1

## Add the following:

## 〈1092〉 THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION

The USP performance test is one test in a series of tests that form the dosage form's public specification (tests, procedures for the tests, acceptance criteria). To satisfy the performance test, USP provides three general test chapters Disintegration $\langle 701\rangle$, Dissolution $\langle 711\rangle$, and Drug Release $\langle 724\rangle$. These general chapters specify the conditions of the procedure. For dissolution, these include standards that specify the apparatus/agitation rate, medium, study design,
assay, and acceptance criteria. Overall the procedure yields data to allow an accept/reject decision relative to the acceptance criteria. Acceptance criteria are frequently based on a regulatory decision. This general information chapter provides recommendations on how to develop and validate a dissolution procedure.

## GENERAL COMMENTS

The dissolution procedure relies on an apparatus, a medium, and a study design chosen to be transferable and rugged and to yield acceptable data. A discriminating procedure yields data that distinguishes important differences in components and composition and/or method of manufacture between dosage forms. The value of dissolution as a quality control tool for predicting in vivo performance of a drug product is significantly enhanced if an in vitro-in vivo relationship (correlation or association) is established; but this relationship is not required (see FDA Guidances). Occasionally the in vitro dissolution test is found to be more sensitive and discriminating than the in vivo test. From a quality assurance point of view, a more discriminating dissolution method is preferred because the test will indicate possible changes in the quality of the product before in vivo performance is affected.

The discriminatory power of the dissolution method depends on the method's ability to detect changes in the drug product. Ideally, the dissolution test conditions would show discrimination for product changes that may affect biopharmaceutical product performance. However, unless an in vi-tro-in vivo correlation exists for the product, variations in dissolution behavior may or may not reflect variations in the product's in vivo performance. To determine if a dissolution method can show discrimination for product changes, the method should be challenged. There are several ways to challenge the discriminatory power of the method, but the
most common approach is to test formulations manufactured with different parameters. Manufacturing variables can come from many sources, e.g., the drug substance, the drug product's formulation, and/or the drug product's manufacturing process. For example, the ability of the method to detect changes in the drug substance can be evaluated by testing products with drug substances having different particle sizes, crystal habits, solvation, surface areas, or synthetic pathways. The method sensitivity to drug product formulation changes can be challenged by testing products with different amounts or ratios of excipients or by testing formulation changes, such as wet granulation versus dry blend, or intra- versus extra-granulation. The method sensitivity to manufacturing process variables such as lubrication blend time, compression force, addition order, drying methods, coating methods, and equipment capability or size can also be evaluated. As different formulations are made using some of the variables just mentioned; the dissolution data are examined. If the data show a measurable difference for the key variables, then the method may be considered a discriminating test for critical manufacturing variables.

With regard to stability, the dissolution test should appropriately reflect relevant changes in the biopharmaceutical performance caused by temperature, aging, humidity, and photosensitivity. A properly designed dissolution test does not generate highly variable dissolution results nor is it associated with significant analytical solution stability problems. If these issues arise, the dissolution test design should be evaluated and appropriately revised.

## APPARATUS/AGITATION

## Apparatus

The choice of apparatus is based on knowledge of the formulation design and on practical aspects of dosage form performance in the in vitro test system. Apparatus 1 or Ap-
paratus 2 (basket and paddle method, respectively, see Dissolution $\langle 711\rangle$ ) is often suitable, and an increase in the rotation frequency is sometimes advantageous, e.g., paddle at 75 rpm to 100 rpm . Apparatus 3 (reciprocating cylinder, see Drug Release $\langle 724\rangle$ ) has been found to be especially useful for bead-type modified-release dosage forms. Apparatus 4 (flow cell, see Drug Release $\langle 724\rangle$ ) may offer advantages for modified-release dosage forms that contain active ingredients with limited solubility. Apparatus 3 or Apparatus 4 may additionally have utility for soft gelatin capsules, bead products, suppositories, or poorly soluble drugs. Apparatus 5 (paddle over disk, see Drug Release $\langle 724\rangle$ ) and $A p$ paratus 6 (rotating cylinder, see Drug Release $\langle 724\rangle$ ) have been shown to be useful for evaluating and testing transdermal dosage forms. Apparatus 7 (reciprocating disk, see Drug Release $\langle 724\rangle$ ) has been shown to be suitable for nondisintegrating oral modified-release dosage forms and transdermal dosage forms.

Some changes that can be made to the apparatus, when necessary, are as follows:
Basket Mesh Size-A 40-mesh basket screen is used in most cases; however, other mesh sizes ( 10 and 20 mesh) may be used when the need is clearly documented by supporting data. In countries where available mesh sizes vary from the USP specified mesh value, basket material with the nearest metric dimension should be used. Care must be taken that baskets are uniform and meet the dimensions requirements specified under Dissolution $\langle 711\rangle$. If the basket screens become clogged during dissolution of capsule or tablet formulations, it may be advisable to switch to the paddle method.

Minipaddles-A minipaddle in combination with a 200mL vessel may be considered for low-dosage products.

Two- or Four-Liter Vessels-The increased volume made possible by using these vessels can assist in meeting sink conditions for poorly soluble drugs.

Other Apparatus-The rotating bottle or static tubes (jacketed stationary tubes enclosed with a water jacket and equipped with a magnetic stirrer) may also have utility for microspheres and implants.

The aforementioned minipaddle/basket, $200-\mathrm{mL}$ vessel, and rotating bottle are not official apparatus and may only be used in extraordinary conditions accompanied by documentation that they are superior to the standard equipment. There are also noncompendial flow-through cells that are modified for special dosage forms. These cells would also need to be justified.

## Sinkers <br> Detailed sinker descriptions and an explanation of why a

 sinker is used must be stated in the written procedure. When comparing different sinkers-or sinkers versus no sinker-a test should be run concurrently with each sinker. Each sinker type may be evaluated based on its ability to maintain the dosage at the bottom of the vessel without inhibiting drug release.Sinkers can significantly influence the dissolution profile of a drug. The use of sinkers, therefore, may be part of a case-by-case dissolution validation. The sinker design should be stated clearly in the method. When transferring the method, the sinkers should be duplicated as closely as possible in the next facility.

The use of sinkers may be required when using Apparatus 2. For tablets and capsules, sinkers can be used when the formulation floats-typically observed at the very beginning of a run-or to help center a dosage form under the paddle. For example, a sinker may also be useful for film-
coated tablets or soft gelatin capsules that stick to the vessel walls. As a guide, the following is a suggested procedure for making sinkers by hand.

Materials: 316 stainless steel wire, 0.032 inch/20 gauge; one set of cork borers \#1 to \#15.

| Capsule <br> Shell | Cork Bore | Length of Wire in inches (cm) | Diameter <br> Size <br> in inches <br> (cm) |
| :---: | :---: | :---: | :---: |
|  |  |  |  |
| 0 , elongated | \#4 | 4.72 (12) | 0.313 (0.8) |
| 1 and 2 | \#3 | 3.94 (10) | 0.275 (0.7) |
| 3 and 4 | \#2 | 3.15 (8) | 0.215 (0.55) |

Procedure-Cut the specified length of coil length wire around the specified bore of the appropriate size, and use small pliers to curve in the ends. In countries where normal values for wire diameters vary from the tabulated values, use wire with the nearest metric dimension.

There are commercially available sinkers that, if properly validated, may be used. The type of sinker should always be clearly defined in the procedure or test method. If the sinker is handmade, the sinker construction procedure instructions should be documented. If a commercial sinker is used, the vendor specifications should be defined.

## Agitation

For immediate-release products, the basket method (Apparatus 1 ) is routinely used for capsule or tablet formulations at an agitation speed of 50 to 100 rpm , although speeds up to 150 rpm have been used in USP monograph dissolution tests. The paddle method (Apparatus 2) is frequently used for tablet and capsule dosage forms at 50 or 75 rpm . Other agitation speeds and apparatus are acceptable
with justification. Documentation would include the data from the normally accepted apparatus and/or agitation speeds to illustrate that a variation is needed.

Selection of the agitation and other study design elements for modified-release dosage forms is similar to that for im-mediate-release products. When the apparatus has been appropriately calibrated, these elements should conform to the requirements and specifications given under Drug Release〈724〉.
Rates outside of 25 to 150 rpm are usually unacceptable because of inconsistency of the hydrodynamics below 25 rpm and of the turbulence above 150 rpm . Agitation rates between 25 rpm and 50 rpm are generally acceptable for suspensions. For dosage forms that exhibit coning (mounding) under the paddle at 50 rpm , the coning can be reduced by increasing paddle speed to 75 rpm , thus reducing the artifact and improving the data. If justified, 100 rpm may be used, especially for extended-release products. Decreasing or increasing the apparatus rotation speed may be justified if the profiles better reflect in vivo performance and/or the method results in better discrimination.

## MEDIUM

Physical and chemical data for the drug substance and dosage unit should be determined before selecting the dissolution medium. Two key properties of the drug are the solubility and solution state stability of the drug as a function of the pH value. When adjusting the composition of the medium to generate sink conditions, the influence of surfactants, pH value, and buffers on the solubility and stability of the drug should be evaluated. Key properties of the dosage unit that may affect the dissolution, enteric-coating, modified-release mechanism, and disintegration rate are hardness, friability, presence of solubility enhancers, and the presence of other excipients.

Selection of the dissolution medium is based, in part, on the solubility data and the dose range in order to ensure that sink conditions are met. The term sink conditions is defined as the volume of medium at least greater than three times that required to form a saturated solution of drug substance. A medium that fails to provide sink conditions may be justifiable if it is shown to be more discriminating or if it provides reliable data that otherwise can only be obtained with the addition of surfactants.

Using an aqueous-organic solvent mixture as a dissolution medium is discouraged; however, if an in vitro-in vivo relationship is demonstrated that cannot be accomplished with a pure aqueous medium, this type of medium may be acceptable.
Purified water is often used as the dissolution medium but is not ideal for several reasons: the quality of water can vary depending on the source of water; the pH value is inherently difficult to measure because the pH value can vary from day to day and may also change during the run depending on the active substance and excipients; and finally, the surface tension may also be variable and dependent on the excipients in the formulation. Despite these limitations, water is inexpensive, readily available, disposed of easily, ecologically acceptable, and suitable for products with a release rate independent of the pH value of the medium. Further, if water is named as the medium in an official test, it is not necessary to change to another medium unless there is a compelling reason.

The dissolution characteristics of an oral formulation are evaluated over the physiologic pH range of 1.2 to 6.8 (1.2 to 7.5 for modified-release formulations). During method development, it may be useful to measure the pH before and after a run to see if the pH changes during the test. Selection of the most appropriate conditions for routine testing is then
based on discriminatory capability, ruggedness, stability of the analyte in the test medium, and, where possible, relevance to in vivo performance.

Listed below are typical media for a dissolution test. Buffers and acids are prepared as directed for Buffer Solutions and Volumetric Solutions, respectively, under Reagents, Indicators, and Solutions. Simulated gastric fluid and simulated intestinal fluid are prepared as directed for Test Solutions under Reagents, Indicators, and Solutions. The following list is not exhaustive and not in order of preference:

Hydrochloric acid (typically between 0.1 and 0.001 N )
Acetate buffer (with a pH between 4.1 and $5.5 ; 0.05 \mathrm{M}$ ) Phosphate buffer (with a pH between 5.8 and 8.0; 0.05 M )

Purified water
Polysorbate 20, polysorbate 40, polysorbate 60, and polysorbate 80 solutions

Sodium lauryl sulfate solutions
Lauryldimethylamine oxide solutions
Cetrimide solutions
Bile salts solutions and/or lecithin
Combinations of surfactant and acids or buffers
Simulated gastric fluid with or without enzyme
Simulated intestinal fluid with or without enzyme
For very poorly soluble compounds, aqueous solutions may contain a percentage of a surfactant (e.g., sodium lauryl sulfate, polysorbate, or lauryldimethylamine oxide) that is used to enhance drug solubility. The need for surfactants and the concentrations used could be justified by showing profiles at several different concentrations. Surfactants can be used as either a wetting agent or, when the critical micelle
concentration is reached, to solubilize the drug substance. The molarity of the buffers and acids used can influence the solubilizing effect, and this should be evaluated.

The Biopharmaceutics Classification System describes the classification of compounds according to solubility and permeability. "Biorelevant medium" is a term used to describe a medium that has some relevance to the in vivo dissolution conditions for the compound. Choice of a biorelevant medium is based on a mechanistic approach that considers the absorption site, if known, and whether the rate-limiting step to absorption is the dissolution or permeability of the compound. In some cases, the biorelevant medium will be different from the test conditions chosen for the regulatory test, and the time points are also likely to be different. If the compound dissolves quickly in the stomach and is highly permeable, gastric emptying time may be the rate-limiting step to absorption. In this case, the dissolution test is to demonstrate that the drug is released quickly under typical gastric (acidic) conditions. On the other hand, if dissolution occurs primarily in the intestinal tract (e.g., for a poorly soluble, weak acid), a higher pH range (e.g., simulated intestinal fluid with a pH of 6.8 ) will be more appropriate. The "fed" and "fasted state" may also have significant effects on the absorption or solubility of a compound. Compositions of media that simulate the fed and fasted states can be found in the literature. These media reflect changes in the pH , bile concentrations, and osmolarity after meal intake, and, therefore, have a different composition than that of typical compendial media. They are primarily used to establish in vitro-in vivo correlations during formulation development and to assess potential food effects,but are not intended for quality control purposes. For

[^30]quality control purposes, the substitution of natural surfactants (bile components) with appropriate synthetic surfactants is permitted and encouraged because of the expense of the natural substances and the labor-intensive preparation of the biorelevant media.

The use of an enzyme in the dissolution medium is permitted (see Dissolution $\langle 711\rangle$ ) when dissolution failures occur due to pellicle formation with gelatin capsules or gelatin-coated products.

Normally for the basket and paddle apparatus, the volume of the dissolution medium is 500 mL to 1000 mL , with 900 mL as the most common volume. The volume can be raised to between 2 and 4 liters, depending on the concentration and sink conditions of the drug, but proper justification is expected.

The significance of deaeration of the medium may be determined: air bubbles can interfere with the test results, acting as a barrier to dissolution if present on the dosage unit or basket mesh; also, bubbles can cause particles to cling to the apparatus and vessel walls. On the other hand, bubbles on the dosage unit may increase the buoyancy and lead to an increase in the dissolution rate, or, decrease the dissolution rate by decreasing the available surface area. A deaeration method is described as a footnote in Dissolution $\langle 711\rangle$. Typical steps are to heat the medium, filter, and draw a vacuum for a short period of time. Other validated methods of deaeration are available and in routine use throughout the industry. Media containing surfactants are not usually deaerated because of excessive foaming. To determine if deaeration of the medium is necessary, dissolution run in nondeaerated medium versus deaerated medium should be performed.

## STUDY DESIGN

## Time Points

For immediate-release dosage forms, the duration of the procedure is typically 30 to 60 minutes, with a single time point specification that is adequate in most cases for Pharmacopeial purposes. Industrial and regulatory concepts of product comparability and performance may require additional time points, and this may also be a feature required for product registration or approval. Enough time points are to be selected to adequately characterize the ascending and plateau phases of the dissolution curve. According to the Biopharmaceutics Classification System referred to in several FDA guidances, highly soluble, highly permeable drugs formulated with rapidly dissolving products need not be subjected to a profile comparison if they can be shown to release $85 \%$ or more of the active drug substance within 15 minutes. For these types of products a one-point test will suffice. However, most products do not fall into this category. Dissolution profiles of immediate-release products not meeting the highly soluble/highly permeable/rapidly dissolving criteria typically show a gradual increase reaching between $85 \%$ and $100 \%$ at around 30 to 45 minutes. Thus, dissolution time points in the range from 15 (or 20), 30,45 , and 60 minutes are usual for most immediate-release product. Useful information may be obtained from other points, e.g., if dissolution is very rapid, 5 to 10 minutes to obtain more data or for slower-dissolving drugs, additional points after 60 minutes. Dissolution test times for compendial tests are usually then established on the basis of an evaluation of the dissolution profile data.
So-called infinity points can be useful during development studies. To obtain an infinity point, the paddle or basket speed is increased at the end of the run to at least 150 rpm for 30 to 60 minutes, after which time an additional sample is taken. Although there is no requirement for
$100 \%$ dissolution in the profile, the infinity point can provide data that may supplement content uniformity data and may provide useful information about the formulation characteristics during the initial development.

For an extended-release dosage form, at least three test time points are chosen to characterize the in vitro drug release profile for Pharmacopeial purposes. Additional sampling times may be required for drug approval purposes. An early time point, usually 1 to 2 hours, is chosen to show that there is little probability of dose dumping. An intermediate time point is chosen to define the in vitro release profile of the dosage form, and a final time point is chosen to show essentially complete release of the drug. Test times and specifications are usually established on the basis of an evaluation of drug release profile data. For products containing more than a single active ingredient, drug release is determined for each active ingredient. Extended-release specifications are addressed in the general information chapter In Vitro and In Vivo Evaluation of Dosage Forms 〈1088〉 as well as other sources. ${ }^{2}$

## Observations

Visual observations and recordings of the product dissolution and disintegration behavior are very useful because dissolution and disintegration patterns can be indicative of formulation or manufacturing process variables. To accomplish visual observation, proper lighting (with appropriate consideration of photodegradation) of the vessel contents and clear visibility in the bath is essential. Documenting observations by drawing sketches and taking photographs or videos is very instructive and helpful for those who are not able to observe the real time dissolution test. Observa-
tions are especially useful during method development and formulation optimization. Examples of typical observations include, but are not limited to, the following:

1. Uneven distribution of particles throughout the vessel, which could occur if particles cling to the sides of the vessels, if there is coning or mounding directly under the apparatus, if particles float at the surface of the medium, if film-coated tablets stick to the vessel, and/or if off-center mounds are formed;
2. Air bubbles on the inside of the vessel or on the apparatus or dosage unit. Sheen on the apparatus is also a sign of air bubbles. This observation would typically be made when assessing the need to deaerate the medium;
3. Dancing or spinning of the dosage unit, or the dosage unit being hit by the paddle;
4. Adhesion of particles to the paddle or inside of the basket, which may be observed upon removal of the stirring device at the end of the run;
5. Pellicles or analogous formations, such as a transparent sacs that are rubbery, swollen masses surrounding the capsule contents;
6. Presence of large floating particles or chunks of the dosage unit;
7. Observation of the disintegration rate (e.g., percent reduction in size of the dosage unit within a certain time frame);
8. For modified or enteric-coated products, complex disintegration of the coating, e.g., the partial opening and splitting apart (like a clamshell) or incomplete opening of the shell accompanied by the release of air bubbles and excipients.
[^31]
## Sampling

The disturbance of hydrodynamics of the vessel by sampling probes should be considered and adequate validation performed to ensure that the probes are not introducing a significant change in the dissolution rate.
Manual-Manual sampling uses plastic or glass syringes, a stainless steel cannula that is usually curved to allow for vessel sampling, a filter, and/or a filter holder. The sampling site must conform to specifications under Dissolution $\langle 711\rangle$.

Autosampling-Autosampling is a useful alternative to manual sampling, especially if the test includes several time points. However, since regulatory labs may perform the dissolution test using manual sampling, autosampling requires validation with manual sampling.

There are many brands of autosamplers, including semiand fully-automated systems. Routine performance checks, cleaning, and maintenance as described in the pertinent standard operating procedures or metrology documents are useful for reliable operation of these devices.

Some instruments are equipped with sampling through the basket or paddle shaft. Proper validation (e.g., demonstrated equivalence to results with the usual sampling procedure) may be required.

Manual versus automated validation can be done either one of two ways. When the drug dissolution results are not highly variable, two concurrent runs (same sampling intervals, $n=6$ ) using manual and automated sampling methods are compared using the criteria under Intermediate Precision. If the dissolution results are highly variable (i.e., the RSD is above $20 \%$ in time points at 10 minutes or earlier, and at or above $10 \%$ RSD in later time points), the analysis may be performed by pulling the sample from the vessel simultaneously by manual and automated sam-
pling methods for each time point. Note that the correction for the volume withdrawn from the medium is doubled in this case.

If the results are not acceptable for the manual sampling, a discard step may be required or the discard volume may be increased. For the autosampler, a longer priming time may be needed if unacceptable results are obtained. If these changes do not work, then a change to another filter type may be needed.

Other aspects of automated validation may include the carryover of residual drug, the effect of an in-residence probe (simultaneous sampling as mentioned above may not be suitable in this case), adsorption of drug, and cleaning and/or rinse cycles.

## Filters

Filtration of the dissolution samples is usually necessary to prevent undissolved drug particles from entering the analytical sample and further dissolving. Also, filtration removes insoluble excipients that may otherwise cause high background or turbidity. Prewetting of the filter with the medium is usually necessary.

Filters can be in-line or at the end of the sampling probe, or both. The pore size can range from $0.45 \mu \mathrm{~m}$ to $70 \mu \mathrm{~m}$. The usual types are depth, disk, or flow-through filters. However, if the excipient interference is high, if the filtrate has a cloudy appearance, or if the filter becomes clogged, an alternative type of filter or pore size should be evaluated.

Adsorption of the drug(s) onto the filter is also evaluated. If drug absorption occurs, it may be necessary to increase the amount of initial filtrate discarded. If results are still unsuitable, an alternative filter material may be sought.
Filter validation may be accomplished by preparing a $100 \%$ standard solution and a completely dissolved sample solution (e.g., prepared as a typical sample in a vessel or a
sample put in a beaker and stirred with a magnetic stirrer for 1 hour). The solutions are sampled ( $\mathrm{n}=3$ ) by both the selected autosampler and the manual technique. Both sampling techniques may use the same or equivalent type of filter. The autosampler is programmed for a typical sample pull, and the manual method withdraws an aliquot from the solutions. The standard solution results are compared to an unfiltered standard. The analyst may compare the sample solution results to the same sample solution unfiltered and centrifuged. For the filter to be acceptable for use, the results of the filtered portions are to approach (within $98 \%$ to $102 \%$ ) the original concentration of the unfiltered standard solution and the centrifuged sample solution.

## Centrifugation

Centrifugation of samples is not preferred, as dissolution can continue to occur, and there may be a concentration gradient in the supernatant. A possible exception might be compounds that adsorb to all common filters.


#### Abstract

\section*{ASSAY}

The usual assay for a dissolution sample is either by spectrophotometry or high-pressure liquid chromatography (HPLC). The preferred method of analysis is spectrophotometry because results can be obtained faster, the analysis is simpler, and fewer solvents are used. HPLC methods are used when there is significant interference from excipients or among drugs in the formulation and/or to improve analytical sensitivity. It may be useful to have data for the drug obtained with a stability-indicating assay (e.g., HPLC chromatograms) in the medium of choice, even if the primary assay is based on a spectrophotometric method.

The validation topics described in this section are typical but not all-inclusive. The acceptance criteria are guidelines only and may differ for some products. Other considerations


may be important for special dosage forms. The extent of validation depends on the phase of the product development. Full validation takes place at or just before Phase III clinical studies. For profile testing, validation studies may be necessary at each relevant time point. For products containing more than a single active ingredient, the dissolution method should be validated for each active ingredient.

## Specificity/Placebo Interference

The placebo consists of all the excipients and coatings (inks, sinker, and, when appropriate, the capsule shell) without the active ingredient. Placebo interference may be determined by weighing three samples each of the placebo blend, equal to or greater than the highest and lowest strength. Transfer the samples to separate vessels filled with dissolution medium at $37^{\circ}$. Stir for around 30 minutes to 1 hour at 150 rpm using the method apparatus. Observe whether the blend becomes wetted. Analyze and calculate the percent interference at each strength $(\mathrm{n}=3)$ by comparing it to the $100 \%$ standard of that strength (or optionally using the selected $Q$ value) by the formula:

$$
100 C\left(A_{P} / A_{S}\right)(V / L)
$$

in which $C$ is the concentration, in mg per mL , of the standard; $A_{P}$ and $A_{S}$ are the absorbances of the placebo and the standard, respectively; $V$ is the volume, in mL , of the medium; and $L$ is the label claim, in mg. The mean is determined, and the interference does not exceed $2 \%$.
NOTE-For extended-release products, a placebo version of the finished dosage form may be more appropriate to use than blends because this placebo formulation will release the various excipients in a manner more nearly reflecting the product than a simple blend of the excipients. The placebo formulation is necessary particularly if one of the released excipients does influence the baseline of the analytical method. For extended-release products, the interfer-
ence must be determined at each sampling point in the release profile. If the placebo interference exceeds $2 \%$, then HPLC analysis is needed; alternatively, another wavelength, algorithm analysis, or a baseline subtraction (correction factor) may be feasible.

## Spectrophotometric Analysis

Analyses may be performed with spectrophotometers that have diode array or variable wavelength detectors. Samples may be automatically introduced into the spectrophotometer using autosippers and flow cells. Routine performance checks, cleaning, and maintenance as described in the standard operating procedures or metrology documents are useful for reliable operation of these instruments. Flow cells ranging from 0.02 to 1 cm are typically used. Cell alignment and air bubbles could be sources of error. The smaller path length flow cells are used to avoid diluting the sample; however, acceptable linearity and standard error should be demonstrated.

During analysis, standard solutions are typically prepared and analyzed at just one concentration at $100 \%$ of the dosage strength (or the selected $Q$ value). During profile analysis, other concentrations may be useful. The recorded standards are aliquots from the same standard solution. A typical blank, standard, and sample may be analyzed in a sequence that brackets the sample with standards and blanks, especially at the beginning and end of the analysis. In most cases, the mean absorbance of the dissolution medium blank may not exceed $1 \%$ of the standard. Values higher than $1 \%$ must be evaluated on a case-by-case basis. The typical relative standard deviation (RSD) for UV analysis is usually $\leq 2 \%$.

The absorptivity is calculated by dividing the mean standard absorbance by the concentration, in mg per mL, divided by the flow-cell path length in cm . After enough
historical data is accumulated, an acceptable absorptivity range for the analyte (using the appropriate flow cell) may be determined. This value may be useful in troubleshooting aberrant data. Fiber optics as a sampling and determinative method, with proper validation, is an option.

Examine the UV spectrum of the drug in solution to select the wavelength for maximum absorbency. In some cases, there may be other wavelengths chosen, as with measuring degradants along with the intact drug substance.

## HPLC

For HPLC analysis, the compatibility of dissolution media and mobile phase may be examined, especially if large injector volumes (over $100 \mu \mathrm{~L}$ ) are needed. Samples are normally analyzed with HPLC using a spectrophotometric detector and an auto-injector. Single injections of each vessel time point with standards throughout the run constitute a typical run design. System suitability tests include, at a minimum, the retention time window and precision. Typically, the system suitability of an HPLC analysis is less than or equal to $2 \%$ RSD for five or six standard determinations. The standard level is typically at the $100 \%$ label claim level, especially for a single-point analysis.
Preparation of the placebo samples for the HPLC analysis is performed in the same way as the spectrophotometric analysis. Look for peaks eluting at the same retention time as the drug. If there are extraneous peaks, inject the standard solution, and compare retention times. If the retention times are too close, spike the placebo solution with the drug. Chromatograms may also be obtained over an extended run time using the blank (dissolution medium), standard, and sample solution to identify late eluters that may interfere with subsequent analyses.

If possible, the validation documentation may include overlaid representative chromatograms or spectra of blank dissolution medium, a filtered placebo solution, a standard solution, and a filtered dissolution sample. Absence of interfering peaks in the placebo chromatogram or lack of absorbance by the placebo at the analytical wavelength demonstrates specificity.

## Linearity and Range

Organic solvents may be used to enhance drug solubility for the preparation of the standard solutions; however, no more than $5 \%(\mathrm{v} / \mathrm{v})$ of organic solvent in the final solution should be used, unless validated.

Linearity and range are typically established by preparing five standard solutions of the drug, ranging in concentration from approximately $\pm 20 \%$ below the lowest expected concentration to $\pm 20 \%$ above the highest concentration during release from the specific dosage unit strength. As further dosage strengths are added, the same testing scheme applies, unless some concentrations have already been tested. For spectrophotometric analysis, this scheme may be altered if different flow-cell sizes are used.

All solutions are made from a common stock if possible. The diluted solutions may be read, at least, in duplicate (two test tubes of the same solution) with spectrophotometric analysis and two injections of the same solution in different vials for HPLC analysis. For the highest concentration, the absorbance values may not exceed the linearity limits of the instrument.

Linearity is typically calculated by using an appropriate least-squares regression program. Typically, a square of the correlation coefficient $\left(\mathrm{r}^{2} \geq 0.98\right)$ demonstrates linearity. In addition, the $y$-intercept must not be significantly different from zero at the $95 \%$ confidence limit.

## Accuracy/Recovery

For full validation, drug powder at $\pm 20 \%$ of the lowest expected concentration to $\pm 20 \%$ of the highest concentration during release from the specific dosage unit strength is typically used. A minimum of three concentration levels is evaluated. The capsule shell, coating blend, inks, and sinker are also added where appropriate. Each level is tested as $\mathrm{n}=$ 3. The amount of placebo blend weighed for each level is the same as the total excipient weight of each tablet or capsule for the dosage strength being validated. For Apparatus 1 and Apparatus 2, the mixture of excipients and drug powder may be tested according to the conditions specified in the method.

In cases of poor drug solubility, if feasible, the stock solution may be prepared by dissolving the drug substance in a small amount of organic solvent and diluting to the final concentration with dissolution medium. An amount of stock solution equivalent to the targeted label claim may be added to the vessel instead of drug powder. [NOTE-The solutions may be made in volumetric flasks instead of vessels.] The percentage of organic solvent should be minimized (ideally $\leq 5 \%$ of the final medium composition) as it may change the solubility of the excipients and bias the results.

The measured recovery is typically $95 \%$ to $105 \%$ of the weighed amounts. Bracketing or matrixing of multiple strengths may be useful.

A special case for validation is the acid stage (see $D e$ -layed-Release (Enteric-Coated) Articles-General Drug Release Standard under Drug Release $\langle 724\rangle$. The limit of not more than $10 \%$ should be validated. If the compound degrades in acid, the validation of the method is complicated but usually can be performed using the degradant, especially if $100 \%$ rapid degradation in-situ occurs.

## Precision

## REPEATABILITY

Repeatability is determined by replicate measurements of a standard solution. It can be measured by calculating the RSD of the multiple injections, by spectrophotometric readings for each standard solution, or from the accuracy or linearity data.

## INTERMEDIATE PRECISION

Intermediate precision may be evaluated to determine the effects of random events on the precision of the analytical procedure. The precision can be across the range of product strengths. Typical variations to study include days, analysts, and equipment. The use of an experimental matrix design is encouraged for evaluation of intermediate precision. If possible, the intermediate precision can be performed using a well-characterized lot of drug product of tight content uniformity. In cases where this well-characterized product is not available, placebo and active ingredient may be used to identify intermediate precision.
The dissolution profiles on the same sample (run twice, $\mathrm{n}=12$ ) may be run by at least two different analysts, with each analyst preparing the standard solutions and the medium. The analysts typically use different dissolution baths, spectrophotometers or HPLC equipment (including columns), and autosamplers and perform the test on different days. This procedure may not be necessary to perform for each strength; instead bracketing with high and low strengths may be acceptable.

Typical acceptance criteria for this type of precision are that the difference in the mean value between the dissolution results from the first analyst to the second analyst does not exceed an absolute $10 \%$ at time points with less than $85 \%$
dissolved and does not exceed $5 \%$ for those remaining time points above $85 \%$. Acceptance criteria may be product specific, and other statistical tests and limits may be used.

## Robustness

The evaluation of robustness may be considered during the development phase but more typically is done at the time of full validation. This assesses the impact of making small, deliberate changes to the dissolution conditions. Experiments to test for robustness can use $\mathrm{n}=3$ if the product exhibits normal variability and $\mathrm{n}=6$ for highly variable products (i.e., the RSD is above $20 \%$ in time points at 10 minutes or earlier, and $10 \%$ or above RSD in later time points).
One run each may be performed using $90 \%, 100 \%$, and $110 \%$ of the medium concentration (e.g., surfactant, w/v $\%$ ) in the method. For buffered media, runs of 0.5 pH units above and below the method pH can be performed. The buffer capacity may be varied by changing the total buffer concentration while keeping the relative amounts of each buffer component the same (see above for suitable variations).

HPLC includes variations of the mobile phase composition, flow rate, pH changes, and column type, brand, lot, or age. System suitability criteria assess acceptability of the method. For a more in-depth discussion of robustness and other validation topics for HPLC, refer to the general information chapter Validation of Compendial Methods $\langle 1225\rangle$. UV could include a variation of wavelength of $\pm 2 \mathrm{~nm}$, depending on the absorbance profile.

## Standard and Sample Solution Stability

The standard solution is stored under conditions that ensure stability. The stability of the standard is analyzed over a specified period of time, using a freshly prepared standard
solution at each time interval for comparison. The acceptable range for standard solution stability is typically between $98 \%$ and $102 \%$.

The sample solution is stored at room temperature in a glass test tube wrapped securely in paraffin or in a capped vial. The sample is analyzed over a specified period of time using the original sample solution response for comparison. The typical acceptable range for sample solution stability may be between $98 \%$ and $102 \%$ when compared to the initial analysis of the sample solutions. If the solution is not stable, aspects to consider could be temperature (refrigeration needed), light protection, or container material (plastic or glass).

The method may state that the standards and samples should be analyzed within the time period demonstrating acceptable standard and sample solution stability.

## ACCEPTANCE CRITERIA

Typical acceptance criteria for the amount of active ingredient dissolved, expressed as a percentage of the labeled content $(Q)$, are in the range of $75 \%$ to $80 \%$ dissolved. A $Q$ value in excess of $80 \%$ is not generally used because allowance should be made for assay and content uniformity ranges. ${ }^{3}$ Acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data.

High variability in results can make it difficult to identify trends or effects of formulation changes. Dissolution results may be considered highly variable if the RSD is greater than
$20 \%$ at timepoints 10 minutes or earlier and greater than $10 \% \mathrm{RSD}$ in later time points. The source of the variability could be investigated, when practical, and one should strive to reduce variability whenever possible. The two most likely causes are the formulation itself or mechanical artifacts associated with the test procedure (e.g., coning or tablets sticking to the vessel wall).

Occurrences such as those mentioned in the previous section on observations can be a strong indication that the dissolution test itself is creating variability. Any time the dosage contents do not disperse freely throughout the vessel in a uniform fashion, aberrant test results could occur. Depending on the problem, the usual remedies include changing the apparatus type, speed of agitation (flowrate), deaeration, consideration and/or examination of sinker type, or changing the composition of the medium. Modifications to apparatus may be useful, with proper justification and validation.

Many causes of variability can come from the formulation and manufacturing process. For example, poor content uniformity, process inconsistencies, a reaction taking place at different rates during dissolution, excipient interactions or interference, film coating, capsule shell aging, or hardening or softening of the dosage form as it ages may be sources of variability and interferences. During routine testing of the product, variability outside of the expected range should be investigated in terms of both analytical and formulation issues.

[^32]
## STIMULI TO THE REVISION PROCESS

This section may contain the following:

- reports or statements of authoritative committees
- original research reports
- evaluations of new and existing pharmacopeial methods
- commentaries
- articles relevant to compendial issues

These items are published to stimulate discussion and continual review of Pharmacopeial standards. Generally, if an Expert Committee publishes an article on which they are specifically seeking comment, this will be clearly stated in the article. Readers may submit comments on issues raised in this section, but comment is not as critical as that for the In-Process Revision and Pharmacopeial Previews sections. Readers interested in submitting comments should see Instructions to Authors.
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## Instructions to Authors

Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to $U S P-N F$ revision will be considered for publication in the Pharmacopeial Forum under the section Stimuli to the Revision Process. Manuscripts are received with the explicit understanding that they have not been published previously and that they are not simultaneously under consideration by any other publication.

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Abstract-Include an abstract of not more than 250 words stating the purpose and the results or conclusions of the article.
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## NOMENCLATURE

This section includes supplements to the latest edition of the USP Dictionary of USAN and International Drug Names that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

## USP Dictionary of USAN and International Drug Names 2003 USP DICTIONARY SUPPLEMENT 5

IMPORTANT-Save this Supplement. This and all supplements appearing in $P F$ are needed to keep the 2003 edition of the USP Dictionary (USPD) up to date. The cumulative contents of the supplements to the current (2003) edition will be included in the next complete edition of the Dictionary.

## New United States Adopted Names (USAN)

The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of $P F$ for other new USAN to supplement the Dictionary main volume.

Arformoterol Tartrate [2003] (ar for moe' ter ole).
$\mathrm{C}_{19} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{O}_{4} . \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6} .494 .49$. (1) Formamide, $N$-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methy-lethyl]amino]ethyl]phenyl]-, $(2 R, 3 R)$-2,3-dihydroxybutanedioate (1:1) (salt); (2) (-)-N-[2-Hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl $]$ amino $]$ ethyl $]$ phenyl]formamide hydrogen $(2 R, 3 R)$-2,3-dihydroxybutanedioate (salt). CAS-200815-49-2. Anti-asthmatic and bronchodilator. (Sepracor, Canada)


Batabulin Sodium [2003] (bat a bue' lin). $\mathrm{C}_{13} \mathrm{H}_{6} \mathrm{~F}_{6} \mathrm{NNaO}_{3} \mathrm{~S}$. 393.24. (1) Benzenesulfonamide, 2,3,4,5,6-pentafluoro- N -(3-fluoro-4-methoxyphenyl)-, sodium salt; (2) Sodium 2,3,4,5,6-pentafluoro- $N$-(3-fluoro-4-methoxyphenyl)benzenesulfonamidate; (3) 2-Fluoro-1-methoxy-4-pentafluorophenylsulfonamidobenzene, sodium salt. CAS-195533-98-3. Treatment of various refractory cancers, including hepatocellular carcinoma, breast, colon and non-small cell lung cancer. (Tularik) $\diamond$ T138067-sodium


Lumiliximab [2003] (loo mil ix' i mab). Immunoglobulin G1, anti-(human immunoglobulin E receptor type II) (human-Macaca irus monoclonal IDEC-152 $\gamma 1$-chain), disulfide with hu-man-Macaca irus monoclonal IDEC-152 $\kappa$-chain, dimer. CAS-357613-86-6. Treatment of allergic asthma, allergic rhinitis, and chronic lymphocytic leukemia. (IDEC) $\triangleleft I D E C-152$

Miglustat [2003] (mi gloo' stat). $\mathrm{C}_{10} \mathrm{H}_{21} \mathrm{NO}_{4}$. 219.28. (1) 3,4,5Piperidinetriol, 1-butyl-2-(hydroxymethyl)-, $(2 R, 3 R, 4 R, 5 S)$-; (2) $(2 R, 3 R, 4 R, 5 S)$-1-Butyl-2-(hydroxymethyl)piperidine-3,4,5-triol. CAS-72599-27-0. INN; BAN. Treatment of glycolipid storage diseases. Zavesca (Lonza, Switzerland) $\diamond O G T$ 918


Mubritinib [2003] (mue bri tye' nib). $\mathrm{C}_{25} \mathrm{H}_{23} \mathrm{~F}_{3} \mathrm{~N}_{4} \mathrm{O}_{2}$. 468.47. (1) 1H-1,2,3-Triazole, 1-[4-[4-[[2-[(1E)-2-[4-(trifluoromethyl)-phenyl]ethenyl]-4-oxazolyl]methoxy]phenyl]butyl]-; (2) 1-[4-[4-[[2-[(E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole. CAS-366017-09-6. Treatment of cancer. (Takeda) $\diamond$ TAK-165


Parathyroid Hormone [2003] (par a thye' roid). Parathormone (human recombinant). Molecular weight is 9414 daltons. CAS-68893-82-3 [human]; CAS-345663-45-8 [human recombinant]; CAS-9002-64-6 [parathyroid]. USP XXI; MI. Treatment of osteoporosis, as an antiosteoporotic, in the treatment of bone and mineral disease and disorders, bone metabolism regulator, blood calcium regulator, and as a diagnostic aid (pseudohypoparathyroidism; hypocalcemia). (SynCo BV); Paroidin (Parke-Davis $\dagger$ ) $\triangleleft A L X 1-11$

Pixantrone [2003] (pix' an trone). $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{5} \mathrm{O}_{2}$. 325.37. (1) Benz $[g]$ isoquinoline-5,10-dione, 6,9 -bis [(2-aminoethyl)amino $]-;$ (2) 6,9-Bis[(2-aminoethyl)amino]benzo[ $g]$ isoquino-line-5,10-dione.CAS-144510-96-3. BAN. Anti-neoplastic. (Novuspharma SpA) $\diamond B B R 2778$


Razaxaban Hydrochloride [2003] (ra zax' a ban).
$\mathrm{C}_{24} \mathrm{H}_{20} \mathrm{~F}_{4} \mathrm{~N}_{8} \mathrm{O}_{2}$. HCl . 564.92. (1) 1 H -Pyrazole- 5 -carboxamide, 1-(3-amino-1,2-benzisoxazol-5-yl)- N -[4-[2-[(dimethylami-no)methyl]-1 H -imidazol-1-yl]-2-fluorophenyl]-3-[trifluoro-methyl)-, monohydrochloride; (2) 1-(3-Amino-1,2-benzisoxazol-5-yl)- N -[4-[2-[(dimethylamino)methyl $]-1 \mathrm{H}$ -imidazol-1-yl]-2-fluorophenyl]-3-(trifluoromethyl)-1H-pyra-zole-5-carboxamide monohydrochloride. CAS-405940-76-3. Anticoagulant; antithrombotic (Factor Xa inhibitor). (Bris-tol-Myers Squibb) $\diamond B M S$-561389


Revaprazan Hydrochloride [2003] (re va' pra zan).
$\mathrm{C}_{22} \mathrm{H}_{23} \mathrm{FN}_{4}$.HCl. 398.90. (1) 2-Pyrimidinamine, 4-(3,4-dihy-dro-1-methyl-2( 1 H )-isoquinolinyl)- N -(4-fluorophenyl)-5,6-dimethyl-, monohydrochloride; (2) $N$-(4-Fluorophenyl)-5,6-dimethyl-4-[(1RS)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl]pyrimidin-2-amine monohydrochloride. CAS-178307-421. Treatment of peptic ulcer, gastric ulcer, duodenal ulcer, and GERD (acid pump antagonist). (Yuhan, Korea) $\diamond$ YH1885


Solabegron Hydrochloride [2003] (soe la beg' ron).
$\mathrm{C}_{23} \mathrm{H}_{23} \mathrm{ClN}_{2} \mathrm{O}_{3}$. HCl. 447.35. (1) [1,1'-Biphenyl $]$-3-carboxylic acid, $3^{\prime}-[[2-[[(2 R)-2-(3$-chlorophenyl)-2-hydroxyethyl]amino ]ethyl $]$ amino $]-$, hydrochloride; (2) 3'-[[2-[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl] amino]ethyl]amino]biphenyl-3-carboxylic acid hydrochloride. CAS-451470-34-1. Antidiabetic ( $\beta 3$ adrenoreceptor agonist). (GlaxoSmithKline) $\checkmark G W 427353 B$


## Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

## Dextiopronin

Change the chemical structure to read:


Eniporide
Change the chemical structure to read:


Esonarimod
Change the chemical structure to read:


Fenoprofen
Change the chemical structure to read:


Iosulamide Meglumine
Change the chemical structure to read:


Iosumetic Acid
Change the chemical structure to read:


Iotasul
Change the chemical structure to read:


Josamycin
Change the chemical structure to read:


## Kainic Acid

Change the chemical structure to read:


## Lotrafiban Hydrochloride

## Add the following chemical structure:



## Maridomycin

Change the chemical structure to read:


## Mazaticol

Change the chemical structure to read:


## Suggested United States Adopted Names

The United States Adopted Names (USAN) program is the specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs while the drugs are still in the investigational stages. The American Medical Association (AMA), the American Pharmaceutical Association (APhA), and the United States Pharmacopeial Convention (USPC) jointly sponsor the USAN program with representation from the FDA.

Each U.S. Adopted Name is chosen with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official United States Pharmacopeia or National Formulary. A measure of the prestige and recognition of the value of the USAN program can be found in the following regulations published by the Commissioner of Food and Drugs and the Secretary of Health and Human Services in the Federal Register of February 1988.

All who are concerned with the prescription, dispen-
sing, use, sale or manufacture of drugs may, in the absence of the designation of an official name by the FDA, rely on the current compendial name or the U.S. Adopted Name (USAN) listed in this volume as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act.
A formal procedure ${ }^{1}$ is followed by the USAN Council in selecting an established name for a drug. The USAN Council Secretary is also an ex officio member of the International Nonproprietary Names (INN) Committee. USAN Guiding Principles are concordant with World Health Organization (WHO) principles, and all USANs for substances also named by the INN Committee are sys-

| Suggested USAN | Category |
| :--- | :--- |
| Abacumab | Treatment of anthrax infection |
| Abbacumab |  |
| Agobacumab |  |
| Aribacumab |  |
| Raxibacumab |  |
| Abatapcept Alfa | Treatment of juvenile arthritis |
| Abatapcim Alfa | and autoimmune diseases |
| Abatapcimus Alfa |  |
| Abatapfusim Alfa |  |
| Signatapcim Alfa |  |
| Signatapcimus Alfa |  |
| Antineoplastic |  |
| Lanimostim |  |
| Abtumumab |  |
| Antineoplastic |  |
| Atumumumab |  |
| Hutumumab |  |
| Paritumumab |  |
| Ulatumumab |  |

[^33]tematically processed through the INN Committee. This ensures that, with very rare exceptions, USANs are identical to INNs and available for world-wide use.
A suggestion for a USAN originates usually from a firm or an individual who has developed a substance of potential therapeutic utility to the point where there is a distinct possibility of its being marketed in the United States of America. Occasionally, the initiative is taken by the USAN Council in the form of a request to parties interested in a substance for which a nonproprietary name appears to be lacking.

Submissions to the USAN Council are expected to conform to the established Guiding Principles ${ }^{2}$ and to be reasonably free from conflict with other names, including both trademarks and nonproprietary names. An effort is made to discourage the occasional, undesirable practice of incorporating in trademarks the syllables used in an established nonproprietary name, or syllables recommended for USAN. Such trademarks may act as a bar to the subsequent adoption of appropriate nonproprietary names for closely related drugs.

The suggested nonproprietary names for the drugs described in the following list are under consideration by the USAN Council. The name(s) being considered for each drug substance, and the applicable category, are separated by double spacing from the name(s) and category for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.
Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Suggested USAN | Category |
| :--- | :--- |
| Aclogrel Hydrochloride | Platelet aggregation inhibitor |
| Cicloflugrel Hydrochloride |  |
| Flosulagrel Hydrochloride |  |
| Losulagrel Hydrochloride |  |
| Prasugrel Hydrochloride |  |
| Prasulagrel Hydrochloride |  |
| Prosulagrel Hydrochloride |  |
| Prosulgrel Hydrochloride |  |
|  |  |
| Adafaxine Hydrochloride | Antidepressant; antianxiety |
| Aldafaxine Hydrochloride |  |
| Atafaxine Hydrochloride |  |
| Edanfaxine Hydrochloride |  |
| Efdanfaxine Hydrochloride |  |
| Radafaxine Hydrochloride |  |
| Sunefaxine Hydrochloride |  |
| Vadafaxine Hydrochloride |  |
| Zunefaxine Hydrochloride |  |
|  |  |
| Adv-2,5-huE1B-deleted-2 | Antineoplastic |
| Adv-2,5-hup53-2 |  |
| Ixadusugene (E1B deleted) |  |
| Ixadusugene (p53) |  |
| Lontucirev (Replicating Ade- |  |
| novirus) |  |
| Padtucirev (Replicating Ade- |  |
| novirus) |  |

[^34]| Suggested USAN | Category |
| :---: | :---: |
| Afboximab | Anti-angiogenic agent to treat |
| Afotuximab | solid tumors and age-related |
| Boxatuximab | macular degeneration |
| Valiximab |  |
| Volotuximab |  |
| Afrexagliptin | Treatment of type-2 diabetes |
| Axagliptin | mellitus and metabolic syn- |
| Cedagliptin | drome |
| Cideptagliptin |  |
| Alagebrax Chloride | Treatment of cardiovascular |
| Alahebrax Chloride | complications of aging, dia- |
| Altagebrax Chloride | betes, and end-stage renal dis- |
| Atagebrax Chloride | ease |
| Atagebraxe Chloride |  |
|  |  |
| Elagebraxe Chloride |  |
| Alovindase | Clearance of intravitrial blood |
| Hyaluronidase | clots |
| Hyaluronidase (sheep testis) |  |
| Ovase |  |
| Ovinase |  |
| Ronovinase |  |
| Aprocitidim | Anti-infective (antimicrobial |
| Aptolactide Alfa | and antiviral); anti-inflamma- |
| Lactoferrin Alfa | tory; antineoplastic |
| Lactofertide Alfa |  |
| Atamcimod Acetate | Treatment of chemotherapy- |
| Binamcimod Acetate | induced diarrhea (CID) |
| Delamcimod Acetate Delamgatide Acetate |  |
|  |  |
| Avanafil | Treatment of erectile dysfunc- |
| Vitanafil | tion |
| Xyanafil |  |
| Avicurium Chloride | Neuromuscular blocker |
| Bantacurium Chloride |  |
| Benecurium Chloride |  |
| Bravacurium Chloride |  |
| Brevicurium Chloride |  |
| Brosacurium Chloride |  |
| Gantacurium Chloride |  |
| Nexicurium Chloride |  |
| Revacurium Chloride |  |
| Vantacurium Chloride |  |
| Velocurium Chloride |  |
| Zelacurium Chloride |  |
| Becorotan Hydrochloride | Treatment of Alzheimer's dis- |
| Becorotane Hydrochloride | ease |
| Lecorotan Hydrochloride |  |
| Lecorotane Hydrochloride |  |
| Lecozotan Hydrochloride |  |
| Lecozotane Hydrochloride |  |
| Bectapitant Mesylate | Antiemetic |
| Vestipitant Mesylate |  |
| Vintapitant Mesylate |  |


| Suggested USAN | Category |
| :--- | :--- |
| Bitafosol Tetrasodium | Treatment of rhinitis, URI and |
| Denufosol Tetrasodium | lung disease, including cystic |
| Dinufosol Tetrasodium | fibrosis; also retinal detach- |
| Dipirafosol Tetrasodium | ment and edema |
| Dipirfosol Tetrasodium |  |
| Calimumab |  |
| Relimumab |  |
| Rolimumab |  |
| Zolimumab |  |
| Zylimumab |  |
| Cefamersan Hydrochloride |  |
| Cefametsan Hydrochloride |  |
| Cefazom Hydrochloride |  |
| Cefazome Hydrochloride |  |
| Cefazomethine Hydrochloride |  |


| Suggested USAN | Category |
| :---: | :---: |
| Ezadenosant | Adenosine ${ }_{2 a}$ receptor antago- |
| Ezadenoson | nist intended for use in treat- |
| Ispredenosant | ment of Parkinson's disease |
| Sodenosant |  |
| Xodenosant |  |
| Xodenoson |  |
| Zadenosant |  |
| Ferric Ferrocyanide | Antidote indicated for the treat- |
| Ferric Hexacyanoferrate (II) | ment of patients with known or |
| Ferric Hexacyanoferrate III | suspected internal contamina- |
| Insoluble Prussian Blue | tion with radioactive cesium and/or radioactive or nonradioactive thallium to increase their rates of elimination |
| Fexifotel | Treatment of neuropathic pain |
| Perzinfotel |  |
| Veramafotel |  |
| Veramfotel |  |
| Fidexaban | Anticoagulant |
| Hioxifilcon C | Hydrophilic contact lens material |
| Levtofisopam | Anxiolytic, treatment of autonomic instability |
| Linxotecan | Antineoplastic |
| Pegbetotecan |  |
| Pegcamotecan |  |
| Pegcamtecan |  |
| Peglinxotecan |  |
| Liritrexate | Treatment of patients with ma- |
| Panatrexate | lignancies |
| Piritrexate |  |
| Travitrexate |  |
|  |  |
| Metazamulin | Topical antibiotic for seconda- |
| Prusarimulin | rily infected traumatic lesions |
| Retazamulin | (SITL) and secondarily infected |
| Retezamulin | dermatoses (SID) or impetigo |
| Tezapimulin |  |
| Zapimulin |  |


| Suggested USAN | Category |
| :---: | :---: |
| Midostaurin | Antineoplastic; protein kinase $C$ inhibition |
| Paliperidone | Treatment of schizophrenia |
| Paliperidone Palmitate | Treatment of schizophrenia |
| Panglitazar <br> Peliglitazar <br> Periglitazar <br> Puliglitazar | Treatment of type- 2 diabetes mellitus, mixed dyslipidemia, atherosclerosis and metabolic syndrome |
| Probucol Hemisuccinate <br> Resibucol <br> Succinbucol <br> Sucinbucol <br> Tebucolide | Prevention of restenosis, progression of risk in patients at risk for cardiovascular disease |
| Procarogammadex Pronagammadex Sunagammadex | Reversal agent for neuromuscular blocking agent |
| Ranolazine | Anti-anginal; anti-ischemic |
| Rotigotine | Treatment of Parkinson's disease and Restless Legs Syndrome |
| Stabaczumab <br> Stafabaczumab <br> Staphbaczumab <br> Stefbaczumab <br> Stefibaczumab | Treatment of Staphylococcus aureus infections |
| Stenavancin Hydrochloride | Antibacterial agent active against gram-positive pathogens |
| Sultaminase Sultamitase | Treatment of Maroteaux-Lamy syndrome (Mucopolysaccharidosis [MPS] VI) |
| Yttrium Y90 Lecratuzumab <br> Yttrium Y90 Tacatuzumab <br> Yttrium Y90 Tactuzumab <br> Yttrium Y90 Vintuzumab | Tumor eradication via selective targeting of AFP-positive cancers by radiolabeled hAFP-31 |

## Suggested International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO). INNs for substances originating within the United States are applied for through the USAN Council. INN and USAN Guiding Principles are concordant, which assures that, with very few exceptions, INNs and USANs are identical.

Under its charter, the WHO is empowered simply to recommend specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as proposals ("Proposed International Nonproprietary Names"). A period of four months from the date of publication in WHO Drug Information is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event
that no objection is received, the WHO proceeds with listing and publishing the names so devised as recommendations ("Recommended International Nonproprietary Names"), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

The names for the drugs that are categorized in the following list are under consideration for the selection of new Proposed International Nonproprietary Names. The name(s) being considered for each drug substance, and the applicable category, are separated by double spacing from the name(s) and category for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Suggested INN | Category |
| :---: | :---: |
| Abatapcept | Treatment of juvenile arthritis and autoimmune disease |
| Accodopram Asaropride Asarotiamide | Treatment of functional dyspepsia |
| Alagebrax Chloride | Prevention and treatment of cardiovascular complications of aging, diabetes, and endstage renal disease ( $A G E$ crosslink breaker) |
| Amidostaurin Indolstatin Midostaurin Staurostatin | Antineoplastic |
| Belotecan Pamitecan Travitecan | Antineoplastic |
| Bivirumab Exbivirumab Libivirumab | Prevention of hepatitis $B$ virus reinfection in patients who have received liver transplantation for end-stage hepatitis $B$ infection, and for treatment of chronic hepatitis $B$ virus infection |
| Botadopa <br> Botagolide <br> Protaline <br> Protiamine <br> Protioline <br> Retadopa <br> Rotigotine | Antiparkinsonian |
| Cenalidomide | Treatment of multiple myeloma, myelodysplastic syndromes, solid tumors including glioma and metastatic melanoma, Crohn's disease, and congestive heart failure |


| Suggested INN | Category |  |
| :---: | :---: | :---: |
| Cerfluticasone | Corticosteroid for the treat- |  |
| Delfluticasone | ment of inflammatory condi- |  |
| Rafluticasone | tions such as asthma, allergy, and COPD |  |
| Dalipronil | Anti-parasitic |  |
| Fampronil |  |  |
| Zenapronil |  |  |
| Dasantafil | Treatment of erectile dysfunction |  |
| Delamcimod Acetate | Treatment of chemotherapyinduced diarrhea |  |
| Denufosol | Treatment of rhinitis, URI and lung disease, including Cystic Fibrosis. Also, retinal detachment and edema |  |
| Deuperison Deuperisone | Sodium-channel blocker; centrally acting muscle relaxant for the symptomatic treatment of spasticity and muscle spasm |  |
| Diphentrone <br> Disphenitrone <br> Disufenton <br> Phenitrone | Neuroprotectant agent used to treat ischemic stroke |  |
| Epelestat | Treatment of bronchopulmonary inflammatory damage, specifically Cystic Fibrosis |  |
| Fenobegron | Treatment of over-active blad- |  |
| Ritabegron | der and urinary incontinence |  |
| Ritobegron |  |  |
| Fidexaban | Direct, selective, reversible, small molecule inhibitor of Factor Xa (anticoagulant) |  |


| Suggested INN | Category | Suggested INN | Category |
| :---: | :---: | :---: | :---: |
| Gadodendrimer Gadodenterate Gadomer | Macro-molecular blood pool contrast agent for magnetic resonance imaging in adult patients | Prasugrel | Inhibition of platelet aggregation; platelet ADPP 2 Y12 antagonist |
| Gantacurium Chloride | Induce muscle paralysis as surgical adjunct; neuromuscular blocker | Radafaxine Ranolazine | Anti-depressant; treatment of anxiety disorders <br> Anti-anginal; anti-ischemic |
| Glucarpidase | Adjunctive treatment of patients at risk of methotrexate toxicity | Regadenoson | Adenosine $A_{2 A}$ agonist; use as an adjunctive pharmacologic agent in cardiac perfusion imaging studies |
| Ispredenosant | An adenosine $2_{A}$ receptor antagonist intended for use in the treatment of Parkinson's disease | Retazamulin | Pleuromutilin derivative; topical antibiotic for secondarily infected traumatic lesions and secondarily infected derma- |
| Lactofertide Alfa | Anti-infective (antimicrobial and antiviral); anti-inflammatory, antineoplastic | Rolimumab | toses or impetigo <br> Treatment of rheumatoid arthritis, uvetis, asthma and |
| Lanimostim | Antineoplastic; anti-infective growth factor that acts on both progenitor and mature cells of the macrophage line | Stefbaczumab | Crohn's disease <br> Treatment of Staphylococcus aureus infections |
| Lecozotan | Treatment of Alzheimer's disease | Stenavancin | Antibacterial agent active against gram-positive pathogens |
| Levtofisopam | Anxiolytic, treatment of autonomic instability | Succinbucol | Prevention of restenosis, progression of atherosclerosis, re- |
| Lontucirev (Replicating Adenovirus) | Treatment of multiple cancers (E1-B deleted adenovirus; replication competent therapeu- |  | duction of risk in patients at risk for cardiovascular disease |
|  | tic virus) | Tandutinib | Treatment of acute myelogenous leukemia |
| Mirotermin | Bone growth; tissue regenera- |  |  |
| Novotermin | tion | Trezdekincept Sudotox | Antineoplastic used to treat malignant glioma, including |
| Paliperidone <br> Paliperidone Palmitate | Treatment of schizophrenia |  | glioblastoma multiforme and anaplastic astrocytoma |
| Paritumumab | Antineoplastic; treatment of subjects with cancers whose tumors express $E G F$ receptors | Vestipitant | Anti-depressant; anti-anxiety; prevention of nausea and vomiting; used in the treatment of functional dyspepsia, irrita- |
| Pegcamotecan | Treatment of small cell lung cancer, and gastric adenocarci- |  | ble bowel syndrome and GERD |
| Perzinfotel | noma Treatment of neuropathic pain | Yttrium Y 90 Tacatuzumab | Tumor eradication via selective targeting of AFP-positive cancers by radiolabeled hAFP-31 |
| Plericixafor | Stem cell mobilization (CXCR4 receptor antagonist) |  |  |

## INDEX

This is a cumulative directory for the content of all issues of $P F$ beginning with $P F$ 30(1).
[Note—This index covers Vol. 30 No. 1, pp. 1-381]

## MONOGRAPHS

Acetaminophen and Aspirin Tablets (USP)
Tablets Containing at Least Three of the Following-
Acetaminophen and Salts of Chlorpheniramine,
Dextromethorphan, and Phenylpropanolamine (USP)
Capsules Containing at Least Three of the FollowingAcetaminophen and Salts of Chlorpheniramine,
Dextromethorphan, and Pseudoephedrine (USP)
Oral Powder Containing at Least Three of the FollowingAcetaminophen and Salts of Chlorpheniramine,
Dextromethorphan, and Pseudoephedrine (USP)
Following-
Oral Solution Containing at Least Three of the Following-
Acetaminophen and Salts of Chlorpheniramine,
Dextromethorphan, and Pseudoephedrine (USP)
Tablets Containing at Least Three of the Following-
Acetaminophen and Salts of Chlorpheniramine,
Dextromethorphan, and Pseudoephedrine (USP)
Acetaminophen and Codeine Phosphate Capsules (USP)
Acetaminophen and Codeine Phosphate Oral Solution (USP)
Acetaminophen and Codeine Phosphate Oral Suspension (USP)
Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution (USP)
Acetaminophen and Diphenhydramine Citrate Tablets (USP)
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets (USP) . . . . . . .
Acetaminophen Oral Solution (USP)
Acetaminophen Oral Suspension (USP)
P) ${ }^{-}$

Acetaminophen and Pseudoephedrine Hydrochloride Tablets (USP)
Acetohydroxamic Acid Tablets (USP)
Albuterol Tablets (USP)
Alfadex (NF)
Alprazolam Tablets (USP)
Amantadine Hydrochloride Capsules (USP)
Amifostine (USP)
Aminosalicylate Sodium Tablets (USP)
Amoxicillin and Clavulanate Potassium for Oral Suspension (USP)
Amphetamine Sulfate Tablets (USP)
Ampicillin Capsules (USP)
Ampicillin Tablets (USP)
Antithrombin III Human (USP)
Ascorbic Acid Tablets (USP)
L-Asparagine (NF)
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Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules (USP)
Aztreonam (USP) . . . . . . . . . . . . . . . . . . . . . . . . .
Baclofen Tablets (USP)
Betadex (NF)
Betamethasone Tablets (USP)
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Biological Indicators for Moist Heat, Dry Heat, and Gaseous
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## USP CATALOG

## New Items at a Glance

See what's new in USP Reference Standards. For your convenient and quick reference, here's a list of Reference Standards released by USP over the past year.

This list is continuously updated with the newest Reference Standards released within the past 12 months.

| Cat.No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1002505 | Acesulfame Potassium (200 mg) | F0C136 | \$260 |
| 1012780 | Alendronate Sodium (200 mg) | F0B315 | \$156 |
| 1012939 | Allantoin (200 mg) | F0C169 | \$156 |
| 1019417 | Amifostine Disulfide (25 mg) | F0C152 | \$487 |
| 1028000 | Amitraz (200 mg) | F0C042 | \$156 |
| 1029953 | Ammonium Chloride (200 mg) | F0C134 | \$156 |
| 1043750 | Aspartame Acesulfame (200 mg) | F0C137 | \$156 |
| *1048619 | Benazepril Hydrochloride (125 mg) | F0C250 | \$156 |
| 1048620 | Benazepril Related Compound A ( 15 mg ) | F0C252 | \$487 |
| 1048630 | Benazepril Related Compound B ( 15 mg ) | F0C256 | \$487 |
| 1065618 | Betahistine Hydrochloride (200 mg) | F0C105 | \$156 |
| 1076363 | Brinzolamide (200 mg) | F0C034 | \$156 |
| 1076374 | Brinzolamide Related Compound A ( 50 mg ) | F0C033 | \$487 |
| 1076385 | Brinzolamide Related Compound B ( 50 mg ) | F0C035 | \$487 |
| *1078733 | Bupropion Hydrochloride (200 mg) | F0C123 | \$208 |
| 1097636 | Cefepime Hydrochloride (500 mg) | F0C063 | \$156 |
| 1097647 | Cefepime Hydrochloride System Suitability ( 25 mg ) | F0C095 | \$156 |
| 1103105 | Cetyl Palmitate (50 mg) | F0B241 | \$156 |
| *1111001 | Chlorhexidine (200 mg) | F0C306 | \$156 |
| *1111103 | Chlorhexidine Acetate (500 mg) | F0C281 | \$156 |
| 1133536 | Choline Bitartrate ( 200 mg ) | F0C057 | \$156 |
| 1133547 | Choline Chloride (200 mg) | F0C058 | \$156 |
| 1140247 | Clomipramine Hydrochloride ( 200 mg ) | F0C075 | \$156 |
| *1140349 | Clonazepam Related Compound C ( 25 mg ) | F0C340 | \$487 |
| *1140418 | Clonidine Related Compound A ( 25 mg ) | F0C373 | \$487 |
| 1142107 | Clozapine (100 mg) | F0C032 | \$260 |
| 1148500 | Copovidone ( 100 mg ) | F0C194 | \$156 |
| 1171900 | Desflurane ( 0.5 mL ) | F0C187 | \$156 |
| 1171910 | Desflurane Related Compound A ( 0.1 mL ) | F0C031 | \$487 |
| 1179708 | Dextran 40 (50 mg) | F0C247 | \$156 |
| 1179741 | Dextran 70 (50 mg) | F0C260 | \$156 |
| 1179854 | Dextran 4 Calibration (100 mg) | F0C002 | \$156 |
| 1179865 | Dextran 10 Calibration (100 mg) | F0C010 | \$156 |
| 1179876 | Dextran 40 Calibration (100 mg) | F0C011 | \$156 |
| 1179887 | Dextran 70 Calibration (100 mg) | F0C013 | \$156 |
| 1179898 | Dextran 250 Calibration (100 mg) | F0C039 | \$156 |
| 1204805 | Diloxanide Furoate (200 mg) | F0C026 | \$156 |
| 1213103 | Dinoprostone (50 mg) | F0C030 | \$1,525 |
| *1224959 | Dolasetron Mesylate (200 mg) | F0C319 | \$156 |
| *1224960 | Dolasetron Mesylate Related Compound A ( 25 mg ) | F0C321 | \$487 |
| 1225281 | Dorzolamide Hydrochloride ( 500 mg ) | F0C040 | \$156 |


| Cat.No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1225292 | Dorzolamide Hydrochloride Related Compound A ( 20 mg ) | F0C068 | \$487 |
| 1225419 | Doxazosin Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | F0C079 | \$156 |
| *1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | \$520 |
| 1234806 | Emedastine Difumarate ( 100 mg ) | F0C059 | \$156 |
| 1260012 | Ethinyl Estradiol Related Compound A ( 20 mg ) | F0B252 | \$487 |
| 1269458 | Fenoldopam Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | F0C125 | \$156 |
| 1269469 | Fenoldopam Related Compound A ( 20 mg ) | F0C124 | \$487 |
| 1269470 | Fenoldopam Related Compound B $(20 \mathrm{mg})$ ( 20 mg ) | F0C126 | \$487 |
| 1273808 | Flumazenil ( 200 mg ) | F0C305 | \$780 |
| *1279837 | Fluoxetine Related Compound C ( 15 mg ) | F0C352 | \$487 |
| 1286060 | Formononetin ( 50 mg ) | F0C196 | \$520 |
| 1286366 | Fosphenytoin Sodium ( 250 mg ) | F0C156 | \$156 |
| 1287675 | Gadoversetamide ( $200 \mathrm{mg} \mathrm{)}$ | F0C172 | \$156 |
| 1287686 | Gadoversetamide Related Compound A ( 200 mg ) | F0C173 | \$487 |
| 1288306 | Ganciclovir (200 mg) | F0C287 | \$364 |
| *1288317 | Ganciclovir Related Compound A ( 15 mg ) | F0C288 | \$624 |
| 1288510 | Gemfibrozil Related Compound A ( 20 mg ) | F0C101 | \$487 |
| *1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 | \$156 |
| 1294976 | Glutamic Acid ( 200 mg ) | F0C069 | \$156 |
| 1295888 | Glycyrrhizic Acid (25 mg) | FOC006 | \$487 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) | F0C214 | \$513 |
| 1348907 | Isoflupredone Acetate ( $200 \mathrm{mg} \mathrm{)}$ | F0C109 | \$156 |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 | \$260 |
| 1355753 | Kawain (200 mg) | F0C160 | \$208 |
| 1356020 | Ketamine Related Compound A ( 50 mg ) | F0C118 | \$487 |
| *1356836 | Lamivudine ( 200 mg ) | F0C361 | \$156 |
| 1356916 | Lansoprazole (200 mg) | F0B310 | \$156 |
| 1356927 | Lansoprazole Related Compound A ( 25 mg ) | F0B311 | \$487 |
| 1370906 | Lynestrenol ( 20 mg ) | F0B314 | \$203 |
| 1392454 | Meropenem ( 300 mg ) | F0C201 | \$182 |
| 1396309 | Metformin Hydrochloride (200 mg) | F0C209 | \$182 |
| 1396310 | Metformin Related Compound A ( 50 mg ) | F0C210 | \$487 |
| *1441232 | Metoprolol Related Compound A ( 20 mg ) | F0C343 | \$520 |
| *1441254 | Metoprolol Related Compound C ( 20 mg ) | F0C344 | \$520 |
| *1443850 | Powdered Milk Thistle Extract ( 250 mg ) | F0B321 | \$260 |
| 1443908 | Milrinone ( 500 mg ) | F0C050 | \$260 |
| 1443919 | Milrinone Related Compound A $(50 \mathrm{mg})$ | F0C051 | \$487 |
| 1449518 | Nabumetone (200 mg) | F0C072 | \$156 |
| 1471914 | Norgestimate (200 mg) | F0C086 | \$156 |
| 1478582 | Ondansetron Hydrochloride ( 300 mg ) | F0C222 | \$208 |
| 1478593 | Ondansetron Related Compound A ( 50 mg ) | F0C191 | \$487 |

## New Items at a Glance (Continued)

| Cat.No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1478618 | Ondansetron Related Compound C ( 50 mg ) | F0C251 | \$487 |
| 1478629 | Ondansetron Related Compound D ( 50 mg ) | F0C226 | \$487 |
| 1482207 | Oxaprozin (200 mg) | F0C115 | \$156 |
| 1483301 | Oxfendazole (200 mg) | F0C128 | \$156 |
| 1491332 | Paclitaxel ( 200 mg ) | F0C180 | \$1,508 |
| 1491343 | Paclitaxel Related Compound A (20 mg) | F0C179 | \$754 |
| 1491354 | Paclitaxel Related Compound B (20 mg) | F0C181 | \$754 |
| 1500251 | Paroxetine Related Compound D ( 15 mg ) | F0C228 | \$487 |
| 1535019 | Phenytoin Related Compound A ( 50 mg ) | F0C155 | \$487 |
| *1535020 | Phenytoin Related Compound B ( 50 mg ) | F0C157 | \$487 |
| 1546106 | Poloxalene (500 mg) | F0C009 | \$156 |
| 1593412 | Quinapril Related Compound A ( 50 mg ) | F0C114 | \$487 |
| 1593423 | Quinapril Related Compound B ( 50 mg ) | F0C116 | \$487 |
| *1596807 | Quinine Hydrochloride Dihydrate $(1 \mathrm{~g})$ | F0C108 | \$156 |
| 1598303 | Ramipril (200 mg) | F0C099 | \$156 |
| 1598314 | Ramipril Related Compound A ( 20 mg ) | F0C100 | \$487 |
| 1599500 | Powdered Red Clover Extract ( 500 mg ) | F0C188 | \$260 |
| *1604508 | Rimantadine Hydrochloride ( 300 mg ) | F0C266 | \$156 |
| 1610090 | Scopoletin (20 mg) | F0C329 | \$156 |
| 1612540 | Sevoflurane (1 mL) | F0C219 | \$156 |
| 1612550 | Sevoflurane Related Compound A ( 0.2 mL ) | F0C261 | \$487 |
| 1614669 | Sodium Starch Glycolate (400 mg) | F0C087 | \$156 |
| 1617408 | Sotalol Hydrochloride (300 mg) | F0C234 | \$182 |
| 1617419 | Sotalol Related Compound A ( 50 mg ) | F0C235 | \$487 |
| 1617420 | Sotalol Related Compound B ( 50 mg ) | F0C236 | \$487 |
| 1617430 | Sotalol Related Compound C ( 50 mg ) | F0C237 | \$487 |
| 1621507 | Stearoyl Polyoxyglycerides ( 100 mg ) | F0C286 | \$156 |
| 1642154 | Sumatriptan (50 mg) | F0C220 | \$208 |


| Cat.No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1642201 | Sumatriptan Succinate ( 200 mg ) | F0C231 | \$208 |
| 1642212 | Sumatriptan Succinate Related Compound A (15 mg) | F0C221 | \$624 |
| 1642223 | Sumatriptan Succinate Related Compound C ( 50 mg ) | F0C230 | \$624 |
| 1642700 | Tacrine Hydrochloride ( 500 mg ) | F0C119 | \$156 |
| 1643361 | Taurine ( 100 mg ) | F0C104 | \$156 |
| 1643452 | Terazosin Hydrochloride ( 200 mg ) | F0C244 | \$156 |
| 1643463 | Terazosin Related Compound A ( 50 mg ) | FOC245 | \$487 |
| 1643474 | Terazosin Related Compound B ( 50 mg ) | F0C218 | \$487 |
| 1643485 | Terazosin Related Compound C $(25 \mathrm{mg})$ | F0C257 | \$487 |
| 1652500 | Thalidomide ( 200 mg ) | F0C107 | \$182 |
| 1667290 | Tiamulin Fumarate ( $250 \mathrm{mg} \mathrm{)}$ | F0C327 | \$156 |
| *1667337 | $\begin{aligned} & \text { Tiamulin Related Compound A } \\ & (50 \mathrm{mg}) \end{aligned}$ | F0C328 | \$494 |
| 1667359 | Tiletamine Hydrochloride (200 mg) | F0C019 | \$156 |
| 1667520 | Tinidazole ( 200 mg ) | F0C093 | \$156 |
| 1667530 | Tinidazole Related Compound A ( 100 mg ) | F0C091 | \$487 |
| 1703805 | Tylosin (250 mg) | F0C008 | \$156 |
| 1706701 | Urea C $13(100 \mathrm{mg}$ ) | F0C078 | \$182 |
| 1708773 | Valsartan Related Compound A (20 mg) | F0C215 | \$624 |
| 1708795 | Valsartan Related Compound C ( 10 mg ) | F0C208 | \$624 |
| 1711461 | Verteporfin (200 mg) | F0C166 | \$156 |
| 1711472 | Verteporfin Related Compound A ( 50 mg ) | F0C167 | \$487 |
| 1714506 | Vinorelbine Tartrate (200 mg) | F0C243 | \$156 |
| 1714528 | Vinorelbine Related Compound A ( 25 mg ) | F0C242 | \$487 |
| 1717708 | Vitexin ( 30 mg ) | F0C142 | \$520 |
| 1724656 | Zileuton ( 150 mg ) | F0C062 | \$156 |
| 1724667 | Zileuton Related Compound A ( 50 mg ) | F0B316 | \$487 |
| 1724678 | Zileuton Related Compound B ( 50 mg ) | F0B313 | \$487 |
| 1724689 | Zileuton Related Compound C ( 50 mg ) | F0B299 | \$487 |

## USING AND ORDERING USP REFERENCE STANDARDS

## Official Reference Standards

USP Reference Standards are required for use in pharmacopeial assays and tests in the official standards publication, the United States Pharmacopeia-National Formulary (USP-NF). USP Reference Standards help to ensure compliance with the official, FDA-enforceable quality requirements in the $U S P-N F$. The Reference Standards also lend themselves to many other applications, including measurements required to attain accurate and reproducible results in modern chromatographic and spectrophotometric methods.

## Rigorous Testing and Quality Control

USP Reference Standards are selected for their high purity, critical characteristics, and suitability for the intended purpose. Unless a USP Reference Standard label states a specific potency or content, the USP Reference Standard is taken as being $100 \%$ pure for the USP purposes for which it is provided.

Heterogeneous substances, of natural origin, are also designated "Reference Standards" where needed. Usually these are the counterparts of international standards.

USP Reference Standards are established through a process of rigorous testing, evaluation, and quality control (See page 6 for a process overview). They are independently tested in three or more laboratories-USP, FDA, and academic and industrial laboratories throughout the United States. The Reference Standards are released under the authority of USP's Board of Trustees, on the recommendation of the USP Reference Standards Expert Committee, which approves selection and suitability of each lot.

## Reference Standards Categories

USP offers more than 1,510 Reference Standards for pharmaceuticals, excipients, and dietary supplements. On pages 12-50 of this catalog, you'll find a full list of available USP and NF Reference Standards, with information updated through Nov. 2003. The list includes:

- Reference Standards required by the current official edition of $U S P-N F$.
- Reference Standards not required in the current $U S P-N F$, but for which sufficient demand remains.
- Reference Standards specified in the current edition of the Food Chemicals Codex (FCC).
- Authentic Substances (AS)—highly purified samples of chemicals, including substances of abuse, required by analytical, clinical, pharmaceutical, and research laboratories.

The distribution of controlled substances is subject to the regulations and licensing provisions of the Drug Enforcement Administration (DEA) of the U.S. Department of Justice.

USP also collaborates with the World Health Organization in its program to provide international biological standards and chemical reference materials for antibiotics, biologicals, and chemotherapeutic agents. Some USP Reference Standards are standardized in terms of the corresponding international standards.

## Proper Use of USP Reference Standards

USP Reference Standards are provided primarily for quality control use in conducting the pharmacopeial assays and tests described in the $U S P-N F$. Neither Reference Standards nor Authentic Substances are intended for use as drugs, dietary supplements, or medical devices.

To serve its intended purpose, each USP Reference Standard must be properly stored, handled, and used. Users of USP Reference Standards should refer to General Chapter $\langle 11\rangle$ in the $U S P-N F$ :

## Listing and directions in USP-NF

- Refer to the list of revisions, additions, and deletions of individual USP Reference Standards in USP 27-NF 22. Individual $U S P$ or $N F$ monographs specify the USP Reference Standard(s) required for assay and test procedures. The USP 27-NF 22 General Test Chapter $\langle 11\rangle$ USP Reference Standards provides additional information and instructions for proper use and storage. Note that if specific instructions for use appearing on the label of a USP Reference Standard differ from the instructions in Chapter $\langle 11\rangle$, the instructions on the label take precedence.
- Consult the cumulative updates to Reference Standards information provided in USP-NF Supplements and also in $U S P-N F$ Interim Revision Announcements, which are published in USP's bimonthly journal, Pharmacopeial Forum.


## Suitability for use

- The user must ascertain that the Reference Standards they are using are an official lot.
- The user must determine the suitability of Reference Standards for applications and uses not in the $U S P-N F$.


## USING AND ORDERING USP REFERENCE STANDARDS

## Storing

- Ensure that the USP Reference Standards are stored in their original stoppered containers, according to any special label directions, away from heat and humidity, and protected from light.


## Weighing

- Ensure that Reference Standard substances are accurately weighed-taking due account of relatively large errors potentially associated with weighing small masses-where it is directed that a standard solution or a standard preparation be prepared for a quantitative determination. See USP 27-NF 22 General Chapters $\langle 41\rangle$ Weights and Balances and $\langle 31\rangle$ Volumetric Apparatus, and USP-NF General Notices, for information regarding appropriate use of USP Reference Standards.


## Drying

- Use a clean and dry vessel, and not the original container, as the drying vessel where a USP Reference Standard is required to be dried before use.
- Make sure not to dry a specimen repeatedly at temperatures above 25 degrees.
- Follow any special drying requirements specified on the Reference Standards label or in specific sections of USP or NF monographs (note that any specific instructions on the label or in the monograph supersede the usual instructions in Procedures under Tests and Assays in USP-NF General Notices).
- Follow Method I under $U S P-N F$ General Chapter $\langle 921\rangle$ Water Determination where the titrimetric determination of water is required at the time a Reference Standard is to be used.
Instrumental or microanalytical methods are acceptable for this purpose. When using typical amounts, users must titrate about 50 mg of the Reference Standard with a fourfold dilution of the reagent.


## ORDERING USP REFERENCE STANDARDS

## Four convenient ways to order

1. Phone: Call USP with your requirements: (800) 227-8772 from the U.S. or Canada and (301) 881-0666 from other countries. Please note that DEA controlled substances cannot be placed over the phone.

Hours of operation:
Monday-Friday
8:30AM-6:00PM

Fax: Fax your orders to (301) 816-8148.
Online: Order through the World Wide Web at
http://www.usp.org/products. Please note that DEA controlled substances cannot be ordered online.
Mail: Send all mail orders to:
U.S. Pharmacopeia

Customer Service Department
12601 Twinbrook Parkway
Rockville, MD 20852, USA

## Important Order/Policy Information

For fax and mail orders, please use the order form at the back of this catalog. Official purchase orders on company letterhead may also be used to order USP Reference Standards. The purchase orders must have billing and shipping addresses and should include the catalog number, the name of the official Reference Standard, and the number of units ordered. Lot numbers need not be specified on written purchase orders as USP only ships current official lots. Confirmation orders may be sent and must clearly be designated as such. The USP does not assume responsibility for duplication of orders not clearly marked as confirmation orders.

## Pricing

USP Reference Standards must be ordered in whole units. Please note that one unit may include several individual containers.

Reference Standards unit prices included in the product listings from pages $12-50$ of this catalog are effective until December 31, 2003. Please note that prices and package sizes are subject to change without notice.

## No Returns or Exchanges

USP Reference Standards may not be returned or exchanged for refund.

## Quantity Discounts

A 5\% discount is allowed for 5-24 units of any one Reference Standard in a single order, and a $10 \%$ discount for 25 or more units of any one Reference Standard in a single order. These discounts are subject to change without notice.

## Shipping

- Reference Standards orders can only be shipped to a street address and not to P.O. boxes.


## USING AND ORDERING USP REFERENCE STANDARDS

- Orders to the U.S. and Ontario, Canada are shipped via air courier of USP's choice at a charge of $\$ 11$ or via air courier of the customer's choice at an additional $\$ 25$ charge.
- Non-controlled substance orders to Canadian provinces other than Ontario are shipped via air courier of USP's choice at a charge of U.S. $\$ 70$. Carriers of the customer's choice incur an additional $\$ 25$ charge.
- Non-controlled substance orders to be shipped outside the U.S. and Canada are accepted directly by USP only when customs forms related to export are not required. They are shipped via air courier of USP's choice at a charge of U.S. $\$ 70$. Carriers of the customer's choice incur an additional $\$ 25$ charge.
- Shipping in cold pack can be done at customer request for an extra charge of \$25.
- Controlled substance orders to anywhere outside the U.S. are shipped via air courier of USP's choice with a charge of U.S. $\$ 220$.
- An additional shipping charge may be assessed for dangerous goods shipments.
- An additional shipping charge of $\$ 75$ will be assessed for rush/ same-day shipments.
- Customers may provide their shipping account numbers to have shipping charged directly.


## Payment

- Full payment in advance, in U.S. dollars, is required for all U.S. orders unless open account status has been granted by USP's Finance Department. To apply for open account status, an application can be requested by calling (301) 816-8177.
- Full payment in advance, in U.S. dollars, is required for all non-U.S. orders.
- Payment may be made by check, money orders, credit cards (VISA, MasterCard, American Express), and electronic wire transfer (please call (301) 816-8177 to get bank information for wire transfers). The customer is responsible for any bank fees and must include it in the payment. The customer is also responsible for any other fees such as customs duties, taxes, or tariffs.


## List Chemicals

The following Reference Standards are "List Chemicals": Dihydroergotamine Mesylate
*Ephedrine Sulfate
Ergonovine Maleate

[^35]Ergotamine Tartrate<br>Methylergonovine Maleate<br>Phenylpropanolamine Bitartrate<br>Phenylpropanolamine HCl<br>Pseudoephedrine HCl<br>Pseudoephedrine Sulfate

An organization in the United States seeking to purchase a List Chemical Reference Standard for resale to another customer must have a DEA registration (either a controlled substance or List Chemical registration). If an organization in the United States is purchasing the List Chemical Reference Standard for its own analytical use, it must provide USP with a letter on company letterhead describing the reason for the purchase.

## CONTROLLED DRUG SUBSTANCE ORDER

## DEA Requirements (U.S. Orders)

For all orders for controlled drug substances-regulated by the U.S. Drug Enforcement Administration (DEA)-to be shipped within the U.S., a copy of the customer's current DEA Registration Certificate must be on file with USP. To order Schedule I and II standards, customers must submit, with their order forms or purchase orders, a DEA Form 222-C, properly completed. In addition, customers ordering DEA Schedules III and IV must provide appropriate DEA registration numbers for those schedules on their order forms or purchase orders.

## DEA Requirements (International Orders)

For all international controlled drug substance orders, please contact Julie Smith at (301) 816-8164 or foreigncontrols@ usp.org.

All orders for controlled drug substances-regulated by the U.S. Drug Enforcement Administration (DEA)-to be shipped outside the U.S. must be accompanied by:

1. Full payment.
2. An import permit (in English or with an English translation attached) valid at least 6 months from the date of its receipt by USP Customer Service.
3. A statement of non-reexport and use for medical or scientific purposes (in English or with an English translation attached).
4. Purchase Order or Price Quote given by USP.

## USING AND ORDERING USP REFERENCE STANDARDS

On receiving the order, USP takes 2-3 business days to:

- Review all documents to make sure they are adequate and appropriate.
- Complete and legally approve the required DEA forms.
- Forward the forms to the DEA office to obtain the necessary Export Permits.

USP cannot ship items without an Export Permit. While it typically takes 6-10 weeks to get the permit from the DEA, USP has no control over the time in which permits are issued. On receiving the Export Permit, USP completes processing of the order in 1-3 days and ships out the materials through its freight forwarder.

Controlled substances (CI, CII, CIII, CIV, CV) shipped to an international address, including Canada, add $\$ 25$ per unit.

For controlled substance orders to be shipped to Mexico, in addition to the DEA processing period, an additional week is required to obtain a certificate from the Mexican Embassy, authorizing the shipment to enter the country. Customers will pay an additional $\$ 114$ to cover the fee charged by the Mexican Embassy per import permit.

## Back Orders

USP will ship a back-ordered item if that item becomes available within 30 days of the date the order is placed if there is a valid open P.O. or payment for the item. If the order is more than 30 days old when the item becomes available, the customer will receive a Notice of Availability (NOA), indicating that the item is available. Such items will be shipped only after USP receives written authorization by the customer. The order will be canceled if the Reference Standard does not become available within six months of the original order. NOAs not replied to within 45 days of generation will be cancelled, and the customer account will be credited appropriately.

Customers may send confirmation orders for back-ordered Reference Standards that subsequently become available. They must clearly designate the confirmation orders as such-USP is not responsible for duplication of orders not clearly designated.

## HOW TO READ PRODUCT LISTINGS

Column 1 (Catalog Number): Catalog number currently assigned to each Reference Standard and Authentic Substance. Please include this number in your orders.

Column 2 (Former Catalog Number): Catalog numbers assigned prior to July 2002. These numbers are provided for your convenience so you can easily cross-reference current numbers against your earlier orders.

Column 3 (Description): Product description as designated in $U S P-N F$, the product label, and / or the Drug Enforcement Administration Control Schedule, as applicable. The quantity of material per container follows the name in parentheses (all materials are in single containers unless otherwise specified).

Column 4 (Current Lot): Current lot designation of each official item being distributed as of the date of this catalog. If the current lot is blank, the item is not in distribution.

Column 5 (Change Code): Codes that identify any change in USP Reference Standards status or information since the Nov./Dec. 2003, official Catalog. Code interpretations are as follows:

| Change <br> Code | Interpretation |
| :---: | :--- |
| 1 | New Reference Standard |
| 2 | New lot |
| 3 | Change in package size or description |
| 4 | Correction of typographical error |
| 5 | New catalog number-use for all orders |
| 6 | Previous lot no longer official; only <br> current lot to be used |
| 7 | Valid use date of previous lot extended <br> 8 |
| Change in catalog number and / or name, <br> see cross-reference section |  |
| 9 | Discontinued |

Column 6 (Previous Lot/Valid Use Date): Identifies lots no longer being distributed. The indicated month and in parenthesis indicates the date (last day of the month) through which that lot was valid as an official USP Reference Standard. (e.g. "F-1 (06/ 00 )" means lot F-1 is no longer being distributed, but was considered official through June 30, 2000.)

Column 7 (CAS Number) ${ }^{*}$ : Chemical Abstracts Service number, when available, for USP Reference Standards and Authentic Substances. In case of mixtures, typically, the CAS number of the analyte of interest is listed.

Column 8 (Price) lists the price of the reference standard.

[^36]
## New Lots in Distribution

| Cat. <br> No. | Description | Curr. <br> Lot. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \hline \text { CAS } \\ \text { No. } \\ \hline \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1048619 | Benazepril Hydrochloride ( 125 mg ) | F0C250 | 1 |  | [86541-74-4] | \$156 |
| 111001 | Chlorhexidine ( 200 mg ) | F0C306 | 1 |  | [55-56-1] | \$156 |
| 111103 | Chlorhexidine Acetate ( 500 mg ) | F0C281 | 1 |  | [56-95-1] | \$156 |
| 1140349 | Clonazepam Related Compound C (25 mg) (2-Bromo-2'-(2-chloroben-zoyl)-4'-nitroacetanilide) | F0C340 | 1 |  | n/f | \$487 |
| 1140418 | Clonidine Related Compound A (25 mg) (Acetylclonidine) | F0C373 | 1 |  | [54707-71-0] | \$487 |
| 1224959 | Dolasetron Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | F0C319 | 1 |  | [115956-13-3] | \$156 |
| 1224960 | Dolasetron Mesylate Related Compound A ( 25 mg ) (Hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3(4H)-one hydrochloride) | F0C321 | 1 |  | n/f | \$487 |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | 1 |  | [84696-12-5] | \$520 |
| 1279837 | Fluoxetine Related Compound C (15 mg) (N-Methyl-N-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-succinamic acid) | F0C352 | 1 |  | n/f | \$487 |
| 1288317 | Ganciclovir Related Compound A (15 mg) ((RS)-2-Amino-9-(2,3-dihy-droxy-propoxymethyl)-1,9-dihydro-purin-6-one) | F0C288 | 1 |  | n/f | \$624 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 | 1 |  | [66-84-2] | \$156 |
| 1356836 | Lamivudine ( 200 mg ) | F0C361 | 1 |  | [134678-17-4] | \$156 |
| 1441232 | Metoprolol Related Compound A (20 mg) ((+/-)1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol) | F0C343 | 1 |  | n/f | \$520 |
| 1441254 | Metoprolol Related Compound C (20 mg) ((+/-)4-[2-Hydroxy-3-(1-methylethyl)aminopropoxy]benzaldehyde) | F0C344 | 1 |  | n/f | \$520 |
| 1535020 | Phenytoin Related Compound B ( 50 mg ) (alpha-((aminocarbonyl)ami-no)-alpha-phenyl benzeneacetic acid) | F0C157 | 1 |  | [6802-95-5] | \$487 |
| 1604508 | Rimantadine Hydrochloride ( 300 mg ) | F0C266 | 1 |  | [1501-84-4] | \$156 |
| 1610090 | Scopoletin (20 mg) | F0C329 | 1 |  | [92-61-5] | \$156 |
| 1667290 | Tiamulin Fumarate ( 250 mg ) | F0C327 | 1 |  | [55297-96-6] | \$156 |
| 1667337 | Tiamulin Related Compound A (50 mg) (Tosyl pleuromutilin) | F0C328 | 1 |  | n/f | \$494 |
| 1019803 | Aminobenzoic Acid (200 mg) (p-aminobenzoic acid) | H1C083 | 2 | $\begin{array}{\|l} \hline H(10 / 04) \\ G(10 / 00) \\ \hline \end{array}$ | [150-13-0] | \$156 |
| 1046056 | Azithromycin (100 mg) | H0C212 | 2 | $\begin{aligned} & \hline \text { G (11/04) } \\ & \text { F (06/00) } \end{aligned}$ | [117772-70-0] | \$156 |
| 1047503 | Bacitracin (1 g) (Susceptibility disk standard) | G1C254 | 2 | G (07/04) | [1405-87-4] | \$156 |
| 1061005 | Benztropine Mesylate (200 mg) | 10 C 038 | 2 | H (09/04) | [132-17-2] | \$156 |
| 1066009 | Betamethasone (200 mg) | K2C204 | 2 | $\begin{array}{\|l\|l\|} \hline \text { K-1 (10/04) } \\ \text { K (11/02) } \\ \hline \end{array}$ | [378-44-9] | \$156 |
| 1076501 | Bromocriptine Mesylate ( 150 mg ) | 11C197 | 2 | I (09/04) | [22260-51-1] | \$156 |
| 1098049 | Cefprozil E-Isomer ( 50 mg ) | F2C284 | 2 | $\begin{array}{\|l} \hline \text { F-1 (10/04) } \\ \text { F (05/01) } \\ \hline \end{array}$ | [121123-17-9] | \$156 |
| 1107004 | Chloramphenicol (200 mg) | N1C074 | 2 | $\begin{aligned} & \hline N(10 / 04) \\ & M(03 / 00) \\ & \hline \end{aligned}$ | [56-75-7] | \$156 |
| 1119309 | Chlorthalidone Related Compound A (25 mg) (4'-Chloro-3'-sulfamoyl-2benzophenone Carboxylic Acid) | G0C376 | 2,3 | F-3 (07/04) | n/f | \$487 |
| 1144000 | Codeine Phosphate CII (100 mg) | J0C200 | 2 | $\begin{array}{\|l} \hline \text { I-1 (10/04) } \\ \text { I (09/02) } \\ \text { H-1 }(01 / 00) \\ \hline \end{array}$ | [41444-62-6] | \$207 |
| 1162320 | Dacarbazine Related Compound A (50 mg) (5-aminoimidazole-4-carboxamide Hydrochloride) | H0C052 | 2,4 | $\begin{array}{\|l} \hline G(03 / 04) \\ F(03 / 00) \\ \hline \end{array}$ | [72-40-2] | \$487 |
| 1166502 | Dehydrocholic Acid (200 mg) | F-1 | 2,4 | F (03/04) | [81-23-2] | \$156 |
| 1179504 | Dexpanthenol ( 500 mg ) | J0C293 | 2 | $\begin{array}{\|l\|} \hline \text { I (08/04) } \\ H(02 / 02) \\ \hline \end{array}$ | [81-13-0] | \$160 |
| 1189009 | Dicloxacillin Sodium ( 500 mg ) | J0C182 | 2 | $\begin{aligned} & \text { IOB142 (09/04) } \\ & \text { H (05/03) } \end{aligned}$ | [13412-64-1] | \$156 |

New Lots in Distribution

| Cat. No. | Description | $\begin{array}{\|l\|l} \text { Curr. } \\ \text { Lot. } \end{array}$ | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \hline \text { CAS } \\ \text { No. } \\ \hline \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1316004 | Hydrocortisone (200 mg) | M1C110 | 2 | $\begin{array}{\|l\|l\|} \hline \text { M (10/04) } \\ \text { L (09/00) } \\ \hline \end{array}$ | [50-23-7] | \$156 |
| 1324002 | Hydroquinone ( 500 mg ) | H0C249 | 2 | $\begin{array}{\|l} \hline \text { G-1 }(10 / 04) \\ \text { G }(11 / 01) \\ \text { F-4 }(02 / 99) \\ \hline \end{array}$ | [123-31-9] | \$156 |
| 1337004 | Iminodibenzyl (25 mg) | 10C253 | 2 | H (11/04) | [494-19-9] | \$487 |
| 1420006 | Levodopa Related Compound B (50 mg) (3-Methoxytyrosine) | 10C300 | 2,8 | H (07/04) |  | \$487 |
| 1370000 | Loperamide Hydrochloride (200 mg) | H0C202 | 2 | $\begin{array}{\|l} \hline \text { G-2 }(09 / 04) \\ \text { G-1 }(02 / 03) \\ \hline \end{array}$ | [34552-83-5] | \$156 |
| 1370611 | Lovastatin Related Compound A (20 mg) (Butanoic acid, 2-methyl-,1,2,3,4,4a,7,8,8a-octahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[alpha(R*), 3alpha,7beta,8beta( $\left.2 \mathrm{~S}^{*}, 4 \mathrm{~S}^{*}\right)$, 8alpha beta]]-) | G0C326 | 2 | F0B235 (09/04) | n/f | \$487 |
| 1392002 | Mercaptopurine ( 500 mg ) | I2C263 | 2 | $\begin{array}{\|l\|} \hline \text { I-1 (10/04) } \\ \text { I (07/02) } \\ \text { H (12/99) } \\ \hline \end{array}$ | [6112-76-1] | \$156 |
| 1412008 | Methocarbamol (200 mg) | H2B029 | 2,4 | H-1 (03/04) | [532-03-6] | \$156 |
| 1473002 | Noroxymorphone Hydrochloride CII ( 50 mg ) | H1C177 | 2 | H (11/04) | n/f | \$560 |
| 1502552 | Penicillin G Procaine ( 200 mg ) | G0C271 | 2 | $\begin{array}{\|l\|l\|} \hline F-1(08 / 04) \\ F & (03 / 99) \\ \hline \end{array}$ | [6130-64-9] | \$156 |
| 1522301 | Pheniramine Maleate ( 100 mg ) | F1C342 | 2 | F (08/04) | [132-20-7] | \$156 |
| 1561008 | Prilocaine Hydrochloride (200 mg) | F3B215 | 2,4 | F-2 (03/04) | [1786-81-8] | \$156 |
| 1574000 | Propoxyphene Hydrochloride CII (1 g) | LOC285 | 2 | K (09/04) | [1639-60-7] | \$207 |
| 1597504 | Quininone ( 50 mg ) | H0B034 | 2,4 | G-1 (03/04) | [84-31-1] | \$487 |
| 1603006 | Riboflavin ( 500 mg ) (Vitamin B2) | N0C021 | 2 | $\begin{array}{\|l\|} \hline \text { M-1 (09/04) } \\ \text { M (11/00) } \\ \hline \end{array}$ | [83-88-5] | \$156 |
| 1624006 | Sulfacetamide Sodium (500 mg) | 11B318 | 2 | $\begin{array}{\|l\|l\|} \hline I(09 / 04) \\ H & (08 / 01) \\ \hline \end{array}$ | [6209-17-2] | \$156 |
| 1625009 | Sulfadiazine ( 200 mg ) | J | 2,4 | 1 (03/04) | [68-35-9] | \$156 |
| 1686003 | Triflupromazine Hydrochloride ( 200 mg ) | F-2 | 2,4 | F-1 (03/04) | [1098-60-8] | \$156 |
| 1705505 | Undecylenic Acid (200 mg) | G2C018 | 2 | $\begin{array}{\|l} \hline \text { G-1 (11/04) } \\ \text { G (01/02) } \end{array}$ | [112-38-9] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1000601 | Acebutolol Hydrochloride ( 125 mg ) | F-1 |  |  | [34381-68-5] | \$156 |
| 1001003 | Acenocoumarol (200 mg) | F |  |  | [152-72-7] | \$156 |
| 1001502 | Acepromazine Maleate ( 250 mg ) | F-2 |  | F-1 (05/02) | [3598-37-6] | \$156 |
| 1002505 | Acesulfame Potassium (200 mg) | F0C136 |  |  | [55589-62-3] | \$260 |
| 1003009 | Acetaminophen (400 mg) | J-1 |  | $\begin{array}{\|l\|} \hline \mathrm{J}(05 / 02) \\ \mathrm{I}(05 / 99) \\ \hline \end{array}$ | [103-90-2] | \$124 |
| 1004001 | Acetanilide Melting Point Standard (500 mg) (Approximately 114 degrees) | M0A029 |  | $\begin{array}{\|l\|} \hline \mathrm{L}(06 / 04) \\ \mathrm{K}(02 / 00) \\ \hline \end{array}$ | [103-84-4] | \$75 |
| 1005004 | Acetazolamide (2 g) | J |  |  | [59-66-5] | \$156 |
| 1006007 | Acetohexamide (250 mg) | H |  | G-1 (06/99) | [968-81-0] | \$156 |
| 1006506 | Acetohydroxamic Acid ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  | F (03/03) | [546-88-3] | \$156 |
| 1007000 | Acetophenazine Maleate ( 200 mg ) | F-1 |  |  | [5714-00-1] | \$156 |
| 1008002 | alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane $(125 \mathrm{mg})$ | G-3 |  |  | n/f | \$487 |
| 1008501 | Acetylcholine Chloride ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | [60-31-1] | \$156 |
| 1009005 | Acetylcysteine (200 mg) | H1B169 |  | H (01/04) | [616-91-1] | \$156 |
| 1009901 | Acetyltributyl Citrate ( 500 mg ) | G0C120 |  | F (05/04) | [77-90-7] | \$156 |
| 1009923 | Acetyltriethyl Citrate ( 500 mg ) | F-1 |  | F (05/02) | [77-89-4] | \$156 |
| 1012065 | Acyclovir (300 mg) | J0C149 |  | 1 (06/04) | [59277-89-3] | \$197 |
| 1012101 | Adenine ( 200 mg ) | G-1 |  | G (06/00) | [73-24-5] | \$156 |
| 1012123 | Adenosine ( 200 mg ) | F1B058 |  | F (04/03) | [58-61-7] | \$156 |
| 1012145 | Agigenin (25 mg) | F |  |  | n/f | \$156 |
| 1012509 | L-Alanine ( 200 mg ) | F-2 |  | F-1 (04/01) | [56-41-7] | \$156 |
| 1012553 | Albendazole (200 mg) | G |  | F-1 (01/00) | [54965-21-8] | \$156 |
| 1012600 | Albuterol ( 200 mg ) | 1 |  | H (12/00) | [18559-94-9] | \$156 |
| 1012633 | Albuterol Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | $J$ |  | I (04/00) | [51022-70-9] | \$156 |
| 1012757 | Alclometasone Dipropionate ( 300 mg ) | H |  | G (01/00) | [66734-13-2] | \$156 |
| 1012780 | Alendronate Sodium (200 mg) | F0B315 |  |  | [121268-17-5] | \$156 |
| 1012906 | Alfentanil Hydrochloride CII ( 500 mg ) | F0B016 |  |  | [70879-28-6] | \$207 |
| 1012939 | Allantoin (200 mg) | FOC169 |  |  | [97-59-6] | \$156 |
| 1012950 | Alliin (25 mg) | F |  |  | [556-27-4] | \$1,525 |
| 1013002 | Allopurinol ( 250 mg ) | I-1 |  | I (07/02) | [315-30-0] | \$156 |
| 1013024 | Allopurinol Related Compound A (50 mg) (3-Amino-4-carboxamidopyrazole Hemisulfate) | G |  | $\begin{array}{\|l} \mathrm{F}-3(05 / 02) \\ \mathrm{F}-2(04 / 99) \\ \hline \end{array}$ | n/f | \$487 |
| 1013057 | S-Allyl-L-Cysteine ( 25 mg ) | F |  |  | n/f | \$487 |
| 1014005 | Alphaprodine Hydrochloride CII ( 250 mg ) | F |  |  | [561-78-4] | \$207 |
| 1015008 | Alprazolam CIV (200 mg) | H |  |  | [28981-97-7] | \$207 |
| 1016000 | Alprostadil ( 25 mg ) | H |  |  | [745-65-3] | \$1,525 |
| 1017105 | Altretamine ( 500 mg ) | F |  |  | [645-05-6] | \$156 |
| 1017502 | Dried Aluminum Hydroxide Gel ( $200 \mathrm{mg} \mathrm{)}$ | F2B120 |  | F-1 (01/04) | [21645-51-2] | \$156 |
| 1018505 | Amantadine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G (04/01) | [665-66-7] | \$156 |
| 1019202 | Amcinonide (200 mg) | G0B260 |  | F-1 (03/04) | [51022-69-6] | \$156 |
| 1019417 | Amifostine Disulfide ( 25 mg ) | F0C152 |  |  | [112901-68-5] | \$487 |
| 1019508 | Amikacin (200 mg) | 1 |  | H (08/00) | [37517-28-5] | \$156 |
| 1019701 | Amiloride Hydrochloride ( 500 mg ) | H |  |  | [17440-83-4] | \$156 |
| 1019756 | Aminobenzoate Potassium (200 mg) | F-1 |  | F (06/01) | [138-84-1] | \$156 |
| 1019767 | Aminobenzoate Sodium (200 mg) | F |  |  | [55-06-6] | \$156 |
| 1019803 |  | H1C083 | 2 | $\begin{array}{r} \mathrm{H}(10 / 04) \\ \mathrm{G}(10 / 00) \\ \hline \end{array}$ | [150-13-0] | \$156 |

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| 1020008 | Aminobutanol ( 500 mg ) | G-1 |  | G (06/99) | [13054-87-0] | \$389 |
| 1021000 | Aminocaproic Acid (200 mg) | F-4 |  |  | [60-32-2] | \$156 |
| 1021703 | N -(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methylene)-amino]-glycine ( 25 mg ) | F-1 |  |  | n/f | \$487 |
| 1022808 | 2-Amino-5-chlorobenzophenone (25 mg) | 1 |  | H-1 (01/03) | [719-59-5] | \$487 |
| 1023403 | 3-Amino-6-chloro-1-methyl-4-phenylcarbostyril ( 25 mg ) | I |  | H (04/01) | [5220-02-0] | \$487 |
| 1025205 | Aminoglutethimide (200 mg) | F |  |  | [125-84-8] | \$156 |
| 1025307 | m-Aminoglutethimide ( 100 mg ) | G |  | F (05/01) | n/f | \$487 |
| 1025351 | Aminohippuric Acid (200 mg) | F-1 |  |  | [61-78-9] | \$156 |
| 1025806 | 2-[3-Amino-5-(n-methylacetamido)-2,4,6-triiodobenzamido]-2-deoxy-dglucose ( 25 mg ) | F |  |  | n/f | \$487 |
| 1025908 | Aminopentamide Sulfate ( 200 mg ) | F0B273 |  |  | [60-46-8] | \$156 |
| 1026004 | m-Aminophenol ( 300 mg ) | F |  |  | [591-27-5] | \$487 |
| 1026401 | Aminosalicylic Acid (125 mg) | F-1 |  | F (03/99) | [65-49-6] | \$124 |
| 1026605 | 3-Amino-2,4,6-triodobenzoic Acid ( 50 mg ) | G |  |  | [3119-15-1] | \$487 |
| 1027007 | 5-Amino-2,4,6-triiodo-N-methylisophthalamic Acid ( 50 mg ) | F-1 |  |  | [2280-89-9] | \$487 |
| 1028000 | Amitraz (200 mg) | F0C042 |  |  | [33089-61-1] | \$156 |
| 1029002 | Amitriptyline Hydrochloride (200 mg) | J0A004 |  | I (03/03) | [549-18-8] | \$156 |
| 1029909 | Ammonio Methacrylate Copolymer Type A (100 mg) | F-1 |  | F (06/01) | [33434-24-1] | \$156 |
| 1029910 | Ammonio Methacrylate Copolymer Type B (100 mg) | F-1 |  | F (05/00) | [33434-24-1] | \$156 |
| 1029953 | Ammonium Chloride (200 mg) | F0C134 |  |  | [12125-02-9] | \$156 |
| 1030001 | Amobarbital CII (200 mg) | F-2 |  |  | [57-43-2] | \$207 |
| 1031004 | Amodiaquine Hydrochloride ( 500 mg ) | H0B238 |  | G-1 (04/03) | [6398-98-7] | \$156 |
| 1031401 | Amoxapine ( 200 mg ) | G |  | F-1 (04/02) | [14028-44-5] | \$156 |
| 1031503 | Amoxicillin ( 200 mg ) | J0C043 |  | I (07/04) | [61336-70-7] | \$156 |
| 1032007 | Amphotericin B (125 mg) | J-2 |  | J-1 (07/02) | [1397-89-3] | \$124 |
| 1033000 | Ampicillin ( 200 mg ) | J-1 |  | $J(12 / 01)$ | [69-53-4] | \$156 |
| 1033203 | Ampicillin Sodium ( 125 mg ) | G-1 |  | G (10/99) | [69-52-3] | \$124 |
| 1033407 | Ampicillin Trihydrate (200 mg) | G |  |  | [7177-48-2] | \$156 |
| 1034002 | Amprolium ( 200 mg ) | F-1 |  | F (04/02) | [121-25-5] | \$156 |
| 1034308 | Amrinone ( 500 mg ) | G |  |  | [60719-84-8] | \$156 |
| 1034320 | Amrinone Related Compound A (100 mg) (5-carboxamide[3,4'-bipyr-idinj-6(1H)-one) | F |  |  | [62749-46-6] | \$487 |
| 1034341 | Amrinone Related Compound B ( 100 mg ) ( N -(1,6-dihydro-6-oxo-( 3,4 '-bipyridine)-5-yl)-2-hydroxypropanamide) | F-1 |  | F (03/00) | n/f | \$487 |
| 1034363 | Amrinone Related Compound C (50 mg) (1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-carbonitrile) | F-1 |  | F (05/00) | n/f | \$487 |
| 1036008 | Anileridine Hydrochloride CII ( $250 \mathrm{mg} \mathrm{)}$ | F |  |  | [126-12-5] | \$207 |
| 1036507 | 3-Anilino-2-(3,4,5-trimethoxybenzyl) acrylonitrile ( 25 mg ) | G-1 |  |  | [30078-48-9] | \$487 |
| 1038003 | Antazoline Phosphate (200 mg) | H |  | G-1 (04/02) | [154-68-7] | \$156 |
| 1039006 | Anthralin (200 mg) | 10B221 |  | H (11/02) | [1143-38-0] | \$156 |
| 1040005 | Antipyrine (200 mg) | G |  | F-4 (09/01) | [60-80-0] | \$156 |
| 1040708 | Apigenin-7-glucoside ( 30 mg ) | F |  |  | n/f | \$487 |
| 1041008 | Apomorphine Hydrochloride ( 250 mg ) | H |  | G (01/03) | [41372-20-7] | \$162 |
| 1041609 | Apraclonidine Hydrochloride ( 100 mg ) | H0B112 |  | G (06/03) | [73218-79-8] | \$479 |
| 1042000 | Aprobarbital CIII ( $200 \mathrm{mg} \mathrm{)} \mathrm{(AS)}$ | F-1 |  |  | [77-02-1] | \$207 |
| 1042500 | L-Arginine (200 mg) | G-1 |  | G (09/00) | [74-79-3] | \$156 |
| 1042601 | Arginine Hydrochloride ( 125 mg ) | G0B060 |  | F-1 (05/03) | [1119-34-2] | \$124 |
| 1042703 | Arsanilic Acid ( 25 mg ) | F |  |  | [98-50-0] | \$156 |
| 1043003 | Ascorbic Acid (1 g) (Vitamin C) | Q0B012 |  | P (04/03) | [50-81-7] | \$156 |

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| 1043706 | Aspartame (200 mg) | H1B125 |  | H (05/03) | [22839-47-0] | \$156 |
| 1043750 | Aspartame Acesulfame (200 mg) | F0C137 |  |  | [106372-55-8] | \$156 |
| 1043728 | Aspartame Related Compound A (75 mg) (5-Benzyl-3,6-dioxo-2piperazineacetic Acid) | H |  | G-1 (10/99) | [5262-10-2] | \$487 |
| 1043819 | Aspartic Acid (100 mg) | F0B087 |  |  | [6899-03-2] | \$156 |
| 1044006 | Aspirin ( 500 mg ) | H |  | G-1 (11/02) | [50-78-2] | \$156 |
| 1044301 | Astemizole ( 200 mg ) | F |  |  | [68844-77-9] | \$156 |
| 1044403 | Atenolol ( 200 mg ) | H |  | G (08/01) | [29122-68-7] | \$156 |
| 1044651 | Atovaquone ( 200 mg ) | FOB190 |  |  | [95233-18-4] | \$156 |
| 1044662 | Atovaquone Related Compound A ( 25 mg ) (cis-2-[4-(4-chlorophenyl)-cyclohexyl]-3-hydroxy-1,4-naphthoquinone) | F0B188 |  |  | n/f | \$487 |
| 1044800 | Atracurium Besylate ( 100 mg ) | F0B143 |  |  | [64228-81-5] | \$156 |
| 1045009 | Atropine Sulfate ( 500 mg ) | M0B098 |  | L-2 (04/03) <br> L-1 (06/02) <br> L (10/00) | [5908-99-6] | \$156 |
| 1045337 | Avobenzone ( 500 mg ) | G0B280 |  | F (09/03) | [70356-09-1] | \$156 |
| 1045508 | Aurothioglucose ( 100 mg ) | H0B224 |  | $\begin{aligned} & \hline \text { G (10/03) } \\ & \text { F (12/01) } \end{aligned}$ | [12192-57-3] | \$156 |
| 1045600 | Azaerythromycin A (100 mg) | G |  | $\begin{array}{\|l} \hline \text { F-1 (02/02) } \\ \text { F (02/99) } \\ \hline \end{array}$ | [76801-85-9] | \$156 |
| 1045756 | Azaperone (200 mg) | F |  |  | [1649-18-9] | \$156 |
| 1045803 | Azatadine Maleate (200 mg) | G0B300 |  | $\begin{array}{\|l\|l\|} \hline \text { F-1 (04/04) } \\ \text { F (06/00) } \\ \hline \end{array}$ | [3978-86-7] | \$156 |
| 1046001 | Azathioprine (200 mg) | H |  | G-1 (02/00) | [446-86-6] | \$156 |
| 1046056 | Azithromycin (100 mg) | H0C212 | 2 | $\begin{array}{\|l\|l\|} \hline G(11 / 04) \\ F(06 / 00) \\ \hline \end{array}$ | [117772-70-0] | \$156 |
| 1046103 | Azlocillin Sodium (200 mg) | F |  |  | [37091-65-9] | \$156 |
| 1046147 | Azo-aminoglutethimide ( 100 mg ) | F |  |  | n/f | \$487 |
| 1046205 | Aztreonam ( 200 mg ) | G0C077 |  | F-1 (03/04) | [78110-38-0] | \$156 |
| 1046307 | Aztreonam E-isomer ( 50 mg ) | F |  |  | n/f | \$156 |
| 1046409 | Open Ring Aztreonam ( 50 mg ) | F |  |  | [87500-74-1] | \$156 |
| 1047300 | Bacampicillin Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G0B053 |  | F (11/02) | [37661-08-8] | \$156 |
| 1047503 | Bacitracin (1 g) (Susceptibility disk standard) | G1C254 | 2 | G (07/04) | [1405-87-4] | \$156 |
| 1048007 | Bacitracin Zinc (200 mg) | N0A024 |  | $\begin{array}{\|l\|} \hline \text { M-1 }(11 / 02) \\ M(02 / 00) \\ \hline \end{array}$ | [1405-89-6] | \$156 |
| 1048200 | Baclofen ( 500 mg ) | 1 |  |  | [1134-47-0] | \$156 |
| 1048222 | Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone) | H |  |  | n/f | \$389 |
| 1048506 | Beclomethasone Dipropionate (200 mg) | K |  | $J$ (12/00) | [5534-09-8] | \$156 |
| 1048619 | Benazepril Hydrochloride ( 125 mg ) | F0C250 | 1 |  | [86541-74-4] | \$156 |
| 1048620 | Benazepril Related Compound A (15 mg) ((3R)-3-[[(1R)-1-(ethoxycar-bonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benaza-pine-1-acetic acid, monohydrochloride) | F0C252 |  |  | n/f | \$487 |
| 1048630 | Benazepril Related Compound B (15 mg) ((3S)-3-[[(1R)-1-(ethoxycar-bonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benaza-pine-1-acetic acid, monohydrochloride) | F0C256 |  |  | n/f | \$487 |
| 1049000 | Bendroflumethiazide ( 200 mg ) | G-1 |  |  | [73-48-3] | \$156 |
| 1050009 | Benoxinate Hydrochloride ( 200 mg ) | F-2 |  | F-1 (10/99) | [5987-82-6] | \$124 |
| 1051001 | Benzalkonium Chloride ( 5 mL of approx. 10\% aqueous solution) | K0B151 |  | J (06/03) | [8001-54-5] | \$156 |
| 1054000 | Benzocaine ( 500 mg ) | 1 |  |  | [94-09-7] | \$156 |

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| 1055002 | Benzoic Acid (300 mg) | F6B173 |  | $\begin{aligned} & \text { F-5 }(03 / 04) \\ & \text { F-4 }(07 / 01) \\ & \hline \end{aligned}$ | [65-85-0] | \$156 |
| 1056005 | Benzonatate (1 g) | IOB003 |  | H (01/03) | [104-31-4] | \$156 |
| 1056504 | 1,4-Benzoquinone (200 mg) | G1B145 |  | $\begin{aligned} & G(01 / 04) \\ & F-1(11 / 01) \\ & F(09 / 00) \\ & \hline \end{aligned}$ | [106-51-4] | \$156 |
| 1057507 | Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide) | H0B069 |  | G-4 (03/03) | [121-30-2] | \$487 |
| 1059003 | Benzphetamine Hydrochloride CIII (200 mg) (AS) | F-1 |  |  | [5411-22-3] | \$207 |
| 1060002 | Benzthiazide (200 mg) | F |  |  | [91-33-8] | \$156 |
| 1061005 | Benztropine Mesylate (200 mg) | 10 CO 38 | 2 | H (09/04) | [132-17-2] | \$156 |
| 1061901 | Benzyl Alcohol ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | G0B306 |  | FOB106 (10/03) | [100-51-6] | \$156 |
| 1062008 | Benzyl Benzoate (5 g) | J0C060 |  | I (05/04) | [120-51-4] | \$156 |
| 1064003 | 1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride ( 25 mg ) | F-1 |  |  | n/f | \$487 |
| 1065006 | Bephenium Hydroxynaphthoate ( 500 mg ) | F |  |  | [3818-50-6] | \$156 |
| 1065618 | Betahistine Hydrochloride ( 200 mg ) | F0C105 |  |  | [5579-84-0] | \$156 |
| 1065709 | Betaine Hydrochloride ( 200 mg ) | F-1 |  | F (11/02) | [590-46-5] | \$156 |
| 1066009 | Betamethasone (200 mg) | K2C204 | 2 | $\begin{aligned} & \text { K-1 (10/04) } \\ & \text { K (11/02) } \\ & \hline \end{aligned}$ | [378-44-9] | \$156 |
| 1067001 | Betamethasone Acetate ( 500 mg ) | J0B079 |  | I (08/03) | [987-24-6] | \$156 |
| 1067307 | Betamethasone Benzoate ( 200 mg ) | F-1 |  |  | [22298-29-9] | \$156 |
| 1067704 | Betamethasone Dipropionate (125 mg) | K0C229 |  | $\begin{aligned} & \mathrm{J}(04 / 04) \\ & \mathrm{I}(03 / 99) \end{aligned}$ | [5593-20-4] | \$124 |
| 1068004 | Betamethasone Sodium Phosphate (500 mg) | J0B043 |  | $\begin{array}{\|l\|l} \hline \text { I-1 (02/03) } \\ \text { I (01/01) } \\ \hline \end{array}$ | [151-73-5] | \$156 |
| 1069007 | Betamethasone Valerate (200 mg) | $J$ |  | 1 (05/00) | [2152-44-5] | \$156 |
| 1069903 | Betaxolol Hydrochloride ( 200 mg ) | G |  | F-1 (06/00) | [63659-19-8] | \$156 |
| 1070006 | Betazole Hydrochloride ( 200 mg ) | H |  |  | [138-92-1] | \$156 |
| 1071009 | Bethanechol Chloride ( 200 mg ) | G |  | F-3 (07/01) | [590-63-6] | \$156 |
| 1071304 | Bile Salts (10 g) | 10C003 |  | $\begin{aligned} & \hline \mathrm{H}-1(05 / 04) \\ & \mathrm{H}(05 / 99) \end{aligned}$ | [145-42-6] | \$124 |
| 1071508 | Biotin (200 mg) | H1B019 |  | H (04/03) | [58-85-5] | \$156 |
| 1072001 | Biperiden ( 200 mg ) | F2B080 |  | F-1 (02/04) | [514-65-8] | \$156 |
| 1073004 | Biperiden Hydrochloride (200 mg) | F-3 |  | F-2 (06/99) | [1235-82-1] | \$156 |
| 1074007 | Bisacodyl (125 mg) | 11B162 |  | $\begin{aligned} & \hline \text { I (01/04) } \\ & \mathrm{H}-1(02 / 99) \\ & \hline \end{aligned}$ | [603-50-9] | \$124 |
| 1074700 | 2,5-Bis(D-arabino-1,2,3,4-tetrahydroxybutyl)pyrazine ( 25 mg ) | F |  |  | n/f | \$487 |
| 1075203 | Bis(2-ethylhexyl)maleate ( 250 mg ) | F-2 |  | F-1 (01/01) | [142-16-5] | \$487 |
| 1075509 | p-Bis(di-n-propyl)carbamylbenzenesulfonamide ( 50 mg ) | F |  |  | n/f | \$487 |
| 1075531 | Bismuth Citrate ( 100 mg ) | F |  |  | [813-93-4] | \$156 |
| 1075553 | Bismuth Subsalicylate ( 100 mg ) | F |  |  | [14882-18-9] | \$156 |
| 1075757 | Bisoprolol Fumarate ( 200 mg ) | F0B038 |  |  | [104344-23-2] | \$156 |
| 1076002 | 4,4'-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone ( 25 mg ) |  |  | G (05/03) | n/f | \$487 |
| 1076308 | Bleomycin Sulfate ( 15 mg ) | J0B213 |  | I (01/04) | [9041-93-4] | \$307 |
| 1076352 | Bretylium Tosylate (200 mg) | F-1 |  |  | [61-75-6] | \$156 |
| 1076363 | Brinzolamide (200 mg) | F0C034 |  |  | [138890-62-7] | \$156 |
| 1076374 | Brinzolamide Related Compound A (50 mg) ((S)-(-)-4-ethylamino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide) | F0C033 |  |  | n/f | \$487 |

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| 1076385 | Brinzolamide Related Compound B (50 mg) ((R)-4-amino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide ethanedioate) | F0C035 |  |  | n/f | \$487 |
| 1076501 | Bromocriptine Mesylate ( 150 mg ) | I1C197 | 2 | I (09/04) | [22260-51-1] | \$156 |
| 1077005 | Bromodiphenhydramine Hydrochloride (200 mg) | F-1 |  |  | [1808-12-4] | \$156 |
| 1077708 | 8-Bromotheophylline ( 400 mg ) | G |  | F (07/02) | [10381-75-6] | \$156 |
| 1078008 | Brompheniramine Maleate ( 125 mg ) | 11A036 |  | $\begin{array}{\|l\|} \hline \mathrm{I}(01 / 03) \\ \mathrm{H}-1(04 / 99) \\ \hline \end{array}$ | [980-71-2] | \$124 |
| 1078303 | Bumetanide (250 mg) | 10 C 111 |  | $\begin{array}{\|l\|} \hline \text { HOBO30 (05/04) } \\ \text { G (03/03) } \\ \hline \end{array}$ | [28395-03-1] | \$156 |
| 1078325 | Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5sulfamoylbenzoic Acid) | F-2 |  | F-1 (05/00) | n/f | \$487 |
| 1078336 | Bumetanide Related Compound B ( 25 mg ) (3-Nitro-4-phenoxy-5sulfamoylbenzoic Acid) | F-2 |  | F-1 (01/03) | [28328-53-2] | \$487 |
| 1078507 | Bupivacaine Hydrochloride (1 g) | H |  | $\begin{array}{ll} \hline \text { G-2 }(03 / 03) \\ \text { G-1 } & (08 / 02) \\ \hline \end{array}$ | [14252-80-3] | \$156 |
| 1078700 | Buprenorphine Hydrochloride CIII ( 50 mg ) | F-1 |  | F (02/99) | [53152-21-9] | \$207 |
| 1078711 | Buprenorphine Related Compound A ( 50 mg ) (21-[3-(1-propenyl)]-7-alpha-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14tetrahydrooripavine) | F1C076 |  | F (04/04) | n/f | \$487 |
| 1078733 | Bupropion Hydrochloride ( 200 mg ) | F0C123 |  |  | [31677-93-7] | \$208 |
| 1078802 | Buspirone Hydrochloride ( 200 mg ) | G |  |  | [33386-08-2] | \$156 |
| 1079000 | Butabarbital CIII (200 mg) | H0C007 |  | G (03/04) | [125-40-6] | \$207 |
| 1080000 | Butacaine Sulfate ( 600 mg ) | F |  |  | [149-15-5] | \$156 |
| 1081002 | Butalbital CIII (200 mg) | H0C054 |  | $\begin{array}{\|l\|} \hline \text { G2B077 (07/04) } \\ \text { G-2 (06/03) } \\ \text { G (05/02) } \\ \hline \end{array}$ | [77-26-9] | \$207 |
| 1081501 | Butamben (200 mg) | F |  |  | [94-25-7] | \$156 |
| 1082300 | Butoconazole Nitrate (200 mg) | F1B097 |  | F (03/03) | [64872-77-1] | \$156 |
| 1082504 | Butorphanol Tartrate CIV (500 mg) | J |  | I (06/00) | [58786-99-5] | \$207 |
| 1082800 | Monotertiary-butyl-p-benzoquinone ( 100 mg ) (FCC) | F |  |  | [3602-55-9] | \$156 |
| 1082901 | Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate ( 25 mg ) | F-1 |  |  | n/f | \$487 |
| 1083008 | 2-tert-Butyl-4-hydroxyanisole ( 200 mg ) | L0C028 |  | K (09/03) | [88-32-4] | \$156 |
| 1083100 | 3-tert-Butyl-4-hydroxyanisole (200 mg) | J |  | I-1 (09/01) | [121-00-6] | \$156 |
| 1084000 | Butylparaben (200 mg) | 10C139 |  | $\begin{array}{\|l\|} \hline \mathrm{H}-1(03 / 04) \\ \mathrm{H}(09 / 01) \\ \hline \end{array}$ | [94-26-8] | \$156 |
| 1085003 | Caffeine (200 mg) | J |  | I (06/02) | [58-08-2] | \$156 |
| 1086006 | Caffeine Melting Point Standard (1 g) (Approximately 236 degrees) | JOB204 |  | 1 (03/04) | [58-08-2] | \$92 |
| 1086108 | Calcifediol ( 75 mg ) | G |  |  | [63283-36-3] | \$156 |
| 1086356 | Calcium Ascorbate ( 200 mg ) | F-1 |  | F (08/01) | [5743-28-2] | \$156 |
| 1086800 | Calcium Gluceptate ( 200 mg ) | F-1 |  | F (09/00) | [29039-00-7] | \$156 |
| 1086902 | Calcium Lactobionate (200 mg) | G0B138 |  | $\begin{aligned} & \hline \text { F-1 (01/04) } \\ & \text { F (11/01) } \\ & \hline \end{aligned}$ | [110638-68-1] | \$156 |
| 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) | N-1 |  | N (06/00) | [137-08-6] | \$156 |
| 1087202 | Calcium Saccharate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [5793-89-5] | \$156 |
| 1088001 | Candicidin (200 mg) | F |  |  | [1403-17-4] | \$156 |
| 1089004 | Cannabidiol CI (25 mg) (AS) | F-2 |  |  | [13956-29-1] | \$207 |
| 1090003 | Cannabinol CI (25 mg) (AS) |  |  | F-2 (05/02) | [521-35-7] | \$207 |
| 1091006 | Capreomycin Sulfate (200 mg) | G |  | F (06/01) | [1405-37-4] | \$156 |

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| 1091108 | Capsaicin (100 mg) | G-1 |  | $\begin{array}{\|l\|l\|} \hline G(03 / 02) \\ F-1(06 / 00) \\ F(03 / 99) \\ \hline \end{array}$ | [404-86-4] | \$156 |
| 1091200 | Captopril (200 mg) | H |  |  | [62571-86-2] | \$156 |
| 1091221 | Captopril Disulfide (100 mg) | G1B066 |  | G (01/04) | [64806-05-9] | \$487 |
| 1092009 | Carbachol ( 200 mg ) | G |  |  | [51-83-2] | \$156 |
| 1093001 | Carbamazepine ( 100 mg ) | $J$ |  | I-1 (02/00) | [298-46-4] | \$156 |
| 1093205 | Carbarsone (200 mg) | F |  |  | [121-59-5] | \$156 |
| 1093500 | Carbenicillin Indanyl Sodium ( 300 mg ) | G |  |  | [26605-69-6] | \$156 |
| 1094004 | Carbenicillin Monosodium Monohydrate ( $200 \mathrm{mg} \mathrm{)}$ | G-2 |  |  | n/f | \$156 |
| 1095506 | Carbidopa ( 400 mg ) | 1 |  | H (10/99) | [38821-49-7] | \$156 |
| 1095517 | Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa) | H0B121 |  | G (04/03) | n/f | \$487 |
| 1096000 | Carbinoxamine Maleate ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G-1 (11/02) | [3505-38-2] | \$156 |
| 1096407 | Carboplatin (100 mg) | H0C240 |  | $\begin{aligned} & \hline \text { G (07/04) } \\ & \text { F (03/00) } \end{aligned}$ | [41575-94-4] | \$159 |
| 1096509 | Carboprost Tromethamine (25 mg) | F-1 |  | F (02/01) | [58551-69-2] | \$487 |
| 1096600 | Carisoprodol (1 g) | G |  | F-2 (05/02) | [78-44-4] | \$156 |
| 1096757 | Carteolol Hydrochloride (200 mg) | F-1 |  | F (11/00) | [51781-21-6] | \$156 |
| 1096804 | Cathinone Hydrochloride $\mathbf{C l}$ ( 50 mg ) (alpha-Aminopropiophenone Hydrochloride) | I |  |  | [76333-53-4] | \$560 |
| 1096906 | Cefaclor ( 400 mg ) | H |  |  | [70356-03-5] | \$156 |
| 1096917 | Cefaclor, Delta-3-Isomer ( 30 mg ) | G |  | F-1 (02/00) | n/f | \$156 |
| 1097104 | Cefadroxil ( 125 mg ) | I |  | H (04/99) | [66592-87-8] | \$124 |
| 1097308 | Cefamandole Lithium (200 mg) | H |  |  | n/f | \$156 |
| 1097400 | Cefamandole Nafate (200 mg) | H |  |  | [42540-40-9] | \$156 |
| 1097501 | Cefamandole Sodium ( 250 mg ) | F |  |  | [30034-03-8] | \$156 |
| 1097603 | Cefazolin (400 mg) | K |  | $J(06 / 00)$ | [25953-19-9] | \$156 |
| 1097636 | Cefepime Hydrochloride ( 500 mg ) | F0C063 |  |  | [123171-59-5] | \$156 |
| 1097647 | Cefepime Hydrochloride System Suitability ( 25 mg ) | F0C095 |  |  | n/f | \$156 |
| 1097658 | Cefixime ( 500 mg ) | F |  |  | [79350-37-1] | \$156 |
| 1097771 | Cefmenoxime Hydrochloride ( 350 mg ) | F |  |  | [75738-58-8] | \$156 |
| 1097782 | Cefmetazole (200 mg) | F-1 |  | F (04/02) | [56796-20-4] | \$156 |
| 1097750 | Cefonicid Sodium (1 g) | G |  |  | [61270-78-8] | \$156 |
| 1097705 | Cefoperazone Dihydrate (200 mg) | H |  | G (12/99) | [62893-19-0] | \$156 |
| 1097807 | Ceforanide ( 200 mg ) | F-1 |  | F (07/00) | [60925-61-3] | \$156 |
| 1097909 | Cefotaxime Sodium ( 250 mg ) | 1 |  |  | [64485-93-4] | \$124 |
| 1097975 | Cefotetan (500 mg) | H0C175 |  | $\begin{array}{\|l\|} \hline G(07 / 04) \\ F(09 / 00) \\ \hline \end{array}$ | [69712-56-7] | \$156 |
| 1098005 | Cefotiam Hydrochloride ( 325 mg ) | G0B050 |  | F (01/03) | [66309-69-1] | \$156 |
| 1098049 | Cefprozil E-Isomer ( 50 mg ) | F2C284 | 2 | $\begin{array}{\|l\|} \hline \text { F-1 (10/04) } \\ \text { F (05/01) } \\ \hline \end{array}$ | [121123-17-9] | \$156 |
| 1098050 | Cefprozil Z-Isomer (200 mg) | G0C037 |  | F (12/03) | [121123-17-9] | \$156 |
| 1098107 | Cefoxitin ( 500 mg ) | 1 |  | H (05/00) | [35607-66-0] | \$156 |
| 1098129 | Ceftazidime, Delta-3-Isomer (25 mg) | G |  | F (03/00) | n/f | \$208 |
| 1098130 | Ceftazidime Pentahydrate ( 300 mg ) | H |  | G (12/99) | [78439-06-2] | \$156 |
| 1098173 | Ceftizoxime (200 mg) | H |  |  | [68401-81-0] | \$156 |
| 1098184 | Ceftriaxone Sodium ( 350 mg ) | G0B264 |  | F (08/03) | [104376-79-6] | \$156 |
| 1098195 | Ceftriaxone Sodium E-Isomer ( 25 mg ) | 10C190 |  | H (07/04) G (08/01) F-1 (02/00) | n/f | \$208 |

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| 1098209 | Cefuroxime Sodium ( 200 mg ) | H |  | G-1 (05/00) | [56238-63-2] | \$156 |
| 1098220 | Cefuroxime Axetil ( 500 mg ) | G |  | F-1 (05/02) | [64544-07-6] | \$156 |
| 1098231 | Cefuroxime Axetil Delta-3-Isomers ( 35 mg ) | H0B160 |  | G (03/03) | n/f | \$156 |
| 1098300 | Cellulose Acetate (125 mg) | F-1 |  | F (11/99) | [9004-35-7] | \$124 |
| 1098355 | Cellulose Acetate Phthalate ( 125 mg ) | F-1 |  | F (03/99) | [9004-38-0] | \$124 |
| 1098708 | Cephaeline Hydrobromide ( 200 mg ) | G-1 |  |  | n/f | \$487 |
| 1099008 | Cephalexin ( 250 mg ) | I-2 |  | I-1 (03/00) | [23325-78-2] | \$156 |
| 1102000 | Cephalothin Sodium ( 200 mg ) | 1 |  |  | [58-71-9] | \$156 |
| 1102408 | Cephapirin Benzathine ( 100 mg ) | F |  |  | [97468-37-6] | \$156 |
| 1102500 | Cephapirin Sodium (200 mg) | I-1 |  | 1 (07/02) | [24356-60-3] | \$156 |
| 1102805 | Cephradine ( 200 mg ) | J |  | I (04/00) | [58456-86-3] | \$156 |
| 1103003 | Cetyl Alcohol ( 100 mg ) | 1 |  | H (03/99) | [36653-82-4] | \$156 |
| 1103105 | Cetyl Palmitate ( 50 mg ) | F0B241 |  |  | [540-10-3] | \$156 |
| 1104006 | Cetylpyridinium Chloride ( 500 mg ) | 1 |  | $\begin{array}{\|l\|} \hline \mathrm{H}-1(06 / 01) \\ \mathrm{H}(08 / 99) \\ \hline \end{array}$ | [6004-24-6] | \$156 |
| 1106001 | Chlorambucil ( 125 mg ) | G |  | F-1 (02/99) | [305-03-3] | \$124 |
| 1107004 | Chloramphenicol (200 mg) | N1C074 | 2 | $\begin{array}{\|l\|} \hline N(10 / 04) \\ M(03 / 00) \\ \hline \end{array}$ | [56-75-7] | \$156 |
| 1107300 | Chloramphenicol Palmitate (200 mg) | G-1 |  |  | [530-43-8] | \$156 |
| 1107401 | Chloramphenicol Palmitate Nonpolymorph A (200 mg) | F-1 |  |  | [530-43-8] | \$487 |
| 1107503 | Chloramphenicol Palmitate Polymorph A (200 mg) | G |  | F (08/99) | [530-43-8] | \$487 |
| 1109000 | Chlordiazepoxide CIV (200 mg) | IOB063 |  | H-1 (03/03) | [58-25-3] | \$207 |
| 1110009 | Chlordiazepoxide Hydrochloride CIV (200 mg) | G-4 |  |  | [438-41-5] | \$207 |
| 1110020 | Chlordiazepoxide Related Compound A (25 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide) | G |  |  | [963-39-3] | \$487 |
| 1111001 | Chlorhexidine ( 200 mg ) | F0C306 | 1 |  | [55-56-1] | \$156 |
| 1111103 | Chlorhexidine Acetate ( 500 mg ) | F0C281 | 1 |  | [56-95-1] | \$156 |
| 1112503 | Chlorobutanol ( 200 mg ) | G |  | F-3 (12/01) | [6001-64-5] | \$156 |
| 1115556 | beta-Chlorogenin (20 mg) | F |  |  | n/f | \$156 |
| 1117008 | Chloroprocaine Hydrochloride (200 mg) | G0B285 |  | $\begin{aligned} & \text { F-3 }(01 / 04) \\ & \text { F-2 }(03 / 99) \\ & \hline \end{aligned}$ | [3858-89-7] | \$156 |
| 1118000 | Chloroquine Phosphate ( 500 mg ) | 1 |  | H (10/99) | [50-63-5] | \$156 |
| 1121005 | Chlorothiazide ( 200 mg ) | H0B161 |  | G (04/03) | [58-94-6] | \$156 |
| 1122008 | Chlorotrianisene (1 g) | F |  |  | [569-57-3] | \$156 |
| 1122700 | Chloroxylenol (125 mg) | F2C259 |  | $\begin{array}{\|l\|} \hline \text { F-1 (07/04) } \\ \text { F (10/99) } \\ \hline \end{array}$ | [88-04-0] | \$124 |
| 1122722 | Chloroxylenol Related Compound A (25 mg) (2-chloro-3,5-dimethylphenol) | G0C275 |  | F-1 (07/04) | [5538-41-0] | \$487 |
| 1123000 | Chlorpheniramine Maleate (125 mg) | M0B020 |  | L-1 (06/03) | [113-92-8] | \$124 |
| 1123102 | Chlorpheniramine Maleate Extended-Release Tablets (Drug Release Calibrator, Single Unit) ( 60 Tablets) | G0B259 |  | F (06/03) | [113-92-8] | \$156 |
| 1124003 | Chlorphenoxamine Hydrochloride (200 mg) | F-1 |  |  | [562-09-4] | \$156 |
| 1125006 | Chlorpromazine Hydrochloride (200 mg) | J |  | I (04/99) | [69-09-0] | \$156 |
| 1126009 | Chlorpropamide (200 mg) | H |  |  | [94-20-2] | \$156 |
| 1127001 | Chlorprothixene (200 mg) | F-1 |  |  | [113-59-7] | \$156 |
| 1129007 | Chlortetracycline Hydrochloride ( 200 mg ) | J-1 |  | J (02/02) | [64-72-2] | \$156 |
| 1130006 | Chlorthalidone ( 125 mg ) | H-1 |  | H (07/99) | [77-36-1] | \$124 |
| 1119309 | Chlorthalidone Related Compound A (25 mg) (4'-Chloro-3'-sulfamoyl-2benzophenone Carboxylic Acid) | G0C376 | 2,3 | F-3 (07/04) | n/f | \$487 |
| 1130505 | Chlorzoxazone ( 500 mg ) | 1 |  | H (07/01) | [95-25-0] | \$156 |

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| 1130527 | Chlorzoxazone Related Compound A (50 mg) (2-Amino-4-chlorophenol) | G-1 |  | G (11/00) | [95-85-2] | \$487 |
| 1131009 | Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3) | M0B157 |  | $\begin{aligned} & \text { L (10/03) } \\ & \text { K (09/99) } \end{aligned}$ | [67-97-0] | \$159 |
| 1131803 | Delta-4,6-cholestadienol ( 30 mg ) | F |  |  | [14214-69-8] | \$156 |
| 1132001 | Cholesteryl Caprylate (200 mg) | F |  |  | [1182-42-9] | \$156 |
| 1133004 | Cholestyramine Resin ( 500 mg ) | 1 |  |  | [11041-12-6] | \$124 |
| 1133503 | Cholic Acid (2 g) (AS) | F3B159 |  | F-2 (01/03) | [81-25-4] | \$156 |
| 1133536 | Choline Bitartrate (200 mg) | F0C057 |  |  | [87-67-2] | \$156 |
| 1133547 | Choline Chloride ( 200 mg ) | F0C058 |  |  | [67-48-1] | \$156 |
| 1133570 | Chondroitin Sulfate Sodium ( 300 mg ) | F0B256 |  |  | [39455-18-0] | \$156 |
| 1133638 | Chromium Picolinate ( 100 mg ) | F |  |  | [14639-25-9] | \$156 |
| 1134007 | Chymotrypsin ( 300 mg ) | 1 |  | H (06/01) | [9004-07-3] | \$156 |
| 1134030 | Ciclopirox Olamine ( 125 mg ) | H0C2O7 |  | G (05/03) | [41621-49-2] | \$124 |
| 1134051 | Cilastatin Ammonium Salt ( 100 mg ) | F-1 |  | F (07/00) | n/f | \$156 |
| 1134062 | Cimetidine ( 200 mg ) | I1C081 |  | I (05/04) | [51481-61-9] | \$156 |
| 1134073 | Cimetidine Hydrochloride ( 200 mg ) | F |  |  | [70059-30-2] | \$156 |
| 1134109 | Cinoxacin (200 mg) | F |  |  | [28657-80-9] | \$156 |
| 1134313 | Ciprofloxacin (125 mg) | G-1 |  | G (05/01) | [85721-33-1] | \$124 |
| 1134324 | Ciprofloxacin Ethylenediamine Analog ( 25 mg ) | J0A030 |  | $\begin{array}{\|l\|} \hline \text { I (01/03) } \\ \text { H-1 (02/99) } \end{array}$ | n/f | \$208 |
| 1134335 | Ciprofloxacin Hydrochloride ( 400 mg ) | H |  | G (04/00) | [86393-32-0] | \$156 |
| 1134357 | Cisplatin ( 100 mg ) | H |  | G (03/01) | [15663-27-1] | \$156 |
| 1134368 | Citric Acid (200 mg) | F1B092 |  | $\begin{aligned} & \text { F-1 (01/04) } \\ & F(07 / 02) \\ & \hline \end{aligned}$ | [77-92-9] | \$156 |
| 1134379 | Clarithromycin (75 mg) | F4B183 |  | $\begin{array}{\|l} \hline \text { F-3 }(01 / 04) \\ \text { F-2 }(09 / 01) \\ \hline \end{array}$ | [81103-11-9] | \$156 |
| 1134380 | Clarithromycin Related Compound A (50 mg) (6,11-di-O-methylerythromycin A) | G |  | F (04/01) | n/f | \$208 |
| 1134404 | Clavam-2-carboxylate Potassium (1 Pellet) | H0C089 |  | $\begin{aligned} & \hline \text { G0B225 (12/03) } \\ & \text { F (10/03) } \\ & \hline \end{aligned}$ | n/f | \$487 |
| 1134426 | Clavulanate Lithium ( 200 mg ) | 1 |  | H (09/02) | n/f | \$156 |
| 1134506 | Clemastine Fumarate ( $250 \mathrm{mg} \mathrm{)}$ | 1 |  | H (10/00) | [14976-57-9] | \$156 |
| 1135000 | Clidinium Bromide ( 2 g ) | G |  |  | [3485-62-9] | \$156 |
| 1135021 | Clidinium Bromide Related Compound A (250 mg) (3-Hydroxy-1methylquinuclindinium Bromide) | I |  |  | [76201-95-1] | \$487 |
| 1136002 | Clindamycin Hydrochloride (200 mg) | G4A017 |  | $\begin{aligned} & \text { G-3 (07/03) } \\ & \text { G-2 (05/99) } \end{aligned}$ | [58207-19-5] | \$428 |
| 1137005 | Clindamycin Palmitate Hydrochloride ( 200 mg ) | F-2 |  |  | [25507-04-4] | \$428 |
| 1138008 | Clindamycin Phosphate (125 mg) | IOC165 |  | $\begin{aligned} & \mathrm{H}-3(04 / 04) \\ & \mathrm{H}-2(07 / 03) \\ & \mathrm{H}-1(02 / 99) \\ & \hline \end{aligned}$ | [24729-96-2] | \$214 |
| 1138201 | Clioquinol ( 500 mg ) | M |  | L-1 (01/03) | [130-26-7] | \$156 |
| 1138405 | Clobetasol Propionate ( 200 mg ) | F-1 |  | F (10/01) | [25122-46-7] | \$156 |
| 1138427 | Clobetasol Propionate Related Compound A ( 50 mg ) (9-alpha-fluoro-11-beta-hydroxy-16-beta-methyl-3-oxo-androsta-1,4-diene-17(R)-spiro-2'-[4'-chloro-5'-ethylfuran-3'(2'H)-one]) | F-1 |  | F (01/03) | n/f | \$208 |
| 1138507 | Clocortolone Pivalate (200 mg) | G |  |  | [34097-16-0] | \$156 |
| 1138904 | Clofazimine ( 200 mg ) | F |  |  | [2030-63-9] | \$156 |
| 1139000 | Clofibrate ( 1 g ) | 1 |  | H (04/01) | [637-07-0] | \$156 |
| 1140000 | Clomiphene Citrate ( 500 mg ) | H |  | G-1 (10/99) | [50-41-9] | \$156 |

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| 1140101 | Clomiphene Related Compound A (100 mg) ((E,Z)-2-[4-(1,2-diphenyle-thenyl)phenoxy]-N,N-diethylethanamine Hydrochloride) | F1B206 |  | F (09/03) | n/f | \$208 |
| 1140247 | Clomipramine Hydrochloride ( 200 mg ) | F0C075 |  |  | [17321-77-6] | \$156 |
| 1140305 | Clonazepam CIV (200 mg) | G1B175 |  | $\begin{array}{\|l\|} \hline \text { G (01/04) } \\ \text { F-2 }(01 / 00) \\ \hline \end{array}$ | [1622-61-3] | \$207 |
| 1140327 | Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chloro-phenyl)-6-nitrocarbostyril) | G2B110 |  | $\begin{aligned} & \text { G-1 (01/04) } \\ & \text { G (02/99) } \\ & \hline \end{aligned}$ | n/f | \$487 |
| 1140338 | Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5nitrobenzophenone) | H |  | G (04/01) | [2011-66-7] | \$487 |
| 1140349 | Clonazepam Related Compound C (25 mg) (2-Bromo-2'-(2-chloro-benzoyl)-4'-nitroacetanilide) | F0C340 | 1 |  | n/f | \$487 |
| 1140407 | Clonidine Hydrochloride (200 mg) | G |  |  | [4205-91-8] | \$156 |
| 1140418 | Clonidine Related Compound A (25 mg) (Acetylclonidine) | F0C373 | 1 |  | [54707-71-0] | \$487 |
| 1140509 | Clorazepate Dipotassium CIV (125 mg) | G0B027 |  | $\begin{array}{\|l} \hline \text { F-1 (06/03) } \\ \text { F (12/99) } \\ \hline \end{array}$ | [57109-90-7] | \$207 |
| 1140702 | Clorsulon (200 mg) | F1B084 |  | F (01/04) | [60200-06-8] | \$156 |
| 1141002 | Clotrimazole (200 mg) | J |  | I (05/99) | [23593-75-1] | \$124 |
| 1141024 | Clotrimazole Related Compound A ( 25 mg ) ((0-chlorophenyl)diphenylmethanol) | I |  | $\begin{aligned} & \hline H(10 / 01) \\ & \text { G-1 (02/99) } \end{aligned}$ | [66774-02-5] | \$487 |
| 1141909 | Cloxacillin Benzathine (200 mg) | F-1 |  | F (03/02) | [23736-58-5] | \$156 |
| 1142005 | Cloxacillin Sodium (200 mg) | LOB086 |  | K (01/04) | [7081-44-9] | \$156 |
| 1142107 | Clozapine ( 100 mg ) | F0C032 |  |  | [5786-21-0] | \$260 |
| 1143008 | Cocaine Hydrochloride CII (250 mg) | IOB074 |  | $\begin{array}{\|l\|l} \hline \mathrm{H}-2(01 / 04) \\ \mathrm{H}-1(02 / 99) \\ \hline \end{array}$ | [53-21-4] | \$207 |
| 1143802 | Codeine N-Oxide Cl (50 mg) | G0A034 |  | F-1 (11/02) | [3688-65-1] | \$207 |
| 1144000 | Codeine Phosphate CII (100 mg) | J0C200 | 2 | $\begin{array}{\|l} \hline \text { I-1 (10/04) } \\ \text { I (09/02) } \\ \text { H-1 }(01 / 00) \\ \hline \end{array}$ | [41444-62-6] | \$207 |
| 1145003 | Codeine Sulfate CII ( 250 mg ) | H-2 |  | H-1 (01/02) | [6854-40-6] | \$207 |
| 1146006 | Colchicine ( 300 mg ) | J |  | I (05/02) | [64-86-8] | \$156 |
| 1146505 | Colestipol Hydrochloride (200 mg) | F-1 |  |  | [37296-80-3] | \$156 |
| 1147009 | Colistimethate Sodium ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  | [8068-28-8] | \$156 |
| 1148001 | Colistin Sulfate (200 mg) | G-1 |  | G (09/99) | [1264-72-8] | \$156 |
| 1148500 | Copovidone ( 100 mg ) | F0C194 |  |  | [2586-89-9] | \$156 |
| 1149004 | Corticotropin (5.6 Units/vial; 5 vials) | M |  | L (06/99) | [9002-60-2] | \$124 |
| 1150003 | Cortisone Acetate ( 150 mg ) | 1 |  |  | [50-04-4] | \$156 |
| 1150353 | Creatinine ( 100 mg ) | F |  |  | [60-27-5] | \$156 |
| 1150502 | Cromolyn Sodium ( 500 mg ) | J |  | I (06/00) | [15826-37-6] | \$156 |
| 1150706 | Crospovidone ( 200 mg ) | G |  |  | [9003-39-8] | \$156 |
| 1151006 | Crotamiton ( 200 mg ) | H-1 |  | H (07/00) | [483-63-6] | \$156 |
| 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) | N |  | M-3 (08/99) | [68-19-9] | \$156 |
| 1152508 | Cyclacillin (200 mg) | G |  |  | [3485-14-1] | \$156 |
| 1153001 | Cyclizine ( 1 g ) DISCONTINUED |  |  | F (04/04) | [82-92-8] | \$156 |
| 1154004 | Cyclizine Hydrochloride (200 mg) | G |  |  | [303-25-3] | \$156 |
| 1154503 | Cyclobenzaprine Hydrochloride ( 200 mg ) | G0A013 |  | F-3 (07/03) | [6202-23-9] | \$156 |
| 1154558 | Alpha Cyclodextrin (50 mg) | F-1 |  | F (10/00) | [10016-20-3] | \$156 |
| 1154569 | Beta Cyclodextrin (250 mg) | G |  | F-1 (12/02) | [7585-39-9] | \$156 |
| 1154707 | Cyclomethicone 4 (200 mg) | F-2 |  | F-1 (06/02) | [69430-24-6] | \$156 |
| 1154809 | Cyclomethicone 5 (125 mg) | F-2 |  | F-1 (09/99) | [69430-24-6] | \$124 |

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| 1154900 | Cyclomethicone 6 (200 mg) | F2B024 |  | F-1 (03/03) | [69430-24-6] | \$156 |
| 1156000 | Cyclopentolate Hydrochloride ( 300 mg ) | H |  | G (04/00) | [5870-29-1] | \$156 |
| 1157002 | Cyclophosphamide ( 500 mg ) | $J$ |  |  | [6055-19-2] | \$124 |
| 1157501 | 2-Cyclopropylmethylamino-5-chlorobenzophenone ( 50 mg ) | F |  |  | n/f | \$487 |
| 1158005 | Cycloserine ( 200 mg ) | G |  |  | [68-41-7] | \$156 |
| 1158504 | Cyclosporine ( 50 mg ) | H-1 |  | $\begin{aligned} & \hline \text { H }(11 / 02) \\ & \text { G-2 }(03 / 00) \\ & \hline \end{aligned}$ | [59865-13-3] | \$479 |
| 1158650 | Cyclosporine Resolution Mixture ( 25 mg ) | F |  |  | $\begin{aligned} & {[108027-45-8]} \\ & \text { (U) } \end{aligned}$ | \$412 |
| 1159008 | Cyclothiazide (200 mg) | F-1 |  |  | [2259-96-3] | \$156 |
| 1161000 | Cyproheptadine Hydrochloride ( 500 mg ) | G |  | F-4 (11/02) | [41354-29-4] | \$156 |
| 1161509 | L-Cysteine Hydrochloride ( 200 mg ) | H |  | G (05/00) | [7048-04-6] | \$156 |
| 1162002 | Cytarabine ( 250 mg ) | G-2 |  | G-1 (07/00) | [147-94-4] | \$156 |
| 1162308 | Dacarbazine ( 125 mg ) | H |  | G (01/99) | [4342-03-4] | \$124 |
| 1162320 | Dacarbazine Related Compound A (50 mg) (5-aminoimidazole-4carboxamide Hydrochloride) | H0C052 | 2,4 | $\begin{aligned} & \hline \mathrm{G}(03 / 04) \\ & \mathrm{F}(03 / 00) \\ & \hline \end{aligned}$ | [72-40-2] | \$487 |
| 1162330 | Dacarbazine Related Compound B (100 mg) (2-azahypoxanthine) | F-1 |  | F (12/01) | [63907-29-9] | \$487 |
| 1162400 | Dactinomycin ( 50 mg ) | I |  |  | [50-76-0] | \$427 |
| 1162501 | Danazol ( 200 mg ) | H |  | G (10/00) | [17230-88-5] | \$156 |
| 1164008 | Dapsone ( 125 mg ) | G-3 |  | G-2 (08/99) | [80-08-0] | \$124 |
| 1164700 | Daunorubicin Hydrochloride (200 mg) | LOB307 |  | $\begin{aligned} & \mathrm{K}(11 / 03) \\ & \mathrm{J}(08 / 00) \end{aligned}$ | [23541-50-6] | \$479 |
| 1165000 | Decamethonium Bromide ( 250 mg ) | F |  |  | [541-22-0] | \$156 |
| 1166003 | Deferoxamine Mesylate ( 500 mg ) | I |  |  | [138-14-7] | \$156 |
| 1166309 | Dehydroacetic Acid ( 200 mg ) | F |  |  | [520-45-6] | \$156 |
| 1166400 | Dehydrocarteolol Hydrochloride (100 mg) | F |  |  | n/f | \$487 |
| 1166502 | Dehydrocholic Acid ( 200 mg ) | F-1 | 2,4 | F (03/04) | [81-23-2] | \$156 |
| 1169001 | Demecarium Bromide ( 250 mg ) | F |  |  | [56-94-0] | \$156 |
| 1170000 | Demeclocycline Hydrochloride (200 mg) | H1C036 |  | $\begin{aligned} & \text { H (08/04) } \\ & \text { G-1 }(08 / 01) \\ & \hline \end{aligned}$ | [64-73-3] | \$156 |
| 1171003 | Denatonium Benzoate ( 200 mg ) | IOB129 |  | H (09/02) | [86398-53-0] | \$156 |
| 1171706 | Desacetyl Diltiazem Hydrochloride ( 50 mg ) | 1 |  | H (08/00) | [23515-45-9] | \$487 |
| 1171900 | Desflurane ( 0.5 mL ) | F0C187 |  |  | [57041-67-5] | \$156 |
| 1171910 | Desflurane Related Compound A ( 0.1 mL ) (bis-(1,2,2,2-tetrafluoroethyl) ether) | F0C031 |  |  | n/f | \$487 |
| 1172006 | Desipramine Hydrochloride ( 125 mg ) | H-1 |  | H (10/99) | [58-28-6] | \$124 |
| 1173009 | Deslanoside ( 100 mg ) | H-1 |  |  | [17598-65-1] | \$156 |
| 1173235 | Desogestrel ( 50 mg ) | F0B282 |  |  | [54024-22-5] | \$156 |
| 1173246 | Desogestrel Related Compound A (15 mg) (13-Ethyl-11-methylene-18, 19-dinor-5alpha, 17alpha-preg-3-en-20-yl-17-ol, desogestrel delta-3 isomer) | F0B279 |  |  | n/f | \$487 |
| 1173257 | Desogestrel Related Compound B (15 mg) (3-Hydroxy-desogestrel) | F0B284 |  |  | n/f | \$487 |
| 1173268 | Desogestrel Related Compound C ( 25 mg ) (3-Keto-desogestrel) | FOB281 |  |  | [54048-10-1] | \$487 |
| 1173508 | Desoximetasone ( 200 mg ) | H0B036 |  | G (01/04) | [382-67-2] | \$156 |
| 1174001 | Desoxycorticosterone Acetate (200 mg) | J0C014 |  | $\begin{aligned} & \text { I (01/04) } \\ & \text { H (05/00) } \end{aligned}$ | [56-47-3] | \$156 |
| 1175004 | Desoxycorticosterone Pivalate ( 125 mg ) | H0C276 |  | G (01/04) | [808-48-0] | \$124 |
| 1176007 | Dexamethasone ( 125 mg ) | $J$ |  |  | [50-02-2] | \$124 |
| 1176506 | Dexamethasone Acetate ( 200 mg ) | G |  | F-1 (06/99) | [55812-90-3] | \$156 |
| 1177000 | Dexamethasone Phosphate (200 mg) | J1B070 |  | $\begin{array}{\|l\|} \hline J(08 / 03) \\ I(03 / 00) \\ \hline \end{array}$ | [312-93-6] | \$156 |

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| 1178002 | Dexbrompheniramine Maleate ( 200 mg ) | $J$ |  | I (03/03) | [2391-03-9] | \$156 |
| 1179005 | Dexchlorpheniramine Maleate ( 500 mg ) | G1A025 |  | G (12/02) | [2438-32-6] | \$156 |
| 1179504 | Dexpanthenol ( 500 mg ) | J0C293 | 2 | $\begin{array}{\|l\|} \hline I \text { (08/04) } \\ H \\ \hline \end{array}$ | [81-13-0] | \$160 |
| 1179708 | Dextran 40 ( 50 mg ) | F0C247 |  |  | [9004-54-0] | \$156 |
| 1179741 | Dextran 70 ( 50 mg ) | F0C260 |  |  | [9004-54-0] | \$156 |
| 1179854 | Dextran 4 Calibration (100 mg) | F0C002 |  |  | [9004-54-0] | \$156 |
| 1179865 | Dextran 10 Calibration ( 100 mg ) | F0C010 |  |  | [9004-54-0] | \$156 |
| 1179876 | Dextran 40 Calibration ( 100 mg ) | F0C011 |  |  | [9004-54-0] | \$156 |
| 1179720 | Dextran 40 System Suitability ( 200 mg ) | F0B181 |  |  | [9004-54-0] | \$156 |
| 1179887 | Dextran 70 Calibration ( 100 mg ) | F0C013 |  |  | [9004-54-0] | \$156 |
| 1179763 | Dextran 70 System Suitability ( 200 mg ) | F0B182 |  |  | [9004-54-0] | \$156 |
| 1179898 | Dextran 250 Calibration ( 100 mg ) | F0C039 |  |  | [9004-54-0] | \$156 |
| 1179800 | Dextran Vo Marker ( 100 mg ) | F0B242 |  |  | [9004-54-0] | \$156 |
| 1180004 | Dextroamphetamine Sulfate CII (500 mg) | H |  | $\begin{array}{\|l\|} \hline G(08 / 03) \\ \text { F-6 (12/99) } \\ \hline \end{array}$ | [51-63-8] | \$216 |
| 1180503 | Dextromethorphan (2 g) | H |  | G (06/00) | [125-71-3] | \$487 |
| 1181007 | Dextromethorphan Hydrobromide ( 500 mg ) | J0B167 |  | I (07/03) | [6700-34-1] | \$156 |
| 1181302 | Dextrose (500 mg) | J-1 |  | $\begin{aligned} & \mathrm{J}(11 / 02) \\ & \mathrm{I}(08 / 99) \\ & \hline \end{aligned}$ | [50-99-7] | \$124 |
| 1181506 | Diacetylated Monoglycerides ( 200 mg ) | G |  |  | [68990-54-5] | \$156 |
| 1182000 | Diacetylfluorescein (200 mg) | H |  | G (01/02) | [596-09-8] | \$156 |
| 1183002 | Diacetylmorphine Hydrochloride CI (25 mg) (AS) (Heroin Hydrochloride) | J |  | I-1 (10/99) | [1502-95-0] | \$207 |
| 1184005 | Diatrizoic Acid ( 100 mg ) | G |  |  | [50978-11-5] | \$156 |
| 1184027 | Diatrizoic Acid Related Compound A ( 50 mg ) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid) | I |  | H (02/00) | [1713-07-1] | \$487 |
| 1185008 | Diazepam CIV (100 mg) | 1 |  | H (12/01) | [439-14-5] | \$207 |
| 1185020 | Diazepam Related Compound A ( 25 mg ) (2-Methyl-amino-5-chlorobenzophenone) | 1 |  | $\begin{array}{\|l} \mathrm{H}-1(11 / 02) \\ \mathrm{H}(04 / 00) \\ \hline \end{array}$ | [1022-13-5] | \$487 |
| 1186000 | Diazoxide (200 mg) | G1C017 |  | G (12/03) | [364-98-7] | \$156 |
| 1187003 | Dibucaine Hydrochloride (200 mg) | 1 |  | H-2 (01/03) | [61-12-1] | \$156 |
| 1187207 | Dichloralphenazone CIV (200 mg) | F0B010 |  |  | [480-30-8] | \$207 |
| 1188006 | Dichlorphenamide ( $200 \mathrm{mg} \mathrm{)}$ | G-1 |  |  | [120-97-8] | \$156 |
| 1188800 | Diclofenac Sodium (200 mg) | H0B150 |  | $\begin{aligned} & \text { G-1 (03/04) } \\ & \text { G (05/01) } \\ & \hline \end{aligned}$ | [15307-79-6] | \$156 |
| 1188811 | Diclofenac Related Compound A (100 mg) ( N -(2,6-dichlorophenyl)-indolin-2-one) | H |  | G (05/02) | [15362-40-0] | \$490 |
| 1189009 | Dicloxacillin Sodium (500 mg) | J0C182 | 2 | $\begin{array}{\|l} \hline \text { IOB142 (09/04) } \\ \text { H (05/03) } \\ \hline \end{array}$ | [13412-64-1] | \$156 |
| 1190008 | Dicumarol (200 mg) | G |  |  | [66-76-2] | \$156 |
| 1191000 | Dicyclomine Hydrochloride ( 125 mg ) | H |  | G (03/99) | [67-92-5] | \$124 |
| 1192003 | Dienestrol ( 125 mg ) | 1 |  |  | [84-17-3] | \$124 |
| 1193006 | Diethylcarbamazine Citrate ( 200 mg ) | G-1 |  |  | [1642-54-2] | \$156 |
| 1193301 | Diethylene Glycol Monoethyl Ether ( $0.5 \mathrm{~mL} / \mathrm{ampule}$ ) | F0B095 |  |  | [111-90-0] | \$156 |
| 1193505 | Diethyl Phthalate ( 200 mg ) | G |  | F-1 (03/00) | [84-66-2] | \$156 |
| 1194009 | Diethylpropion Hydrochloride CIV (200 mg) | H |  |  | [134-80-5] | \$207 |
| 1195001 | Diethylstilbestrol (200 mg) | K5B291 |  | K-4 (05/04) | [56-53-1] | \$156 |
| 1197007 | Diethyltoluamide (3 g) | H |  |  | [134-62-3] | \$124 |
| 1197302 | Diflorasone Diacetate (200 mg) | G |  | F-1 (03/00) | [33564-31-7] | \$156 |

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| 1197506 | Diflunisal ( 200 mg ) | G |  |  | [22494-42-4] | \$156 |
| 1198000 | Digitalis (3 g) | F |  |  | [8031-42-3] | \$156 |
| 1199002 | Digitoxin ( 200 mg ) | M |  |  | [71-63-6] | \$156 |
| 1200000 | Digoxin (250 mg) | O0B096 |  | N-1 (04/03) | [20830-75-5] | \$156 |
| 1200600 | Dihydrocapsaicin (25 mg) | G0C071 |  | $\begin{array}{\|l} \hline \text { F-1 (12/03) } \\ \text { F (01/00) } \\ \hline \end{array}$ | [19408-84-5] | \$156 |
| 1200804 | Dihydrocodeine Bitartrate CII (200 mg) | H |  | G (03/01) | [5965-13-9] | \$207 |
| 1201002 | 17alpha-Dihydroequilin ( 50 mg ) | 10 C 277 |  | H (07/04) | [6639-99-2] | \$208 |
| 1202005 | Dihydroergotamine Mesylate ( 250 mg ) (List Chemical) | J0B085 |  | I (03/03) | [6190-39-2] | \$156 |
| 1203008 | Dihydrostreptomycin Sulfate ( 200 mg ) | J |  |  | [5490-27-7] | \$156 |
| 1204000 | Dihydrotachysterol ( $30 \mathrm{mg} / \mathrm{ampul}$; 4 ampules) | I |  |  | [67-96-9] | \$156 |
| 1204102 | Dihydroxyacetone ( 250 mg ) | F |  |  | [96-26-4] | \$156 |
| 1204805 | Diloxanide Furoate ( $200 \mathrm{mg} \mathrm{)}$ | F0C026 |  |  | [3736-81-0] | \$156 |
| 1205003 | Diltiazem Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  |  | [33286-22-5] | \$156 |
| 1206006 | Dimenhydrinate ( 100 mg ) | J0B055 |  | I (06/03) | [523-87-5] | \$156 |
| 1208001 | Dimethisoquin Hydrochloride (2 g) | G |  |  | [2773-92-4] | \$156 |
| 1210105 | N -(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8-germaspiro [4:5] decane-1,3-dione (AS) | F |  |  | [41992-23-8] | \$156 |
| 1211006 | Dimethyl Sulfoxide (3 g) | G0C198 |  | $\begin{array}{\|l\|l\|} \hline \text { F-3 }(07 / 04) \\ \text { F-2 } & (05 / 02) \\ \hline \end{array}$ | [67-68-5] | \$208 |
| 1213001 | Dinoprost Tromethamine ( 50 mg ) | F |  |  | [38562-01-5] | \$1,525 |
| 1213103 | Dinoprostone ( 50 mg ) | F0C030 |  |  | [363-24-6] | \$1,525 |
| 1214004 | Dioxybenzone ( 150 mg ) | F1B277 |  | F (10/03) | [131-53-3] | \$156 |
| 1216000 | Diphemanil Methylsulfate ( 500 mg ) | H |  |  | [62-97-5] | \$156 |
| 1217909 | Diphenhydramine Citrate ( 125 mg ) | H0B128 |  | G (04/03) | [88637-37-0] | \$124 |
| 1218005 | Diphenhydramine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | J0B013 |  | I (07/03) | [147-24-0] | \$156 |
| 1219008 | Diphenoxylate Hydrochloride CII (200 mg) | I |  | H (03/02) | [3810-80-8] | \$207 |
| 1220302 | Dipivefrin Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | I |  | H (06/99) | [64019-93-8] | \$156 |
| 1220506 | Dipyridamole (200 mg) | H |  | G-1 (01/99) | [58-32-2] | \$156 |
| 1220700 | Dirithromycin (200 mg) | F |  |  | [62013-04-1] | \$156 |
| 1221000 | Disodium Guanylate ( 300 mg ) (FCC) | F-1 |  |  | [5550-12-9] | \$156 |
| 1222002 | Disodium Inosinate ( 500 mg ) (FCC) | F |  |  | [4691-65-0] | \$156 |
| 1222501 | Disopyramide Phosphate (200 mg) | H-1 |  | H (03/02) | [22059-60-5] | \$156 |
| 1223005 | 2,4-Disulfamyl-5-trifluoromethylaniline ( 125 mg ) | G |  |  | [654-62-6] | \$487 |
| 1224008 | Disulfiram (200 mg) | F-3 |  | F-2 (07/02) | [97-77-8] | \$156 |
| 1224507 | Dobutamine Hydrochloride ( 600 mg ) | H-1 |  | H (01/00) | [49745-95-1] | \$156 |
| 1224700 | Docusate Calcium ( 500 mg ) | H0B044 |  | G-1 (07/02) | [128-49-4] | \$156 |
| 1224802 | Docusate Sodium ( 500 mg ) | J |  | I-1 (05/02) | [577-11-7] | \$156 |
| 1224904 | Docusate Potassium ( 100 mg ) | F-1 |  | F (11/99) | [7491-09-0] | \$156 |
| 1224959 | Dolasetron Mesylate (200 mg) | F0C319 | 1 |  | [115956-13-3] | \$156 |
| 1224960 | Dolasetron Mesylate Related Compound A ( 25 mg ) (Hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3(4H)-one hydrochloride) | F0C321 | 1 |  | n/f | \$487 |
| 1225204 | Dopamine Hydrochloride ( 200 mg ) | G |  | F-5 (05/02) | [62-31-7] | \$156 |
| 1225281 | Dorzolamide Hydrochloride ( 500 mg ) | F0C040 |  |  | [130693-82-2] | \$156 |
| 1225292 | Dorzolamide Hydrochloride Related Compound A $(20 \mathrm{mg})((4 R, 6 R)-4-$ (ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide, monohydrochloride) | F0C068 |  |  | n/f | \$487 |
| 1225000 | Doxapram Hydrochloride (200 mg) | F4C053 |  | F-3 (07/04) | [7081-53-0] | \$156 |
| 1225419 | Doxazosin Mesylate (200 mg) | F0C079 |  |  | [77883-43-3] | \$156 |
| 1225500 | Doxepin Hydrochloride ( 500 mg ) | 1 |  |  | [1229-29-4] | \$156 |

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| 1225703 | Doxorubicin Hydrochloride ( 50 mg ) | K |  | J (06/02) | [25316-40-9] | \$479 |
| 1226003 | Doxycycline Hyclate ( 200 mg ) | I |  | H (01/00) | [24390-14-5] | \$156 |
| 1227006 | Doxylamine Succinate ( 300 mg ) | IOB266 |  | H (01/04) | [562-10-7] | \$156 |
| 1229001 | Droperidol ( 250 mg ) | H-1 |  | H (04/99) | [548-73-2] | \$156 |
| 1230000 | Dyclonine Hydrochloride ( 200 mg ) | G |  |  | [536-43-6] | \$156 |
| 1231003 | Dydrogesterone (200 mg) | IOB114 |  | H (01/04) | [152-62-5] | \$156 |
| 1231502 | Dyphylline ( 200 mg ) | G-2 |  | G-1 (11/02) | [479-18-5] | \$156 |
| 1231808 | Econazole Nitrate (200 mg) | G |  |  | [68797-31-9] | \$156 |
| 1232006 | Edetate Calcium Disodium (200 mg) | G-3 |  | G-2 (11/99) | [23411-34-9] | \$156 |
| 1233009 | Edetate Disodium ( 200 mg ) | H |  | G-2 (04/02) | [6381-92-6] | \$156 |
| 1233508 | Edetic Acid ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [60-00-4] | \$156 |
| 1234001 | Edrophonium Chloride ( 200 mg ) | H |  | G (08/99) | [116-38-1] | \$156 |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | 1 |  | [84696-12-5] | \$520 |
| 1234806 | Emedastine Difumarate ( 100 mg ) | F0C059 |  |  | [87233-62-3] | \$156 |
| 1235004 | Emetine Hydrochloride ( 300 mg ) | H0B201 |  | G (05/03) | [316-42-7] | \$156 |
| 1235274 | Enalaprilat ( 300 mg ) | I |  | $\begin{array}{\|l\|} \hline \text { H }(03 / 01) \\ \text { G (08/99) } \\ \hline \end{array}$ | [84680-54-6] | \$124 |
| 1235300 | Enalapril Maleate (200 mg) | $J$ |  | I (06/01) | [76095-16-4] | \$156 |
| 1235503 | Endotoxin (10,000 USP Endotoxin Units) | G2B274 |  | $\begin{array}{\|l\|} \hline \text { G-1 (12/03) } \\ \text { G (06/99) } \\ \hline \end{array}$ | n/f | \$156 |
| 1235809 | Enflurane ( 1 mL ) | G-1 |  | G (02/01) | [13838-16-9] | \$156 |
| 1236007 | Ephedrine Sulfate (200 mg) (List Chemical) | H-2 |  | H-1 (11/02) | [134-72-5] | \$156 |
| 1236506 | 4-Epianhydrotetracycline Hydrochloride ( 50 mg ) | J0C041 |  | $\begin{array}{\|l\|} \hline \text { I-1 (12/03) } \\ \text { I (06/00) } \\ \hline \end{array}$ | [4465-65-0] | \$487 |
| 1236801 | Epilactose (200 mg) | G |  | F-1 (06/00) | [103302-12-1] | \$487 |
| 1237000 | Epinephrine Bitartrate (200 mg) | 0 |  |  | [51-42-3] | \$156 |
| 1237509 | Epitetracycline Hydrochloride (200 mg) | F |  |  | [23313-80-6] | \$487 |
| 1238002 | Equilin ( 25 mg ) | 1 |  | H-1 (05/00) | [474-86-2] | \$208 |
| 1239005 | Ergocalciferol ( $30 \mathrm{mg} / \mathrm{ampule}$; 5 ampules) (Vitamin D2) | P0B275 |  | $\begin{array}{\|l\|} \hline \mathrm{O}(02 / 04) \\ \mathrm{N}(12 / 99) \\ \hline \end{array}$ | [50-14-6] | \$168 |
| 1239504 | Ergoloid Mesylates ( $300 \mathrm{mg} \mathrm{)}$ | 1 |  | H-1 (01/00) | [8067-24-1] | \$156 |
| 1240004 | Ergonovine Maleate (100 mg) (List Chemical) | N |  | M-1 (07/02) | [129-51-1] | \$156 |
| 1241007 | Ergosterol ( 50 mg ) | H |  |  | [57-87-4] | \$156 |
| 1241506 | Ergotamine Tartrate (150 mg) (List Chemical) | IOB174 |  | H (01/04) | [379-79-3] | \$156 |
| 1241550 | Ergotaminine ( 100 mg ) (List Chemical) | G0B177 |  | F-1 (06/04) | [639-81-6] | \$156 |
| 1242000 | Erythromycin (250 mg) | M |  | L (08/99) | [114-07-8] | \$156 |
| 1242010 | Erythromycin B (150 mg) | G |  | $\begin{array}{\|l\|} \hline \text { F-1 (09/01) } \\ \text { F (05/01) } \\ \hline \end{array}$ | [527-75-3] | \$156 |
| 1242021 | Erythromycin C (50 mg) | F-3 |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 (01/03) } \\ \text { F-1 (02/02) } \\ \hline \text { F (02/99) } \\ \hline \end{array}$ | n/f | \$156 |
| 1242032 | Erythromycin Related Compound $\mathrm{N}(50 \mathrm{mg})$ ( N -Demethylerythromycin A) | F2A023 |  | $\begin{array}{\|l} \hline \text { F-1 (06/04) } \\ \text { F (09/99) } \\ \hline \end{array}$ | n/f | \$156 |
| 1243002 | Erythromycin Estolate (200 mg) | H |  | G (01/03) | [3521-62-8] | \$156 |
| 1245008 | Erythromycin Ethylsuccinate ( 200 mg ) | H |  | G-1 (06/01) | [1264-62-6] | \$156 |
| 1246000 | Erythromycin Gluceptate (200 mg) | H |  | G (07/03) | [23067-13-2] | \$156 |
| 1247003 | Erythromycin Lactobionate ( $200 \mathrm{mg} \mathrm{)}$ | H-1 |  | H (01/02) | [3847-29-8] | \$156 |
| 1248006 | Erythromycin Stearate ( 200 mg ) | H0B187 |  | G-1 (05/03) | [643-22-1] | \$156 |
| 1249009 | Erythrosine Sodium ( 100 mg ) | F |  |  | [49746-10-3] | \$156 |
| 1250008 | Estradiol ( 500 mg ) | K1B007 |  | K (04/03) | [50-28-2] | \$156 |

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| 1251000 | Estradiol Benzoate ( 250 mg ) (AS) | G-1 |  |  | [50-50-0] | \$156 |
| 1252003 | Estradiol Cypionate ( 200 mg ) | G-1 |  | G (02/00) | [313-06-4] | \$156 |
| 1254009 | Estradiol Valerate ( 100 mg ) | L |  | K (05/02) | [979-32-8] | \$156 |
| 1254508 | Estriol ( 100 mg ) | J |  | I-1 (06/01) | [50-27-1] | \$156 |
| 1255001 | Estrone (200 mg) | K1B099 |  | $\begin{aligned} & \mathrm{K}(07 / 03) \\ & \mathrm{J}-1(07 / 00) \end{aligned}$ | [53-16-7] | \$156 |
| 1255500 | Estropipate (500 mg) | J0B262 |  | $\begin{aligned} & \hline \text { I (12/03) } \\ & \mathrm{H}(09 / 01) \end{aligned}$ | [7280-37-7] | \$156 |
| 1256004 | Ethacrynic Acid (200 mg) | F |  |  | [58-54-8] | \$156 |
| 1257007 | Ethambutol Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G (08/02) | [1070-11-7] | \$156 |
| 1258305 | Ethchlorvynol CIV ( 0.7 ml ) | F0B011 |  |  | [113-18-8] | \$207 |
| 1260001 | Ethinyl Estradiol ( 150 mg ) | P1B193 |  | $\begin{array}{\|l} \hline \text { P0B052 (01/04) } \\ \text { P (03/03) } \\ \text { O (08/99) } \\ \hline \end{array}$ | [57-63-6] | \$156 |
| 1260012 | Ethinyl Estradiol Related Compound A (20 mg) (6-Keto-ethinyl estradiol) | F0B252 |  |  | n/f | \$487 |
| 1261004 | Ethionamide ( 200 mg ) | H0B148 |  | G (03/03) | [536-33-4] | \$156 |
| 1262801 | Ethopabate ( 125 mg ) | F |  |  | [59-06-3] | \$156 |
| 1262823 | Ethopabate Related Compound A ( 25 mg ) (Methyl-4-acetamido-2hydroxybenzoate) | F |  |  | n/f | \$487 |
| 1263000 | Ethopropazine Hydrochloride ( 300 mg ) | G |  |  | [1094-08-2] | \$156 |
| 1264002 | Ethosuximide ( 125 mg ) | H |  | $\begin{aligned} & \mathrm{G}-2(11 / 01) \\ & \mathrm{G}-1(05 / 99) \\ & \hline \end{aligned}$ | [77-67-8] | \$124 |
| 1264501 | Ethotoin ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [86-35-1] | \$156 |
| 1265005 | Ethoxzolamide ( 200 mg ) | F |  |  | [452-35-7] | \$156 |
| 1265504 | Ethylcellulose (1 g) | $\mathrm{H}-1$ |  | H (06/99) | [9004-57-3] | \$156 |
| 1266008 | Ethyl Maltol (1 g) (FCC) | H |  |  | [4940-11-8] | \$156 |
| 1266507 | Ethylnorepinephrine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [3198-07-0] | \$156 |
| 1267000 | Ethylparaben (200 mg) | IOA016 |  | H (01/04) | [120-47-8] | \$156 |
| 1267500 | Ethyl Vanillin (200 mg) | F2B134 |  | F-1 (04/04) | [121-32-4] | \$156 |
| 1268003 | Ethynodiol Diacetate (200 mg) | 10A033 |  | $\begin{aligned} & \hline \mathrm{H}-1(01 / 03) \\ & \mathrm{H}(04 / 01) \\ & \hline \end{aligned}$ | [297-76-7] | \$156 |
| 1268502 | Etidronate Disodium (200 mg) | G |  | F-2 (02/03) | [7414-83-7] | \$156 |
| 1268604 | Etidronic Acid Monohydrate (1 g) | G |  | F-1 (05/99) | [2809-21-4] | \$156 |
| 1268706 | Etodolac ( 400 mg ) | G |  | F (10/01) | [41340-25-4] | \$156 |
| 1268728 | Etodolac Related Compound A (25 mg) ((+/-)-8-ethyl-1-methyl-1,3,4,9tetrahydropyrano [3,4-b]-indole-1-acetic acid) | F-1 |  | F (05/02) | [109518-50-5] | \$208 |
| 1268808 | Etoposide ( 300 mg ) | G |  |  | [33419-42-0] | \$124 |
| 1268852 | Etoposide Resolution Mixture ( 30 mg ) | F0B209 |  |  | [33419-42-0] | \$208 |
| 1269006 | Evans Blue ( 200 mg ) DISCONTINUED |  |  | G (04/04) | [314-13-6] | \$156 |
| 1269200 | Famotidine ( 125 mg ) | H-1 |  | $\begin{aligned} & \mathrm{H}(11 / 02) \\ & \mathrm{G}(03 / 99) \\ & \hline \end{aligned}$ | [76824-35-6] | \$124 |
| 1269389 | Felodipine (200 mg) | F-1 |  | F (09/02) | [72509-76-3] | \$156 |
| 1269390 | Felodipine Related Compound A ( 100 mg ) (ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate) | F0B207 |  |  | [96302-71-7] | \$487 |
| 1269403 | Fenbendazole ( 100 mg ) | F |  |  | [43210-67-9] | \$487 |
| 1269458 | Fenoldopam Mesylate (200 mg) | F0C125 |  |  | [67227-57-0] | \$156 |
| 1269469 | Fenoldopam Related Compound A ( 20 mg ) (1-Methyl-3-benzazapine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate) | FOC124 |  |  | n/f | \$487 |

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| 1269470 | Fenoldopam Related Compound B (20 mg) (1H-3-Benzazapine-7,8diol, 2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate) | F0C126 |  |  | n/f | \$487 |
| 1269505 | Fenoprofen Calcium ( 500 mg ) | G-1 |  |  | [53746-45-5] | \$156 |
| 1269550 | Fenoprofen Sodium ( 500 mg ) | G |  | F-1 (05/02) | [66424-46-2] | \$156 |
| 1270005 | Fentanyl Citrate CII (100 mg) | J2B227 |  | $\begin{array}{\|l\|} \hline \mathrm{J}-1(09 / 03) \\ \mathrm{J}(05 / 02) \\ \mathrm{I}(06 / 00) \\ \hline \end{array}$ | [990-73-8] | \$207 |
| 1270402 | Finasteride ( 200 mg ) | F |  |  | [98319-26-7] | \$156 |
| 1270800 | Flecainide Acetate ( 200 mg ) | F-1 |  | F (06/03) | [54143-56-5] | \$156 |
| 1270821 | Flecainide Related Compound A (75 mg) (3-[2,5-bis(2,2,2-triflu-oroethoxy)phenyl]-1,5,6,7,8,8a-hexahydroimidazo-[1,5a]pyridine Hydrochloride) | F |  |  | n/f | \$487 |
| 1271008 | Floxuridine ( 250 mg ) | F-2 |  | F-1 (08/01) | [50-91-9] | \$156 |
| 1272000 | Flucytosine ( 200 mg ) | F |  |  | [2022-85-7] | \$156 |
| 1273003 | Fludrocortisone Acetate ( $250 \mathrm{mg} \mathrm{)}$ | H |  | G (08/01) | [514-36-3] | \$156 |
| 1273808 | Flumazenil ( 200 mg ) | F0C305 |  |  | [78755-81-4] | \$780 |
| 1274006 | Flumethasone Pivalate ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  | H (01/02) | [2002-29-1] | \$156 |
| 1274505 | Flunisolide ( 200 mg ) | 1 |  | H (01/01) | [77326-96-6] | \$156 |
| 1274607 | Flunixin Meglumine ( 300 mg ) | G |  | $\begin{aligned} & \hline \text { F-1 (04/02) } \\ & \hline \text { F (09/99) } \\ & \hline \end{aligned}$ | [42461-84-7] | \$156 |
| 1275009 | Fluocinolone Acetonide ( 100 mg ) | J |  | I (11/99) | [67-73-2] | \$156 |
| 1276001 | Fluocinonide ( 100 mg ) | 1 |  |  | [356-12-7] | \$156 |
| 1277004 | Fluorescein (200 mg) | G0B171 |  | F-1 (02/03) | [2321-07-5] | \$156 |
| 1277208 | Fluoride Dentifrice: Sodium Fluoride-Calcium Pyrophosphate (high beta-phase) ( 180 g ) DISCONTINUED |  |  | F (01/04) | n/f | \$487 |
| 1277252 | Fluoride Dentifrice: Sodium Fluoride/Silica (4.5 oz) | J0C294 |  | $\begin{aligned} & \text { I (8/04) } \\ & \mathrm{H}(04 / 99) \\ & \hline \end{aligned}$ | n/f | \$458 |
| 1277274 | Fluoride Dentifrice: Sodium Fluoride/Sodium Bicarbonate Powder (4 oz) | F |  |  | n/f | \$487 |
| 1277300 | Fluoride Dentifrice: Sodium Monofluorophosphate-Calcium Carbonate (4.6 oz) | G |  |  | n/f | \$487 |
| 1277354 | Fluoride Dentifrice: Sodium Monofluorophosphate/Dicalcium Phosphate (4.6 oz) | G |  |  | n/f | \$487 |
| 1277401 | Fluoride Dentifrice: Sodium Monofluorophosphate (1000 ppm)/Silica ( 5.25 oz ) | G-1 |  | G (08/99) | n/f | \$487 |
| 1277423 | Fluoride Dentifrice: Sodium Monofluorophosphate (1500 ppm)/Silica ( 5.25 oz ) | F-1 |  | F (07/99) | n/f | \$487 |
| 1277456 | Fluoride Dentifrice: Stannous Fluoride-Silica (4 oz) | H0B105 |  | G (11/02) | n/f | \$487 |
| 1278007 | Fluorometholone ( $200 \mathrm{mg} \mathrm{)}$ | IOB184 |  | H-1 (11/02) | [426-13-1] | \$156 |
| 1278109 | Fluorometholone Acetate ( 200 mg ) | F |  |  | [3801-06-7] | \$156 |
| 1278302 | Fluoroquinolonic Acid ( 50 mg ) | G |  | F-1 (12/99) | [86393-33-1] | \$487 |
| 1279000 | Fluorouracil ( 250 mg ) | H-1 |  | H (01/02) | [51-21-8] | \$156 |
| 1279804 | Fluoxetine Hydrochloride ( 200 mg ) | F-1 |  | F (11/99) | [59333-67-4] | \$156 |
| 1279815 | Fluoxetine Related Compound A ( 15 mg ) ( N -methyl-3-phenyl-3-[(alpha,alpha,alpha-(trifluoro-m-tolyl)oxy]propylamine Hydrochloride) | H0C131 |  | $\begin{array}{\|l} \hline \text { G (06/04) } \\ \text { F-1 (05/01) } \\ F(06 / 00) \\ \hline \end{array}$ | n/f | \$487 |
| 1279826 | Fluoxetine Related Compound B ( 5 mL of a 0.01 N HCl solution, approx. $2 \mathrm{mg} / \mathrm{mL}$ ) (N-methyl-3-phenylpropylamine) | F3C085 |  | $\begin{aligned} & \hline \text { F-2 (06/04) } \\ & \text { F-1 (09/02) } \\ & \text { F (09/00) } \\ & \hline \end{aligned}$ | [23580-89-4] | \$156 |
| 1279837 | Fluoxetine Related Compound C (15 mg) (N-Methyl-N-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-succinamic acid) | F0C352 | 1 |  | n/f | \$487 |
| 1280009 | Fluoxymesterone CIII ( 200 mg ) | G-2 |  | G-1 (04/00) | [76-43-7] | \$207 |

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| 1280803 | Fluphenazine Decanoate Dihydrochloride ( 500 mg ) | G |  | F-1 (10/01) | n/f | \$159 |
| 1281001 | Fluphenazine Enanthate Dihydrochloride ( 125 mg ) | H |  | G (02/99) | [3105-68-8] | \$124 |
| 1282004 | Fluphenazine Hydrochloride ( 125 mg ) | H |  |  | [146-56-5] | \$124 |
| 1284000 | Flurandrenolide ( 100 mg ) | IOB245 |  | H (09/03) | [1524-88-5] | \$156 |
| 1285002 | Flurazepam Hydrochloride CIV (200 mg) |  | 6 | I (09/03) | [1172-18-5] | \$207 |
| 1285308 | Flurazepam Related Compound C (50 mg) (5-chloro-2-(2-diethyl-aminoethyl(amino)-2'-fluorobenzophenone Hydrochloride) | H-1 |  |  | n/f | \$487 |
| 1285603 | Flurazepam Related Compound F (50 mg) (7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one) | $10 \mathrm{Co92}$ |  | H (01/04) | [2886-65-9] | \$487 |
| 1285750 | Flurbiprofen ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | [5104-49-4] | \$156 |
| 1285760 | Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid) | H |  | G (03/01) | n/f | \$487 |
| 1285807 | Flurbiprofen Sodium (200 mg) | F |  |  | [56767-76-1] | \$156 |
| 1285851 | Flutamide ( 200 mg ) | G |  | F-1 (06/00) | [13311-84-7] | \$156 |
| 1285862 | o-Flutamide ( 50 mg ) | F-1 |  | F (01/00) | n/f | \$156 |
| 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) | P |  | O (07/00) | [59-30-3] | \$156 |
| 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) | IOB176 |  | $\begin{aligned} & \mathrm{H}-1(04 / 04) \\ & \mathrm{H}(01 / 00) \\ & \hline \end{aligned}$ | [1492-18-8] | \$156 |
| 1286060 | Formononetin ( 50 mg ) | F0C196 |  |  | [485-72-3] | \$520 |
| 1286209 | 4-Formylbenzenesulfonamide ( 50 mg ) | F |  |  | n/f | \$487 |
| 1286300 | 10-Formylfolic Acid ( 25 mg ) | F2B226 |  | F-1 (01/4) | [134-05-4] | \$156 |
| 1286366 | Fosphenytoin Sodium ( 250 mg ) | F0C156 |  |  | [92134-98-0] | \$156 |
| 1286504 | Fructose (125 mg) | I-2 |  | $\begin{array}{\|l\|l} \hline \text { I-1 (11/02) } \\ \text { I (08/99) } \\ \hline \end{array}$ | [57-48-7] | \$124 |
| 1286708 | Fumaric Acid (200 mg) | G-1 |  | G (04/02) | [110-17-8] | \$156 |
| 1286800 | Furazolidone ( 200 mg ) | G-2 |  | G-1 (01/01) | [67-45-8] | \$156 |
| 1287008 | Furosemide ( 125 mg ) | J1B131 |  | $J(10 / 03)$ | [54-31-9] | \$124 |
| 1287020 | Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfuryl-amino-5-sulfamoylbenzoic Acid) | J |  | I (08/02) | n/f | \$487 |
| 1287030 | Furosemide Related Compound B ( 100 mg ) (4-Chloro-5-sulfamoylanthranilic Acid) | 10 C 248 |  | $\begin{aligned} & \hline \text { H (08/04) } \\ & \text { G-3 (03/01) } \\ & \hline \end{aligned}$ | [3086-91-7] | \$487 |
| 1287303 | Gabapentin ( 250 mg ) | F |  |  | [60142-96-3] | \$156 |
| 1287325 | Gabapentin Related Compound A (100 mg) (3,3-pentamethylene-5butyrolactam) | F |  |  | [64744-50-9] | \$487 |
| 1287507 | Gadodiamide ( 500 mg ) | F |  |  | [131410-48-5] | \$156 |
| 1287518 | Gadodiamide Related Compound A ( 50 mg ) (gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide) | F |  |  | n/f | \$487 |
| 1287529 | Gadodiamide Related Compound B (50 mg) (gadolinium disodium diethylenetriamine pentaacetic acid) | F |  |  | n/f | \$487 |
| 1287609 | Gadopentetate Monomeglumine ( 500 mg ) | F |  |  | [92923-57-4] | \$156 |
| 1287631 | Gadoteridol ( 500 mg ) | F |  |  | [120066-54-8] | \$156 |
| 1287642 | Gadoteridol Related Compound A ( 50 mg ) (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid) | F0A002 |  |  | [120041-08-9] | \$487 |
| 1287653 | Gadoteridol Related Compound B (50 mg) (1,4,7,10-Tetraazacyclodo-decane-1,4,7-triacetic acid, monogadolinium salt) | FOB198 |  |  | [112188-16-6] | \$487 |
| 1287664 | Gadoteridol Related Compound C (50 mg) (1,4,7,10-Tetraaza-11-oxo-bicyclo[8.2.2]tetradecane-4,7-diacetic acid) | FOB199 |  |  | [220182-19-4] | \$487 |
| 1287675 | Gadoversetamide (200 mg) | F0C172 |  |  | [131069-91-5] | \$156 |
| 1287686 | Gadoversetamide Related Compound A (200 mg) (Hydrogen[8,11,14-tris(carboxymethyl)-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(4-)]gadolinium) | F0C173 |  |  | n/f | \$487 |
| 1287700 | Galactose ( 200 mg ) | F-4 |  | F-3 (05/01) | [59-23-4] | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1288000 | Gallamine Triethiodide ( 200 mg ) | F |  |  | [65-29-2] | \$156 |
| 1288306 | Ganciclovir ( 200 mg ) | F0C287 |  |  | [82410-32-0] | \$364 |
| 1288317 | Ganciclovir Related Compound A (15 mg) ((RS)-2-Amino-9-(2,3-dihydroxy-propoxymethyl)-1,9-dihydro-purin-6-one) | F0C288 | 1 |  | n/f | \$624 |
| 1288500 | Gemfibrozil ( 200 mg ) | H |  |  | [25812-30-0] | \$156 |
| 1288510 | Gemfibrozil Related Compound A (20 mg) (2,2-dimethyl-5-[2,5-dimethyl-4-propene-1-yl)phenoxy]valeric acid) | F0C101 |  |  | n/f | \$487 |
| 1289003 | Gentamicin Sulfate (200 mg) | K |  | J-1 (04/00) | [1405-41-0] | \$156 |
| 1290002 | Gentian Violet ( 650 mg ) | F |  |  | [548-62-9] | \$156 |
| 1291005 | Gibberellic Acid (200 mg) (FCC) | G |  | F (04/01) | [77-06-5] | \$156 |
| 1291504 | Powdered Ginger ( 500 mg ) | F |  |  | n/f | \$156 |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | F0B289 |  |  | [50647-08-0] | \$520 |
| 1292008 | Gitoxin ( 50 mg ) | G |  | F-3 (07/00) | [4562-36-1] | \$487 |
| 1292507 | Glipizide ( 125 mg ) | G1C174 |  | G (07/04) | [29094-61-9] | \$124 |
| 1292609 | Glipizide Related Compound A ( 25 mg ) ( N -\{2-[(4-aminosulfonyl)-phenyl]ethyl\}-5-methyl-pyrazinecarboxamide) | G-1 |  | G (04/99) | n/f | \$487 |
| 1294003 | Glucagon ( $25 \mathrm{mg}, 0.95 \mathrm{U} / \mathrm{mg}$ ) | H |  |  | [16941-32-5] | \$156 |
| 1294207 | Glucosamine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F0C363 | 1 |  | [66-84-2] | \$156 |
| 1294976 | Glutamic Acid ( 200 mg ) | F0C069 |  |  | [56-86-0] | \$156 |
| 1294808 | Glutamine ( 100 mg ) | FOB244 |  |  | [56-85-9] | \$156 |
| 1294848 | gamma-Glutamyl-S-allyl-L-cysteine ( 25 mg ) | F |  |  | n/f | \$675 |
| 1295006 | Glutethimide CII (500 mg) | F |  |  | [77-21-4] | \$207 |
| 1295505 | Glyburide (200 mg) | G |  | F-2 (11/02) | [10238-21-8] | \$156 |
| 1295607 | Glycerin (2 mL) | H0C073 |  | $\begin{array}{\|l\|} \hline \text { G1A001 (04/04) } \\ \text { G (12/02) } \\ \text { F (04/99) } \\ \hline \end{array}$ | [56-81-5] | \$156 |
| 1295709 | Glyceryl Behenate (200 mg) | F3B113 |  | F-2 (03/03) | [18641-57-1] | \$156 |
| 1295800 | Glycine ( 200 mg ) | F-3 |  | F-2 (02/00) | [56-40-6] | \$156 |
| 1296009 | Glycopyrrolate ( 200 mg ) | H0B304 |  | G (05/04) | [596-51-0] | \$156 |
| 1295888 | Glycyrrhizic Acid ( 25 mg ) | F0C006 |  |  | [1405-86-3] | \$487 |
| 1297001 | Human Chorionic Gonadotropin (1 vial, 5,760 USP Units per package) | H |  | G (07/00) | [9002-61-3] | \$156 |
| 1298004 | Gramicidin ( 200 mg ) | 1 |  | H-1 (07/02) | [1405-97-6] | \$156 |
| 1299007 | Griseofulvin (200 mg) | 1 |  | H-1 (09/02) | [126-07-8] | \$156 |
| 1299200 | Griseofulvin Permeability Diameter (2 g) |  |  | $\begin{aligned} & \text { I0C138 (10/04) } \\ & \mathrm{H}(08 / 03) \\ & \hline \end{aligned}$ | [126-07-8] | \$156 |
| 1300004 | Guaiacol (1 g) | K |  | J (04/00) | [90-05-1] | \$156 |
| 1301007 | Guaifenesin (200 mg) | 1 |  | H (09/02) | [93-14-1] | \$156 |
| 1301404 | Guanabenz Acetate ( $200 \mathrm{mg} \mathrm{)}$ | G |  | F-1 (06/00) | [23256-50-0] | \$156 |
| 1301608 | Guanadrel Sulfate (200 mg) | F-1 |  |  | [22195-34-2] | \$156 |
| 1301801 | Guanethidine Monosulfate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [645-43-2] | \$156 |
| 1302000 | Guanethidine Sulfate ( 500 mg ) | G-1 |  |  | [60-02-6] | \$156 |
| 1302101 | Guanfacine Hydrochloride (125 mg) | G0B123 |  | $\begin{array}{\|l\|} \hline \text { F-1 (02/03) } \\ \text { F (11/99) } \\ \hline \end{array}$ | [29110-48-3] | \$124 |
| 1302305 | Halazepam CIV (200 mg) | F |  |  | [23092-17-3] | \$207 |
| 1302509 | Halcinonide ( 300 mg ) | F |  |  | [3093-35-4] | \$156 |
| 1303002 | Haloperidol ( 200 mg ) | 1 |  | H-1 (05/02) | [52-86-8] | \$156 |
| 1303013 | Haloperidol Related Compound A ( 25 mg ) (4,4-Bis[(4-p-chlorophenyl)-4-hydroxy-piperidinoj-butyrophenone) | J |  |  | [67987-08-0] | \$487 |
| 1303308 | Haloprogin (200 mg) | F |  |  | [777-11-7] | \$156 |
| 1303501 | Halothane ( 1 mL ) | F-1 |  |  | [151-67-7] | \$156 |

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| 1304005 | Heparin Sodium ( $10 \times 1 \mathrm{~mL}$ ) | K-5 |  | $\begin{array}{\|l\|l\|} \hline \text { K-4 }(08 / 03) \\ \text { K-3 }(02 / 99) \\ \hline \end{array}$ | [9041-08-1] | \$156 |
| 1305008 | Hexachlorophene ( 500 mg ) | 1 |  | H-2 (01/01) | [70-30-4] | \$156 |
| 1307003 | Hexobarbital CIII ( 500 mg ) | F |  |  | [56-29-1] | \$207 |
| 1308006 | Hexylcaine Hydrochloride (1 g) | F-1 |  |  | [532-76-3] | \$156 |
| 1308200 | Hexylene Glycol (125 mg) | G |  | $\begin{array}{\|l} \mathrm{F}-2(04 / 02) \\ \mathrm{F}-1(04 / 99) \\ \hline \end{array}$ | [107-41-5] | \$156 |
| 1308307 | Hexylresorcinol (200 mg) | F |  |  | [136-77-6] | \$156 |
| 1308505 | L-Histidine (200 mg) | G0A018 |  | $\begin{array}{\|l\|} \hline \text { F-2 (01/03) } \\ \text { F-1 }(04 / 00) \\ \hline \end{array}$ | [71-00-1] | \$156 |
| 1309009 | Histamine Dihydrochloride (250 mg) | M0C280 |  | L (07/04) | [56-92-8] | \$156 |
| 1310008 | Homatropine Hydrobromide ( 200 mg ) | H-1 |  | H (08/02) | [51-56-9] | \$156 |
| 1311000 | Homatropine Methylbromide ( 250 mg ) | $J$ |  | $\begin{array}{\|l} \hline \mathrm{I}-1(06 / 01) \\ \mathrm{H}-1(10 / 01) \\ \hline \end{array}$ | [80-49-9] | \$156 |
| 1311408 | Homosalate ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | F0B102 |  |  | [118-56-9] | \$156 |
| 1312003 | Hyaluronidase ( 500 mg ) | H |  |  | [9001-54-1] | \$156 |
| 1313006 | Hydralazine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | K |  | J-1 (09/02) | [304-20-1] | \$156 |
| 1314009 | Hydrochlorothiazide ( 200 mg ) | 1 |  | H (05/02) | [58-93-5] | \$156 |
| 1315001 | Hydrocodone Bitartrate CII (250 mg) | J0A026 |  | $\begin{array}{\|l\|} \hline \text { I-1 (12/02) } \\ \text { I (07/02) } \\ \text { H-2 (11/99) } \\ \hline \end{array}$ | [34195-34-1] | \$207 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl) | FOC214 |  |  | [847-86-9] | \$513 |
| 1316004 | Hydrocortisone ( 200 mg ) | M1C110 | 2 | $\begin{array}{\|l\|} \hline M(10 / 04) \\ L \\ \hline \end{array}$ | [50-23-7] | \$156 |
| 1317007 | Hydrocortisone Acetate (200 mg) | K |  | J (10/99) | [50-03-3] | \$156 |
| 1317302 | Hydrocortisone Butyrate (200 mg) | H |  |  | [13609-67-1] | \$156 |
| 1318000 | Hydrocortisone Cypionate ( 200 mg ) | F |  |  | [508-99-6] | \$156 |
| 1319002 | Hydrocortisone Hemisuccinate ( 200 mg ) | H |  | $\begin{aligned} & \text { G-3 }(03 / 02) \\ & \text { G-2 }(08 / 99) \\ & \hline \end{aligned}$ | [83784-20-7] | \$156 |
| 1320001 | Hydrocortisone Phosphate Triethylamine (200 mg) | F-1 |  |  | n/f | \$156 |
| 1321004 | Hydrocortisone Valerate (200 mg) | F-1 |  | F (07/02) | [57524-89-7] | \$156 |
| 1322007 | Hydroflumethiazide ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  |  | [135-09-1] | \$156 |
| 1323000 | Hydromorphone Hydrochloride CII (50 mg) | 1 |  | H-2 (03/01) | [71-68-1] | \$207 |
| 1324002 | Hydroquinone ( 500 mg ) | H0C249 | 2 | $\begin{aligned} & \hline \text { G-1 }(10 / 04) \\ & \text { G }(11 / 01) \\ & \text { F-4 (02/99) } \\ & \hline \end{aligned}$ | [123-31-9] | \$156 |
| 1325005 | Hydroxyamphetamine Hydrobromide ( 200 mg ) | G |  | F (06/01) | [306-21-8] | \$156 |
| 1327000 | Hydroxychloroquine Sulfate ( 200 mg ) | J0B297 |  | I (05/04) | [747-36-4] | \$156 |
| 1329006 | Hydroxyprogesterone Caproate ( 200 mg ) | H |  |  | [630-56-8] | \$156 |
| 1329709 | Hydroxypropyl Betadex ( 200 mg ) | F0B295 |  |  | [128446-35-5] | \$156 |
| 1329800 | Hydroxypropyl Cellulose (200 mg) | F-1 |  |  | [9004-64-2] | \$156 |
| 1330005 | Hydroxypropyl Methylcellulose ( 250 mg ) | G-1 |  | G (02/02) | [9004-65-3] | \$156 |
| 1332000 | Hydroxyurea (200 mg) | H |  | G (01/00) | [127-07-1] | \$156 |
| 1333003 | Hydroxyzine Hydrochloride ( 500 mg ) | H |  |  | [2192-20-3] | \$156 |
| 1333058 | Hydroxyzine Related Compound A ( 25 mg ) ( p -Chlorobenzhydrylpiperazine) | H |  |  | [303-26-4] | \$208 |
| 1334006 | Hydroxyzine Pamoate ( 500 mg ) | H0C016 |  | G-1 (07/03) | [10246-75-0] | \$156 |
| 1335009 | Hyoscyamine Sulfate (125 mg) |  |  | $\begin{aligned} & \text { G2A007 (09/04) } \\ & \text { G-1 (08/02) } \\ & \text { G (10/99) } \\ & \hline \end{aligned}$ | [6835-16-1] | \$124 |

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| 1335202 | Hyperoside ( 50 mg ) | F |  |  | [482-36-0] | \$855 |
| 1335304 | Hypromellose Phthalate ( 100 mg ) | F-1 |  | F (12/00) | [9050-31-1] | \$156 |
| 1335508 | Ibuprofen ( 750 mg ) | $J$ |  | I (06/02) | [15687-27-1] | \$156 |
| 1335701 | Idarubicin Hydrochloride ( 50 mg ) | H0C061 |  | $\begin{aligned} & \mathrm{G}(11 / 03) \\ & \mathrm{F}(06 / 00) \\ & \hline \end{aligned}$ | [57852-57-0] | \$479 |
| 1336001 | Idoxuridine ( 250 mg ) | H1B230 |  | H (07/04) | [54-42-2] | \$156 |
| 1336205 | Ifosfamide ( 500 mg ) | G |  | $\begin{aligned} & \hline \text { F-1 (11/00) } \\ & \text { F (02/99) } \\ & \hline \end{aligned}$ | [3778-73-2] | \$156 |
| 1336500 | Imidazole (200 mg) | G1B132 |  | G (01/04) | [288-32-4] | \$487 |
| 1336806 | Imidurea (200 mg) | H |  | G (10/99) | [39236-46-9] | \$156 |
| 1337004 | Iminodibenzyl (25 mg) | 10 C 253 | 2 | H (11/04) | [494-19-9] | \$487 |
| 1337809 | Imipenem Monohydrate ( 100 mg ) | G |  | F (01/01) | [74431-23-5] | \$156 |
| 1338007 | Imipramine Hydrochloride ( 200 mg ) | 1 |  | H (09/01) | [113-52-0] | \$156 |
| 1338801 | Indapamide (250 mg) | H |  | G (07/02) | [26807-65-8] | \$156 |
| 1339000 | Indigotindisulfonate Sodium ( 500 mg ) | H1B153 |  | H (06/03) | [860-22-0] | \$156 |
| 1340009 | Indocyanine Green (200 mg) | IOB045 |  | H (09/01) | [3599-32-4] | \$156 |
| 1341001 | Indomethacin (200 mg) | JOB165 |  | $\begin{aligned} & \text { I (01/04) } \\ & H(05 / 99) \end{aligned}$ | [53-86-1] | \$156 |
| 1342004 | Insulin (100 mg) | H |  |  | [9004-10-8] | \$156 |
| 1342106 | Insulin Human (100 mg) | H1A031 |  | $\begin{aligned} & \mathrm{H}(11 / 02) \\ & \mathrm{G}(04 / 00) \end{aligned}$ | [11061-68-0] | \$156 |
| 1342208 | Insulin (Beef) (100 mg) | F |  |  | [11070-73-8] | \$156 |
| 1342300 | Insulin (Pork) ( 100 mg ) | F |  |  | [12584-58-6] | \$156 |
| 1342503 | locetamic Acid (200 mg) | F |  |  | [16034-77-8] | \$156 |
| 1343007 | lodipamide ( 200 mg ) | G |  |  | [606-17-7] | \$156 |
| 1343517 | lodixanol (200 mg) | FOB240 |  |  | [92339-11-2] | \$156 |
| 1343540 | Iodixanol Related Compound C (25 mg) (5-Acetyl] 3 -[[3,5-bis[[2,3-dihydroxypropyl)amino]carbonyl]-2,4,6-triiodophenyl]amino]-2-hydroxy-propyl]amino]-N,N'-bis-(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B236 |  |  | n/f | \$487 |
| 1343550 | lodixanol Related Compound D (50 mg) (5-[Acetyl(2-hydroxy-3-methyl-propyl)amino]-N,N'-bis(2,3-dihydroxypropyl)2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B231 |  |  | [89797-00-2] | \$487 |
| 1343561 | lodixanol Related Compound E ( 25 mg ) (5-[[3-[[]3-[[(2,3-Dihydoxypro-pyl)amino]carbonyl]-5-[[amino]carbonyl]-2,4,6-triiodophenyl](acetylimi-no)]-2-hydroxypropyl]-(acetylimino)]-N,N'-bis(2,3-dihydoxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B229 |  |  | n/f | \$487 |
| 1344305 | o-lodohippuric Acid ( 100 mg ) | F |  |  | [147-58-0] | \$156 |
| 1344509 | lodoquinol ( 100 mg ) | H |  | G (07/02) | [83-73-8] | \$156 |
| 1344600 | lohexol ( 100 mg ) | F-1 |  | F (01/99) | [66108-95-0] | \$124 |
| 1344622 | Iohexol Related Compound A (100 mg) (5-(acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F-1 |  | F (10/01) | n/f | \$487 |
| 1344644 | Iohexol Related Compound B ( 50 mg ) ( 5 -amino-N,N'-bis(2,3-dihy-droxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F-1 |  | F (01/04) | [76801-93-9] | \$487 |
| 1344666 | lohexol Related Compound C (100 mg) (N,N'-bis(2,3-dihydroxypropyl)-5-nitro-1,3-benzenedicarboxamide) | F-1 |  | F (09/03) | n/f | \$156 |
| 1344702 | lopamidol (200 mg) | G |  |  | [60166-93-0] | \$156 |
| 1344724 | lopamidol Related Compound A (50 mg) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoiso-phthalamide) | G |  |  | [60166-98-5] | \$487 |
| 1344735 | lopamidol Related Compound B (100 mg) (5-Glycolamido-N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodoisophthalamide) | F |  |  | n/f | \$487 |

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| 1344804 | lopromide ( 400 mg ) | F |  |  | [73334-07-3] | \$156 |
| 1344826 | lopromide Related Compound A ( 50 mg ) ( 5 -Amino-N,N'-bis(2,3-dihy-droxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide) | F |  |  | n/f | \$487 |
| 1344837 | lopromide Related Compound B (50 mg) (5-(Acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide) | F |  |  | n/f | \$487 |
| 1345002 | lothalamic Acid (200 mg) | G |  |  | [2276-90-6] | \$156 |
| 1345104 | loversol ( 200 mg ) | F |  |  | [87771-40-2] | \$156 |
| 1345115 | loversol Related Compound A ( 50 mg ) ( 5 -Amino-N,N'-bis(2,3-dihy-droxypropyl)-2,4,6-triiodoisophthalamide) | F |  |  | [76801-93-9] | \$487 |
| 1345126 | loversol Related Compound B ( 50 mg ) (N,N'-bis(2,3-dihydroxypropyl)-5-[(N-(2-hydroxyethyl)-carbonyl)methoxy]-2,4,6-triiodoisophthalamide) | F |  |  | n/f | \$487 |
| 1345159 | Ioxaglic Acid (100 mg) | F |  |  | [59017-64-0] | \$156 |
| 1345206 | loxilan (400 mg) | F |  |  | [107793-72-6] | \$156 |
| 1345228 | Ioxilan Related Compound A (100 mg) (5-amino-2,4,6-triiodo-3 N-(2hydroxyethyl)carbamoyl benzoic acid) | F |  |  | [22871-58-5] | \$487 |
| 1346005 | Ipodate Calcium (200 mg) | F |  |  | [1151-11-7] | \$156 |
| 1347008 | Ipodate Sodium (200 mg) | F-1 |  |  | [1221-56-3] | \$156 |
| 1347755 | Isoamyl Methoxycinnamate ( $750 \mathrm{mg} / \mathrm{ampule} \mathrm{)}$ | F0B017 |  |  | [71617-10-2] | \$156 |
| 1348000 | Isocarboxazid ( 200 mg ) | F-1 |  |  | [59-63-2] | \$156 |
| 1348500 | Isoetharine Hydrochloride ( 250 mg ) | F-2 |  |  | [2576-92-3] | \$156 |
| 1348907 | Isoflupredone Acetate ( 200 mg ) | F0C109 |  |  | [338-98-7] | \$156 |
| 1349003 | Isoflurane ( 1 mL ) | H |  |  | [26675-46-7] | \$156 |
| 1349502 | L-Isoleucine ( 200 mg ) | F-2 |  | F-1 (09/02) | [73-32-5] | \$156 |
| 1349604 | Isomalathion ( 50 mg ) | F1B107 |  | F (01/03) | [3344-12-5] | \$487 |
| 1349659 | Isometheptene Mucate ( 200 mg ) | F |  |  | [7492-31-1] | \$156 |
| 1349706 | Isoniazid (200 mg) | H |  |  | [54-85-3] | \$156 |
| 1350002 | Isopropamide lodide (200 mg) | F-2 |  |  | [71-81-8] | \$156 |
| 1350400 | Isopropyl Myristate ( 500 mg ) | 1 |  |  | [110-27-0] | \$156 |
| 1350603 | Isopropyl Palmitate ( 500 mg ) | 1 |  | H (10/99) | [142-91-6] | \$156 |
| 1351005 | Isoproterenol Hydrochloride ( 125 mg ) | K |  |  | [51-30-9] | \$124 |
| 1352008 | Isosorbide ( $75 \%$ solution, 1 g ) | 1 |  | H-2 (10/00) | [652-67-5] | \$156 |
| 1353000 | Diluted Isosorbide Dinitrate ( 500 mg of $25 \%$ mixture with mannitol) | I-1 |  | I (10/99) | [87-33-2] | \$156 |
| 1353500 | Isotretinoin (200 mg) | 1 |  | H (10/00) | [4759-48-2] | \$156 |
| 1354003 | Isoxsuprine Hydrochloride (200 mg) | F-3 |  |  | [579-56-6] | \$156 |
| 1354207 | Isradipine ( 200 mg ) | G0B054 |  | F (05/03) | [75695-93-1] | \$156 |
| 1354218 | Isradipine Related Compound A ( 25 mg ) (Isopropyl methyl 4-(4-benzofurazanyl)-2,6-dimethyl-3,5-pyridinedicarboxylate) | F | 4 |  | n/f | \$487 |
| 1354309 | Ivermectin (200 mg) | F0B196 |  |  | [70288-86-7] | \$156 |
| 1355006 | Kanamycin Sulfate (200 mg) | J |  | I (06/99) | [25389-94-0] | \$156 |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 |  |  | n/f | \$260 |
| 1355753 | Kawain (200 mg) | F0C160 |  |  | [500-64-1] | \$208 |
| 1356009 | Ketamine Hydrochloride CIII ( 250 mg ) | G-2 |  | G-1 (07/00) | [1867-66-9] | \$207 |
| 1356020 | Ketamine Related Compound A (50 mg) (1-[(2-Chlorophenyl)(methylimino)methyl]cylcopentanol) | F0C118 |  |  | [6740-87-0] | \$487 |
| 1356508 | Ketoconazole (200 mg) | G4B179 |  | $\begin{aligned} & \text { G-3 (01/04) } \\ & \text { G-2 (06/01) } \\ & \text { G-1 }(01 / 99) \end{aligned}$ | [65277-42-1] | \$156 |
| 1356632 | Ketoprofen (200 mg) | H0B216 |  | $\begin{array}{\|l\|} \hline \text { G (07/04) } \\ \text { F-2 (05/99) } \\ \hline \end{array}$ | [22071-15-4] | \$156 |
| 1356643 | Ketoprofen Related Compound A ( 25 mg ) (alpha-Methyl-3-(4-methylbenzoyl) benzeneacetic acid) | G |  |  | [107257-20-5] | \$487 |

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| 1356665 | Ketorolac Tromethamine (200 mg) | G |  | F-2 (04/99) | [74103-07-4] | \$156 |
| 1356654 | Labetalol Hydrochloride ( 200 mg ) | G |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 }(01 / 02) \\ \text { F-1 } & (03 / 01) \\ \hline \end{array}$ | [32780-64-6] | \$156 |
| 1356676 | Anhydrous Lactose ( 100 mg ) | G |  | F (06/01) | [63-42-3] | \$156 |
| 1356687 | Lactitol ( 500 mg ) | F0B005 |  |  | [81025-04-9] | \$156 |
| 1356701 | Lactose Monohydrate ( 500 mg ) | G-1 |  | G (08/02) | [5989-81-1] | \$156 |
| 1356803 | Lactulose (1 g) | H |  | G-1 (08/00) | [4618-18-2] | \$156 |
| 1356836 | Lamivudine ( 200 mg ) | F0C361 | 1 |  | [134678-17-4] | \$156 |
| 1356880 | Lanolin (20 g) | F |  |  | [8006-54-0] | \$156 |
| 1356905 | Lanolin Alcohols (5 g) | F |  |  | [8027-33-6] | \$156 |
| 1356916 | Lansoprazole ( 200 mg ) | F0B310 |  |  | [103577-45-3] | \$156 |
| 1356927 | Lansoprazole Related Compound A (25 mg) (2-[[[3-methyl-4-(2,2,2-triflouroethoxy)-2-pyridyl]methyl]sulfonyl]benzimidazole) | F0B311 |  |  | n/f | \$487 |
| 1356971 | Letrozole ( 200 mg ) | F0B170 |  |  | [112809-51-5] | \$156 |
| 1356982 | Letrozole Related Compound A ( 15 mg ) ( $4,4^{\prime}$-( $1 \mathrm{H}-1,3,4$-triazol- 1 ylmethylene)dibenzonitrile) | F0B168 |  |  | n/f | \$487 |
| 1357001 | L-Leucine (200 mg) | H0B237 |  | $\begin{aligned} & \text { G-1 (04/04) } \\ & \text { G (08/00) } \end{aligned}$ | [61-90-5] | \$156 |
| 1358004 | Leucovorin Calcium ( 500 mg ) | J2B219 |  | $\begin{array}{\|l\|} \hline \mathrm{J}-1(07 / 04) \\ \mathrm{J}(05 / 02) \\ \hline \end{array}$ | [1492-18-8] | \$160 |
| 1359007 | Levallorphan Tartrate (200 mg) DISCONTINUED |  | 9 | $\begin{aligned} & \text { G-1 (09/04) } \\ & \text { G (11/02) } \\ & \hline \end{aligned}$ | [71-82-9] | \$156 |
| 1359302 | Levamisole Hydrochloride ( 125 mg ) | F2C122 |  | F-1 (05/04) | [16595-80-5] | \$124 |
| 1359506 | Levmetamfetamine CII (75 mg) | F |  |  | [33817-09-3] | \$207 |
| 1359801 | Levobunolol Hydrochloride (200 mg) | G |  |  | [27912-14-7] | \$156 |
| 1359903 | Levocarnitine ( 400 mg ) | G0B197 |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 }(06 / 03) \\ \text { F-1 }(12 / 00) \\ \hline \end{array}$ | [541-15-1] | \$156 |
| 1359925 | Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride) | F-1 |  | F (08/01) | [6538-82-5] | \$208 |
| 1361009 | Levodopa ( 200 mg ) | 1 |  | H (09/00) | [59-92-7] | \$156 |
| 1361010 | Levodopa Related Compound A ( 50 mg ) (3-(3,4,6-Trihydroxyphenyl)alanine) | K |  | $\begin{array}{\|l\|} \hline J(01 / 03) \\ I(06 / 00) \\ \hline \end{array}$ | [27244-64-0] | \$487 |
| 1420006 | Levodopa Related Compound B ( 50 mg ) (3-Methoxytyrosine) | $10 C 300$ | 2,8 | H (07/04) |  | \$487 |
| 1362001 | Levo-alpha-acetylmethadol Hydrochloride CII (25 mg) (AS) DISCONTINUED |  | 9 | $\begin{array}{\|l\|} \hline \text { F-1 (08/03) } \\ \text { F (07/01) } \\ \hline \end{array}$ | [43033-72-3] | \$207 |
| 1362500 | Levonordefrin ( 200 mg ) | F-1 |  |  | [829-74-3] | \$156 |
| 1363004 | Levopropoxyphene Napsylate ( 300 mg ) | G |  |  | [55557-30-7] | \$156 |
| 1364007 | Levorphanol Tartrate CII (500 mg) | H |  | G (03/01) | [5985-38-6] | \$207 |
| 1365000 | Levothyroxine ( 500 mg ) | K |  | $J$ (10/00) | [51-48-9] | \$156 |
| 1366002 | Lidocaine ( 250 mg ) | L |  |  | [137-58-6] | \$156 |
| 1367005 | Lincomycin Hydrochloride ( 200 mg ) | H2B130 |  | H-1 (01/04) | [7179-49-9] | \$156 |
| 1367504 | Lindane ( 200 mg ) | F-2 |  |  | [58-89-9] | \$156 |
| 1368008 | Liothyronine (250 mg) | L1C262 |  | $\begin{array}{\|l\|} \hline \text { L (08/04) } \\ \text { K (08/01) } \\ \hline \end{array}$ | [6893-02-3] | \$156 |
| 1368609 | Lisinopril (300 mg) | I |  | $\begin{aligned} & \mathrm{H}(09 / 01) \\ & \mathrm{G}(10 / 99) \end{aligned}$ | [83915-83-7] | \$156 |
| 1369000 | Lithium Carbonate (300 mg) | G0B031 |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 (01/03) } \\ \text { F-1 (01/01) } \\ \hline \end{array}$ | [554-13-2] | \$156 |
| 1370000 | Loperamide Hydrochloride (200 mg) | H0C202 | 2 | $\begin{aligned} & \hline \text { G-2 }(09 / 04) \\ & \text { G-1 }(02 / 03) \\ & \hline \end{aligned}$ | [34552-83-5] | \$156 |
| 1370203 | Loracarbef (200 mg) | F |  |  | [121961-22-6] | \$156 |

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| 1370225 | Loracarbef L-Isomer ( 25 mg ) | F |  |  | n/f | \$156 |
| 1370305 | Lorazepam CIV (200 mg) | 10C048 |  | H0B023 (06/04) | [846-49-1] | \$207 |
| 1370327 | Lorazepam Related Compound A ( 25 mg ) (7-Chloro-5-(0-chloro-phenyl)-1,3-dihydro-3-acetoxy-2H-1,4-benzodiazepin-2-one) | G |  | F-1 (06/01) | [2848-96-6] | \$487 |
| 1370338 | Lorazepam Related Compound B ( 25 mg ) (2-Amino-2',5-dichlorobenzophenone) | G |  | F-2 (01/04) | [2958-36-3] | \$487 |
| 1370349 | Lorazepam Related Compound C (25 mg) (6-Chloro-4-(0-chloro-phenyl)-2-quinazolinecarboxaldehyde) | H |  | $\begin{aligned} & \mathrm{G}(01 / 03) \\ & \mathrm{F}-3(01 / 02) \\ & \hline \end{aligned}$ | n/f | \$487 |
| 1370350 | Lorazepam Related Compound D (25 mg) (6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxylic Acid) | G0A014 |  | F-2 (01/04) | [54643-79-7] | \$487 |
| 1370360 | Lorazepam Related Compound E (25 mg) (6-Chloro-4-(o-chloro-phenyl)-2-quinazoline Methanol) | G |  | $\begin{aligned} & \text { F-3 (07/02) } \\ & \text { F-2 (04/99) } \\ & \hline \end{aligned}$ | n/f | \$487 |
| 1370600 | Lovastatin (125 mg) | H2C012 |  | $\begin{array}{\|l\|} \hline \text { H1B067 (01/04) } \\ \text { H (08/03) } \\ \hline \end{array}$ | [75330-75-5] | \$124 |
| 1370611 | Lovastatin Related Compound A ( 20 mg ) (Butanoic acid, 2-meth-yl-, 1,2,3,4,4a,7,8,8a-octahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[alpha( $\mathrm{R}^{*}$ ), 3alpha,7beta,8beta(2S*,4S*), 8alpha beta]]-) | G0C326 | 2 | F0B235 (09/04) | n/f | \$487 |
| 1370702 | Loxapine Succinate ( 125 mg ) | G0B026 |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 (06/03) } \\ \text { F-1 (07/01) } \\ \text { F (03/99) } \\ \hline \end{array}$ | [27833-64-3] | \$124 |
| 1370906 | Lynestrenol (20 mg) | F0B314 |  |  | [52-76-6] | \$203 |
| 1371002 | Lysergic Acid Diethylamide Tartrate Cl (10 mg) (AS) (LSD) | I |  |  | [50-37-3] | \$207 |
| 1371501 | L-Lysine Acetate ( 200 mg ) | F |  |  | [57282-49-2] | \$156 |
| 1372005 | L-Lysine Hydrochloride (200 mg) | H |  | G (07/00) | [657-27-2] | \$156 |
| 1373008 | Mafenide Acetate (200 mg) | F |  |  | [13009-99-9] | \$156 |
| 1374000 | Magaldrate ( 200 mg ) | F-1 |  |  | [74978-16-8] | \$156 |
| 1374306 | Magnesium Salicylate (200 mg) | F2B081 |  | F-1 (01/04) | [18917-95-8] | \$156 |
| 1374408 | Malathion ( 500 mg ) | F-1 |  | F (08/01) | [121-75-5] | \$156 |
| 1374500 | Maleic Acid ( 300 mg ) | G |  | F-2 (12/00) | [110-16-7] | \$487 |
| 1374601 | Malic Acid (200 mg) | G0B158 |  | F-1 (04/03) | [617-48-1] | \$156 |
| 1374907 | Maltitol (200 mg) | G |  | F-1 (12/99) | [585-88-6] | \$156 |
| 1375003 | Maltol (4 g) (FCC) | G |  | F-1 (12/99) | [118-71-8] | \$156 |
| 1375058 | Mandelic Acid ( 500 mg ) | F |  |  | [90-64-2] | \$156 |
| 1375105 | Mannitol ( 200 mg ) | IOB212 |  | H (03/04) | [69-65-8] | \$156 |
| 1375207 | Maprotiline Hydrochloride ( 200 mg ) | H |  | G (07/02) | [10347-81-6] | \$156 |
| 1375309 | Mazindol CIV ( 350 mg ) | H |  | G (02/03) | [22232-71-9] | \$207 |
| 1375502 | Mebendazole ( 200 mg ) | G |  |  | [31431-39-7] | \$156 |
| 1375706 | Mebrofenin ( 100 mg ) | F |  |  | [78266-06-5] | \$156 |
| 1376006 | Mecamylamine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  |  | [826-39-1] | \$156 |
| 1376505 | Mechlorethamine Hydrochloride ( 100 mg ) | F-1 |  | F (09/00) | [55-86-7] | \$156 |
| 1377009 | Meclizine Hydrochloride ( 500 mg ) | $\mathrm{I}-1$ |  |  | [31884-77-2] | \$156 |
| 1377508 | Meclocycline Sulfosalicylate ( 300 mg ) | G |  |  | [73816-42-9] | \$156 |
| 1377803 | Meclofenamate Sodium ( 500 mg ) | H |  |  | [6385-02-0] | \$156 |
| 1378001 | Medroxyprogesterone Acetate ( 200 mg ) | H-2 |  | H-1 (04/03) | [71-58-9] | \$156 |
| 1379004 | Medrysone ( 500 mg ) | F |  |  | [2668-66-8] | \$156 |
| 1379605 | Mefenamic Acid (200 mg) | G0C025 |  | $\begin{aligned} & \text { F3A032 (08/04) } \\ & \text { F-2 (01/03) } \end{aligned}$ | [61-68-7] | \$156 |
| 1379106 | Megestrol Acetate ( 500 mg ) | 1 |  | H (05/00) | [595-33-5] | \$156 |
| 1379300 | Melphalan Hydrochloride (200 mg) | G |  |  | [3223-07-2] | \$156 |

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| 1381006 | Menadione (200 mg) (Vitamin K3) | H-3 |  | H-2 (02/00) | [58-27-5] | \$156 |
| 1381709 | Menthol (250 mg) | IOB049 |  | H (04/03) | [2216-51-5] | \$156 |
| 1381742 | Menthyl Anthranilate ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | F0B103 |  |  | [134-09-8] | \$156 |
| 1382009 | Mepenzolate Bromide ( 200 mg ) | F |  |  | [76-90-4] | \$156 |
| 1383001 | Meperidine Hydrochloride CII (200 mg) | I |  | H-1 (12/99) | [50-13-5] | \$207 |
| 1384004 | Mephentermine Sulfate ( 250 mg ) | F-1 |  |  | [1212-72-2] | \$156 |
| 1385007 | Mephenytoin ( $250 \mathrm{mg} \mathrm{)}$ | G |  |  | [50-12-4] | \$156 |
| 1386000 | Mephobarbital CIV (250 mg) | G |  | F (01/01) | [115-38-8] | \$207 |
| 1387002 | Mepivacaine Hydrochloride (200 mg) | H |  | G-4 (02/99) | [1722-62-9] | \$156 |
| 1388005 | Meprednisone ( 200 mg ) | G |  |  | [1247-42-3] | \$156 |
| 1389008 | Meprobamate CIV (200 mg) | G-1 |  | G (03/02) | [57-53-4] | \$207 |
| 1390007 | Meprylcaine Hydrochloride (200 mg) | F |  |  | [956-03-6] | \$156 |
| 1391000 | 3-Mercapto-2-methylpropanoic Acid 1,2-Diphenylethylamine Salt ( 75 mg ) | G |  |  | n/f | \$487 |
| 1392002 | Mercaptopurine ( 500 mg ) | 12C263 | 2 | $\begin{array}{\|l\|} \hline \text { I-1 (10/04) } \\ \text { I (07/02) } \\ H(12 / 99) \\ \hline \end{array}$ | [6112-76-1] | \$156 |
| 1392454 | Meropenem ( 300 mg ) | F0C201 |  |  | [119478-56-7] | \$182 |
| 1392705 | Mesalamine ( 200 mg ) | G1B001 |  | $\begin{aligned} & \hline \text { G (01/03) } \\ & \text { F-1 }(03 / 00) \\ & \hline \end{aligned}$ | [89-57-6] | \$156 |
| 1393005 | Mesoridazine Besylate ( 250 mg ) | I-1 |  |  | [32672-69-8] | \$156 |
| 1394008 | Mestranol (200 mg) | K0C065 |  | $\begin{array}{\|l} \hline J(07 / 04) \\ I-1(09 / 99) \\ \hline \end{array}$ | [72-33-3] | \$156 |
| 1395500 | Metaproterenol Sulfate (200 mg) | F-3 |  |  | [5874-97-5] | \$156 |
| 1396003 | Metaraminol Bitartrate ( 200 mg ) | F-3 |  |  | [33402-03-8] | \$156 |
| 1396309 | Metformin Hydrochloride (200 mg) | F0C209 |  |  | [1115-70-4] | \$182 |
| 1396310 | Metformin Related Compound A (50 mg) (1-Cyanoguanidine) | F0C210 |  |  | [461-58-5] | \$487 |
| 1396400 | Methacrylic Acid Copolymer Type A (200 mg) | G0B140 |  | F-2 (04/03) | n/f | \$156 |
| 1396502 | Methacrylic Acid Copolymer Type B (200 mg) | G0B141 |  | F-2 (04/03) | n/f | \$156 |
| 1396604 | Methacrylic Acid Copolymer Type C (100 mg) | G1B088 |  | G (08/03) | n/f | \$124 |
| 1397006 | Methacycline Hydrochloride ( 200 mg ) | H |  | G (04/01) | [3963-95-9] | \$156 |
| 1398009 | Methadone Hydrochloride CII (200 mg) | IOB163 |  | H-1 (08/03) | [1095-90-5] | \$207 |
| 1399001 | Methamphetamine Hydrochloride CII (125 mg) | I |  |  | [51-57-0] | \$207 |
| 1401001 | Methantheline Bromide ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [53-46-3] | \$156 |
| 1402004 | Methapyrilene Fumarate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [33032-12-1] | \$156 |
| 1404000 | Methaqualone Cl ( 500 mg ) | F-1 |  |  | [72-44-6] | \$207 |
| 1405002 | Metharbital CIII ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  | F-1 (07/99) | [50-11-3] | \$207 |
| 1406005 | Methazolamide ( 500 mg ) | H0B239 |  | G-1 (05/04) | [554-57-4] | \$156 |
| 1407008 | Methdilazine (200 mg) | F-1 |  |  | [1982-37-2] | \$156 |
| 1408000 | Methdilazine Hydrochloride (200 mg) | G |  |  | [1229-35-2] | \$156 |
| 1409003 | Methenamine ( 500 mg ) | H0C047 |  | G (05/04) | [100-97-0] | \$156 |
| 1409502 | Methenamine Hippurate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [5714-73-8] | \$156 |
| 1409604 | Methenamine Mandelate ( 200 mg ) | F-2 |  | F-1 (11/00) | [587-23-5] | \$156 |
| 1410002 | Methicillin Sodium ( 500 mg ) |  |  | $\begin{aligned} & \text { I1B186 (11/04) } \\ & \text { I (03/03) } \\ & \text { H (03/00) } \\ & \hline \end{aligned}$ | [7246-14-2] | \$156 |
| 1411005 | Methimazole (200 mg) | G |  | F (02/01) | [60-56-0] | \$156 |
| 1411504 | L-Methionine (200 mg) | G |  | F-2 (11/99) | [63-68-3] | \$156 |
| 1412008 | Methocarbamol (200 mg) | H2B029 | 2,4 | H-1 (03/04) | [532-03-6] | \$156 |

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| 1413000 | Methohexital CIV (500 mg) | F-2 |  |  | [18652-93-2] | \$207 |
| 1414003 | Methotrexate ( 500 mg ) | I |  |  | [59-05-2] | \$156 |
| 1415006 | Methotrimeprazine ( 125 mg ) | F-2 |  | F-1 (05/99) | [60-99-1] | \$124 |
| 1416009 | Methoxamine Hydrochloride ( 200 mg ) | F |  |  | [61-16-5] | \$156 |
| 1417001 | Methoxsalen ( 500 mg ) | H |  |  | [298-81-7] | \$156 |
| 1418004 | Methoxyflurane ( 1 mL ) | G |  |  | [76-38-0] | \$156 |
| 1419007 | Methoxyphenamine Hydrochloride ( 250 mg ) | F |  |  | [5588-10-3] | \$156 |
| 1421009 | Methscopolamine Bromide (200 mg) | G |  |  | [155-41-9] | \$156 |
| 1422001 | Methsuximide ( 500 mg ) | F-2 |  | F-1 (08/99) | [77-41-8] | \$156 |
| 1424007 | Methyclothiazide ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | [135-07-9] | \$156 |
| 1424018 | Methyclothiazide Related Compound A (100 mg) (4-amino-6-chloro-N-3-methyl-m-benzenedisulfonamide) | G |  | F-2 (12/00) | n/f | \$487 |
| 1424222 | Methyl Benzylidene Camphor (200 mg) | F0B118 |  |  | [36861-47-9] | \$156 |
| 1424233 | Methyl Caprate ( 300 mg ) | F |  |  | [110-42-9] | \$156 |
| 1424244 | Methyl Caproate ( 300 mg ) | F |  |  | [106-70-7] | \$156 |
| 1424255 | Methyl Caprylate ( 300 mg ) | F |  |  | [111-11-5] | \$156 |
| 1424506 | Methylcellulose (1 g) (AS) | G0B222 |  | F-2 (05/03) | [9004-67-5] | \$156 |
| 1425000 | 4-Methyl-2,5-dimethoxyamphetamine Hydrochloride CI (25 mg) (AS) (STP) | F |  |  | [15589-00-1] | \$207 |
| 1426002 | Methyldopa ( 500 mg ) | 1 |  |  | [41372-08-1] | \$156 |
| 1427005 | Methyldopate Hydrochloride ( 200 mg ) | G-2 |  |  | [2508-79-4] | \$156 |
| 1428008 | Methylene Blue ( 250 mg ) | G |  |  | [7220-79-3] | \$156 |
| 1429000 | Methylenedioxy-3,4-amphetamine Hydrochloride $\mathbf{C l}(25 \mathrm{mg})$ (AS) (MDA) | F-1 |  |  | [6292-91-7] | \$207 |
| 1430000 | Methylergonovine Maleate ( 50 mg ) (List Chemical) | J |  | I (05/02) | [57432-61-8] | \$156 |
| 1430305 | Methyl Laurate ( 500 mg ) | F |  |  | [111-82-0] | \$156 |
| 1430327 | Methyl Linoleate ( $5 \times 50 \mathrm{mg}$ ) | F |  |  | [112-63-0] | \$156 |
| 1430349 | Methyl Linolenate ( $5 \times 50 \mathrm{mg}$ ) | F |  |  | [301-00-8] | \$156 |
| 1430509 | $3-\mathrm{O}-\mathrm{Methylmethyldopa} \mathrm{( } 50 \mathrm{mg}$ ) | G-1 |  |  | n/f | \$487 |
| 1431002 | Methyl 5-methyl-3-isoxazolecarboxylate ( 25 mg ) | F-1 |  | F (01/01) | n/f | \$487 |
| 1431501 | Methyl Myristate ( 300 mg ) | F |  |  | [124-10-7] | \$156 |
| 1431556 | Methyl Oleate ( 500 mg ) | G0C148 |  | F (04/04) | [112-62-9] | \$156 |
| 1431603 | Methyl Palmitate ( 300 mg ) | F |  |  | [112-39-0] | \$156 |
| 1431625 | Methyl Palmitoleate ( $300 \mathrm{mg} \mathrm{)}$ | F |  |  | n/f | \$156 |
| 1432005 | Methylparaben ( 125 mg ) | J-1 |  | J (03/03)) | [99-76-3] | \$124 |
| 1433008 | Methylphenidate Hydrochloride CII (125 mg) | 1 |  | H (05/01) | [298-59-9] | \$165 |
| 1434000 | Methylphenidate Hydrochloride Erythro Isomer CII ( 25 mg ) | J0B294 |  | $\begin{array}{\|l} \hline \text { IOA006 (09/03) } \\ \text { H-1 (01/03) } \\ \text { H (06/01) } \\ \hline \end{array}$ | [298-59-9] | \$560 |
| 1434022 | Methylphenidate Related Compound A (50 mg) (alpha-Phenyl-2piperidineacetic Acid Hydrochloride) | G |  | F-2 (10/99) | n/f | \$487 |
| 1435003 | Methylprednisolone ( 200 mg ) | H |  |  | [83-43-2] | \$156 |
| 1436006 | Methylprednisolone Acetate ( 200 mg ) | G-2 |  | G-1 (02/00) | [53-36-1] | \$156 |
| 1437009 | Methylprednisolone Hemisuccinate ( 200 mg ) | IOC146 |  | H (07/04) | [2921-57-5] | \$156 |
| 1437508 | Methyl Stearate ( 300 mg ) | F |  |  | [112-61-8] | \$156 |
| 1438001 | Methyltestosterone CIII (200 mg) | J |  | I (11/01) | [58-18-4] | \$207 |
| 1440003 | Methysergide Maleate ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  | [129-49-7] | \$156 |
| 1440808 | Metoclopramide Hydrochloride ( 500 mg ) | G |  | F-2 (06/99) | [54143-57-6] | \$156 |
| 1441006 | Metocurine lodide ( $300 \mathrm{mg} \mathrm{)}$ | G |  |  | [7601-55-0] | \$156 |
| 1441200 | Metolazone ( 200 mg ) | G0B246 |  | F-1 (05/03) | [17560-51-9] | \$156 |

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| 1441287 | Metoprolol Fumarate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [119637-66-0] | \$156 |
| 1441232 | Metoprolol Related Compound A (20 mg) ((+/-)1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol) | F0C343 | 1 |  | n/f | \$520 |
| 1441254 | Metoprolol Related Compound C (20 mg) ((+/-)4-[2-Hydroxy-3-(1methylethyl)aminopropoxy]benzaldehyde) | F0C344 | 1 |  | n/f | \$520 |
| 1441301 | Metoprolol Tartrate (200 mg) | H1B059 |  | $\begin{aligned} & \hline \text { H (01/04) } \\ & \text { G-1 (11/99) } \\ & \hline \end{aligned}$ | [56392-17-7] | \$156 |
| 1441505 | Metrizamide ( 500 mg ) | F |  |  | [31112-62-6] | \$156 |
| 1442009 | Metronidazole ( 100 mg ) | 1 |  |  | [443-48-1] | \$156 |
| 1443001 | Metyrapone ( 200 mg ) | H |  | G (06/01) | [54-36-4] | \$156 |
| 1443205 | Metyrosine ( 200 mg ) | F |  |  | [672-87-7] | \$156 |
| 1443250 | Mexiletine Hydrochloride (200 mg) | F-2 |  | F-1 (09/02) | [5370-01-4] | \$156 |
| 1443307 | Mezlocillin Sodium ( 350 mg ) | G |  |  | [59798-30-0] | \$156 |
| 1443409 | Miconazole ( 200 mg ) | G-1 |  | G (07/02) | [22916-47-8] | \$156 |
| 1443500 | Miconazole Nitrate (200 mg) | I |  | H (06/99) | [22832-87-7] | \$156 |
| 1443850 | Powdered Milk Thistle Extract (250 mg) | F0B321 |  |  | [84604-20-6] | \$260 |
| 1443908 | Milrinone ( 500 mg ) | F0C050 |  |  | [78415-72-2] | \$260 |
| 1443919 | Milrinone Related Compound A ( 50 mg ) (1,6-Dihydro-2-methyl-6-oxo(3,4'-bipyridine)-5-carboxamide) | F0C051 |  |  | [80047-24-1] | \$487 |
| 1444004 | Minocycline Hydrochloride (200 mg) | 10C178 |  | $\begin{array}{\|l\|l\|} \hline \mathrm{H}-3(04 / 04) \\ \mathrm{H}-2(07 / 02) \\ \hline \end{array}$ | [13614-98-7] | \$156 |
| 1444208 | Minoxidil ( 125 mg ) | H1C168 |  | $\begin{array}{\|l\|} \hline \mathrm{H}(03 / 04) \\ \mathrm{G}(05 / 99) \\ \hline \end{array}$ | [38304-91-5] | \$124 |
| 1444707 | Mitomycin ( 50 mg ) | K |  | $J(07 / 01)$ | [50-07-7] | \$479 |
| 1445007 | Mitotane ( 500 mg ) | GOC044 |  | F (07/04) | [53-19-0] | \$156 |
| 1445200 | Mitoxantrone Hydrochloride ( 400 mg ) | H |  | G (03/01) | [70476-82-3] | \$498 |
| 1445222 | Mitoxantrone Related Compound A Hydrochloride ( 30 mg ) ( 8 -amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione Hydrochloride) |  |  | $\begin{aligned} & \hline \text { F-1 (07/04) } \\ & \text { F (03/01) } \end{aligned}$ | n/f | \$208 |
| 1445459 | Molindone Hydrochloride ( 500 mg ) | F |  |  | [15622-65-8] | \$156 |
| 1445470 | Mometasone Furoate (200 mg) | G0B073 |  | $\begin{aligned} & \hline \text { F-1 (04/03) } \\ & \text { F (02/01) } \\ & \hline \end{aligned}$ | [83919-23-7] | \$156 |
| 1445481 | Monensin Sodium (200 mg) | F0B293 |  |  | [22373-78-0] | \$156 |
| 1445506 | Monobenzone ( 200 mg ) | F |  |  | [103-16-2] | \$156 |
| 1445801 | Mono- and Di-acetylated Monoglycerides (200 mg) | F |  |  | [68990-54-5] | \$156 |
| 1446000 | Monoglycerides (125 mg) | H |  |  | [68990-53-4] | \$124 |
| 1446804 | Monostearyl Maleate ( 100 mg ) | G |  | F-2 (04/00) | [2424-62-6] | \$487 |
| 1446950 | Moricizine Hydrochloride ( 100 mg ) | F |  |  | [29560-58-5] | \$156 |
| 1447002 | Morphine Monohydrate CII (50 mg) (AS) | G |  |  | [6009-81-0] | \$207 |
| 1448005 | Morphine Sulfate CII (500 mg) | LOB056 |  | $\begin{aligned} & \mathrm{K}(06 / 03) \\ & \mathrm{J}-1(07 / 00) \\ & \hline \end{aligned}$ | [6211-15-0] | \$332 |
| 1448504 | Moxalactam Disodium ( 500 mg ) | F-1 |  |  | [64953-12-4] | \$156 |
| 1448901 | Mupirocin ( 50 mg ) | F-1 |  | F (03/02) | [12650-69-0] | \$156 |
| 1448923 | Mupirocin Lithium (100 mg) | G |  | F (02/01) | [73346-79-9] | \$156 |
| 1449008 | Myristyl Alcohol (1 g) | G |  | F (02/02) | [112-72-1] | \$156 |
| 1449518 | Nabumetone (200 mg) | F0C072 |  |  | [42924-53-8] | \$156 |
| 1449700 | Nadolol (200 mg) | F-3 |  | F-2 (04/02) | [42200-33-9] | \$156 |
| 1450007 | Nafcillin Sodium (200 mg) | H |  |  | [7177-50-6] | \$156 |
| 1450404 | Naftifine Hydrochloride ( 200 mg ) | F |  |  | [65473-14-5] | \$156 |
| 1451000 | Nalidixic Acid (200 mg) | G |  |  | [389-08-2] | \$156 |

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| 1452002 | Nalorphine Hydrochloride CIII (250 mg) | I |  |  | [57-29-4] | \$207 |
| 1453005 | Naloxone (125 mg) | LOB124 |  | $\begin{aligned} & \hline \text { K-1 (12/02) } \\ & \text { K (07/01) } \\ & \hline \end{aligned}$ | [465-65-6] | \$124 |
| 1453504 | Naltrexone (200 mg) | H0C150 |  | $\begin{aligned} & \text { G1B039 (03/04) } \\ & \text { G (02/03) } \end{aligned}$ | [16590-41-3] | \$156 |
| 1453526 | Naltrexone Related Compound A CII (30 mg) (N-(3-butenyl)-noroxymorphone Hydrochloride) | F |  |  | n/f | \$207 |
| 1454008 | Nandrolone CIII ( 50 mg ) | F-3 |  |  | [434-22-0] | \$560 |
| 1455000 | Nandrolone Decanoate CIII ( 250 mg ) | I |  |  | [360-70-3] | \$207 |
| 1456003 | Nandrolone Phenpropionate CIII (250 mg) | H |  |  | [62-90-8] | \$207 |
| 1457006 | Naphazoline Hydrochloride (200 mg) | K |  |  | [550-99-2] | \$156 |
| 1457301 | Naproxen (200 mg) | I-1 |  | $\begin{aligned} & \mathrm{I}(03 / 03) \\ & \mathrm{H}-1(01 / 01) \end{aligned}$ | [22204-53-1] | \$156 |
| 1457403 | Naproxen Sodium (200 mg) | 1 |  |  | [26159-34-2] | \$156 |
| 1457505 | Natamycin (200 mg) | 1 |  | H (11/99) | [7681-93-8] | \$156 |
| 1458009 | Neomycin Sulfate (200 mg) | L-2 |  | $\begin{aligned} & \mathrm{L}-1(09 / 01) \\ & \mathrm{L}(02 / 99) \\ & \hline \end{aligned}$ | [1405-10-3] | \$156 |
| 1459001 | Neostigmine Bromide (200 mg) | G |  |  | [114-80-7] | \$156 |
| 1460000 | Neostigmine Methylsulfate ( 200 mg ) | 1 |  | H (07/00) | [51-60-5] | \$156 |
| 1460500 | Netilmicin Sulfate ( 500 mg ) | H |  | G (05/02) | [56391-57-2] | \$156 |
| 1461003 | Niacin (200 mg) | H-1 |  |  | [59-67-6] | \$156 |
| 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) | M-1 |  | M (02/01) | [98-92-0] | \$156 |
| 1463304 | Nicotine Bitartrate Dihydrate ( 500 mg ) | G |  | F (05/99) | [6019-06-3] | \$156 |
| 1463508 | Nifedipine ( 125 mg ) | J0B243 |  | I-1 (04/04) | [21829-25-4] | \$124 |
| 1463600 | Nifedipine Nitrophenylpyridine Analog (25 mg) | K |  | $J(04 / 01)$ | n/f | \$487 |
| 1463701 | Nifedipine Nitrosophenylpyridine Analog ( 25 mg ) | K |  | $J$ (07/02) | n/f | \$487 |
| 1464001 | Nitrofurantoin ( 500 mg ) | J |  | I-1 (11/02) | [67-20-9] | \$156 |
| 1465004 | Nitrofurazone ( $200 \mathrm{mg} \mathrm{)}$ | H-1 |  | H (09/01) | [59-87-0] | \$156 |
| 1465503 | Nitrofurfural Diacetate ( 100 mg ) | F-1 |  |  | [92-55-7] | \$487 |
| 1466007 | Nitrofurazone Related Compound A ( 500 mg ) (5-Nitro-2-furfuraldazine) | H0B100 |  | G (07/03) | n/f | \$487 |
| 1466506 | Diluted Nitroglycerin ( 5 ampules, approx. 200 mg of a $0.948 \%$ solution in propylene glycol each) | G |  |  | [55-63-0] | \$156 |
| 1467804 | Nizatidine ( 200 mg ) | G |  | F-1 (06/00) | [76963-41-2] | \$156 |
| 1467950 | Nonoxynol 9 ( 0.5 mL ) | H-1 |  | H (03/02) | [26027-38-3] | \$156 |
| 1468002 | Nonoxynol 10 (200 mg) | F |  |  | [26027-38-3] | \$156 |
| 1468400 | Nordazepam CIV (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-ben-zodiazepin-2-one) | H1B035 |  | $\begin{aligned} & \hline \mathrm{H}(03 / 03) \\ & \mathrm{G}(03 / 00) \\ & \hline \end{aligned}$ | [1088-11-5] | \$560 |
| 1468501 | Norepinephrine Bitartrate ( 125 mg ) | H |  |  | [69815-49-2] | \$124 |
| 1469005 | Norethindrone ( 200 mg ) | J1B065 |  | $\begin{aligned} & \hline \mathrm{J}-1(05 / 03) \\ & \mathrm{J}(07 / 02) \\ & \mathrm{I}-1(03 / 01) \\ & \hline \end{aligned}$ | [68-22-4] | \$156 |
| 1470004 | Norethindrone Acetate ( 100 mg ) | J0B072 |  | $\begin{aligned} & \hline \mathrm{I}(04 / 03) \\ & \mathrm{H}(06 / 99) \\ & \hline \end{aligned}$ | [51-98-9] | \$156 |
| 1471007 | Norethynodrel (200 mg) | G |  |  | [68-23-5] | \$156 |
| 1471506 | Norfloxacin ( 200 mg ) | H |  | G (04/01) | [70458-96-7] | \$156 |
| 1471914 | Norgestimate ( 200 mg ) | F0C086 |  |  | [35189-28-7] | \$156 |
| 1472000 | Norgestrel (125 mg) | J0C269 |  | $\begin{aligned} & \hline \text { I (07/04) } \\ & H(05 / 99) \end{aligned}$ | [6533-00-2] | \$124 |
| 1473002 | Noroxymorphone Hydrochloride CII (50 mg) | H1C177 | 2 | H (11/04) | n/f | \$560 |
| 1474005 | Nortriptyline Hydrochloride (200 mg) | 1 |  | H (04/00) | [894-71-3] | \$156 |
| 1474504 | Noscapine ( 500 mg ) | G |  |  | [128-62-1] | \$156 |

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| 1475008 | Novobiocin ( 200 mg ) | G-2 |  |  | [303-81-1] | \$156 |
| 1476000 | Nylidrin Hydrochloride (200 mg) | F-2 |  |  | [849-55-8] | \$156 |
| 1477003 | Nystatin ( 200 mg ) | N1B004 |  | N (01/03) | [1400-61-9] | \$156 |
| 1477900 | Octinoxate ( 500 mg ) (Octyl Methoxycinnamate) | G0C024 |  | FOB032 (12/03) | [5466-77-3] | \$156 |
| 1477411 | Octocrylene ( 500 mg ) | G0C211 |  | F0B104 (05/04) | [6197-30-4] | \$156 |
| 1477502 | Octoxynol 9 ( 200 mg ) | G |  | F-2 (07/00) | [9002-93-1] | \$156 |
| 1477808 | Octyldodecanol (200 mg) | G |  | F-1 (07/99) | [5333-42-6] | \$156 |
| 1477943 | Octyl Salicylate (400 mg) | F0B091 |  |  | [118-60-5] | \$156 |
| 1478108 | Ofloxacin (200 mg) | F-2 |  | F-1 (08/02) | [82419-36-1] | \$156 |
| 1478505 | Omeprazole (200 mg) | H1B211 |  | $\begin{aligned} & \text { H (05/04) } \\ & \text { G-1 (04/02) } \\ & \text { G (09/01) } \\ & \hline \end{aligned}$ | [73590-58-6] | \$156 |
| 1478582 | Ondansetron Hydrochloride ( 300 mg ) | F0C222 |  |  | [103639-04-9] | \$208 |
| 1478593 | Ondansetron Related Compound A ( 50 mg ) (3[(Dimethylamino)-methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride) | FOC191 |  |  | [119812-29-2] | \$487 |
| 1478618 | Ondansetron Related Compound C (50 mg) (1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4-one) | F0C251 |  |  | [27397-31-1] | \$487 |
| 1478629 | Ondansetron Related Compound D (50 mg) (1,2,3,9-Tetrahydro-9-methyl-3-methylene-4H-carbazol-4-one) | F0C226 |  |  | n/f | \$487 |
| 1479009 | Orphenadrine Citrate (200 mg) | G |  | F-4 (05/02) | [4682-36-4] | \$156 |
| 1481000 | Oxacillin Sodium (200 mg) | $J$ |  | I (03/02) | [7240-38-2] | \$156 |
| 1481500 | Oxamniquine (200 mg) | F |  |  | [21738-42-1] | \$156 |
| 1481703 | Oxamniquine Related Compound A (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolinemethyl methanesulfonate) | F |  |  | n/f | \$487 |
| 1481805 | Oxamniquine Related Compound B (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-5-nitro-6-quinolinemethanol) | F |  |  | n/f | \$487 |
| 1482003 | Oxandrolone CIII ( 50 mg ) | G0B220 |  | F-4 (07/03) | [53-39-4] | \$207 |
| 1482207 | Oxaprozin (200 mg) | F0C115 |  |  | [21256-18-8] | \$156 |
| 1483006 | Oxazepam CIV (200 mg) | G-1 |  | G (12/00) | [604-75-1] | \$207 |
| 1483301 | Oxfendazole (200 mg) | FOC128 |  |  | [53716-50-0] | \$156 |
| 1483505 | Oxprenolol Hydrochloride (200 mg) | H |  |  | [6452-73-9] | \$156 |
| 1484009 | Oxtriphylline ( 500 mg ) | G |  |  | [4499-40-5] | \$156 |
| 1485001 | Oxybenzone ( 150 mg ) | H0B263 |  | $\begin{aligned} & \hline \mathrm{G}(11 / 03) \\ & \mathrm{F}-2(12 / 99) \\ & \hline \end{aligned}$ | [131-57-7] | \$156 |
| 1485103 | Oxybutynin Chloride (200 mg) | G-1 |  | G (11/02) | [1508-65-2] | \$156 |
| 1485114 | Oxybutynin Related Compound A ( 100 mg ) (Phenylcyclohexylglycolic Acid) | G |  | F-2 (01/00) | [4335-77-7] | \$487 |
| 1485191 | Oxycodone CII (200 mg) | 10B046 |  | $\begin{aligned} & \mathrm{H}(01 / 03) \\ & \mathrm{G}-1(01 / 01) \end{aligned}$ | [76-42-6] | \$207 |
| 1486004 | Oxymetazoline Hydrochloride (200 mg) | 1 |  |  | [2315-02-8] | \$156 |
| 1487007 | Oxymetholone CIII (200 mg) | G1B247 |  | G (10/03) | [434-07-1] | \$207 |
| 1488000 | Oxymorphone CII ( 500 mg ) | H0B214 |  | G (03/03) | [76-41-5] | \$207 |
| 1489002 | Oxyphenbutazone (1 g) | H |  |  | [7081-38-1] | \$156 |
| 1490103 | Oxyquinoline Sulfate (200 mg) | F-1 |  | F (07/02) | [134-31-6] | \$156 |
| 1491004 | Oxytetracycline (200 mg) | I-1 |  |  | [6153-64-6] | \$156 |
| 1491300 | Oxytocin (5 vials, 46 USP units per vial) | F |  |  | [50-56-6] | \$156 |
| 1491332 | Paclitaxel ( 200 mg ) | F0C180 |  |  | [33069-62-4] | \$1,508 |
| 1491343 | Paclitaxel Related Compound A (20 mg) (Cephalomannine) | F0C179 |  |  | [71610-00-9] | \$754 |
| 1491354 | Paclitaxel Related Compound B (20 mg) (10-Deacetyl-7-epipaclitaxel) | F0C181 |  |  | nf | \$754 |
| 1491503 | Padimate O (300 mg) | H0B154 |  | G (04/03) | [21245-02-3] | \$156 |

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| 1492007 | Palmitic Acid ( 500 mg ) | 1 |  |  | [57-10-3] | \$156 |
| 1493000 | Pamoic Acid (250 mg) | G-4 |  | G-3 (01/03) | [130-85-8] | \$156 |
| 1494057 | Pancreatin Amylase and Protease (2 g) | 1 |  | H (10/00) | [8049-47-6] | \$156 |
| 1494079 | Pancreatin Lipase (2 g) | 1 |  | H-1 (03/01) | [8049-47-6] | \$156 |
| 1494501 | Panthenol, Racemic (200 mg) | G |  | F-1 (02/00) | [16485-10-2] | \$156 |
| 1494807 | Pantolactone ( 500 mg ) | F |  |  | [599-04-2] | \$487 |
| 1495005 | Papain (1 g) | H |  | G (12/01) | [9001-73-4] | \$156 |
| 1496008 | Papaverine Hydrochloride (200 mg) | H |  |  | [61-25-6] | \$156 |
| 1497000 | Paramethadione ( 500 mg ) | G |  |  | [115-67-3] | \$156 |
| 1498003 | Paramethasone Acetate ( 200 mg ) | G |  | F-1 (05/01) | [1597-82-6] | \$156 |
| 1498706 | Parbendazole ( 200 mg ) | F |  |  | [14255-87-9] | \$156 |
| 1499006 | Pargyline Hydrochloride (200 mg) | F-1 |  |  | [306-07-0] | \$156 |
| 1500003 | Paromomycin Sulfate ( 125 mg ) | G |  | F-3 (01/01) | [1263-89-4] | \$156 |
| 1500218 | Paroxetine Hydrochloride ( 500 mg ) |  |  | FOB288 (09/04) | [110429-35-1] | \$156 |
| 1500229 | Paroxetine Related Compound A (20 mg) (trans-4-(p-methoxyphenyl)-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine Hydrochloride) | F0B172 |  |  | n/f | \$487 |
| 1500230 | Paroxetine Related Compound B (20 mg) (trans-4-phenyl-3-[[(3,4methylenedioxy)phenoxy]methylpiperidine acetate) | F0B189 |  |  | n/f | \$487 |
| 1500240 | Paroxetine Related Compound C (25 mg) ((+)-trans-Paroxetine hydrochloride) | F0B192 |  |  | [130855-30-0] | \$487 |
| 1500251 | Paroxetine Related Compound D (15 mg) ((-)-cis-Paroxetine hydrochloride) | F0C228 |  |  | n/f | \$487 |
| 1500400 | Parthenolide ( 25 mg ) | F |  |  | [20554-84-1] | \$156 |
| 1500502 | Particle Count Set (2 blanks and 2 suspensions) | 1 |  | H (09/02) | n/f | \$487 |
| 1500808 | Penbutolol Sulfate (200 mg) | F |  |  | [38363-32-5] | \$156 |
| 1501006 | Penicillamine (200 mg) | H1B164 |  | H (01/04) | [52-67-5] | \$156 |
| 1501108 | Penicillamine Disulfide ( 100 mg ) | H |  | G (07/00) | [20902-45-8] | \$487 |
| 1502009 | Penicillin G Benzathine ( $200 \mathrm{mg} \mathrm{)}$ | J |  |  | [41372-02-5] | \$156 |
| 1502508 | Penicillin G Potassium ( 200 mg ) | 1 |  | H (02/99) | [113-98-4] | \$156 |
| 1502552 | Penicillin G Procaine (200 mg) | G0C271 | 2 | $\begin{array}{\|l} \hline F-1(08 / 04) \\ F(03 / 99) \\ \hline \end{array}$ | [6130-64-9] | \$156 |
| 1502701 | Penicillin G Sodium ( 200 mg ) | L-3 |  | L-2 (09/01) | [69-57-8] | \$156 |
| 1504489 | Penicillin V ( 200 mg ) | F |  |  | [87-08-1] | \$156 |
| 1504503 | Penicillin V Potassium ( 200 mg ) | H0C213 |  | $\begin{aligned} & \text { G-1 (06/04) } \\ & \text { G (06/00) } \end{aligned}$ | [132-98-9] | \$156 |
| 1505007 | Pentazocine CIV (500 mg) | H |  | G-1 (11/00) | [359-83-1] | \$207 |
| 1505506 | Pentetic Acid (100 mg) | F-1 |  | F (09/01) | [67-43-6] | \$156 |
| 1507002 | Pentobarbital CII (200 mg) | H3C144 |  | $\begin{array}{ll} \mathrm{H}-2(07 / 04) \\ \mathrm{H}-1 & (08 / 02) \\ \hline \end{array}$ | [76-74-4] | \$207 |
| 1508901 | Pentoxifylline (200 mg) | F0B202 |  |  | [6493-05-6] | \$156 |
| 1510007 | Pepsin (5 g) | F-2 |  |  | [9001-75-6] | \$156 |
| 1510801 | Perflubron ( 0.5 mL ) | G0C103 |  | F (04/04) | [423-55-2] | \$156 |
| 1510845 | Pergolide Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | F1C225 |  | F (07/04) | [66104-23-2] | \$194 |
| 1510867 | Pergolide Sulfoxide ( 50 mg ) | F0B014 |  |  | [72822-01-6] | \$194 |
| 1511000 | Perphenazine ( 200 mg ) | J0B249 |  | I (10/03) | [58-39-9] | \$156 |
| 1511203 | Perphenazine Sulfoxide ( $100 \mathrm{mg} \mathrm{)}$ | G-1 |  | G (07/02) | [10078-25-8] | \$487 |
| 1512002 | Phenacemide ( 250 mg ) | F |  |  | [63-98-9] | \$156 |
| 1513005 | Phenacetin ( 500 mg ) | H-1 |  | H (09/00) | [62-44-2] | \$156 |
| 1514008 | Phenacetin Melting Point Standard ( 500 mg ) (Approximately 135 degrees) | H3A009 |  | $\begin{array}{ll} \hline \mathrm{H}-2 & (02 / 03) \\ \mathrm{H}-1 & (06 / 01) \\ \hline \end{array}$ | [62-44-2] | \$92 |

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| 1515000 | Phenazopyridine Hydrochloride ( 200 mg ) | G-4 |  |  | [136-40-3] | \$156 |
| 1516003 | Phencyclidine Hydrochloride CII ( 25 mg ) (AS) | G1B025 |  | G (12/02) | [956-90-1] | \$207 |
| 1516502 | Phendimetrazine Tartrate CIII ( 350 mg ) | G |  | F (01/01) | [50-58-8] | \$207 |
| 1517006 | Phenelzine Sulfate (200 mg) | G |  | F-1 (04/02) | [156-51-4] | \$156 |
| 1517301 | D-Phenethicillin Potassium (200 mg) | F |  |  | n/f | \$487 |
| 1517607 | L-Phenethicillin Potassium (200 mg) | F |  |  | n/f | \$156 |
| 1520000 | Phenformin Hydrochloride ( 200 mg ) | G |  |  | [834-28-6] | \$156 |
| 1522006 | Phenindione ( 250 mg ) | F |  |  | [83-12-5] | \$156 |
| 1522301 | Pheniramine Maleate ( 100 mg ) | F1C342 | 2 | F (08/04) | [132-20-7] | \$156 |
| 1523009 | Phenmetrazine Hydrochloride CII (200 mg) | F-2 |  |  | [1707-14-8] | \$207 |
| 1524001 | Phenobarbital CIV (200 mg) | $J$ |  |  | [50-06-6] | \$207 |
| 1524908 | Phenolphthalein ( $250 \mathrm{mg} \mathrm{)}$ | F-3 |  |  | [77-09-8] | \$156 |
| 1525004 | Phenolsulfonphthalein ( 100 mg ) | F-2 |  |  | [143-74-8] | \$156 |
| 1526007 | Phenoxybenzamine Hydrochloride ( $250 \mathrm{mg} \mathrm{)}$ | G |  |  | [63-92-3] | \$156 |
| 1527000 | Phenprocoumon (200 mg) DISCONTINUED |  |  | F-1 (02/04) | [435-97-2] | \$156 |
| 1528002 | Phensuximide ( 500 mg ) | G |  | F-1 (03/01) | [86-34-0] | \$156 |
| 1528501 | Phentermine Hydrochloride CIV (200 mg) | H0B309 |  | G (08/03) | [1197-21-3] | \$207 |
| 1529005 | Phentolamine Hydrochloride ( 300 mg ) | F |  |  | [73-05-2] | \$156 |
| 1530004 | Phentolamine Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  |  | [65-28-1] | \$156 |
| 1530503 | L-Phenylalanine (200 mg) | H |  | G (02/02) | [63-91-2] | \$156 |
| 1530809 | Phenylbenzimidazole Sulfonic Acid ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [27503-81-7] | \$156 |
| 1531007 | Phenylbutazone ( 250 mg ) | J0A008 |  | I-1 (02/03) | [50-33-9] | \$156 |
| 1533002 | Phenylephrine Hydrochloride ( 125 mg ) | K |  | J (02/99) | [61-76-7] | \$124 |
| 1533308 | 5 -Phenylhydantoin (100 mg) | F |  |  | [89-24-7] | \$487 |
| 1533851 | Phenylpropanediol ( 100 mg ) | F |  |  | n/f | \$487 |
| 1533909 | Phenylpropanolamine Bitartrate ( 100 mg ) (List Chemical) | F |  |  | [67244-90-0] | \$156 |
| 1534005 | Phenylpropanolamine Hydrochloride (250 mg) (List Chemical) | J |  | 1 (02/02) | [154-41-6] | \$156 |
| 1535008 | Phenytoin (200 mg) | I2B233 |  | $\begin{array}{\|l\|} \hline \text { I-1 (03/04) } \\ \text { I (04/01) } \\ \hline \end{array}$ | [57-41-0] | \$156 |
| 1535507 | Phenytoin Sodium (200 mg) | H |  | G (05/99) | [630-93-3] | \$156 |
| 1535019 | Phenytoin Related Compound A (50 mg) (2,2-Diphenylglycine) | F0C155 |  |  | [3060-50-2] | \$487 |
| 1535020 | Phenytoin Related Compound B ( 50 mg ) (alpha-((aminocarbonyl)ami-no)-alpha-phenyl benzeneacetic acid) | F0C157 | 1 |  | [6802-95-5] | \$487 |
| 1535700 | Phosphated Riboflavin ( 100 mg ) | G1B286 |  | G (07/04) | [6184-17-4] | \$124 |
| 1537003 | Physostigmine Salicylate ( 200 mg ) | H-1 |  | H (06/00) | [57-64-7] | \$156 |
| 1538006 | Phytonadione ( 500 mg ) (Vitamin K1) | N0B303 |  | $\begin{aligned} & \hline \text { M-1 (07/04) } \\ & M(09 / 01) \\ & \hline \end{aligned}$ | [84-80-0] | \$156 |
| 1538505 | Pilocarpine ( 300 mg ) | F |  |  | [92-13-7] | \$156 |
| 1538902 | Pilocarpine Hydrochloride ( 200 mg ) | H |  |  | [54-71-7] | \$156 |
| 1539009 | Pilocarpine Nitrate (200 mg) | 1 |  |  | [148-72-1] | \$156 |
| 1539508 | Pimozide ( 200 mg ) | G |  |  | [2062-78-4] | \$156 |
| 1539701 | Pindolol ( 200 mg ) | H-1 |  |  | [13523-86-9] | \$156 |
| 1541000 | Piperacetazine (250 mg) | F |  |  | [3819-00-9] | \$156 |
| 1541500 | Piperacillin ( 500 mg ) | H |  |  | [66258-76-2] | \$156 |
| 1541703 | Piperazine Adipate ( 200 mg ) | F |  |  | [142-88-1] | \$156 |
| 1541805 | Piperazine Citrate ( 200 mg ) | F |  |  | [144-29-6] | \$156 |
| 1541907 | Piperazine Dihydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [142-64-3] | \$156 |
| 1542003 | Piperazine Phosphate (200 mg) | F |  |  | [14538-56-8] | \$156 |
| 1543006 | Piperidolate Hydrochloride (200 mg) | F |  |  | [129-77-1] | \$156 |

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| 1544508 | Piroxicam ( 200 mg ) | H |  | G (01/99) | [36322-90-4] | \$156 |
| 1545205 | Plicamycin ( 50 mg ) | H |  | G (04/00) | [18378-89-7] | \$479 |
| 1545409 | Polacrilex Resin (100 mg) | F |  |  | n/f | \$156 |
| 1545500 | Polacrilin Potassium (200 mg) | F-2 |  | F-1 (09/00) | n/f | \$156 |
| 1546106 | Poloxalene ( 500 mg ) | FOC009 |  |  | [9003-11-6] | \$156 |
| 1546300 | Polydimethylsiloxane ( 500 mg ) | H0C020 |  | $\begin{aligned} & \text { G-5 (05/04) } \\ & \text { G-4 (06/01) } \\ & \hline \end{aligned}$ | [9016-00-6] | \$156 |
| 1546707 | Polyethylene, High Density (3 strips) | G |  | F-1 (04/01) | [9002-88-4] | \$156 |
| 1546809 | Polyethylene, Low Density (3 strips) | G1B166 |  | $\begin{array}{\|l\|} \hline \text { G (06/04) } \\ \text { F-2 (12/99) } \\ \hline \end{array}$ | [9002-88-4] | \$156 |
| 1546853 | Polyethylene Oxide ( 100 mg ) | F-1 |  |  | [25322-68-3] | \$156 |
| 1546900 | Polyethylene Terephthalate (PET) (3 Strips) | F |  |  | [25038-59-9] | \$156 |
| 1546922 | Polyethylene Terephthalate G (PETG) (3 Strips) | F |  |  | [25640-14-6] | \$156 |
| 1547007 | Polymyxin B Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | K |  | J-1 (09/99) | [1405-20-5] | \$156 |
| 1547404 | Polyoxyl 50 Stearate ( 200 mg ) | F |  |  | [9004-99-3] | \$156 |
| 1547903 | Polyoxyl 40 Stearate ( 200 mg ) | F-2 |  | F-1 (05/00) | [9004-99-3] | \$156 |
| 1548000 | Polythiazide ( 200 mg ) | F-1 |  |  | [346-18-9] | \$156 |
| 1550001 | Potassium Gluconate (200 mg) | H0C064 |  | G (06/04) | [299-27-4] | \$156 |
| 1551004 | Potassium Guaiacolsulfonate ( 500 mg ) | J0B292 |  | $\begin{array}{\|l\|} \hline \text { I-1 (07/03) } \\ \text { I (11/00) } \\ \hline \end{array}$ | [78247-49-1] | \$156 |
| 1551150 | Potassium Sucrose Octasulfate ( 300 mg ) | 10B283 |  | $\begin{array}{\|l} \hline \text { H0B119 (04/04) } \\ \text { G-1 (04/03) } \\ \text { G (02/01) } \\ \hline \end{array}$ | [76578-81-9] | \$156 |
| 1551300 | Potassium Trichloroammineplatinate ( $20 \mathrm{mg} \mathrm{)}$ | H0B149 |  | $\begin{aligned} & \text { G-1 (01/03) } \\ & \text { G (07/99) } \end{aligned}$ | [13820-91-2] | \$487 |
| 1551503 | Povidone (100 mg) | F-1 |  | F (11/01) | [9003-39-8] | \$156 |
| 1553000 | Pralidoxime Chloride ( $200 \mathrm{mg} \mathrm{)}$ | G-2 |  | $\begin{aligned} & \text { G-1 (03/01) } \\ & \text { G (08/99) } \\ & \hline \end{aligned}$ | [51-15-0] | \$156 |
| 1554002 | Pramoxine Hydrochloride ( 500 mg ) | 1 |  | H (11/02) | [637-58-1] | \$156 |
| 1554501 | Prazepam CIV ( 500 mg ) | G0C066 |  | F-1 (11/02) | [2955-38-6] | \$207 |
| 1554603 | Praziquantel ( 200 mg ) | G |  | $\begin{array}{\|l\|} \hline \text { F-3 (07/02) } \\ \text { F-2 (09/00) } \\ \hline \end{array}$ | [55268-74-1] | \$156 |
| 1554658 | Praziquantel Related Compound A (50 mg) (2-benzoyl-1,2,3,6,7,11b-hexahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one) | F-1 |  |  | n/f | \$487 |
| 1554669 | Praziquantel Related Compound B ( 50 mg ) (2-(cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one) | F-2 |  | F-1 (06/00) | n/f | \$487 |
| 1554670 | Praziquantel Related Compound C ( 50 mg ) ( 2 -( $N$-formylhexahydrohip-puroyl-1,2,3,4-tetrahydroisoquinolin-1-one) | F-2 |  | F-1 (06/00) | n/f | \$487 |
| 1554705 | Prazosin Hydrochloride ( 500 mg ) | G-1 |  | G (02/01) | [19237-84-4] | \$156 |
| 1555005 | Prednisolone (200 mg) | M |  | L-1 (04/02) | [50-24-8] | \$156 |
| 1556008 | Prednisolone Acetate (200 mg) | $J$ |  | I-1 (02/02) | [52-21-1] | \$156 |
| 1556507 | Prednisolone Hemisuccinate ( 125 mg ) | H-1 |  | H (02/99) | [2920-86-7] | \$124 |
| 1558003 | Prednisolone Tebutate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [7681-14-3] | \$156 |
| 1559006 | Prednisone ( 250 mg ) | L |  | $\begin{array}{\|l\|} \hline \text { K-1 (01/02) } \\ \text { K (02/00) } \\ \hline \end{array}$ | [53-03-2] | \$156 |
| 1559505 | Prednisone Tablets (Dissolution Calibrator, Disintegrating) (30 tablets) | O0C056 |  | $\begin{aligned} & \hline \text { N (06/04) } \\ & \text { M (09/02) } \\ & \text { L (11/00) } \\ & \hline \end{aligned}$ | [53-03-2] | \$180 |
| 1561008 | Prilocaine Hydrochloride (200 mg) | F3B215 | 2,4 | F-2 (03/04) | [1786-81-8] | \$156 |
| 1561507 | Primaquine Phosphate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [63-45-6] | \$156 |
| 1562000 | Primidone (200 mg) | G |  | F-6 (04/99) | [125-33-7] | \$156 |

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| 1563003 | Probenecid ( $200 \mathrm{mg} \mathrm{)}$ | IOA011 |  | H-1 (03/03) | [57-66-9] | \$156 |
| 1563309 | Probucol (200 mg) | G |  | F-1 (01/02) | [23288-49-5] | \$156 |
| 1563320 | Probucol Related Compound A (25 mg) (2,2',6,6'-tetra-tert-butyldiphenoquinone) | F-1 |  |  | n/f | \$487 |
| 1563331 | Probucol Related Compound B (25 mg) (4,4'-dithio-bis(2,6-di-tertbutylphenol)) | F-2 |  | F-1 (08/03) | n/f | \$487 |
| 1563342 | Probucol Related Compound C ( 25 mg ) (4-[(3,5-di-tert-butyl-2-hy-droxyphenylthio)isopropylidenethio]-2,6-di-tert-butylphenol) | F-2 |  | F-1 (05/00) | n/f | \$487 |
| 1563502 | Procainamide Hydrochloride ( 200 mg ) | H1B117 |  | H (04/03) | [614-39-1] | \$156 |
| 1564006 | Procaine Hydrochloride (200 mg) | H |  |  | [51-05-8] | \$156 |
| 1565009 | Procarbazine Hydrochloride ( 200 mg ) | F |  |  | [366-70-1] | \$156 |
| 1566001 | Prochlorperazine Maleate ( 200 mg ) | H-1 |  |  | [84-02-6] | \$156 |
| 1567004 | Procyclidine Hydrochloride ( 200 mg ) | G |  |  | [1508-76-5] | \$156 |
| 1568007 | Progesterone ( 200 mg ) | H-5 |  | H-4 (07/02) | [57-83-0] | \$124 |
| 1568506 | L-Proline ( 200 mg ) | F-2 |  | F-1 (01/02) | [147-85-3] | \$156 |
| 1569000 | Promazine Hydrochloride ( 200 mg ) | H0B261 |  | G (10/03) | [53-60-1] | \$156 |
| 1570009 | Promethazine Hydrochloride ( 500 mg ) | K |  | J-1 (10/00) | [58-33-3] | \$156 |
| 1570304 | Propafenone Hydrochloride (200 mg) | G |  | F-1 (01/01) | [34183-22-7] | \$156 |
| 1570508 | Propantheline Bromide ( 200 mg ) | IOA019 |  | H (11/02) | [50-34-0] | \$156 |
| 1329505 | Propantheline Bromide Related Compound A ( 50 mg ) (9-Hydroxypropantheline bromide) | G0B258 |  | F-1 (12/03) | n/f | \$487 |
| 1571001 | Proparacaine Hydrochloride ( 200 mg ) | G |  |  | [5875-06-9] | \$156 |
| 1573007 | Propoxycaine Hydrochloride ( 200 mg ) | F |  |  | [550-83-4] | \$156 |
| 1574000 | Propoxyphene Hydrochloride CII (1 g) | L0C285 | 2 | K (09/04) | [1639-60-7] | \$207 |
| 1575002 | Propoxyphene Napsylate CII (1 g) | H |  |  | [26570-10-5] | \$207 |
| 1575206 | Propoxyphene Related Compound A ( 50 mg ) (alpha-d-4-dimethyl-amino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride) | G-5 |  |  | n/f | \$487 |
| 1576005 | Propranolol Hydrochloride (200 mg) | H-1 |  | H (09/01) | [318-98-9] | \$156 |
| 1576504 | Propylene Carbonate (200 mg) | F |  |  | [108-32-7] | \$156 |
| 1576708 | Propylene Glycol (1 mL) | $10 \mathrm{CO22}$ |  | $\begin{array}{\|l\|} \hline \mathrm{H}(03 / 04) \\ \mathrm{G}(02 / 99) \\ \hline \end{array}$ | [57-55-6] | \$156 |
| 1576720 | Propylene Glycol Diacetate ( 250 mg ) | F |  |  | [623-84-7] | \$156 |
| 1576800 | Propyl Gallate ( 200 mg ) | G-1 |  | G (01/03) | [121-79-9] | \$156 |
| 1577008 | Propylparaben (200 mg) | 1 |  | H (02/00) | [94-13-3] | \$156 |
| 1578000 | Propylthiouracil (200 mg) | G |  | F-1 (01/00) | [51-52-5] | \$156 |
| 1578500 | Prostaglandin A1 ( 25 mg ) | H0B108 |  | G (04/03) | [14152-28-4] | \$529 |
| 1580002 | Protriptyline Hydrochloride (200 mg) | F-1 |  |  | [1225-55-4] | \$156 |
| 1581005 | Pseudoephedrine Hydrochloride (125 mg) (List Chemical) | J1B203 |  | $\begin{array}{\|l\|} \hline J(01 / 04) \\ I(05 / 02) \\ \hline \end{array}$ | [345-78-8] | \$124 |
| 1581504 | Pseudoephedrine Sulfate (200 mg) (List Chemical) | G1C135 |  | $\begin{aligned} & \hline G(06 / 04) \\ & F-2(05 / 02) \\ & \hline \end{aligned}$ | [7460-12-0] | \$156 |
| 1584003 | Pyrantel Pamoate (1 g) | 1 |  | H-1 (04/00) | [22204-24-6] | \$156 |
| 1585006 | Pyrazinamide ( 200 mg ) | G |  | F-2 (02/00) | [98-96-4] | \$156 |
| 1586009 | Pyridostigmine Bromide ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  | [101-26-8] | \$156 |
| 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) | P |  | O-1 (04/00) | [58-56-0] | \$156 |
| 1588004 | Pyrilamine Maleate ( $200 \mathrm{mg} \mathrm{)}$ | 10B276 |  | H (12/03) | [59-33-6] | \$156 |
| 1589007 | Pyrimethamine ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G (07/02) | [58-14-0] | \$156 |
| 1592001 | Pyrvinium Pamoate ( 500 mg ) | G |  |  | [3546-41-6] | \$156 |
| 1592205 | Quazepam CIV (200 mg) | F |  |  | [36735-22-5] | \$207 |

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| 1592227 | Quazepam Related Compound A (30 mg) (7-Chloro-1-(2,2,2-triflu-oroethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one) | F |  |  | n/f | \$487 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 |  |  | [6151-25-3] | \$156 |
| 1593004 | Quinacrine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [6151-30-0] | \$156 |
| 1593412 | Quinapril Related Compound A (50 mg) (Ethyl[3S-[2(R*),3a,11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-phenylethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate) | F0C114 |  |  | [103733-49-9] | \$487 |
| 1593423 | Quinapril Related Compound B ( 50 mg ) ( 3 -Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetra-hydro-,[3S-[2[R*( $\left.\left.\left.\left.\left.\mathrm{R}^{*}\right)\right], 3 \mathrm{R}^{*}\right]\right]-\right)$ | F0C116 |  |  | [85441-60-7] | \$487 |
| 1594007 | Quinethazone ( 1.5 g ) | G |  |  | [73-49-4] | \$156 |
| 1594506 | Quinic Acid ( 200 mg ) | F |  |  | [77-95-2] | \$156 |
| 1595000 | Quinidine Gluconate (200 mg) | H1A028 |  | H (04/03) | [7054-25-3] | \$156 |
| 1595509 | Quinidine Sulfate ( 500 mg ) | H-1 |  | H (12/99) | [6591-63-5] | \$156 |
| 1596807 | Quinine Hydrochloride Dihydrate (1 g) | F0C108 |  |  | [6119-47-7] | \$156 |
| 1597005 | Quinine Sulfate (200 mg) | H |  |  | [6119-70-6] | \$156 |
| 1597504 | Quininone ( 50 mg ) | H0B034 | 2,4 | G-1 (03/04) | [84-31-1] | \$487 |
| 1598008 | 3-Quinuclidinyl Benzilate ( 25 mg ) | H |  | G (11/01) | [6581-06-2] | \$515 |
| 1598303 | Ramipril ( 200 mg ) | F0C099 |  |  | [87333-19-5] | \$156 |
| 1598314 | Ramipril Related Compound A (20 mg) ((2S,3aS,6aS)-1-[(S)2-[[(S)1-(methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclo-penta[b]pyrrole-2-carboxylic acid) | F0C100 |  |  | [91224-69-0] | \$487 |
| 1598405 | Ranitidine Hydrochloride (200 mg) | H0B268 |  | G (01/04) | [66357-59-3] | \$156 |
| 1598507 | Ranitidine Related Compound A (50 mg) (5-[[(2-aminoethyl)thio]-methyl]-N,N-dimethyl-2-furanmethanamine hemifumarate) | H1B137 |  | $\begin{array}{\|l} \hline \mathrm{H}(01 / 04) \\ \mathrm{G}(01 / 01) \\ \hline \end{array}$ | [91224-69-0] | \$487 |
| 1598609 | Ranitidine Related Compound B ( 50 mg ) ( $\mathrm{N}, \mathrm{N}$ '-bis[2-[[[5-[(dimethyl-amino)methyl]-2-furanyl]methyl]thio]ethyl]-2-nitro-1,1-ethenediamine) | G |  | F-4 (04/02) | [72126-78-4] | \$487 |
| 1598700 | Ranitidine Related Compound C (50 mg) ( N -[2-[[[5-[(dimethylamino)-methyl]-2-furanyl]methyl]sulfinyl]ethyl]-N-methyl-2-nitro-1,1-ethenediamine) | 11B136 |  | $\begin{aligned} & \text { I (01/04) } \\ & \text { H (05/01) } \end{aligned}$ | [73851-70-4] | \$487 |
| 1599000 | Rauwolfia Serpentina (15 g) | G |  |  | [8063-17-0] | \$156 |
| 1599500 | Powdered Red Clover Extract ( 500 mg ) | FOC188 |  |  | n/f | \$260 |
| 1600813 | Repaglinide ( 200 mg ) | F0B265 |  |  | [135062-02-1] | \$156 |
| 1600824 | Repaglinide Related Compound A (50 mg) ((S)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butylamine, N -acetyl-L-glutamate salt) | F0B267 |  |  | n/f | \$487 |
| 1600835 | Repaglinide Related Compound B (50 mg) (3-Ethoxy-4-ethoxycarbo-nyl-phenylacetic acid) | F0B269 |  |  | [99469-99-5] | \$487 |
| 1600846 | Repaglinide Related Compound C (25 mg) ((S)-2-Ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl] benzoic acid) | F0B271 |  |  | [107362-12-9] | \$487 |
| 1601000 | Reserpine (200 mg) | O0C106 |  | N (06/03) | [50-55-5] | \$156 |
| 1602003 | Resorcinol ( 200 mg ) | H-1 |  | H (04/01) | [108-46-3] | \$156 |
| 1602706 | Ribavirin (200 mg) | H |  | G (08/01) | [36791-04-5] | \$289 |
| 1603006 | Riboflavin (500 mg) (Vitamin B2) | N0C021 | 2 | $\begin{aligned} & \text { M-1 (09/04) } \\ & \mathrm{M}(11 / 00) \\ & \hline \end{aligned}$ | [83-88-5] | \$156 |
| 1603800 | Rifabutin ( 50 mg ) | G0B040 |  | F (11/02) | [72559-06-9] | \$156 |
| 1604009 | Rifampin ( 300 mg ) | $J$ |  | $1(09 / 00)$ | [13292-46-1] | \$156 |
| 1604202 | Rifampin Quinone ( 50 mg ) | H |  | G (12/01) | [13983-13-6] | \$156 |
| 1604508 | Rimantadine Hydrochloride ( 300 mg ) | F0C266 | 1 |  | [1501-84-4] | \$156 |
| 1604600 | Rimexolone ( 100 mg ) | F |  |  | [49697-38-3] | \$156 |
| 1604701 | Ritodrine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G-1 |  |  | [23239-51-2] | \$156 |
| 1606208 | Roxarsone ( 200 mg ) | F |  |  | [121-19-7] | \$156 |
| 1606503 | Rutin ( 100 mg ) | F |  |  | [153-18-4] | \$156 |

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| 1607007 | Saccharin (200 mg) | G-3 |  | G-2 (12/01) | [81-07-2] | \$156 |
| 1608000 | Salicylamide (200 mg) | F-4 |  | F-3 (05/03) | [65-45-2] | \$156 |
| 1609002 | Salicylic Acid (125 mg) | J2B147 | 7 | $\begin{array}{\|l} \hline \mathrm{J}-1(10 / 03) \\ \mathrm{J}(10 / 02) \\ \mathrm{I}(07 / 99) \\ \hline \end{array}$ | [69-72-7] | \$124 |
| 1609501 | Salicylic Acid Tablets (Dissolution Calibrator, Non-disintegrating) (33 tablets) | 0 |  | N(02/02) | [69-72-7] | \$156 |
| 1609807 | Salsalate ( 125 mg ) | G |  |  | [552-94-3] | \$124 |
| 1609829 | Saquinavir Mesylate ( 200 mg ) | FOB008 |  |  | [149845-06-7] | \$156 |
| 1609831 | Saquinavir Related Compound A ( 25 mg ) ( N -tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-D-asparaginyl]-amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide) | FOB009 |  |  | n/f | \$487 |
| 1610001 | Scopolamine Hydrobromide ( 250 mg ) | J0B051 |  | I-1 (01/03) | [6533-68-2] | \$156 |
| 1610090 | Scopoletin (20 mg) | F0C329 | 1 |  | [92-61-5] | \$156 |
| 1611004 | Secobarbital CII (200 mg) | H |  |  | [76-73-3] | \$207 |
| 1611900 | Selegiline Hydrochloride ( 200 mg ) | G |  |  | [14611-52-0] | \$156 |
| 1611955 | Selenomethionine ( 100 mg ) | FOB006 |  |  | [1464-42-2] | \$156 |
| 1612007 | Sennosides (250 mg) | H1B223 |  | H (04/04) | $\begin{aligned} & {[81-27-6] \quad(A)} \\ & {[128-57-4] \text { (B) }} \end{aligned}$ | \$156 |
| 1612506 | L-Serine ( 200 mg ) | G |  | F-3 (11/00) | [56-45-1] | \$156 |
| 1612540 | Sevoflurane ( 1 mL ) | F0C219 |  |  | [28523-86-6] | \$156 |
| 1612550 | Sevoflurane Related Compound A ( 0.2 mL ) (1,1,3,3,3-Pentafluoroisopropenyl fluoromethyl ether) | F0C261 |  |  | [58109-34-5] | \$487 |
| 1612608 | Silver Sulfadiazine ( 200 mg ) | 1 |  | H (04/01) | [22199-08-2] | \$156 |
| 1612630 | Silybin ( 50 mg ) | F |  |  | [22888-70-6] | \$156 |
| 1612641 | Silydianin ( 20 mg ) | F |  |  | [29782-68-1] | \$156 |
| 1612652 | Simethicone (50 g) | G |  | F (07/00) | [8050-81-5] | \$156 |
| 1612700 | Simvastatin (200 mg) | H1B093 |  | $\begin{array}{\|l\|} \hline \text { H (07/03) } \\ \text { G (02/02) } \\ \text { F-1 (05/99) } \\ \hline \end{array}$ | [79902-63-9] | \$156 |
| 1612801 | Sisomicin Sulfate ( 500 mg ) | 10 C 238 |  | $\begin{aligned} & \text { H (04/04) } \\ & \text { G }(10 / 00) \\ & \hline \end{aligned}$ | [53179-09-2] | \$156 |
| 1613509 | Sodium Ascorbate (200 mg) | G-1 |  |  | [134-03-2] | \$156 |
| 1613600 | Sodium Butyrate ( 25 mg ) | F |  |  | [156-54-7] | \$156 |
| 1614002 | Sodium Fluoride ( 1 g ) | H-1 |  | H (05/01) | [7681-49-4] | \$156 |
| 1614308 | Sodium Lactate (200 mg) | H |  | G (06/00) | [867-56-1] | \$156 |
| 1614501 | Sodium Nitroprusside ( 500 mg ) | H |  | G (11/99) | [13755-38-9] | \$156 |
| 1614603 | Sodium Propionate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  | F (03/02) | [6700-17-0] | \$156 |
| 1614669 | Sodium Starch Glycolate ( 400 mg ) | F0C087 |  |  | [9063-38-1] | \$156 |
| 1614705 | Sodium Stearyl Fumarate ( 200 mg ) | G |  | F-2 (05/01) | [4070-80-8] | \$156 |
| 1616008 | 1,4-Sorbitan (200 mg) | 10A003 |  | $\begin{array}{\|l\|} \hline \text { H }(04 / 03) \\ \text { G }(02 / 00) \\ \hline \end{array}$ | [27299-12-3] | \$156 |
| 1617000 | Sorbitol ( 125 mg ) | H1B139 |  | H (01/04) | [50-70-4] | \$124 |
| 1617408 | Sotalol Hydrochloride ( 300 mg ) | F0C234 |  |  | [959-24-0] | \$182 |
| 1617419 | Sotalol Related Compound A (50 mg) (N-[4-[[(1-Methylethyl)amino]acetyl]phenyl]methanesulfonamide monohydrochloride) | F0C235 |  |  | n/f | \$487 |
| 1617420 | Sotalol Related Compound B ( 50 mg ) ( N -(4-Formylphenyl)methanesulfonamide) | F0C236 |  |  | n/f | \$487 |
| 1617430 | Sotalol Related Compound C ( 50 mg ) ( N -[4-[2-[(1-Methylethyl)amino]ethyl]phenyl]methanesulfonamide hydrochloride) | F0C237 |  |  | n/f | \$487 |
| 1618003 | Spectinomycin Hydrochloride (200 mg) | F-2 |  |  | [22189-32-8] | \$156 |

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| 1619006 | Spironolactone ( 125 mg ) | J-1 |  |  | [52-01-7] | \$124 |
| 1619505 | Squalane ( 500 mg ) | G-1 |  |  | [111-01-3] | \$156 |
| 1620005 | Stanozolol CIII (200 mg) | F-3 |  | F-2 (02/01) | [10418-03-8] | \$207 |
| 1621008 | Stearic Acid ( 500 mg ) | J |  | I (10/01) | [57-11-4] | \$156 |
| 1621507 | Stearoyl Polyoxyglycerides (100 mg) | F0C286 |  |  | n/f | \$156 |
| 1622000 | Stearyl Alcohol ( 125 mg ) | H-1 |  | H (09/99) | [112-92-5] | \$124 |
| 1623003 | Streptomycin Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | J0B195 |  | I (04/03) | [3810-74-0] | \$156 |
| 1623502 | Succinylcholine Chloride ( 500 mg ) | H |  |  | [71-27-2] | \$156 |
| 1623604 | Succinylmonocholine Chloride ( 150 mg ) | G |  | F-1 (02/01) | n/f | \$487 |
| 1623626 | Sucralose ( 400 mg ) | G0B028 |  | F (04/03) | [56038-13-2] | \$156 |
| 1623637 | Sucrose ( 100 mg ) | H0B002 |  | $\begin{aligned} & \text { G-1 (03/03) } \\ & \text { G (05/99) } \end{aligned}$ | [57-50-1] | \$156 |
| 1623648 | Sufentanil Citrate ClI (25 mg) | H0B208 |  | $\begin{aligned} & \text { G (05/03) } \\ & \text { F-1 (04/02) } \\ & F(09 / 99) \\ & \hline \end{aligned}$ | [60561-17-3] | \$207 |
| 1623670 | Sulbactam ( 250 mg ) | G |  | F-1 (05/00) | [68373-14-8] | \$156 |
| 1623681 | Sulconazole Nitrate ( 200 mg ) | F-1 |  | F (05/02) | [61318-91-0] | \$156 |
| 1623706 | Sulfabenzamide (200 mg) | G |  |  | [127-71-9] | \$156 |
| 1623808 | Sulfacetamide ( 300 mg ) | G-1 |  |  | [144-80-9] | \$156 |
| 1624006 | Sulfacetamide Sodium ( 500 mg ) | 11B318 | 2 | $\begin{array}{\|l\|} \hline \text { I (09/04) } \\ H(08 / 01) \\ \hline \end{array}$ | [6209-17-2] | \$156 |
| 1624505 | Sulfachlorpyridazine ( 200 mg ) | F |  |  | [80-32-0] | \$156 |
| 1625009 | Sulfadiazine ( 200 mg ) | J | 2,4 | $1(03 / 04)$ | [68-35-9] | \$156 |
| 1626001 | Sulfadimethoxine ( 200 mg ) | F-3 |  | F-2 (03/99) | [122-11-2] | \$156 |
| 1626500 | Sulfadoxine ( 200 mg ) | F-2 |  | F-1 (07/02) | [2447-57-6] | \$156 |
| 1628007 | Sulfamerazine ( 1 g ) | H |  |  | [127-79-7] | \$156 |
| 1629000 | Sulfamethazine (1 g) | G-3 |  |  | [57-68-1] | \$156 |
| 1630009 | Sulfamethizole (200 mg) | F-3 |  | F-2 (01/03) | [144-82-1] | \$156 |
| 1631001 | Sulfamethoxazole ( 200 mg ) | I-1 |  | I (04/02) | [723-46-6] | \$156 |
| 1631500 | Sulfamethoxazole N4-glucoside ( 25 mg ) | H |  | G (11/01) | n/f | \$487 |
| 1632004 | Sulfanilamide (5 g) | O0B047 |  | $\mathrm{N}(01 / 04)$ | [63-74-1] | \$156 |
| 1633007 | Sulfanilamide Melting Point Standard ( 500 mg ) (Approximately 165 degrees) | K0B133 |  | $\begin{aligned} & \hline \mathrm{J}-1(03 / 04) \\ & \mathrm{J}(09 / 99) \\ & \hline \end{aligned}$ | [63-74-1] | \$75 |
| 1633506 | Sulfanilic Acid ( 200 mg ) | G |  | F-2 (09/00) | [121-57-3] | \$487 |
| 1634000 | Sulfapyridine (200 mg) | IOB298 |  | H (07/04) | [144-83-2] | \$156 |
| 1635002 | Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees) | J |  | I (07/00) | [144-83-2] | \$92 |
| 1635206 | Sulfaquinoxaline ( 200 mg ) | F0A005 |  |  | [59-40-5] | \$156 |
| 1636005 | Sulfasalazine ( 125 mg ) | G-2 |  | G-1 (06/99) | [599-79-1] | \$124 |
| 1636504 | Sulfathiazole ( 350 mg ) | H |  | G (08/00) | [72-14-0] | \$156 |
| 1637008 | Sulfinpyrazone ( 200 mg ) | G |  |  | [57-96-5] | \$156 |
| 1638000 | Sulfisoxazole (200 mg) | $J$ |  | I-1 (06/99) | [127-69-5] | \$156 |
| 1639003 | Sulfisoxazole Acetyl ( 200 mg ) | H-1 |  |  | [80-74-0] | \$156 |
| 1640002 | Sulfisoxazole Diolamine ( 500 mg ) | F |  |  | [4299-60-9] | \$156 |
| 1642008 | Sulindac ( 200 mg ) | H |  | G-1 (12/01) | [38194-50-2] | \$156 |
| 1642154 | Sumatriptan ( 50 mg ) | F0C220 |  |  | [103628-46-2] | \$208 |
| 1642201 | Sumatriptan Succinate ( 200 mg ) | F0C231 |  |  | [103628-48-4] | \$208 |
| 1642212 | Sumatriptan Succinate Related Compound A (15 mg) ([3-[2-(dimeth-ylamino)ethyl]-2-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-1H-indol-5-yl]-N-methylmethansulfonamide, succinate salt) | F0C221 |  |  | n/f | \$624 |

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| 1642223 | Sumatriptan Succinate Related Compound C ( 50 mg ) ([3-[2-(dimeth-ylamino)ethyl]-1-(hydroxymethyl)-1H-indol-5-yl]-N-methylmethanesulfonamide succinate salt) | F0C230 |  |  | n/f | \$624 |
| 1642507 | Suprofen (200 mg) | F |  |  | [40828-46-4] | \$156 |
| 1642700 | Tacrine Hydrochloride ( 500 mg ) | F0C119 |  |  | [1684-40-8] | \$156 |
| 1643000 | Talbutal CIII (250 mg) | F |  |  | [115-44-6] | \$207 |
| 1643306 | Tamoxifen Citrate (200 mg) | H |  | $\begin{array}{ll} \text { G-2 }(09 / 01) \\ \text { G-1 } & (05 / 00) \\ \hline \end{array}$ | [54965-24-1] | \$156 |
| 1643361 | Taurine ( 100 mg ) | F0C104 |  |  | [107-35-7] | \$156 |
| 1643408 | Temazepam CIV (200 mg) | H0C205 |  | $\begin{aligned} & \hline \text { G (06/04) } \\ & \text { F (12/99) } \end{aligned}$ | [846-50-4] | \$207 |
| 1643452 | Terazosin Hydrochloride (200 mg) | F0C244 |  |  | [70024-40-7] | \$156 |
| 1643463 | Terazosin Related Compound A (50 mg) (1-(4-Amino-6,7-dimethoxy-2quinazolinyl)piperazine dihydrochloride) | F0C245 |  |  | n/f | \$487 |
| 1643474 | Terazosin Related Compound B (50 mg) (1-(4-hydroxy-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]piperazine) | F0C218 |  |  | n/f | \$487 |
| 1643485 | Terazosin Related Compound C (25 mg) (1,4-bis(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine dihydrochloride) | F0C257 |  |  | n/f | \$487 |
| 1643500 | Terbutaline Sulfate ( 125 mg ) | H |  | G (04/99) | [23031-32-5] | \$124 |
| 1643703 | Terconazole (200 mg) | G-2 |  | $\begin{aligned} & \text { G-1(04/01) } \\ & \text { G (03/99) } \\ & \hline \end{aligned}$ | [67915-31-5] | \$156 |
| 1643805 | Terfenadine (200 mg) | H |  | G (12/99) | [50679-08-8] | \$156 |
| 1643907 | Terfenadine Related Compound A (100 mg) (1-[4-(1,1-dimethylethyl)-phenyl]-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-butanone) | G |  |  | n/f | \$487 |
| 1643929 | Terfenadine Related Compound B (50 mg) (Terfenadine-N-oxide) | F |  |  | n/f | \$487 |
| 1644003 | Terpin Hydrate ( 750 mg ) | G |  |  | [2451-01-6] | \$156 |
| 1645006 | Testolactone CIII ( 125 mg ) | F-1 |  |  | [968-93-4] | \$165 |
| 1646009 | Testosterone CIII (125 mg) | 11B253 |  | I (08/04) | [58-22-0] | \$165 |
| 1647001 | Testosterone Cypionate CIII ( 200 mg ) | G-1 |  | G (08/01) | [58-20-8] | \$207 |
| 1648004 | Testosterone Enanthate CIII ( 200 mg ) | $J$ |  |  | [315-37-7] | \$207 |
| 1649007 | Testosterone Propionate CIII ( 200 mg ) | L1C005 |  | $\begin{array}{\|l\|} \hline \mathrm{L}(08 / 04) \\ \mathrm{K}-1(11 / 01) \\ \hline \end{array}$ | [57-85-2] | \$207 |
| 1650006 | Tetracaine Hydrochloride ( 200 mg ) | J |  |  | [136-47-0] | \$156 |
| 1651009 | Tetracycline Hydrochloride ( 200 mg ) | K |  |  | [64-75-5] | \$156 |
| 1652001 | Tetrahydrozoline Hydrochloride ( 200 mg ) | G1A015 |  | G (03/03) | [522-48-5] | \$156 |
| 1652500 | Thalidomide ( 200 mg ) | F0C107 |  |  | [50-35-1] | \$182 |
| 1653004 | Theophylline ( 200 mg ) | J0B180 |  | I (01/04) | [58-55-9] | \$156 |
| 1653106 | Theophylline Extended-Release Beads (Drug Release Calibrator, Multiple Unit) ( 20 g ) |  |  | F-1 (11/04) | [58-55-9] | \$156 |
| 1655000 | Thiabendazole (100 mg) | G0A027 |  | $\begin{array}{\|l\|} \hline \text { F-1 (04/03) } \\ \text { F (04/01) } \\ \hline \end{array}$ | [148-79-8] | \$156 |
| 1656002 | Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride) | 0 |  | $\begin{array}{\|l\|l} \hline N(11 / 02) \\ M-1(04 / 99) \\ \hline \end{array}$ | [67-03-8] | \$156 |
| 1656308 | Thiamylal CIII ( 200 mg ) | F |  |  | [77-27-0] | \$207 |
| 1657005 | Thiethylperazine Malate ( $200 \mathrm{mg} \mathrm{)}$ | G |  | F-1 (09/00) | [52239-63-1] | \$156 |
| 1658008 | Thiethylperazine Maleate ( 200 mg ) | F-1 |  |  | [1179-69-7] | \$156 |
| 1659000 | Thimerosal ( 500 mg ) | H1B205 |  | $\begin{aligned} & \text { H (09/04) } \\ & \text { G (12/99) } \end{aligned}$ | [54-64-8] | \$156 |
| 1660000 | Thioguanine ( 200 mg ) | F-1 |  |  | [154-42-7] | \$156 |
| 1661002 | Thiopental CIII ( 250 mg ) | 1 |  |  | [76-75-5] | \$207 |
| 1662504 | Thioridazine ( 200 mg ) | H |  |  | [50-52-2] | \$156 |

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| 1663008 | Thioridazine Hydrochloride (200 mg) | H |  |  | [130-61-0] | \$156 |
| 1663700 | Thiostrepton (200 mg) | F1B022 |  | F (11/02) | [1393-48-2] | \$156 |
| 1664000 | Thiotepa ( 500 mg ) | 1 |  | H (01/99) | [52-24-4] | \$156 |
| 1665003 | Thiothixene ( 250 mg ) | G |  |  | [3313-26-6] | \$156 |
| 1666006 | (E)-Thiothixene (100 mg) | H |  | G-1 (05/00) | [3313-27-7] | \$487 |
| 1667100 | Thonzonium Bromide ( 200 mg ) | F |  |  | [553-08-2] | \$156 |
| 1667202 | L-Threonine ( 200 mg ) | G |  | F-3 (12/00) | [72-19-5] | \$156 |
| 1667279 | Thromboplastin, Human Recombinant (set) (1 vial Thromboplastin and 1 vial Diluent) DISCONTINUED |  | 9 | F (10/04) | [9002-05-5] | \$156 |
| 1667290 | Tiamulin Fumarate ( $250 \mathrm{mg} \mathrm{)}$ | F0C327 | 1 |  | [55297-96-6] | \$156 |
| 1667337 | Tiamulin Related Compound A (50 mg) (Tosyl pleuromutilin) | FOC328 | 1 |  | n/f | \$494 |
| 1667304 | Ticarcillin Monosodium Monohydrate ( 200 mg ) | H |  | G-1 (03/99) | [74682-62-5] | \$156 |
| 1667359 | Tiletamine Hydrochloride ( 200 mg ) | F0C019 |  |  | [14176-50-2] | \$156 |
| 1667406 | Timolol Maleate (200 mg) | G-1 |  |  | [26921-17-5] | \$156 |
| 1667520 | Tinidazole (200 mg) | F0C093 |  |  | [19387-91-8] | \$156 |
| 1667530 | Tinidazole Related Compound A (100 mg) (2-methyl-5-nitroimidazole) | F0C091 |  |  | [696-23-1] | \$487 |
| 1667439 | Tioconazole ( 200 mg ) | H |  | G (04/02) | [65899-73-2] | \$156 |
| 1667450 | Tioconazole Related Compound A (25 mg) (1-[2,4-Dichloro-beta-[(3-thenyl)-oxy]phenethyl]imidazole Hydrochloride) | G |  |  | n/f | \$487 |
| 1667461 | Tioconazole Related Compound B (25 mg) (1-[2,4-Dichloro-beta-[(2,5-dichloro-3-thenyl)oxy]phenethyl]imidazole Hydrochloride) | G |  |  | n/f | \$487 |
| 1667472 | Tioconazole Related Compound C (25 mg) (1-[2,4-Dichloro-beta-[(5-bromo-2-chloro-3-thenyl)-oxy]-phenethyl]imidazole Hydrochloride) | G |  |  | n/f | \$487 |
| 1667508 | Tobramycin (250 mg) | K0B248 |  | $J(08 / 03)$ | [32986-56-4] | \$156 |
| 1667552 | Tocainide Hydrochloride ( 125 mg ) | F-1 |  | F (04/99) | [35891-93-1] | \$124 |
| 1667600 | Alpha Tocopherol (250 mg) (Vitamin E Alcohol) | M |  | L-1 (01/00) | [10191-41-0] | \$156 |
| 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) | K |  | J (06/99) | [7695-91-2] | \$156 |
| 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) | F-5 |  | F-4 (01/02) | [4345-03-3] | \$156 |
| 1668001 | Tolazamide (200 mg) | G-2 |  | G-1 (06/00) | [1156-19-0] | \$156 |
| 1669004 | Tolazoline Hydrochloride ( 300 mg ) | F |  |  | [59-97-2] | \$156 |
| 1670003 | Tolbutamide (200 mg) | 1 |  | H (06/00) | [64-77-7] | \$156 |
| 1670502 | Tolmetin Sodium ( 500 mg ) | IOB064 |  | H (09/03) | [64490-92-2] | \$156 |
| 1671006 | Tolnaftate (200 mg) | I |  |  | [2398-96-1] | \$156 |
| 1672009 | Toluenesulfonamides, ortho and para (200 mg of each supplied in a set) | F-4 |  | F-3 (11/99) | $\begin{aligned} & {[88-19-7](\mathrm{o})} \\ & {[70-55-3](\mathrm{p})} \\ & \hline \end{aligned}$ | \$487 |
| 1672304 | Torsemide ( 200 mg ) | F0B090 |  |  | [56211-40-6] | \$156 |
| 1672315 | Torsemide Related Compound A (75 mg) (4-[(3-methylphenyl)amino]-3-pyridinesulfonamide) | F0B071 |  |  | n/f | \$487 |
| 1672326 | Torsemide Related Compound B (75 mg) (N-[(n-butylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide) | F0B083 |  |  | n/f | \$487 |
| 1672337 | Torsemide Related Compound C (75 mg) (N-[(ethylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide) | F0B078 |  |  | n/f | \$487 |
| 1672803 | Transplatin ( 25 mg ) | H0B287 |  | G (03/04) | [14913-33-8] | \$487 |
| 1673500 | Trazodone Hydrochloride ( 200 mg ) | F-2 |  |  | [25332-39-2] | \$156 |
| 1674004 | Tretinoin ( $30 \mathrm{mg} / \mathrm{ampule;} 5$ ampules) | I2B185 |  | $\begin{aligned} & \hline \text { I-1 (01/04) } \\ & \text { I (01/02) } \\ & H(06 / 01) \\ & \hline \end{aligned}$ | [302-79-4] | \$156 |
| 1675007 | Triacetin (1 g) | G-1 |  | G (06/01) | [102-76-1] | \$156 |
| 1676000 | Triamcinolone ( 250 mg ) | H-1 |  |  | [124-94-7] | \$156 |
| 1677002 | Triamcinolone Acetonide ( 500 mg ) | K |  | J (03/99) | [76-25-5] | \$156 |
| 1678005 | Triamcinolone Diacetate (200 mg) | G |  |  | [67-78-7] | \$156 |

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| 1679008 | Triamcinolone Hexacetonide (125 mg) | G |  |  | [5611-51-8] | \$124 |
| 1680007 | Triamterene (200 mg) | 1 |  |  | [396-01-0] | \$156 |
| 1680506 | Triazolam CIV (200 mg) | H0B041 |  | G-1 (03/03) | [28911-01-5] | \$207 |
| 1680608 | Tributyl Citrate ( 500 mg ) | F |  |  | [77-94-1] | \$156 |
| 1680801 | Trichlorfon ( 200 mg ) | F |  |  | [52-68-6] | \$156 |
| 1681000 | Trichlormethiazide ( 200 mg ) | H |  |  | [133-67-5] | \$156 |
| 1682206 | Triclosan (200 mg) | F0B135 |  |  | [3380-34-5] | \$156 |
| 1683005 | Tridihexethyl Chloride ( 200 mg ) | F-1 |  |  | [4310-35-4] | \$156 |
| 1683504 | Trientine Hydrochloride (125 mg) | F2B257 |  | $\begin{array}{\|l} \hline \text { F-1 (09/03) } \\ \text { F (08/96) } \\ \hline \end{array}$ | [38260-01-4] | \$124 |
| 1683606 | Triethyl Citrate ( 500 mg ) | F-1 |  | F (03/02) | [77-93-0] | \$156 |
| 1685000 | Trifluoperazine Hydrochloride (200 mg) | H0A010 |  | G (03/03) | [440-17-5] | \$156 |
| 1685500 | 2-[ N -(2,2,2-Trifluoro-ethyl)amino-5]-chlorobenzophenone ( 25 mg ) | F |  |  | n/f | \$487 |
| 1686003 | Triflupromazine Hydrochloride (200 mg) | F-2 | 2,4 | F-1 (03/04) | [1098-60-8] | \$156 |
| 1686309 | Trifluridine ( 200 mg ) | F |  |  | [70-00-8] | \$156 |
| 1686310 | Trifluridine Related Compound A (20 mg) (5-Carboxy-2'-deoxyuridine) | F |  |  | [14599-46-3] | \$487 |
| 1687006 | Trihexyphenidyl Hydrochloride ( 200 mg ) | $J$ |  | I (07/01) | [52-49-3] | \$156 |
| 1689001 | Trimeprazine Tartrate ( 200 mg ) | F-3 |  | F-2 (08/01) | [4330-99-8] | \$156 |
| 1690000 | Trimethadione (200 mg) | G |  |  | [127-48-0] | \$156 |
| 1692006 | Trimethobenzamide Hydrochloride ( 500 mg ) | H-2 |  | H-1 (06/02) | [554-92-7] | \$156 |
| 1692505 | Trimethoprim ( 300 mg ) | J0B228 |  | I (01/04) | [738-70-5] | \$156 |
| 1693009 | Trioxsalen (200 mg) | H0C278 |  | G (04/04) | [3902-71-4] | \$156 |
| 1694001 | Tripelennamine Citrate ( 200 mg ) | G |  | F (02/03) | [6138-56-3] | \$156 |
| 1695004 | Tripelennamine Hydrochloride ( 200 mg ) | $J$ |  |  | [154-69-8] | \$156 |
| 1696007 | Triprolidine Hydrochloride ( 500 mg ) | 1 |  | H-1 (02/02) | [6138-79-0] | \$156 |
| 1696109 | Triprolidine Hydrochloride Z-Isomer (100 mg) | G |  | F-1 (02/02) | n/f | \$487 |
| 1696200 | Trisalicylic Acid (100 mg) | G |  | F-1 (10/99) | n/f | \$487 |
| 1697000 | Troleandomycin (250 mg) | F-1 |  |  | [2751-09-9] | \$156 |
| 1698002 | Tromethamine (125 mg) | G |  | F-3 (07/99) | [77-86-1] | \$124 |
| 1699005 | Tropicamide ( 125 mg ) | G-1 |  | G (02/99) | [1508-75-4] | \$124 |
| 1700002 | Trypsin Crystallized ( 300 mg ) | H |  | G (12/99) | [9002-07-7] | \$156 |
| 1700501 | L-Tryptophan (200 mg) | G-1 |  | G (09/00) | [73-22-3] | \$156 |
| 1702008 | Tubocurarine Chloride ( 250 mg ) | K-1 |  |  | [6989-98-6] | \$156 |
| 1703805 | Tylosin (250 mg) | F0C008 |  |  | [1401-69-0] | \$156 |
| 1704003 | Tyloxapol (600 mg) | H |  | G (02/00) | [25301-02-4] | \$156 |
| 1704502 | Tyropanoate Sodium ( 500 mg ) | F |  |  | [7246-21-1] | \$156 |
| 1705006 | L-Tyrosine ( 500 mg ) | $J$ |  |  | [60-18-4] | \$156 |
| 1705301 | Ubidecarenone (200 mg) | F0B191 |  |  | [303-98-0] | \$156 |
| 1705312 | Ubidecarenone for System Suitability ( 25 mg ) | FOB194 |  |  | [303-98-0] | \$156 |
| 1705505 | Undecylenic Acid (200 mg) | G2C018 | 2 | $\begin{aligned} & \text { G-1 (11/04) } \\ & \text { G (01/02) } \\ & \hline \end{aligned}$ | [112-38-9] | \$156 |
| 1705800 | Uracil Arabinoside ( 50 mg ) | G |  | F-1 (06/99) | [3083-77-0] | \$156 |
| 1706009 | Uracil Mustard ( 500 mg ) | F |  |  | [66-75-1] | \$156 |
| 1706701 | Urea C 13 (100 mg) | F0C078 |  |  | [57-13-6] | \$182 |
| 1707806 | Ursodiol ( 125 mg ) | G |  | $\begin{aligned} & \hline \text { F-1 (11/01) } \\ & \text { F (09/99) } \end{aligned}$ | [128-13-2] | \$124 |
| 1707908 | Valerenic Acid (25 mg) | G0B146 |  | F (01/04) | [3569-10-6] | \$696 |
| 1708503 | L-Valine ( 200 mg ) | F-2 |  | F-1 (05/02) | [72-18-4] | \$156 |

## USP Reference Standards and Authentic Substances

| Cat. No. | Description | Curr. <br> Lot. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \text { CAS } \\ \text { No. } \\ \hline \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1708707 | Valproic Acid (500 mg) | J1B127 |  | $\begin{array}{\|l} \hline J(01 / 04) \\ I-1(11 / 00) \\ \hline \end{array}$ | [99-66-1] | \$156 |
| 1708729 | Valproic Acid Related Compound A ( 0.25 mL ) (diallylacetic acid) | F1B156 |  | F (01/03) | [99-67-2] | \$208 |
| 1708773 | Valsartan Related Compound A (20 mg) ((R)-N-Valeryl-N-([2'-(1-H-tetrazole)-5-yl)-biphenyl-4-yl]-methyl)-valine) | F0C215 |  |  | n/f | \$624 |
| 1708795 | Valsartan Related Compound C (10 mg) ((S)-N-Valeryl-N-([2'-(1-H-tetrazole)-5-yll-biphenyl-4-yll]-methyl)-valine benzyl ester) | F0C208 |  |  | n/f | \$624 |
| 1709007 | Vancomycin Hydrochloride (4 vials, each vial contains $100,500 \mathrm{mcg}$ of vancomycin activity) | L |  | K (08/01) | [1404-93-9] | \$156 |
| 1710006 | Vanillin (200 mg) | 1 |  | H (04/99) | [121-33-5] | \$156 |
| 1711009 | Vanillin Melting Point Standard (1 g) (Approximately 82 degrees) | J |  | $\begin{aligned} & \text { I-1 (03/03) } \\ & \text { I (11/00) } \\ & \hline \end{aligned}$ | [121-33-5] | \$92 |
| 1711166 | Vecuronium Bromide Related Compound A ( 25 mg ) (3alpha, 17beta-diacetyl-oxy-2beta, 16beta-bispiperidinyl-5alpha-androstan) | F0B178 |  |  | n/f | \$487 |
| 1711202 | Verapamil Hydrochloride ( 200 mg ) | G |  | F-4 (06/00) | [152-11-4] | \$156 |
| 1711304 | Verapamil Related Compound A (50 mg) (3,4-Dimethoxy-alpha-[3-(methylamino)propyl]-alpha-(1-methylethyl)-benzeneacetonitrile monoHydrochloride) | H |  | G (01/01) | n/f | \$487 |
| 1711406 | Verapamil Related Compound B (50 mg) (alpha-[2-[[2-(3,4-dimeth-oxyphenyl)-ethyl]methylamino]ethyl]-3,4-dimethoxy-alpha-(1-methyl-ethyl)-benzeneacetonitrile monoHydrochloride) | G |  |  | [1794-55-4] | \$487 |
| 1711461 | Verteporfin ( 200 mg ) | FOC166 |  |  | [129497-78-5] | \$156 |
| 1711472 | Verteporfin Related Compound A (50 mg) ((+/-)18-Ethenyl-4,4a-dihy-dro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23H,25H-ben-zo[b]prophine-9,13-dipropanoic acid) | F0C167 |  |  | n/f | \$487 |
| 1711508 | Vidarabine ( 200 mg ) | G-1 |  |  | [24356-66-9] | \$156 |
| 1713004 | Vinblastine Sulfate ( $50 \mathrm{mg} / \mathrm{ampule}$ ) | L |  | K (05/99) | [143-67-9] | \$354 |
| 1714007 | Vincristine Sulfate ( $50 \mathrm{mg} / \mathrm{mmpule)}$ | O0B062 |  | $\begin{aligned} & \mathrm{N}(01 / 03) \\ & \mathrm{M}(04 / 99) \end{aligned}$ | [2068-78-2] | \$479 |
| 1714506 | Vinorelbine Tartrate ( 200 mg ) | F0C243 |  |  | [125317-39-7] | \$156 |
| 1714528 | Vinorelbine Related Compound A ( 25 mg ) (4-O-Deacetylvinorelbine tartrate) | F0C242 |  |  | n/f | \$487 |
| 1715000 | Viomycin Sulfate (200 mg) | F |  |  | [37883-00-4] | \$156 |
| 1716002 | Vitamin A (10 ampules containing vitamin A acetate in cottonseed/ peanut oil) | V0C258 |  | U (04/04) | [127-47-9] | \$156 |
| 1717504 | Vitamin D Assay System Suitability (1.5 g) | F |  |  | [67-97-0] | \$156 |
| 1717708 | Vitexin ( 30 mg ) | F0C142 |  |  | [3681-93-4] | \$520 |
| 1719000 | Warfarin ( 200 mg ) | 10B305 |  | $\begin{array}{ll} \hline \text { H-2 } & (08 / 04) \\ \text { H-1 } & (11 / 01) \\ \hline \end{array}$ | [81-81-2] | \$156 |
| 1719102 | Warfarin Related Compound A (50 mg) (3-(0-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one) | G1B111 |  | G (01/04) | [37209-23-7] | \$156 |
| 1720000 | Xanthanoic Acid (100 mg) | G-1 |  | G (12/00) | [82-07-5] | \$487 |
| 1720203 | Xanthone ( 100 mg ) | F-1 |  |  | [90-47-1] | \$487 |
| 1720407 | Xylazine ( 200 mg ) | F |  |  | [7361-61-7] | \$156 |
| 1720429 | Xylazine Hydrochloride ( 200 mg ) | F |  |  | [23076-35-9] | \$156 |
| 1720600 | Xylitol (1 g) | G0B037 |  | $\begin{aligned} & \text { F-3 }(11 / 02) \\ & \text { F-2 (05/00) } \end{aligned}$ | [87-99-0] | \$156 |
| 1721002 | Xylometazoline Hydrochloride (125 mg) | IOB101 |  | H-1 (05/03) | [1218-35-5] | \$124 |
| 1722005 | Xylose (1 g) | F |  |  | [58-86-6] | \$156 |
| 1724000 | Yohimbine Hydrochloride (200 mg) | F |  |  | [65-19-0] | \$156 |
| 1724306 | Zalcitabine (200 mg) | F |  |  | [7481-89-2] | \$156 |

## USP Reference Standards and Authentic Substances

| Cat. No. | Description | Curr. <br> Lot. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1724317 | Zalcitabine Related Compound A (50 mg) (2',3'-Didehydro-2',3'-dideoxycytidine) | F0B234 |  |  | [7481-88-1] | \$487 |
| 1724500 | Zidovudine ( 400 mg ) | G |  | F (09/01) | [30516-87-1] | \$156 |
| 1724521 | Zidovudine Related Compound B (25 mg) (3'-chloro-3'-deoxythymidine) | G0B116 |  | $\begin{array}{\|l} \hline \text { F-1 (03/03) } \\ \text { F (06/01) } \end{array}$ | [25526-94-7] | \$487 |
| 1724532 | Zidovudine Related Compound C (100 mg) (thymine) | F-1 |  | F (09/01) | [65-71-4] | \$487 |
| 1724656 | Zileuton ( 150 mg ) | F0C062 |  |  | [111406-87-2] | \$156 |
| 1724667 | Zileuton Related Compound A (50 mg) (N-(1-Benzo[b]thien-2-ylethyl) urea) | F0B316 |  |  | n/f | \$487 |
| 1724678 | Zileuton Related Compound B (50 mg) (2-(Benzo[b]thien-2-oyl)benzo[b]thiophene) | F0B313 |  |  | n/f | \$487 |
| 1724689 | Zileuton Related Compound C (50 mg) (1-Benzo[b]thien-2-ylethanone) | F0B299 |  |  | n/f | \$487 |
| 1724805 | Zolazepam Hydrochloride ( 500 mg ) | G0C023 |  | $\begin{array}{\|l} \hline \text { F-1 (03/04) } \\ \text { F (05/02) } \\ \hline \end{array}$ | [33754-49-3] | \$156 |

## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. <br> No. | New Description |
| :---: | :---: | :---: | :---: |
| 00200-6 | 5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid ( 50 mg ) (Limit Test) | 1184027 | Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3 amino-2,4,6-triiodobenzoic Acid) |
| 02200-3 | 3-Amino-4-carboxamidopyrazole Hemisulfate ( 50 mg ) (Limit Test) | 1013024 | Allopurinol Related Compound A ( 50 mg ) (3-Amino-4-carboxamidopyrazole Hemisulfate) |
| 02250-2 | 4-Amino-6-chloro-1,3-benzenedisulfonamide ( 100 mg ) (Limit Test) | 1057507 | Benzothiadiazine Related Compound A (100 mg) (4-Amino-6 chloro-1,3-benzenedisulfonamide) |
| 02380-0 | 2-Amino-2'-chloro-5-nitrobenzophenone (25 mg) (Limit Test) | 1140338 | Clonazepam Related Compound B (25 mg) (2-Amino-2' chloro-5-nitrobenzophenone) |
| 02420-2 | 4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide ( 100 mg ) (Limit Test) | 1424018 | Methyclothiazide Related Compound A (100 mg) (4-Amino-6 chloro-N-3-methyl-m-benzenedisulfonamide) |
| 02240-6 | 2-Amino-4-chlorophenol (50 mg) (Limit Test) | 1130527 | Chlorzoxazone Related Compound A ( 25 mg ) (2-Amino-4 chlorophenol) |
| 02460-0 | 3-Amino-4-(2-chloro-phenyl)-6-nitrocarbostyril (25 mg) <br> (Limit Test) | 1140327 | Clonazepam Related Compound A (25 mg) (3-Amino-4-(2 chlorophenyl)-6-nitrocarbostyril) |
| 02490-5 | 2-Amino-2',5-dichlorobenzophenone (25 mg) (Limit Test) | 1370338 | Lorazepam Related Compound B ( 25 mg ) (2-Amino-2',5 dichlorobenzophenone) |
| 02610-6 | 3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid ( 25 mg ) (Limit Test) | 1078325 | Bumetanide Related Compound A ( 25 mg ) (3-Amino-4-phe-noxy-5-sulfamoylbenzoic Acid) |
| 02620-8 | alpha-Aminopropiophenone Hydrochloride ( 50 mg ) (Limit Test) | 1096804 | Cathinone Hydrochloride $\mathbf{C l}(50 \mathrm{mg})$ (alpha-Aminopropiophenone Hydrochloride) |
| 06300-0 | 5-Benzyl-3,6-dioxo-2-piperazineacetic Acid ( 250 mg ) (Limit Test) | 1043728 | Aspartame Related Compound A (75 mg) (5-Benzyl-3,6 dioxo-2-piperazineacetic Acid) |
| 07350-3 | 2-(4-Biphenylyl)propionic Acid (100 mg) (Limit Test) | 1285760 | Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid) |
| 07480-1 | N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide ( 50 mg ) (Limit Test) | 1344724 | lopamidol Related Compound A ( 50 mg ) (N,N'-Bis-(1,3 dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide) |
| 07500-4 | 4,4'-Bis[4-(p-chlorophenyl)-4-hydroxypiperidino]-butyrophenone ( 25 mg ) (Limit Test) | 1303013 | Haloperidol Related Compound A (25 mg) (4,4-Bis[4-p-chlor-ophenyl)-4-hydroxypiperidinoj-butyrophenone |
| 08650-5 | Calcium Formyltetrahydrofolate ( 50 mg ) (AS) (For Qualitiative Use Only) | 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) |
| 11230-0 | p -Chlorobenzhydrylpiperazine ( 25 mg ) | 1333058 | Hydroxyzine Related Compound A ( 25 mg ) (p-Chlorobenzhydrylpiperazine) |
| 11310-9 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxaldehyde ( 25 mg ) (Limit Test) | 1370349 | Lorazepam Related Compound C ( 25 mg ) (6-Chloro-4-(0 chlorophenyl)-2-quinazolinecarboxaldehyde) |
| 11320-0 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxylic Acid ( 25 mg ) (Limit Test) | 1370350 | Lorazepam Related Compound D ( 25 mg ) ( 6 -Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid) |
| 11330-2 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazoline Methanol ( 25 mg ) (Limit Test) | 1370360 | Lorazepam Related Compound E ( 25 mg ) (6-Chloro-4-(0 chlorophenyl)-2-quinazoline Methanol) |
| 11400-0 | 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one ( 50 mg ) (Limit Test) | 1468400 | Nordazepam CIV ( 50 mg ) (7-Chloro-1,3-dihydro-5-phenyl-2H- 1,4-benzodiazepin-2-one) |
| 11500-2 | 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4 -oxide ( 25 mg ) (Limit Test) | 1110020 | Chlordiazepoxide Related Compound A ( 25 mg ) (7-Chloro 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide) |
| 11510-4 | 2-Chloro-4-N-furfuryl-amino-5-sulfamolybenzoic acid ( 50 mg ) (Limit Test) | 1287020 | Furosemide Related Compound A ( 50 mg ) ( 2 -Chloro-4-N furfurylamino-5-sulfamoylbenzoic Acid) |
| 11550-1 | 2-Chloro-3,5-dimethyl-phenol (50 mg) (Limit Test) | 1122722 | Chloroxylenol Related Compound A (50 mg) (2-Chloro-3,5 dimethyl-phenol) |
| 11650-4 | (o-Chlorophenyl)diphenyl-methanol (25 mg) (Limit Test) | 1141024 | Clotrimazole Related Compound A ( 25 mg ) ( (o-Chlorophe-nyl)diphenyl-methanol ) |
| 11670-8 | 4-(4-Chlorophenyl)-2-pyrrolidinone (75 mg) (Limit Test) | 1048222 | Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)- <br> 2-pyrrolidinone) |
| 11900-3 | 4-Chloro-5-sulfamoylanthranilic Acid (100 mg) (Limit Test) | 1287030 | Furosemide Related Compound B (100 mg) (4-Chloro-5 sulfamoylanthranilic Acid) |
| 1119309 | 4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid ( 100 mg ) | 1119309 | Chlorthalidone Related Compound A ( 25 mg ) ( 4 '-Chloro- $3^{\prime}$ -sulfamoyl-2-benzophenone Carboxylic Acid) |

## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. <br> No. | New Description |
| :---: | :---: | :---: | :---: |
| 15870-8 | Cyclosporine U (25 mg) DISCONTINUED | 1158650 | Cyclosporine Resolution Mixture ( 25 mg ) (Replaces Cat. No. 15870-8 Cyclosporine U ( 25 mg )) |
| 21000-3 | alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride (125 mg) (Limit Test) | 1575206 | Propoxyphene Related Compound A ( 50 mg ) (alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride) |
| 1268820 | Etoposide Related Compound A (25 mg) (4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-alpha-D-glucopyranoside) DISCONTINUED | 1268852 | Etoposide Resolution Mixture ( 30 mg ) |
| 32720-4 | 3-Hydroxy-1-methylquinuclidinium Bromide ( 250 mg ) (Limit Test) | 1135021 | Clidinium Bromide Related Compound A ( 250 mg ) (3-Hydroxy -1-methylquinuclindinium Bromide) |
| 1329505 | 9-Hydroxypropantheline Bromide ( 50 mg ) | 1329505 | Propantheline Bromide Related Compound A ( 50 mg ) (9Hydroxypropantheline bromide) |
| 33010-7 | Hydroxypropyl Methylcellulose Phthalate ( 100 mg ) | 1335304 | Hypromellose Phthalate ( 100 mg ) |
|  | Melting Point Standard - Acetanilide ( 500 mg ; approximately 114 degrees) | 1004001 | Acetanilide Melting Point Standard ( 500 mg ) (Approximately 114 degrees) |
|  | Melting Point Standard - Caffeine (1 g; approximately 236 degrees) | 1086006 | Caffeine Melting Point Standard (1 g) (Approximately 236 degrees) |
|  | Melting Point Standard - Phenacetin ( 500 mg ; approximately 135 degrees) | 1514008 | Phenacetin Melting Point Standard ( 500 mg ) (Approximately 135 degrees) |
|  | Melting Point Standard - Sulfanilamide (1 g; approximately 165 degrees) | 1633007 | Sulfanilamide Melting Point Standard ( 500 mg ) (Approximately 165 degrees) |
|  | Melting Point Standard - Sulfapyridine (2 g; approximately 191 degrees) | 1635002 | Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees) |
|  | Melting Point Standard - Vanillin (1 g; approximately 82 degrees) | 1711009 | Vanillin Melting Point Standard (1 g) (Approximately 82 degrees) |
| 1420006 | 3 -Methoxytyrosine ( 50 mg ) | 1420006 | Levodopa Related Compound B (50 mg) (3-Methoxytyrosine) |
| 42420-0 | 2-Methylamino-5-chlorobenzophenone (25 mg) (Limit Test) | 1185020 | Diazepam Related Compound A ( 25 mg ) <br> (2-Methylamino-5-chlorobenzophenone) |
| 42430-2 | 3-O-Methylcarbidopa ( 50 mg ) | 1095517 | Carbidopa Related Compound A ( 50 mg ) (3-O-Methylcarbidopa) |
| 46600-7 | 5-Nitro-2-furfuraldazine ( 500 mg ) | 1466007 | Nitrofurazone Related Compound A ( 500 mg ) (5-Nitro-2-furfuraldazine) |
| 46660-8 | 3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid ( 25 mg ) (Limit Test) | 1078336 | Bumetanide Related Compound B ( 25 mg ) (3-Nitro-4-phe-noxy-5-sulfamoylbenzoic Acid) |
| 1477900 | Octyl Methoxycinnamate ( 500 mg ) | 1477900 | Octinoxate ( 500 mg ) (Octyl Methoxycinnamate) |
| 49400-2 | Pancreatin (2 g) | 1494057 and/or 1494079 | Pancreatin Amylase and Protease (2 g) and/or Pancreatin Lipase (2 g) |
| 53180-1 | Phenylcyclohexylglycolic Acid (100 mg) (Limit Test) | 1485114 | Oxybutynin Related Compound A ( 100 mg ) (Phenylcyclohexylglycolic Acid) |
| 53350-1 | alpha-Phenyl-2-piperidineacetic Acid Hydrochloride ( 50 mg ) (Limit Test) | 1434022 | Methylphenidate Related Compound A ( 50 mg ) (alpha-Phe-nyl-2-piperidineacetic Acid Hydrochloride) |
| 54500-1 | Plastic, Negative Control | 1546707 | Polyethylene, High Density (3 strips) |
| 61500-5 | Sodium Taurocholate (20 g) | 1071304 | Bile Salts (10 g) (Sodium Taurocholate) |
| 68800-9 | 3 -(3,4,6-Trihydroxyphenyl)-alanine (50 mg) (Limit Test) | 1361010 | Levodopa Related Compound A (50 mg) (3-(3,4,6- <br> Trihydroxyphenyl)-alanine) |
|  | Vitamin B1 Hydrochloride | 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) |
|  | Vitamin B2 | 1603006 | Riboflavin ( 500 mg ) (Vitamin B2) |
|  | Vitamin B3 | 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) |
|  | Vitamin B5 | 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) |
|  | Vitamin B6 | 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) |
|  | Vitamin B12 | 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) |

## Cross Reference List

| Former <br> Cat. No. | Former Description/Cross Reference | Cat. <br> No. | New Description |
| :--- | :--- | :--- | :--- |
|  | Vitamim Bc | 1286005 | Folic Acid (500 mg) (Vitamin M or Vitamin Bc) |
|  | Vitamin C | 1043003 | Ascorbic Acid (1 g) (Vitamin C) |
|  | Vitamin D2 | 1239005 | Ergocalciferol ( $150 \mathrm{mg} ; 30 \mathrm{mg} / \mathrm{ampule} ; 5$ ampules) (Vitamin <br> D2) |
|  | Vitamin D3 | 1131009 | Cholecalciferol (30 mg/ampul; 5 ampuls) (Vitamin D3) |
|  | Vitamin E Alcohol | 1667600 | Alpha Tocopherol (250 mg) (Vitamin E Alcohol) |
|  | Vitamin E Acetate | 1667701 | Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate) |
|  | Vitamin E Acid Succinate | 1667803 | Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E <br> Succinate) |
|  | Vitamin K1 | 1538006 | Phytonadione (500 mg) (Vitamin K1) |
|  | Vitamin K3 | 1381006 | Menadione (200 mg) (Vitamin K3) |
|  | Vitamin M | 1286005 | Folic Acid ( 500 mg$)$ (Vitamin M or Vitamin Bc) |

## Dietary Supplement Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| AMINO ACIDS |  |  |  |
| 1012509 | L-Alanine (200 mg) | F-2 | \$156 |
| 1021000 | Aminocaproic Acid (200 mg) | F-4 | \$156 |
| 1042500 | L-Arginine (200 mg) | G-1 | \$156 |
| 1042601 | Arginine Hydrochloride ( 125 mg ) | G0B060 | \$124 |
| 1161509 | L-Cysteine Hydrochloride ( 200 mg ) | H | \$156 |
| 1294976 | Glutamic Acid ( 200 mg ) | F0C069 | \$156 |
| 1294808 | Glutamine ( 100 mg ) | FOB244 | \$156 |
| 1295800 | Glycine ( 200 mg ) | F-3 | \$156 |
| 1308505 | L-Histidine ( 200 mg ) | G0A018 | \$156 |
| 1349502 | L-Isoleucine ( 200 mg ) | F-2 | \$156 |
| 1357001 | L-Leucine (200 mg) | H0B237 | \$156 |
| 1359903 | Levocarnitine ( 400 mg ) | G0B197 | \$156 |
| 1359925 | Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride) | F-1 | \$208 |
| 1371501 | L-Lysine Acetate ( 200 mg ) | F | \$156 |
| 1372005 | L-Lysine Hydrochloride (200 mg) | H | \$156 |
| 1411504 | L-Methionine ( 200 mg ) | G | \$156 |
| 1530503 | L-Phenylalanine ( 200 mg ) | H | \$156 |
| 1568506 | L-Proline (200 mg) | F-2 | \$156 |
| 1612506 | L-Serine (200 mg) | G | \$156 |
| 1667202 | L-Threonine ( 200 mg ) | G | \$156 |
| 1700501 | L-Tryptophan (200 mg) | G-1 | \$156 |
| 1705006 | L-Tyrosine ( 500 mg ) | $J$ | \$156 |
| 1708503 | L-Valine ( 200 mg ) | F-2 | \$156 |
| BOTANICALS |  |  |  |
| CAPSAICIN/CAPSICUM |  |  |  |
| 1091108 | Capsaicin (100 mg) | G-1 | \$156 |
| 1200600 | Dihydrocapsaicin (25 mg) | G0C071 | \$156 |
| CHAMOMILE |  |  |  |
| 1040708 | Apigenin-7-Glucoside ( 30 mg ) | F | \$487 |
| CRANBERRY LIQUID |  |  |  |
| 1134368 | Citric Acid ( 200 mg ) | F1B092 | \$156 |
| 1181302 | Dextrose ( 500 mg ) | J-1 | \$124 |
| 1286504 | Fructose ( 125 mg ) | I-2 | \$124 |
| 1374601 | Malic Acid (200 mg) | G0B158 | \$156 |
| 1594506 | Quinic Acid ( 200 mg ) | F | \$156 |
| 1617000 | Sorbitol ( 125 mg ) | H1B139 | \$124 |
| 1623637 | Sucrose ( 100 mg ) | H0B002 | \$156 |
| ELEUTHERO |  |  |  |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | \$520 |
| FEVERFEW |  |  |  |
| 1500400 | Parthenolide (25 mg) | F | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| GARLIC |  |  |  |
| 1012145 | Agigenin (25 mg) | F | \$156 |
| 1012950 | Alliin (25 mg) | F | \$1,525 |
| 1115556 | beta-Chlorogenin ( $20 \mathrm{mg} \mathrm{)}$ | F | \$156 |
| 1294848 | gamma-Glutamyl-S-allyl-L-cysteine ( 25 mg ) | F | \$675 |
| 1411504 | L-Methionine (200 mg) | G | \$156 |

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## Dietary Supplement Reference Standards Available from USP

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| :---: | :---: | :---: | :---: |
| GARLIC FLUID EXTRACT |  |  |  |
| 1013057 | S-Allyl-L-Cysteine (25 mg) | F | \$487 |
| GINGER |  |  |  |
| 1091108 | Capsaicin (100 mg) | G-1 | \$156 |
| 1291504 | Powdered Ginger ( 500 mg ) | F | \$156 |
| GINKGO |  |  |  |
| 1592409 | Quercetin (500 mg) | F0B015 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| AMERICAN GINSENG |  |  |  |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | F0B289 | \$520 |
| ASIAN GINSENG |  |  |  |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | FOB289 | \$520 |
| HAWTHORN LEAF WITH FLOWER |  |  |  |
| 1335202 | Hyperoside ( 50 mg ) | F | \$855 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 | \$156 |
| 1717708 | Vitexin ( 30 mg ) | F0C142 | \$520 |
| KAVA |  |  |  |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 | \$260 |
| KAWAIN |  |  |  |
| 1355753 | Kawain (200 mg) | F0C160 | \$208 |
| LICORICE |  |  |  |
| 1295888 | Glycyrrhizic Acid (25 mg) | FOC006 | \$487 |
| MILK THISTLE |  |  |  |
| 1443850 | Powdered Milk Thistle Extract (250 mg) | F0B321 | \$260 |
| 1612630 | Silybin ( 50 mg ) | F | \$156 |
| 1612641 | Silydianin ( 20 mg ) | F | \$156 |
| RED CLOVER |  |  |  |
| 1286060 | Formononetin ( 50 mg ) | F0C196 | \$520 |
| 1599500 | Powdered Red Clover Extract (500 mg) | F0C188 | \$260 |
| SAW PALMETTO |  |  |  |
| 1424233 | Methyl Caprate ( 300 mg ) | F | \$156 |
| 1424244 | Methyl Caproate ( 300 mg ) | F | \$156 |
| 1424255 | Methyl Caprylate ( 300 mg ) | F | \$156 |
| 1430305 | Methyl Laurate ( 500 mg ) | F | \$156 |
| 1430327 | Methyl Linoleate ( $5 \times 50 \mathrm{mg}$ ) | F | \$156 |
| 1430349 | Methyl Linolenate ( $5 \times 50 \mathrm{mg}$ ) | F | \$156 |
| 1431501 | Methyl Myristate ( 300 mg ) | F | \$156 |
| 1431556 | Methyl Oleate ( 500 mg ) | G0C148 | \$156 |
| 1431603 | Methyl Palmitate ( 300 mg ) | F | \$156 |
| 1431625 | Methyl Palmitoleate ( $300 \mathrm{mg} \mathrm{)}$ | F | \$156 |
| 1437508 | Methyl Stearate ( 300 mg ) | F | \$156 |
| ST. JOHN S WORT |  |  |  |
| 1335202 | Hyperoside ( 50 mg ) | F | \$855 |
| 1485001 | Oxybenzone ( 150 mg ) | H0B263 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| VALERIAN |  |  |  |
| 1707908 | Valerenic Acid (25 mg) | G0B146 | \$696 |
| MISCELLANEOUS DIETARY SUPPLEMENTS |  |  |  |
| 1133570 | Chondroitin Sulfate Sodium ( 300 mg ) | F0B256 | \$156 |

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## Dietary Supplement Reference Standards Available from USP

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| :---: | :---: | :---: | :---: |
| 1133638 | Chromium Picolinate ( 100 mg ) | F | \$156 |
| 1150353 | Creatinine ( 100 mg ) | F | \$156 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 | \$156 |
| 1611955 | Selenomethionine ( 100 mg ) | FOB006 | \$156 |
| VITAMINS-MINERALS |  |  |  |
| 1043003 | Ascorbic Acid (1 g) (Vitamin C) | Q0B012 | \$156 |
| 1071508 | Biotin ( 200 mg ) | H1B019 | \$156 |
| 1086356 | Calcium Ascorbate (200 mg) | F-1 | \$156 |
| 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) | N-1 | \$156 |
| 1131009 | Cholecalciferol ( $30 \mathrm{mg} / \mathrm{ampule}$; 5 ampules) (Vitamin D3) | M0B157 | \$159 |
| 1131803 | Delta-4,6-cholestadienol ( 30 mg ) | F | \$156 |
| 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) | N | \$156 |
| 1179504 | Dexpanthenol ( 500 mg ) | J0C293 | \$160 |
| 1239005 | Ergocalciferol ( $30 \mathrm{mg} / \mathrm{ampule}$; 5 ampules) (Vitamin D2) | P0B275 | \$168 |
| 1241007 | Ergosterol ( 50 mg ) | H | \$156 |
| 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) | P | \$156 |
| 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) | IOB176 | \$156 |
| 1381006 | Menadione (200 mg) (Vitamin K3) | H-3 | \$156 |
| 1461003 | Niacin (200 mg) | H-1 | \$156 |
| 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) | M-1 | \$156 |
| 1494501 | Panthenol, Racemic ( $200 \mathrm{mg} \mathrm{)}$ | G | \$156 |
| 1494807 | Pantolactone ( 500 mg ) | F | \$487 |
| 1538006 | Phytonadione ( 500 mg ) (Vitamin K1) | N0B303 | \$156 |
| 1550001 | Potassium Gluconate (200 mg) | H0C064 | \$156 |
| 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) | P | \$156 |
| 1603006 | Riboflavin ( 500 mg ) (Vitamin B2) | N0C021 | \$156 |
| 1613509 | Sodium Ascorbate (200 mg) | G-1 | \$156 |
| 1614002 | Sodium Fluoride (1 g) | H-1 | \$156 |
| 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) | 0 | \$156 |
| 1667600 | Alpha Tocopherol (250 mg) (Vitamin E Alcohol) | M | \$156 |
| 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) | K | \$156 |
| 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) | F-5 | \$156 |
| 1716002 | Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil) | V0C258 | \$156 |
| 1717504 | Vitamin D Assay System Suitability (1.5 g) | F | \$156 |

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| Cat. <br> No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1012906 | Alfentanil Hydrochloride CII (500 mg) | F0B016 | \$207 |
| 1014005 | Alphaprodine Hydrochloride CII (250 mg) | F | \$207 |
| 1015008 | Alprazolam CIV (200 mg) | H | \$207 |
| 1030001 | Amobarbital CII (200 mg) | F-2 | \$207 |
| 1036008 | Anileridine Hydrochloride CII ( 250 mg ) | F | \$207 |
| 1042000 | Aprobarbital CIII ( 200 mg ) (AS) | F-1 | \$207 |
| 1059003 | Benzphetamine Hydrochloride CIII (200 mg) (AS) | F-1 | \$207 |
| 1078700 | Buprenorphine Hydrochloride CIII ( 50 mg ) | F-1 | \$207 |
| 1079000 | Butabarbital CIII ( 200 mg ) | H0C007 | \$207 |
| 1081002 | Butalbital CIII ( 200 mg ) | H0C054 | \$207 |
| 1082504 | Butorphanol Tartrate CIV (500 mg) | J | \$207 |
| 1089004 | Cannabidiol CI (25 mg) (AS) | F-2 | \$207 |
| 1090003 | Cannabinol CI (25 mg) (AS) |  | \$207 |
| 1096804 | Cathinone Hydrochloride CI (50 mg) (alpha-Aminopropiophenone Hydrochloride) | 1 | \$560 |
| 1109000 | Chlordiazepoxide CIV ( 200 mg ) | IOB063 | \$207 |
| 1110009 | Chlordiazepoxide Hydrochloride CIV (200 mg) | G-4 | \$207 |
| 1140305 | Clonazepam CIV (200 mg) | G1B175 | \$207 |
| 1140509 | Clorazepate Dipotassium CIV (125 mg) | G0B027 | \$207 |
| 1143008 | Cocaine Hydrochloride CII (250 mg) | IOB074 | \$207 |
| 1143802 | Codeine N-Oxide CI (50 mg) | G0A034 | \$207 |
| 1144000 | Codeine Phosphate CII (100 mg) | J0C200 | \$207 |
| 1145003 | Codeine Sulfate CII ( 250 mg ) | H-2 | \$207 |
| 1180004 | Dextroamphetamine Sulfate CII (500 mg) | H | \$216 |
| 1183002 | Diacetylmorphine Hydrochloride (Heroin Hydrochloride) CI (25 mg) (AS) | J | \$207 |
| 1185008 | Diazepam CIV (100 mg) | 1 | \$207 |
| 1187207 | Dichloralphenazone CIV (200 mg) | F0B010 | \$207 |
| 1194009 | Diethylpropion Hydrochloride CIV (200 mg) | H | \$207 |
| 1200804 | Dihydrocodeine Bitartrate CII (200 mg) | H | \$207 |
| 1219008 | Diphenoxylate Hydrochloride CII (200 mg) | 1 | \$207 |
| 1258305 | Ethchlorvynol CIV ( 0.7 ml ) | F0B011 | \$207 |
| 1270005 | Fentanyl Citrate CII (100 mg) | J2B227 | \$207 |
| 1280009 | Fluoxymesterone CIII ( 200 mg ) | G-2 | \$207 |
| 1285002 | Flurazepam Hydrochloride CIV ( $200 \mathrm{mg} \mathrm{)}$ |  | \$207 |
| 1295006 | Glutethimide CII ( 500 mg ) | F | \$207 |
| 1302305 | Halazepam CIV ( 200 mg ) | F | \$207 |
| 1307003 | Hexobarbital CIII ( 500 mg ) | F | \$207 |
| 1315001 | Hydrocodone Bitartrate ClI (250 mg) | J0A026 | \$207 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl) | F0C214 | \$513 |
| 1323000 | Hydromorphone Hydrochloride CII (50 mg) | 1 | \$207 |
| 1356009 | Ketamine Hydrochloride CIII ( $250 \mathrm{mg} \mathrm{)}$ | G-2 | \$207 |
| 1359506 | Levmetamfetamine CII ( 75 mg ) | F | \$207 |
| 1364007 | Levorphanol Tartrate CII ( 500 mg ) | H | \$207 |
| 1370305 | Lorazepam CIV (200 mg) | $10 \mathrm{CO48}$ | \$207 |
| 1371002 | Lysergic Acid Diethylamide Tartrate (LSD) Cl (10 mg) (AS) | 1 | \$207 |
| 1375309 | Mazindol CIV ( 350 mg ) | H | \$207 |
| 1383001 | Meperidine Hydrochloride CII (200 mg) | 1 | \$207 |
| 1386000 | Mephobarbital CIV (250 mg) | G | \$207 |
| 1389008 | Meprobamate CIV (200 mg) | G-1 | \$207 |
| 1398009 | Methadone Hydrochloride CII (200 mg) | IOB163 | \$207 |

## Controlled Substances Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1399001 | Methamphetamine Hydrochloride CII (125 mg) | I | \$207 |
| 1404000 | Methaqualone $\mathbf{C l}(500 \mathrm{mg}$ ) | F-1 | \$207 |
| 1405002 | Metharbital CIII ( $200 \mathrm{mg} \mathrm{)}$ | F-2 | \$207 |
| 1413000 | Methohexital CIV ( 500 mg ) | F-2 | \$207 |
| 1425000 | 4-Methyl-2,5-dimethoxyamphetamine Hydrochloride (STP) CI (25 mg) (AS) | F | \$207 |
| 1429000 | Methylenedioxy-3,4-amphetamine Hydrochloride (MDA) CI (25 mg) (AS) | F-1 | \$207 |
| 1433008 | Methylphenidate Hydrochloride CII (125 mg) | 1 | \$165 |
| 1434000 | Methylphenidate Hydrochloride Erythro Isomer CII ( 25 mg ) | J0B294 | \$560 |
| 1438001 | Methyltestosterone CIII (200 mg) | J | \$207 |
| 1447002 | Morphine Monohydrate CII (50 mg) (AS) | G | \$207 |
| 1448005 | Morphine Sulfate CII (500 mg) | LOB056 | \$332 |
| 1452002 | Nalorphine Hydrochloride CIII (250 mg) | 1 | \$207 |
| 1453526 | Naltrexone Related Compound A CII ( 30 mg ) ( $N$-(3-butenyl)-noroxymorphone hydrochloride) | F | \$207 |
| 1454008 | Nandrolone CIII ( 50 mg ) | F-3 | \$560 |
| 1455000 | Nandrolone Decanoate CIII (250 mg) | 1 | \$207 |
| 1456003 | Nandrolone Phenpropionate CIII (250 mg) | H | \$207 |
| 1468400 | Nordazepam CIV (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) | H1B035 | \$560 |
| 1473002 | Noroxymorphone Hydrochloride CII ( 50 mg ) | H1C177 | \$560 |
| 1482003 | Oxandrolone CIII ( 50 mg ) | G0B220 | \$207 |
| 1483006 | Oxazepam CIV (200 mg) | G-1 | \$207 |
| 1485191 | Oxycodone CII (200 mg) | IOB046 | \$207 |
| 1487007 | Oxymetholone CIII (200 mg) | G1B247 | \$207 |
| 1488000 | Oxymorphone CII ( 500 mg ) | H0B214 | \$207 |
| 1505007 | Pentazocine CIV ( 500 mg ) | H | \$207 |
| 1507002 | Pentobarbital CII (200 mg) | H3C144 | \$207 |
| 1516003 | Phencyclidine Hydrochloride CII (25 mg) (AS) | G1B025 | \$207 |
| 1516502 | Phendimetrazine Tartrate CIII ( 350 mg ) | G | \$207 |
| 1523009 | Phenmetrazine Hydrochloride Cll ( 200 mg ) | F-2 | \$207 |
| 1524001 | Phenobarbital CIV (200 mg) | J | \$207 |
| 1528501 | Phentermine Hydrochloride CIV (200 mg) | H0B309 | \$207 |
| 1554501 | Prazepam CIV (500 mg) | G0C066 | \$207 |
| 1574000 | Propoxyphene Hydrochloride CII (1 g) | L0C285 | \$207 |
| 1575002 | Propoxyphene Napsylate CII (1 g) | H | \$207 |
| 1592205 | Quazepam CIV (200 mg) | F | \$207 |
| 1611004 | Secobarbital CII (200 mg) | H | \$207 |
| 1620005 | Stanozolol CIII (200 mg) | F-3 | \$207 |
| 1623648 | Sufentanil Citrate CII ( 25 mg ) | H0B208 | \$207 |
| 1643000 | Talbutal CIII ( 250 mg ) | F | \$207 |
| 1643408 | Temazepam CIV (200 mg) | H0C205 | \$207 |
| 1645006 | Testolactone CIII (125 mg) | F-1 | \$165 |
| 1646009 | Testosterone CIII (125 mg) | 11B253 | \$165 |
| 1647001 | Testosterone Cypionate CIII ( $200 \mathrm{mg} \mathrm{)}$ | G-1 | \$207 |
| 1648004 | Testosterone Enanthate CIII ( 200 mg ) | J | \$207 |
| 1649007 | Testosterone Propionate CIII ( 200 mg ) | L1C005 | \$207 |
| 1656308 | Thiamylal CIII ( 200 mg ) | F | \$207 |
| 1661002 | Thiopental CIII (250 mg) | 1 | \$207 |
| 1680506 | Triazolam CIV (200 mg) | H0B041 | \$207 |

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[^40]
# CHROMATOGRAPHIC REAGENTS USED IN $\boldsymbol{U S P} \boldsymbol{- N F}$ AND PHARMACOPEIAL FORUM 

This is an update based on the proposals published in this issue of $P F$.

## CHROMATOGRAPHIC REAGENTS

## Chromatographic Reagents Used in USP-NF and Pharmacopeial Forum

January-February 2004

| PF | AMIFOSTINE |  | Type of Test | Comments DSD Mgh \#2600 |
| :---: | :---: | :---: | :---: | :---: |
| 30(1) | L1 | Luna C18 | Assay \& Chrom. purity | $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}, 5 \mu \mathrm{~m}$, manufacturer Phenomenex. |
|  | ANTITHROMBIN III HUMAN |  |  | DSD Mgh \#5390 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(1) | L\# \# | TSK-Gel G3000SW | Mol w distrib, Ave mol wt | Analytical column $7.5 \mathrm{~mm} \times 30 \mathrm{~cm}, 10 \mu \mathrm{~m}$; guard column $7.5 \mathrm{~mm} \times 7.5 \mathrm{~cm}, 10 \mu \mathrm{~m}$, manufacturer Tosoh Biosep. |
|  | CLONIDINE TRANSDERMAL SYSTEM |  |  | DSD Mgh \#18610 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(1) | L1 | Capcell UG C18 | Assay and Related Compounds | $4.6 \mathrm{~mm} \times 15 \mathrm{~cm}, 5$ : m, manufacturer Shiseido. |
|  | FLUCONAZOLE |  |  | DSD Mgh \#33240 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(1) | L1 | Symmetry C18 | Related compounds | $4.6 \mathrm{~mm} \times 15 \mathrm{~cm}, 3.5$ : m, manufacturer Waters. |
|  | IRBESARTAN |  |  | DSD Mgh \#42410 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(1) | L1 | Nucleosil C18 | Assay and Related Compounds | $4.0 \mathrm{~mm} \times 25 \mathrm{~cm}, 7$ : m, manufacturer MachereyNagel. |
|  | NETILMICIN SULFATE |  |  | DSD Mgh \#56470 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(1) | L1 | Luna C18 | Assay \& Chrom. purity | $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}, 5$ : m, manufacturer Phenomenex. |
|  | NETILMICIN SULFATE INJECTION |  |  | DSD Mgh \#56476 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(1) | L1 | Luna C18 | Assay \& Chrom. purity | $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}, 5: \mathrm{m}$, manufacturer Phenomenex. |
|  | NYSTATIN |  |  | DSD Mgh \#58060 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(1) | L1 | Hypersil C18 | Composition | $4.6 \mathrm{~mm} \times 15 \mathrm{~cm}, 5: \mathrm{m}$, manufacturer ThermoHypersil-Keystone. |
|  | OXANDROLONE |  |  | DSD Mgh \#59110 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(1) | L1 | Xterra MS C18 | Assay \& Chrom. Purity | $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}, 5 \mu \mathrm{~m}$, manufacturer Waters. |


| PF | PHENOXYETHANOL |  | Type of Test | Comments ${ }^{\text {DSD Mgh \#381 }}$ |
| :---: | :---: | :---: | :---: | :---: |
|  | LGS\# | Reagent Brand |  |  |
| 30(1) | G27 | Chrompack CP-Sil 8 CB | Assay, Chromatographic purity, and Limit of . | $0.32 \mathrm{~mm} \times 10 \mathrm{~m}, 5: \mathrm{m}$, manufacturer VarianChrompack |
|  | VECURONIUM BROMIDE |  |  | DSD Mgh \#88050 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(1) | L1 | Alltima C-18 | Related compounds | $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}, 5 \mu \mathrm{~m}$, manufacturer Alltech |

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Pharmacopeial Forum is covered in Current Contents/Life Sciences and in the Science Citation Index (SCI), in International Pharmaceutical Abstracts, and in Current Awareness in Biological Sciences.

The United States Pharmacopeial Convention comprises representatives from colleges and national and state organizations of medicine and pharmacy. It publishes the U.S. Pharmacopeia and National Formulary, the legally recognized compendia of standards for drugs and products of other health care technologies. The USP and NF include assays and tests for the determination of strength, quality, and purity and requirements for packaging and labeling.

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## Moving?

Our subscribers' records and publication labels are computergenerated. Please send your new address, and your latest label, or an exact copy of it, to: USPC, PF Customer Service Dept., 12601 Twinbrook Parkway, Rockville, MD 20852. Fax: (301) 816-8148.

## STANDARDS DEVELOPMENT

This section presents an overview of the public review and comment process, conducted through Pharmacopeial Forum $(P F)$, for the development of official pharmaceutical standards.

USP publishes Pharmacopeial Forum ( $P F$ ) bimonthly as the working vehicle of the USP Council of Experts. PF provides interested parties an opportunity to review and comment as the Council of Experts develops or revises standards for the United States Pharmacopeia and the National Formulary (USP-NF).
$P F$ includes the following:

1. Potential revisions-entirely new standards, revision ideas, and drafts not yet targeted for official adoption (Pharmacopeial Previews)
2. Proposed revisions - new or revised standards targeted for official adoption (In-Process Revision)
3. Adopted revisions-new or revised standards that become official and binding before the publication of the next $U S P$ NF or Supplement (Interim Revision Announcement)
USP welcomes comments and data on potential, proposed, or official standards. ${ }^{*}$ Comments, along with USP's responses, will be published either in PF Briefings, the Commentary section of $P F$, the Commentary section of Supplements to USP-NF, or the Commentary section of $U S P-N F$.
[^42]The chart below shows the public review and comment process and its relationship to standards development.

# Public Review and Comment Process for Standards Development 



Questions on the process should be addressed to John W. Gasper, M.A., J.D., Director, Office of the Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: jg@usp.org).

## HOW TO USE PF

This section provides descriptions of the various parts of $P F$. It also includes Committee Designations and the Staff Directory.

The contents of the different sections of $P F$ are briefly described below. Readers will get an idea of how each section is relevant to their job functions. They may contact USP scientific staff liaisons or staff members of the Executive Secretariat (listed in the Staff Directory) if they have any questions. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a Request for Revision is available on the USP website (www.usp.org/standards/revisionguideline/).

Proposed and Adopted Revisions

| Section | Content | How Readers Can Respond |
| :---: | :---: | :---: |
| Pharmacopeial <br> Previews <br> Early ideas for revisions | -Briefing: Scientific rationale for potential inclusion or change. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -Potential revisions not yet targeted for official adoption that require a longer public review and comment process because of issues such as: <br> - the controversial nature of an item; <br> - the application of new technologies that require further study; and <br> - articles produced by multiple sources. | Review drafts and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview. |
| In-Process Revision Revisions targeted for adoption | -Briefing: Scientific rationale for proposed changes. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -New and revised standards that have been approved for publication by the appropriate USP Committee when it is considering whether to advance standards to official status (see Standards Development). New or revised text is marked with symbols ( ${ }^{\square}$ or ) to specify the tentative earliest date on which the revision would be officially adopted. | Review material and send comments promptly to USP staff liaison (see the Staff Directory). Guidelines on how to comment are found at the end of the Policies and Announcements section. |
| Harmonization <br> Items the Pharmacopeial Discussion Group (PDG) is trying to harmonize internationally | - Briefing: Scientific rationale for the potential inclusion or change or for the proposed change. The designated stage of harmonization. The stage determines whether an item appears under Pharmacopeial Previews or under In-Process Revision, both separate sections of Harmonization. <br> -For In-Process Revision, new or revised text is marked with symbols (■) to specify the tentative, earliest date on which the revision would be officially adopted. | Review material and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview or In-Process Revision. |
| Interim Revision <br> Announcement <br> Adopted standards | Standards that have been adopted and will become officially binding on the specified date. Effective date is specified in the section's introductory page or within parentheses following a particular item. New or revised text is set off by the symbols ${ }^{\circ}$. | Review to see if affected by any of the changes. Note effective date when standards become official and ensure compliance. |

## Other Sections

## Committee Designations

Names of the committees (composed of volunteer scientific experts) that USP staff work with on the development of standards.

## Staff Directory

Names of all USP scientific staff liaisons with contact information.

## Policies and Announcements

- General scientific and policy issues affecting $U S P-N F$ standards and processes
- Update on standards-related issues being considered by USP
- Summaries of meetings of the Council of Experts
- Guidelines on how to comment
- Publication and comment schedules


## Stimuli to the Revision Process

- Articles on standards development issues authored by the USP Council of Experts, USP staff, or other interested parties
- Discussions of issues on which USP desires public input prior to further development


## Nomenclature

- Latest adopted United States Adopted Names (USAN) and International Nonproprietary Names (INN) for drugs
- Revisions to existing names as a supplement to the USP Dictionary of USAN and International Drug Names
- Suggested, proposed, and recommended USAN and INN
- Information on how nonproprietary drug names are devised
- Articles relevant to compendial nomenclature issues


## Index

Cumulative directory for the content of all issues of $P F$ beginning with $P F 30(1)$.

## Reference Standards Catalog

List of official USP Reference Standards specified in $U S P-N F$, along with availability and ordering information.

## Chromatographic Reagents Used in USP-NF and Pharmacopeial Forum

Update of chromatographic reagents based on the proposals published in this issue of $P F$.

## EXPERT COMMITTEE DESIGNATIONS*

The names of the Committees and their abbreviations are as follows:

| AER | Aerosols |
| :--- | :--- |
| AMB | Analytical Microbiology |
| BBP | Blood and Blood Products |
| BNA | Bioavailability and Nutrient Absorption |
| BNT | Biotechnology and Natural Therapeutics and Diagnostics |
| BPC | Biopharmaceutics |
| BST | Biostatistics |
| CRX | Compounding Pharmacy |
| DSB | Dietary Supplements-Botanicals |
| DSI | Dietary Supplements-Information |
| DSN | Dietary Supplements-Non-Botanicals |
| EMC | Excipient Monograph Content ${ }^{\dagger}$ |
| ESC | Excipients-Substances and Characterization ${ }^{\dagger}$ |
| ETM | Excipients-Test Methods |
| GCT | Gene Therapy, Cell Therapy, and Tissue Engineering |
| GTB | General Toxicity and Biocompatibility |
| NL | Nomenclature and Labeling |
| PA1 | Pharmaceutical Analysis 1 |
| PA2 | Pharmaceutical Analysis 2 |
| PA3 | Pharmaceutical Analysis 3 |
| PA4 | Pharmaceutical Analysis 4 |
| PA5 | Pharmaceutical Analysis 5 |
| PA6 | Pharmaceutical Analysis 6 |
| PA7 | Pharmaceutical Analysis 7-Antibiotics |
| PDF | Pharmaceutical Dosage Forms |
| PPC | Parenteral Products-Compounding and Preparation |
| PPI | Parenteral Products-Industrial |
| PSD | Packaging, Storage, and Distribution |
| PW | Pharmaceutical Waters |
| RMI | Radiopharmaceuticals and Medical Imaging |
| SMU | Safe Medication Use |
| VET | Veterinary Drugs |
| VVI | Vaccines, Virology, and Immunology |
|  |  |

[^43]
## STAFF DIRECTORY

This is an updated directory that reflects assignment changes based on the reorganization of USP. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Committee is not identified. The Fax number is (301) 816-8373.

| STAFF | E-MAIL | PHONE | ASSIGNMENT |
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\(\left.$$
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\text { cals (DSB); Dietary } \\
\text { Siaison }\end{array}
$$ <br>

abilements-Biaavail-\end{array}\right]\)| Absorption (BNA) |
| :---: |

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| William W. Wright, Scientific Fellow | www@usp.org | (301) 816-8335 | Pharmaceutical Analysis 7Antibiotics (PA7a) |
| Kahkashan Zaidi, Scientist | kxz@usp.org | (301) 816-8269 | Aerosols (AER) |

## POLICIES AND ANNOUNCEMENTS

In this section, readers may find statements about general scientific and policy issues that may have an impact on $U S P-N F$ standards and processes, announcements about issues being considered by USP, and summaries of Council of Experts meetings. This section also includes publication and comment schedules.

NOTICE OF REVISION PERTAINING TO THE PACKAGING AND STORAGE STATEMENTS FOR EXCIPIENT ARTICLES. Changes in the Packaging and Storage sections of the following excipient monographs will appear in Pharmacopeial Forum 30(3) [May-June 2004].

This will apply to the following new excipient monographs, which became official in USP27-NF22: Ammonium Sulfate, Candelilla Wax, Cetrimonium Bromide, Hydrogenated Cottonseed Oil, Tribasic Sodium Phosphate, Glyceryl Distearate, Glyceryl Monolinoleate, and Glyceryl Monooleate.

It will also apply to the following new and revised excipient monographs, which will become official in the First Supplement to USP27-NF22: Dibutyl Phthalate, Diethylene Glycol Stearates, Ethylene Glycol Stearates, Hydrogenated Soybean Oil, Hymetellose, Low-Substituted Carboxymethylcellulose Sodium, Medium-Chain Triglycerides, Polyisobutylene, Sodium Cetostearyl Sulfate, Sorbitol, Sorbitol Solution, Maltitol Solution, and Noncrystallizing Sorbitol Solution.

As well, it will apply to the following official excipient monographs for which revision proposals are currently presented in Pharmacopeial Forum: Pregelatinized Starch and Tapioca Starch.

Lastly, the Committee wishes to apply this principle to proposed new excipient monographs for which revision proposals are currently presented in Pharmacopeial Forum: Copovidone, Modified Starch, Pregelatinized Modified Starch, Maltose, Anhydrized Liquid Sorbitol, Phenolsulfonphthalein, and Hypromellose Acetate Succinate.
For more information, please contact Catherine Sheehan at 301-816-8262 or cxs@usp.org.

USP GUIDELINE FOR SUBMITTING REQUESTS FOR REVISION TO THE USP-NF. We are pleased to announce the availability of the USP Guideline for Submitting Requests for Revision to the $U S P-N F$. This document was developed in conjunction with the USP Council of Experts and its Expert Committees, USP Staff, and the Drug Substance, Complex Actives, and Excipients Project Teams of the Prescription/Nonprescription Stakeholders Forum. This document includes information to aid submission of new monographs and revisions to existing monographs for Non-Complex Active Substances and Products, Biological and Biotech Substances and Products, Excipients, and Vaccines. It incorporates many of the concepts and suggestions included in the ICH Q3A, Q3B, Q3C, Q6A, and Q6B guidelines. These include the definition of a specification and incorporate much of the terminology of Q3A for the control of impurities. The guideline clearly defines the information needed for the USP's Council of Experts and its Expert Committees to evaluate a request for revision. The document is approximately 75 pages in length with about 25 pages of addenda and is available in PDF format from the USP website at www.usp.org. Hard copies will be provided upon request.

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education series has been developed to enhance the knowledge, skills, and expertise of pharmaceutical industry personnel.

The following list indicates tentatively scheduled course dates. For further information, contact Barbara B. Hubert, Director, Pharmacopeial Education, BBH@usp.org, 301-816-8333, or Diana Lenahan, Program Associate, DPL@ usp.org, 301-816-8530. Call 301-816-8530 to get information on customized courses offered at USP or at your site.

Calendar of Pharmacopeial Education Courses, 2004

| Date | Name of course | Location |
| :---: | :---: | :---: |
| March 22 and 23 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| March 24 | Fundamentals of Microbiological Testing | USP Headquarters, Rockville, MD |
| April 1 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| April 21 and 22 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| May 19 | Standards 100: Fundamentals of the Use of $U S P$ $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| May 20 | Standards 101: Advanced Use of $U S P-N F$, General Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| June 10 | Fundamentals of Microbiological Testing | USP Headquarters, Rockville, MD |
| July 19 and 20 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| August 10 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| August 11 | Standards 100: Fundamentals of the Use of $U S P$ $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| August 12 | Standards 101: Advanced Use of $U S P-N F$, General Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| October 14 | Fundamentals of Microbiological Testing | USP Headquarters, Rockville, MD |
| October 18 and 19 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| November 11 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| November 11 | Standards 100: Fundamentals of the Use of $U S P$ $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| November 12 | Standards 101: Advanced Use of $U S P-N F$, General Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| November 12 | Fundamentals of Dissolution (Lecture) | USP Headquarters, Rockville, MD |
| December 2 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| December 8 | Standards 100: Fundamentals of the Use of $U S P$ $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| December 9 | Standards 101: Advanced Use of $U S P-N F$, General Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |

VISIT THE USP WEB SITE AT 〈http://www.usp.org〉. Various resources related to Pharmacopeial standards are presented, including highlights from $P F$.

## $\boldsymbol{U S P}-\boldsymbol{N F}$ AVAILABLE IN THREE ELECTRONIC

FORMATS. The trusted reference for official pharmaceutical standards is available in three convenient electronic formats- CD , intranet, and online. The CD is ideal for single users who prefer to have $U S P-N F$ on their hard drives. The intranet format allows Web browser-based access to multiple users within a company, through their own intranet server. The online format can be accessed by individual registered users through the World Wide Web. All three electronic formats provide fast and easy access to official $U S P-N F$ content. More information can be
obtained by visiting www.usp.org/products or by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

CHROMATOGRAPHIC REAGENTS NOW AVAILABLE. Chromatographic Reagents lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic test methods that has been published in Pharmacopeial Forum ( $P F$ ) since 1980. Chromatographic Reagents also helps to track which column reagents were used to validate methods that have become official and are included in $U S P-N F$. The branded column reagents list is updated bimonthly through Pharmacopeial Forum. Chromatographic Reagents can be ordered by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

INTERNATIONAL CORRESPONDENCE. Individuals who wish to correspond with the European and Japanese Pharmacopoeias concerning monographs in the Official Inquiry and Consensus stages of international harmonization should address their comments to the coordinating pharmacopeia for a given article. The addresses for the European and Japanese Pharmacopoeias are as follows:

Technical Secretariat of the European Pharmacopoeia Commission B.P. 907

F 67029 Strasbourg Cedex 1
France

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E-mail: nakashima-nobumasa@mhlw.go.jp

HOW TO SUBMIT COMMENTS. The USP welcomes and encourages interested parties to submit comments and data regarding potential, proposed, or adopted (official) standards. Submissions concerning a particular item that has appeared in a $P F$ should be submitted to the appropriate USP scientific staff liaison identified at the end of the Briefing accompanying each item. To submit comments and data to a liaison, use the e-mail address and telephone numbers listed in the Staff Directory included in every $P F$.

Please note that $U S P-N F$ is being published in an annual edition with one main book and two Supplements a year. In addition, the following schedule will repeat every year so that users will know what to expect and become familiar with the deadlines.

The publication and comment schedule for USP 27-NF 22 is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2003 | November 2003 | January 2004 |
| Supplement One | October 15, 2003 | February 2004 | April 2004 |
| Supplement Two | February 17, 2004 | June 2004 | August 2004 |

The publication and comment schedule for USP 28-NF 23 is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2004 | November 2004 | January 2005 |
| Supplement One | October 15, 2004 | February 2005 | April 2005 |
| Supplement Two | February 17, 2005 | June 2005 | August 2005 |

In the future, USP anticipates including the comment submission deadline in each briefing of every revision proposal when it is published for public review and comment.

For general inquiries or in cases where a particular liaison is not identified, use the general USP telephone number 301-881-0666 or FAX number 301-816-8373.

All official revisions are published in Supplements to $U S P-N F$ (twice yearly). Between Supplements, official revisions are published in $P F$ in the Interim Revision Announcement; these revisions are also incorporated in the upcoming Supplement. The electronic version of $U S P-N F$ is updated as each Supplement becomes available and, therefore, contains all official text up to and including the contents of the latest Supplement.

Publication Schedules

| Publication | Publication Date | Official Date |
| :---: | :---: | :---: |
| $1{ }^{\text {st }}$ Supplement | Feb. 2004 | Apr. 1, 2004 |
| PF 30(2) [Mar.-Apr. 2004] | Mar. 2004 | Not Applicable |
| $2^{\text {nd }} I R A$ [published in PF 30(2)] | Mar. 2004 | Apr. 1, 2004 |
| PF 30(3) [May-June 2004] | May 2004* | Not Applicable |
| $3{ }^{\text {rd }}$ IRA [published in PF 30(3)] | May 2004* | June 1, 2004* |
| $2^{\text {nd }}$ Supplement | June 2004* | Aug. 1, $2004{ }^{*}$ |
| PF 30(4) [July-Aug. 2004] | July 2004* | Not Applicable |
| $4^{\text {th }} I R A$ [published in $P F 30(4)$ ] | July 2004* | Aug. 1, 2004* |
| $P F$ 30(5) [Sept.-Oct. 2004] | Sept. 2004* | Not Applicable |
| $5^{\text {th }}$ IRA [published in PF 30(5)] | Sept. 2004* | Oct. 1, 2004* |
| PF 30(6) [Nov.-Dec. 2004] | Nov. 2004* | Not Applicable |
| $6^{\text {th }}$ IRA [published in PF 30(6)] | Nov. 2004* | Dec. 1, 2004* |

* Tentative


## INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

- The list of new USP Reference Standards that have become available
- The list of assays or tests that are adopted but held in abeyance pending availability of required USP Reference Standards
- New adopted (official) revisions to the $U S P-N F$ that become effective before the effective date of the next Supplement or that were not ready for adoption by the closing date for the upcoming Supplement. (The effective date for these revisions is stated on the next page.)

Readers should review this section to determine if they are affected by any of the changes.
Symbols-Interim revisions are shown with new text (if any) enclosed in circles, ${ }^{\bullet}$ new text $\boldsymbol{m}_{\bullet}$. Text enclosed in squares, $\boldsymbol{\square}_{\text {new }}$ text $_{\boldsymbol{\bullet}}$, has already been adopted in a Supplement. Where the symbols appear together with no enclosed text, such as ${ }^{\bullet}$ • or $\boldsymbol{m}^{\boldsymbol{\bullet}} \boldsymbol{\square}$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the $I R A$ or Supplement in which the revision first appeared. For example, $\bullet 2$ indicates that the revision was officially adopted in the Second Interim Revision Announcement, and $\boldsymbol{m}_{2 \mathrm{~S}(\text { USP27) }}$ indicates that the revision was officially adopted in the Second Supplement to USP 27.

Errata-At the end of the Interim Revision Announcement section is a list of errata and corrections to USP 27-NF 22. The page number indicates where the item is found in $U S P-N F$. If necessary, this list will be updated with every issue of $P F$. This information will also be cumulative in the next available Supplement, and will appear in its corrected form in the next annual edition of $U S P-N F$. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.
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# SECOND INTERIM REVISION <br> ANNOUNCEMENT <br> to USP 27 and to NF 22 

By authority of the United States Pharmacopeial Convention, Inc. Prepared by the Council of Experts and published by the Board of Trustees

Larry L. Braden, Chair<br>USP Board of Trustees<br>Roger L. Williams, Executive Vice President and Chairman, USP Council of Experts<br>John W. Gasper, Director, Executive Secretariat

Official April 1, 2004.
Released March 1, 2004.

[^44]
## New USP Reference Standards

The following USP Reference Standards, which were indicated in past Supplements to $U S P-N F$ as being not yet available, have since become available. Thus, the official date of each USP 27 or NF 22 standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list.

USP Allantoin RS (March 1, 2004)
USP Amifostine Disulfide RS (March 1, 2004)
USP Ammonium Chloride RS (March 1, 2004)
USP Aspartame Acesulfame RS (March 1, 2004)
USP Benazepril Hydrochloride RS (July 1, 2004)
USP Benazepril Related Compound A RS (May 1, 2004)
USP Benazepril Related Compound B RS (May 1, 2004)
USP Bupropion Hydrochloride RS (March 1, 2004)
USP Cefpiramide RS (September 1, 2004)
USP Chlorhexidine RS (July 1, 2004)
USP Chlorhexidine Acetate RS (July 1, 2004)
USP Choline Chloride RS (March 1, 2004)
USP Clonazepam Related Compound C RS (July 1, 2004)
USP Clonidine RS (September 1, 2004)
USP Clonidine Related Compound A RS (September 1, 2004)
USP Copovidone RS (March 1, 2004)
USP Cyclandelate RS (September 1, 2004)
USP Desflurane RS (May 1, 2004)
USP Desflurane Related Compound A RS (March 1, 2004)
USP Dextran 40 RS (May 1, 2004)
USP Dextran 70 RS (May 1, 2004)
USP Dolasetron Mesylate RS (July 1, 2004)
USP Dolasetron Mesylate Related Compound A RS (July 1, 2004)
USP Doxazosin Mesylate RS (March 1, 2004)
USP Powdered Eleuthero Extract RS (July 1, 2004)
USP Fenoldopam Mesylate RS (March 1, 2004)
USP Fludarabine RS (September 1, 2004)
USP Flumazenil RS (May 1, 2004)
USP Fluoxetine Related Compound C RS (July 1, 2004)
USP Formononetin RS (March 1, 2004)
USP Fosphenytoin Sodium RS (March 1, 2004)
USP Gadoversetamide RS (March 1, 2004)
USP Gadoversetamide Related Compound A RS (March 1, 2004)
USP Ganciclovir RS (May 1, 2004)
USP Ganciclovir Related Compound A RS (July 1, 2004)
USP Glucosamine Hydrochloride RS (July 1, 2004)
USP Hydrocodone Bitartrate Related Compound A CII RS (March 1, 2004)
USP Isoflurane Related Compound A RS (September 1, 2004)
USP Isoflurane Related Compound B RS (September 1, 2004)
USP Powdered Kava Extract RS (March 1, 2004)
USP Kawain RS (March 1, 2004)
USP Lamivudine RS (July 1, 2004)
USP Loratadine RS (September 1, 2004)
USP Meropenem RS (March 1, 2004)
USP Metformin Hydrochloride RS (March 1, 2004)
USP Metformin Related Compound A RS (March 1, 2004)
USP Metoprolol Related Compound A RS (July 1, 2004)
USP Metoprolol Related Compound B RS (September 1, 2004)
USP Metoprolol Related Compound C RS (September 1, 2004)
USP Metoprolol Related Compound D RS (September 1, 2004)
USP Ondansetron Hydrochloride RS (March 1, 2004)
USP Ondansetron Related Compound A RS (March 1, 2004)
USP Ondansetron Related Compound C RS (March 1, 2004)
USP Ondansetron Related Compound D RS (March 1, 2004)
USP Oxfendazole RS (March 1, 2004)

USP Paclitaxel RS (March 1, 2004)
USP Paclitaxel Related Compound A RS (March 1, 2004)
USP Paclitaxel Related Compound B RS (March 1, 2004)
USP Paroxetine Related Compound D RS (May 1, 2004)
USP Phenytoin Related Compound A RS (March 1, 2004)
USP Phenytoin Related Compound B RS (July 1, 2004)
USP Quinine Hydrochloride Dihydrate RS (March 1, 2004)
USP Powdered Red Clover Extract RS (May 1, 2004)
USP Rimantidine Hydrochloride RS (July 1, 2004)
USP Scopoletin RS (July 1, 2004)
USP Sevoflurane RS (May 1, 2004)
USP Sevoflurane Related Compound A RS (May 1, 2004)
USP Sotalol Hydrochlride RS (July 1, 2004)
USP Sotalol Related Compound A RS (May 1, 2004)
USP Sotalol Related Compound B RS (May 1, 2004)
USP Sotalol Related Compound C RS (May 1, 2004)
USP Stearoyl Polyoxyglycerides RS (May 1, 2004)
USP Sumatriptan RS (March 1, 2004)
USP Sumatriptan Succinate RS (March 1, 2004)
USP Sumatriptan Succinate Related Compound A RS (March 1, 2004)

USP Sumatriptan Succinate Related Compound C RS (March 1, 2004)

USP Terazosin Hydrochloride RS (March 1, 2004)
USP Terazosin Related Compound A RS (March 1, 2004)
USP Terazosin Related Compound B RS (March 1, 2004)
USP Terazosin Related Compound C RS (March 1, 2004)
USP Tiamulin Fumarate RS (July 1, 2004)
USP Tiamulin Related Compound A RS (July 1, 2004)
USP Valsartan Related Compound A RS (March 1, 2004)
USP Valsartan Related Compound C RS (March 1, 2004)
USP Vecuronium Bromide RS (September 1, 2004)
USP Verteporfin RS (March 1, 2004)
USP Verteporfin Related Compound A RS (March 1, 2004)
USP Vinorelbin Related Compound A RS (March 1, 2004)
USP Vinorelbine Tartrate RS (May 1, 2004)
USP Vitexin RS (March 1, 2004)

The official dates of any USP 27 or NF 22 standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards.

[^45]USP Sargramostim RS
USP Sulisobenzone RS
USP $\Delta^{8}$-tetrahydrocannabinol RS
USP $\Delta^{9}$-tetrahydrocannabinol RS
USP Thiacetarsamide RS
USP Tilmicosin RS

USP Tinidazole Related Compound B RS
USP Trenbolone RS
USP Trenbolone Acetate RS
USP Powdered Valerian RS
USP Vasopressin RS

## MONOGRAPHS (USP)

## Glucagon

## Change to read:

Assay-[NOTE-All buffers have a final pH of 7.4, unless otherwise indicated.]

HEPATOCYTE PREPARATION-
Calcium-free perfusion buffer with dextrose-Prepare a solution containing, in each $\mathrm{L}, 7.92 \mathrm{~g}$ of sodium chloride, 0.35 g of potassium chloride, 1.80 g of dextrose, 0.19 g of edetic acid, and 2.38 g of $N$-2-hydroxyethylpiperazine- $N^{\prime}-2$-ethanesulfonic acid. Oxygenate prior to circulation.

Collagenase buffer-Prepare a solution containing, in each L, 3.62 g of sodium chloride, 23.83 g of $N$-2-hydroxyethylpipera-zine- $N^{\prime}$-2-ethanesulfonic acid, 0.35 g of potassium chloride, 0.52 g of calcium chloride, and 1.8 g of dextrose. Adjust to a pH of 7.6, and oxygenate. Immediately before perfusion, dissolve a quantity of collagenase in this solution to obtain a concentration of $0.02 \%$ to $0.05 \%$.

Wash buffer-Prepare a solution containing, in each L, 7.92 g of sodium chloride, 0.35 g of potassium chloride, 0.19 g of edetic acid, 2.38 g of $N$-2-hydroxyethylpiperazine- $N^{\prime}$-2-ethanesulfonic acid, 0.22 g of calcium chloride, and 0.12 g of magnesium sulfate.

Incubation buffer-Prepare a solution containing, in each L, 6.19 g of sodium chloride, 0.35 g of potassium chloride, 0.22 g of calcium chloride, 0.12 g of magnesium sulfate, 0.16 g of monobasic potassium phosphate, 11.915 g of $N$-2-hydroxyethylpipera-zine- $N^{\prime}-2$-ethanesulfonic acid, and $1 \%$ bovine serum albumin (BSA). Adjust to a pH of 7.5 .

Test animals-Male Sprague-Dawley rats are maintained on a standard rat chow diet and freely given water. On the morning of the test, select a healthy rat weighing approximately 300 g , and administer 100 Units of Heparin Sodium subcutaneously.

Procedure - [NOTE-Conduct this procedure in the morning to ensure that the rat has optimal glycogen in its liver.] Anesthetize the rat with an appropriate anesthetic. Open the abdominal cavity, and isolate the portal vein. Insert an angiocatheter connected to a perfusion pump, and tie into the portal vein at the general location of the lienal branch. Start the perfusion ( 25 mL per minute) in situ with Calcium-free perfusion buffer with dextrose, equilibrated with oxygen, at a temperature of $37^{\circ}$. As the liver enlarges, cut the inferior vena cava to allow pressure equilibrium. [NOTE-About 300 mL of the perfusate is needed to clear the liver of red blood cells at a flow rate of 30 to 60 mL per minute.] Then circulate Collagenase buffer at a flow rate of 30 to 60 mL per minute for about $10 \mathrm{~min}-$ utes. The exact concentration of collagenase (within the range of $0.02 \%$ to $0.05 \%$ ) is determined empirically for each lot of enzyme. The concentration of collagenase is that necessary to consistently cause a breakdown of the liver about 10 minutes after initial entry of the Collagenase buffer into the liver. When the liver significantly increases in size, changes color and consistency, and starts to leak perfusate out of the lobes, change the system to the oxygenated prewarmed Wash buffer. About 100 mL of Wash buffer is needed to wash the liver of collagenase at a flow rate of 25 mL per minute. Surgically remove the liver from the animal and place in a prewarmed tray containing oxygenated Wash buffer $\left(37^{\circ}\right)$. Gently comb the liver with a stainless steel, fine-toothed comb to free the hepatocytes. Wash the hepatocytes with Wash buffer, and filter through cheesecloth (or a $150-\mu \mathrm{m}$ mesh polyethylene net) into a plastic beaker. Centrifuge the cell suspension for about 2 minutes at about $25 \times g$ to form a loosely packed pellet. Discard the supernatant, and resuspend the pellet in Wash buffer. Repeat the washing procedure twice for a total of three washes. Resuspend the final pellet in 100 to 200 mL of Incubation buffer depending on cell yield. [NOTE-If the Assay procedure is interrupted, cool the cells by collecting the cells in a beaker placed in ice. The cells are
washed with ice-cold Wash buffer, and stored on ice until ready for use. At that point the cells are pelleted once more, and resuspended in ice-cold Incubation buffer.]
Suitability- The concentrations of cells may vary due to the collagenase activity and the viability of the hepatocytes. To check cell viability and to determine viable cell concentration, dilute duplicate $100-\mu \mathrm{L}$ aliquots of cell suspension with $400 \mu \mathrm{~L}$ of Wash buffer and $500 \mu \mathrm{~L}$ of isotonic $0.4 \%$ trypan blue. The aliquots are counted in a hemocytometer. The cells are suspended in Incubation buffer to obtain a viable cell concentration of not less than $3 \times 10^{6}$ per mL . Count several distinct fields. [NOTE-Viable cells are those cells that exclude the trypan blue.]

NEGATIVE CONTROL SOLUTION-Prepare a solution containing $0.5 \%$ bis(trimethylsilyl)acetamide (BSA) in sterile water.

INCUBATION FLASKS-Use $25-\mathrm{mL}$ conical flasks, the bottoms of which have been heated and pushed inward to form a conically raised center.

STANDARD PREPARATIONS- ${ }^{\bullet}$ In duplicate, dissolve a suitable quantity of USP Glucagon RS, accurately measured, in 0.01 N hydrochloric acid or other suitable diluent to obtain a solution containing 1.0 USP Glucagon Unit per mL. $\bullet 2$ All dilutions thereafter are made using $0.5 \%$ BSA ( $\mathrm{w} / \mathrm{v}$ ) in water. Dilute accurately measured volumes of each solution with Negative control solution to obtain five concentrations-200, 100, 50, 25 and 12.5 micro-Units per $\mathrm{mL}-$ of each solution (Standard preparations). Pipet 0.2 mL of each Standard preparation into separate Incubation flasks. Pipet 0.2 mL of Negative control solution into each of two flasks (Negative control solution 1 and 2). Then add the hepatocytes into each of the twelve flasks.

ASSAY PREPARATIONS-Using accurately weighed quantities of Glucagon, proceed as directed for Standard preparations.

D-GLUCOSE DETERMINATION-
Standard stock solution-Transfer 2.0 g of USP Dextrose RS, accurately weighed, to a $200-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with saturated benzoic solution to volume.

Standard solutions-Transfer suitable quantities of Standard stock solution to three flasks, and dilute with saturated benzoic acid solution to obtain solutions having known concentrations of 0.5 , 1.0 , and 1.5 times the typical sample glucose concentration.

Potassium ferrocyanide solution-Dissolve 1.25 g of trihydrate potassium ferrocyanide in 125 mL of Sterile Water for Injection.

System suitability-Analyze the Potassium ferrocyanide solution, the Standard solutions, and five replicates of the middle Standard solution. Prepare a standard curve using the Standard solutions as directed for Procedure: the relative standard deviation of the standard curve is not more than $2.0 \%$; the response of the Potassium ferrocyanide solution is not more than 30 mg per L; and the relative standard deviation is not more than $2.0 \%$ for the replicate analyses of the middle Standard solution.

PROCEDURE-Dispense 5 mL of Hepatocyte preparation into the special incubation flasks in sequence from high glucagon concentration to low glucagon concentration alternating the Standard preparations with the Assay preparations. The flasks are swirled in an orbiting water bath at 125 rpm at $30^{\circ}$ for approximately 30 to 60 minutes. [NOTE-The exact incubation time must be determined to optimize the signal-to-noise ratio.] Following incubation place 0.5 to $1.0-\mathrm{mL}$ aliquots, in duplicate, from each incubation flask into labeled tubes, and centrifuge at $12,500 \times g$. Determine the percentage of glucose concentration in each flask's supernatant.

To conform to the linear range of the instrument being used, it may be necessary to adjust by dilution each of the preparations. Use a glucose analyzer that has demonstrated appropriate specificity, accuracy, precision, and linear response over the range of concentrations being determined. [NOTE-A suitable analyzer may use an immobilized, oxidase-enzyme membrane or jacket-generating hydrogen peroxide, which is then detected at the electrode.] Perform the glucose analysis in the following sequence: Negative control solution 1, Standard preparations, Assay preparations, and Negative control solution 2. Determine the percentage of glucose against the Negative control solution for each preparation.

CALCULATIONS-
Linearity test-Use an analysis of variance (ANOVA) with one sample assayed against a standard, and using two replicates each, construct a table (see Table 1). Compare the value of the ratio MSNL/MSRES ${ }_{1}$ to a critical value obtained from a table for an $F$ distribution with $m-2$ and $3 m-3$ degrees of freedom where $m$ is the number of dose levels for each preparation. If the ratio MSNL/MSRES does not indicate the presence of significant nonlinearity (ratio value is lower than the critical value), then proceed to the test for parallelism. If the ratio exceeds the critical value (significance level of 0.05 ), the nonlinearity is statistically significant and the test is repeated, discarding the results from either the highest or lowest dose of both the Standard preparations and the Assay preparations (four dose levels). If the ratio MSNL/MSRES does not indicate the presence of significant nonlinearity, then proceed to the test for parallelism.

Parallelism test-Compare the ratio MSNP/MSRES 2 to a critical value obtained from an $F$ distribution having 1 and $4 m-5$ degrees of freedom. If the ratio MSNP/MSRES ${ }_{2}$ does not indicate the presence of significant nonparallelism, then the assay is considered valid. Use the appropriate dose levels for the estimation of the relative potency.

Relative potency-Calculate the relative potency, $R$, of the Assay preparations as compared to the Standard preparations as follows.
(1) $X_{j}$ is defined as the $\log _{10}$ of the $j^{\text {th }}$ dose of the Standard preparations or the Assay preparations. The glucagon dose varies from 12.5 to $200 \times 10^{-6}$ USP Glucagon Units per mL. For ease in the subsequent calculations, these doses are respectively represented by 1 through 5 as shown in the table below.

| $j$ | 1 | 2 | 3 | 4 | 5 |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Dose | 12.5 | 25 | 50 | 100 | 200 |
| $X_{j}$ | 1.10 | 1.40 | 1.70 | 2.00 | 2.30 |

(2) To differentiate between the Standard preparations and the Assay preparations in the calculations, the subscript " $i$ " will be used with $i=1$ to designate the Standard preparations and $i=2$ to designate the Assay preparations. $Y_{i j k}$ will denote the glucose concentration associated with the $k^{\text {th }}$ replicate of the $j^{\text {th }}$ dose of the $i^{\text {th }}$ preparation. For example, $Y_{l j}$ is the glucose concentration associated with the $k^{\text {th }}$ replicate of the $j^{\text {th }}$ dose of the appropriate Standard preparation; $Y_{11 k}$ is the glucose concentration associated with the $k^{\text {th }}$ replicate of dose 1 of the Standard preparation and $Y_{21 k}$ would denote the glucose concentration associated with the $k^{\text {th }}$ replicate of dose 1 of the Assay preparation. Dose 1 represents a glucose dose of $12.5 \times 10^{-6}$ USP Glucagon Units per mL. Finally, $Y_{132}$ would represent the glucose concentration associated with the $2^{\text {nd }}$ replicate of dose 3 for the Standard preparation.
(3) $Y_{S}$ and $Y_{t}$ denote the average glucose concentrations for the Standard preparations and the Assay preparations, respectively.
(4) Calculate the least-squares slope estimate, $b$, for a linear regression relating the $Y_{i j k}$ 's to the $X_{j}$ 's as follows: $b=S_{x y} / S_{x x}$ with $S_{x y}$ and $S_{x x}$ calculated using the equations in Table 2.
(5) The $\log$ potency, $M$, is calculated using $M=-1\left[\left(Y_{S^{-}} Y_{t}\right) / b\right]$.
(6) $R=\operatorname{antilog}(M)$.
(7) Calculate the confidence limits (upper and lower) for the relative potency, $R$, using the value $s^{2}=\mathrm{MSRES}_{3}$ (see Table 1 and Table 2) as follows. Obtain $t$ from a table for a $t$ distribution having $4 m-4$ degrees of freedom. For the $95 \%$ limits, the $t$ values can be obtained from Table 9 under Design and Analysis of Biological Assays $\langle 111\rangle$.

NOTE-For confidence limits having other probability levels (i.e., $100(1-\mathrm{a}) \%$ ), the right tail $t$ critical value having a/2 area to its right is used.

Calculate $g=t^{2} S^{2} / b^{2} S_{x x}$

$$
\text { and } F=(t s / b) \sqrt{(1 / m)(1-g)+\left(M^{2} / S_{x x}\right)}
$$

and calculate

$$
M_{L}=(M-F) /(1-g)
$$

and

$$
M_{U}=(M+F) /(1-g)
$$

where $M$ is the $\log$ potency and $M_{L}$ and $M_{U}$ are the $\log$ potency lower and upper confidence limits. The lower and upper confidence limits for the relative potency, $R$, are given by

$$
R L=\operatorname{antilog}\left(M_{L}\right)
$$

$$
R U=\operatorname{antilog}\left(M_{U}\right)
$$

It meets the requirements if the potency is between 0.8 to 1.25 USP Glucagon Units per mg , and the confidence interval width at $P=$ 0.95 does not exceed $45 \%$ of the computed potency.

Table 1. ANOVA for the Rat Hepatocyte Assay for Glucagon

| Source | Degrees of <br> Freedom | SS (Sum of <br> Squares) | MS (Mean <br> Square) |
| :--- | :---: | :---: | :---: |
| Preparations | 1 | SSPREP | MSPREP |
| Replicates | 1 | SSREP | MSREP |
| Linear Slope | 1 | SSLIN | MSLIN |
| Residual $_{3}$ | $4 m-4$ | SSRES $_{3}$ | MSRES $_{3}$ |
| Nonparallelism $_{\text {Residual }_{2}}$ | 1 | SSNP $_{2}$ | MSNP |
| Nonlinearity $_{\text {Residual }_{1}}$ | $m-5$ | SSRES $_{2}$ | MSRES $_{2}$ |
| TOTAL $^{2 m-2}$ | SSNL $_{1}$ | MSNL $_{1}$ |  |

NOTES-This analysis pertains to one sample assayed against a standard, using two replicates each.

The number of dose levels for each preparation is denoted by $m$. Table 2 gives the equations for calculating the SS terms. In each row of the ANOVA table, the MS is obtained by dividing the SS term by the degrees of freedom.

Table 2. Equations for Calculating the Sums of Squares in the Analysis of Variance*

$$
\begin{aligned}
& \mathrm{Y}_{\mathrm{i} .}=\sum_{\mathrm{j} k} \mathrm{y}_{\mathrm{ijk}} \\
& Y_{j}=\sum \sum y_{i k} \\
& Y_{k}=\sum_{i j} y_{i j k} \\
& C F=\frac{\left(\sum \sum_{\mathrm{ijk}} \sum \mathrm{y}_{\mathrm{ijk}}\right)^{2}}{4 \mathrm{~m}} \\
& S_{x y}^{s}=\sum_{j k} x_{j_{j} y_{j k}}-\frac{\left(\sum_{j} x_{j}\right)\left(Y_{1 . .}\right)}{m} \\
& S_{x y}^{T}=\sum_{j k} x_{j} y_{2 j k}-\frac{\left(\sum_{j} x_{j}\right)\left(Y_{2}\right)}{m} \\
& S_{x y}=S_{x y}^{s}+S_{x y}^{\top} \\
& S_{x x}^{s}=2 \sum_{j} x_{j}^{2}-\frac{2\left(\sum_{j} x_{j}\right)^{2}}{m} \\
& S_{x x}^{\top}=S_{x x}^{s} \\
& S_{\mathrm{xx}}=S_{\mathrm{xx}}^{\mathrm{s}}+\mathrm{S}_{\mathrm{xx}}^{\top}
\end{aligned}
$$

## Lithium Carbonate Extended-Release Tablets

## Change to read:

## Drug release $\langle 724\rangle$ -

TEST 1-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 1.

Medium: dilute hydrochloric acid (7 in 1000); 800 mL .
Apparatus 1: 100 rpm .
Times: $15,45,90$, and 120 minutes.
Procedure-At each Time, withdraw 8.0 mL of the solution under test, and pass through a filter having a $35-\mu \mathrm{m}$ or finer porosity. Using the filtrate as the Assay preparation, suitably diluted with Dissolution Medium if necessary, and using Dissolution Medium to prepare the Standard preparation, determine the amount of $\mathrm{Li}_{2} \mathrm{CO}_{3}$ dissolved by employing a flame photometer, as directed in the Assay.
Tolerances-The percentages of the labeled amount of $\mathrm{Li}_{2} \mathrm{CO}_{3}$ dissolved at the specified times conform to Acceptance Table 1.

| Time (minutes) | Amount dissolved |
| :---: | :--- |
| 15 | between $2 \%$ and $16 \%$ |
| 45 | between $25 \%$ and $45 \%$ |
| 90 | between $60 \%$ and $85 \%$ |
| 120 | not less than $85 \%$ |

TEST 2-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 2.

Apparatus and Procedure-Proceed as directed for Test 1.
Medium: water; 900 mL .
Times: 1,3 , and 7 hours.
Tolerances-The percentages of the labeled amount of $\mathrm{Li}_{2} \mathrm{CO}_{3}$ dissolved at the specified times conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | not more than $40 \%$ |
| 3 | between $45 \%$ and $75 \%$ |
| 7 | not less than $70 \%$ |

TEST 3-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 3.

Medium: water; 250 mL .
Apparatus 3: 6 dips per minute, 20 -mesh top screen and 100 mesh bottom screen.

Procedure-Proceed as directed for Test 1.
Times and Tolerances-The percentages of the labeled amount of $\mathrm{Li}_{2} \mathrm{CO}_{3}$ dissolved at the specified times conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $10 \%$ and $45 \%$ |
| 2 | between $25 \%$ and $75 \%$ |
| 6 | not less than $70 \%$ |

${ }^{\bullet}$ TEST 4-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 4.

Medium, Apparatus, Times, and Procedure-Proceed as directed for Test 1 .

[^46]Tolerances-The percentages of the labeled amount of $\mathrm{Li}_{2} \mathrm{CO}_{3}$ dissolved at the specified times conform to Acceptance Table 1.

| Time (minutes) | Amount dissolved |
| :---: | :--- |
| 15 | between $2 \%$ and $16 \%$ |
| 45 | between $25 \%$ and $45 \%$ |
| 90 | between $60 \%$ and $85 \%$ |
| 120 | not less than $80 \%$ |

## Loratadine Oral Solution

## Change to read:

Packaging and storage-Preserve in tight containers, and store between $2^{\circ}$ and ${ }^{\circ} 25^{\circ} \cdot{ }^{\circ}$

## Mephobarbital Tablets

## Delete the following:

${ }^{\bullet}$ Dissolution $\langle 711\rangle$ -
Medium: pH 6.8 phosphate buffer (see under Buffer Solutions in the section Reagents, Indicators, and Solutions); 900 mL .

Apparatus 2: 75 rpm .
Time: 75 minutes.
Procedure-Determine the amount of $\mathrm{C}_{13} \mathrm{H}_{14} \mathrm{~N}_{2} \mathrm{O}_{3}$ dissolved by employing UV absorption at the wavelenth of maximum absorbance at about 242 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, in comparison with a Standard solution having a known concentration of USP Mephobarbital RS in the same Medium.

Tolerances-Not less than $70 \%(Q)$ of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{14} \mathrm{~N}_{2} \mathrm{O}_{3}$ is dissolved in 75 minutes. $\bullet 2$

## Nalidixic Acid Oral Suspension

## Change to read:

Assay-
Mobile phase-Prepare a solution of 784 mg of dibasic potassium phosphate in 325 mL of water. To this solution add a solution of 2.62 g of hexadecyltrimethylammonium bromide in 350 mL of methanol. To the combined solution add ${ }^{\bullet} 325 \mathrm{~mL}_{\bullet 2}$ of methanol, mix, filter, and degas. This solution has an apparent pH of about 10. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard solution-Prepare a solution of sulfanilic acid in Mobile phase containing about 0.8 mg per mL .

Standard preparation - Prepare a solution having a known concentration of about 0.18 mg per mL of USP Nalidixic Acid RS in methanol. Transfer 5.0 mL of this solution and 1.0 mL of Internal standard solution to a $25-\mathrm{mL}$ volumetric flask, dilute with methanol to volume, and mix.

Assay preparation-Transfer an accurately measured volume of freshly mixed Oral Suspension, equivalent to about 150 mg of nalidixic acid, to a $500-\mathrm{mL}$ volumetric flask, add about 400 mL of methanol, and sonicate for about 30 minutes. Shake by mechanical means for about 30 minutes, sonicate again for about 30 minutes, dilute with methanol to volume, mix, and filter. Transfer 3.0 mL of the clear filtrate and 1.0 mL of Internal standard solution to a 25 mL volumetric flask, dilute with methanol to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for sulfanilic acid and 1.0 for nalidixic acid; the resolution, $R$, between sulfanilic acid and nalidixic acid is not less than 1 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{12} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{3}$ in each mL of the Oral Suspension taken by the formula:

$$
(12,500 / 3)(C / V)\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Nalidixic Acid RS in the Standard preparation; $V$ is the volume, in mL , of Oral Suspension taken to prepare the Assay preparation; and $R_{U}$ and $R_{S}$ are the ratios of the peak areas for nalidixic acid and sulfanilic acid in the chromatograms obtained from the Assay preparation and the Standard preparation, respectively.

## Vitamin A

## Change to read:

## Identification-

A: To 1 mL of a chloroform solution of it containing the equivalent of approximately $6 \mu \mathrm{~g}$ of retinol, add 10 mL of antimony trichloride TS: a transient blue color appears at once.

B: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ Test solution-
FOR LIQUID FORM OF VITAMIN A-Dissolve a volume equivalent to about 15,000 USP Units in chloroform to obtain 10 mL of solution.

FOR SOLID FORM OF VITAMIN A-Weigh a quantity equivalent to about 15,000 USP Units, place in a separator, add 75 mL of water, shake vigorously for 1 minute, extract with 10 mL of chloroform by shaking for 1 minute, and centrifuge to clarify the chloroform extract.

Standard solution-Dissolve the contents of $1^{\bullet}$ ampul $_{\bullet 2}$ of USP Vitamin A RS in chloroform to obtain 25.0 mL .

Developing solvent system: a mixture of cyclohexane and ether (4:1).

Procedure-Apply at the starting point of the chromatogram 0.015 mL of the Standard solution and 0.01 mL of the Test solution, and proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$. Allow the solvent front to move a distance of 10 cm , remove the plate, and air dry. Spray with phosphomolybdic acid TS: the blue-green spot formed is indicative of the presence of retinol. The approximate $R_{F}$ values of the predominant spots, corresponding to the different forms of retinol, are 0.1 for the alcohol form, 0.45 for the acetate, and 0.7 for the palmitate.

## GENERAL CHAPTERS

## General Tests and Assays

## General Requirements for Tests and Assays

## 〈11〉 USP REFERENCE STANDARDS

## Add the following:

${ }^{\bullet}$ USP Ammonium Chloride RS——Dry over silica gel for 4 hours. This material is hygroscopic. Keep container tightly closed. Store at room temperature. $\bullet 2$

## Change to read:

USP Cefpiramide RS-- Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. Store in a freezer. $\bullet 2$

## Change to read:

USP 4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid RS-- (NAME CHANGE) See USP Chlorthalidone Related Compound $A R S . \bullet 2$

## Add the following:

${ }^{\bullet}$ USP Chlorthalidone Related Compound A RS——Do not dry. Keep container tightly closed. Store in a desiccator. $\bullet 2$

Change to read:
${ }^{\mathbf{4}}$ USP Clonidine RS-- Do not dry before using.e2 Keep container tightly closed. Protect from light. $\triangle U S P 27$

## Change to read:

USP Enalapril Maleate RS-- Do not dry. $\bullet 2$ Keep container tightly closed.

## Change to read:

USP Fentanyl Citrate RS-- Do not dry before using.@2 Keep container tightly closed. Protect from light.

## Change to read:

${ }^{\boldsymbol{A}}$ USP Fluoxetine Related Compound C RS [ $N$-Methyl- $N-[3-$ phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-succinamic acid] $\left(\mathrm{C}_{21} \mathrm{H}_{22} \mathrm{~F}_{3} \mathrm{NO}_{4} \diamond 409.40\right)$ - $\quad$ USP27 ${ }^{\circ}$ Do not dry. Keep container tightly closed. Protect from light.e2

## Change to read:

USP Hydroxypropyl Methylcellulose RS——(NAME CHANGE) See USP Hypromellose RS. $\bullet 2$

## Add the following:

${ }^{\bullet}$ USP Hypromellose RS-Dry portion at $105^{\circ}$ for 2 hours before using. Keep container tightly closed. This material is hygroscopic. 22

## Change to read:

USP Isoflurane Related Compound B RS [2,2,2-trifluoroethyldifluoromethyl ether] $\left(\mathrm{C}_{3} \mathrm{H}_{3} \mathrm{~F}_{5} \mathrm{O} \diamond 150.05\right)$ - Do not dry before using. Keep container tightly closed. Protect from light. [Cau-tion-Extremely volatile liquid. Cool contents before opening ampul.] ${ }_{\bullet 2}$

## Change to read:

-USP Loratadine RS ${ }_{\mathbf{1 S}\left(U S P^{277}\right)}{ }^{\bullet}$ Do not dry. Keep container tightly closed. Protect from light. ${ }^{2}$

## Change to read:

USP Metoprolol Related Compound B RS [ $\pm$ )1-chloro-2-hy-droxy-3-[4-(2-methoxyethyl)phenoxy]-propane] $\left(\mathrm{C}_{12} \mathrm{H}_{17} \mathrm{ClO}_{3} \diamond\right.$ 244.71)-Do not dry. Keep container tightly closed. Protect from light. ${ }^{\circ}$ Store in a freezer. ${ }^{2}$

## Change to read:

USP Metoprolol Related Compound C RS [( $\pm$ )4-[2-Hydroxy-3-(1-methylethyl)aminopropoxy]benzaldehyde] $\left(\mathrm{C}_{13} \mathrm{H}_{19} \mathrm{NO}_{3} \diamond\right.$ 237.29)-Do not dry. Keep container tightly closed. Protect from light. ${ }^{\circ}$ Store in a freezer. ${ }^{\circ}$

## Change to read:

USP Metoprolol Related Compound D RS [( $\pm$ ) N,N-bis[2-hy-droxy-3-[4-(2-methoxyethyl)phenoxy]propyl](1methylethyl)amine] $\left(\mathrm{C}_{27} \mathrm{H}_{41} \mathrm{NO}_{6} \diamond 475.62\right)$-Do not dry. Keep container tightly closed. Protect from light. ${ }^{\circ}$ Store in a freezer. $\bullet 2$

## Change to read:

USP Saccharin RS-- Do not dry ${ }_{\bullet 2}$ Keep container tightly closed.

## Change to read:

USP Sotalol Hydrochloride RS-- Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator. $\bullet 2$

## Change to read:

USP Sotalol Hydrochloride Related Compound A RS [ $N[(4-$ [[(1-methylethyl)amino]acetyl]phenyl]methanesulfonamide monohydrochloride] $\left(\mathrm{C}_{12} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{~S} \cdot \mathrm{HCl} \diamond 306.81\right)$ - Do not dry. Keep container tightly closed. Store in a refrigerator. $\bullet 2$

## Change to read:

USP Sotalol Hydrochloride Related Compound B RS [ $N$-(4formylphenyl)methanesulfonamidel $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{3} \mathrm{~S} \diamond 199.23\right)$ ${ }^{\bullet}$ Do not dry. Keep container tightly closed. Store in a refrigerator. $\bullet_{2}$

## Change to read:

USP Sotalol Hydrochloride Related Compound C RS [ $N$-[4-[2-[(1-methylethyl)amino]ethyl]phenyl]methanesulfonamide monohydrochloride] $\left(\mathrm{C}_{12} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{O}_{2} \mathrm{~S} \cdot \mathrm{HCl} \diamond 292.83\right)$ - ${ }^{\circ}$ Do not dry. Keep container tightly closed. Store in a refrigerator. $\bullet 2$

## Change to read:

USP Sulfinpyrazone RS- ${ }^{\bullet}$ Do not dry. Keep container tightly closed. $\bullet 2$

## Change to read:

USP Tolnaftate RS-Dry portion in vacuum at $65^{\circ}$ for 3 hours before using. Keep container tightly closed. ${ }^{\circ}$ Store in a refrigerator. $\bullet 2$

## ERRATA

Following is a list of errata and corrections to USP 27-NF 22. The page number indicates where the item is found in USP 27-NF 22. If necessary, this list will be updated with every issue of $P F$. This information will also be available as a cumulative table in the next available Supplement and will appear in its corrected form in the next annual edition of $U S P-N F$. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff are available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

| Page | Title | Section | Description |
| :--- | :--- | :--- | :--- |
| 256 | Bisoprolol Fumarate | Specific rotation | Change "between $-0.2^{\circ}$ and $+0.2^{\circ}$ " to: $-2^{\circ}$ and $+2^{\circ}$ |
| 387 | Cefuroxime Axetil for Oral <br> Suspension | Dissolution | Line 3 under Medium: Change "dibasic <br> sodium phosphate" to: anhydrous dibasic sodium phos- <br> phate |
| 2373 | $\langle 811\rangle$ Powder Fineness | Classification of Powder | Line 13: Change "of $850-80 \mu \mathrm{~m}$. " to : of $850-1180 \mu \mathrm{~m}$. |
| 2658 | Reagents, Indicators, and | Introduction | Line 7 under Water: reinsert the new text made <br> official in First Supplement to USP 26, which appears <br> Solutions |
|  |  | after: "from the atmosphere." to read:, or purified water <br> which has a resistivity of not less than 18 Mohm-cm. |  |

## IN-PROCESS REVISION

This section contains proposals for adoption as official USP or NF standards (either proposed new standards or proposed revisions of current $U S P$ or $N F$ standards). These may be any of the following: (1) items that previously appeared under Pharmacopeial Previews and are now formally proposed as revisions; (2) proposed revisions placed directly under In-Process Revision; or (3) modifications of revisions previously proposed under In-Process Revision. Readers should review material in this section and provide comments to the staff liaison (use the Staff Directory to find the contact information). Information on how to comment is found in the Policies and Announcements section. It is important to send comments promptly so that the Committee members can consider readers' input as they are deciding whether to advance standards to official status.

Briefings Each Proposal is preceded by a Briefing in the following format:

## BRIEFING

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being proposed, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see How to Use $P F$ ), the name of the scientific staff liaison who handled the particular issue, and the USP tracking correspondence number, as shown in the example below:
(PA5: K. Russo) RTS-55678-1

Symbols Proposed revisions are shown with language proposed for deletion or replacement crossed off. New text (if any) follows, and is enclosed in symbols and set off from the current official text by a paragraph break and by larger type, thus:

- new text.
if slated for an Interim Revision Announcement to USP 27-NF 22 (IRA), thus:
${ }^{\Delta_{n e w}}$ text $_{\mathbf{\Delta U S P 2 8}}$
if slated for $U S P 28-N F 23$, and thus:
-new text.
if slated for a Supplement to $U S P-N F$. The same symbols not set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as ${ }^{\bullet}$ 。 or $\boldsymbol{\bullet}^{\boldsymbol{n}}$ or $^{\boldsymbol{\Delta}}$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular IRA or Supplement or indicates the USP or NF as the publication where the revision will appear if approved. For example, $\bullet 2$ indicates that the revision is proposed for the Second Interim Revision Announcement, and $\boldsymbol{n}_{2 S}$ (USP 27) indicates that the proposed revision is slated for the Second Supplement to USP 27, and $\Delta_{\Delta S P 28}$ and $\Delta_{\Delta F 23}$ indicate that the revisions are proposed for USP 28 and $N F 23$, respectively.

Official Title Changes Where the specification "Monograph title change" is found, it indicates that the official title stated after that specification will be substituted for the former title in the appropriate places throughout that monograph once this revision becomes official.
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## Briefing

General Notices and Requirements, $U S P 27$ page 3 and page 1823 of $P F 29(6)$ [Nov.-Dec. 2003]. It is proposed to include in the Labeling section of Preservation, Packaging, Storage, and Labeling a warning statement to be applied to the label of all herbs or botanicals intended for use as a dietary supplement.
(DSI: J. Salguero) RTS-40895-1

## Change to read:

## SIGNIFICANT FIGURES AND TOLERANCES

Where limits are expressed numerically herein, the upper and lower limits of a range include the two values themselves and all intermediate values, but no values outside the limits. The limits expressed in monograph definitions and tests, regardless of whether the values are expressed as percentages or as absolute numbers, are considered significant to the last digit shown.

Equivalence Statements in Titrimetric Procedures-The directions for titrimetric procedures conclude with a statement of the weight of the analyte that is equivalent to each mL of the standardized titrant. In such an equivalence statement, it is to be understood that the number of significant figures in the concentration of the titrant corresponds to the number of significant figures in the weight of the analyte. Blank corrections are to be made for all titrimetric assays where appropriate (see Titrimetry $\langle 541\rangle$ ).

Tolerances-The limits specified in the monographs for Pharmacopeial articles are established with a view to the use of these articles as drugs, nutritional or dietary supplements, or devices, except where it is indicated otherwise. The use of the molecular formula for the active ingredient(s) named in defining the required strength of a Pharmacopeial article is intended to designate the chemical entity or entities, as given in the complete chemical name of the article, having absolute ( 100 percent) purity.

A dosage form shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label. The tolerances and limits stated in the definitions in the monographs for Pharmacopeial articles allow for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions. Where the minimum amount of a substance present in a nutritional or dietary supplement is required to be higher than the lower tolerance limit allowed for in the monograph because of applicable legal requirements, then the upper tolerance limit contained in the monograph shall be increased by a corresponding amount.

The specified tolerances are based upon such attributes of quality as might be expected to characterize an article produced from suitable raw materials under recognized principles of good manufacturing practice.

The existence of compendial limits or tolerances does not constitute a basis for a claim that an official substance that more nearly approaches 100 percent purity "exceeds" the Pharmacopeial quality. Similarly, the fact that an article has been prepared to closer tolerances than those specified in the monograph does not constitute a basis for a claim that the article "exceeds" the Pharmacopeial requirements.

Interpretation of Requirements-Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated limits to determine whether there is conformance with compendial assay or test requirements. The ob-
served or calculated values usually will contain more significant figures than there are in the stated limit, and an observed or ealeut tated
$■_{\text {a reportable }}^{\mathbf{m}_{2 S}(U S P 27)}$ result is to be rounded off to the number of places that is in agreement with the limit expression by the following procedure. [NOTE-Limits, which are fixed numbers, are not rounded off.]
-Intermediate calculations (e.g., slope for linearity in Validation of Compendial Methods $\langle 1225\rangle$ ) may be rounded for reporting purposes, but the original value (not rounded) should be used for any additional required calculations. Rounding off should not be done until the final calculations for the reportable value have been completed. [NOTE-Limits, which are fixed numbers, are not rounded off.]

A reportable value is often a summary value for several individual determinations. It is the end result of a completed measurement method, as documented. It is the value compared with the acceptance criterion. In most cases, the reportable value is used as documentation for internal or external
users.m2S (USP27)
When rounding off is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5 , it is eliminated and the preceding digit is unchanged. If this digit is greater than 5 , it is eliminated and the preceding digit is increased by one. If this digit equals 5 , the 5 is eliminated and the preceding digit is increased by one.

| Illustration of Rounding Numerical Values <br> for Comparison with Requirements |  |  |  |
| :---: | :---: | :---: | :---: |
| Compendial | Unrounded | Rounded |  |
| Requirement | Value | Result | Conforms |
| Assay limit $\geq 98.0 \%$ | $97.96 \%$ | $98.0 \%$ | Yes |
|  | $97.92 \%$ | $97.9 \%$ | No |
|  | $97.95 \%$ | $98.0 \%$ | Yes |
| Assay limit $\leq 101.5 \%$ | $101.55 \%$ | $101.6 \%$ | No |
|  | $101.46 \%$ | $101.5 \%$ | Yes |
|  | $101.45 \%$ | $101.5 \%$ | Yes |
| Limit test $\leq 0.02 \%$ | $0.025 \%$ | $0.03 \%$ | No |
|  | $0.015 \%$ | $0.02 \%$ | Yes |
|  | $0.027 \%$ | $0.03 \%$ | No |
| Limit test $\leq 3 \mathrm{ppm}$ | $0.00035 \%$ | $0.0004 \%$ | No |
|  | $0.00025 \%$ | $0.0003 \%$ | Yes |
|  | $0.00028 \%$ | $0.0003 \%$ | Yes |

## Change to read:

## GENERAL CHAPTERS

Each general chapter is assigned a number that appears in brackets adjacent to the chapter name (e.g., $\langle 621\rangle$ Chromatography). General chapters that inelude general requirements for tests and assays are numbered frem $\langle 1\rangle$ to $\langle 999\rangle$, chapters that are informa tional are numbered from $\langle 1000$ ) to $\langle 1999$ ), and chapters pertaining to nutritional supplements are numbered above- $\langle\mathcal{Z 0 0 \theta})$ :
－Articles recognized in this compendia must comply with the official standards and tests and assays in the General No－ tices，relevant monographs，and General Chapters numbered below 1000．General Chapters numbered above 1000 are considered to be interpretive and are intended to provide in－ formation on，give definition to，or describe a particular sub－ ject．They contain no official standards，tests，assays，or other mandatory requirements applicable to any pharmaco－ peial article unless specifically referenced in a monograph
or elsewhere in the Pharmacopeia．m2S（USP27）
The use of the general chapter numbers is encouraged for the identification and rapid access to general tests and information．It is especially helpful where monograph section headings and chap－ ter names are not the same（e．g．，Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ in a monograph refers to method $\langle 197 \mathrm{U}\rangle$ under general tests chapter〈197〉Spectrophotometric Identification Tests；Specific rotation $\langle 781 \mathrm{~S}\rangle$ in a monograph refers to method $\langle 781 \mathrm{~S}\rangle$ under general tests chapter $\langle 781\rangle$ Optical Rotation；and Calcium $\langle 191\rangle$ in a mono－ graph refers to the tests for Calcium under general tests chapter〈191〉 Identification Tests－General）．

## Change to read：

## TESTS AND ASSAYS

Apparatus－A specification for a definite size or type of con－ tainer or apparatus in a test or assay is given solely as a recommen－ dation．Where volumetric flasks or other exact measuring， weighing，or sorting devices are specified，this or other equipment of at least equivalent accuracy shall be employed．（See also Ther－ mometers $\langle 21\rangle$ ，Volumetric Apparatus $\langle 31\rangle$ ，and Weights and Bal－ ances $\langle 41\rangle$ ．）Where low－actinic or light－resistant containers are specified，clear containers that have been rendered opaque by ap－ plication of a suitable coating or wrapping may be used．

Where an instrument for physical measurement，such as a spec－ trophotometer，is specified in a test or assay by its distinctive name， another instrument of equivalent or greater sensitivity and accuracy may be used．In order to obtain solutions having concentrations that are adaptable to the working range of the instrument being used，solutions of proportionately higher or lower concentrations may be prepared according to the solvents and proportions thereof that are specified for the procedure．

Where a particular brand or source of a material，instrument，or piece of equipment，or the name and address of a manufacturer or distributor，is mentioned（ordinarily in a footnote），this identifica－ tion is furnished solely for informational purposes as a matter of convenience，without implication of approval，endorsement，or cer－ tification．Items capable of equal or better performance may be used if these characteristics have been validated．

Where the use of a centrifuge is indicated，unless otherwise spe－ cified，the directions are predicated upon the use of apparatus hav－ ing an effective radius of about 20 cm （ 8 inches）and driven at a speed sufficient to clarify the supernatant layer within 15 minutes．

Unless otherwise specified，for chromatographic tubes and col－ umns the diameter specified refers to internal diameter（ID）；for other types of tubes and tubing the diameter specified refers to out－ side diameter（OD）．

Steam Bath－Where the use of a steam bath is directed，exposure to actively flowing steam or to another form of regulated heat，cor－ responding in temperature to that of flowing steam，may be used．

Water Bath－Where the use of a water bath is directed without qualification with respect to temperature，a bath of vigorously boil－ ing water is intended．

Foreign Substances and Impurities－Tests for the presence of foreign substances and impurities are provided to limit such sub－ stances to amounts that are unobjectionable under conditions in which the article is customarily employed（see also Impurities in Official Articles $\langle 1086\rangle$ ）．

While one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity，strength，quality， and purity，it is manifestly impossible to include in each mono－ graph a test for every impurity，contaminant，or adulterant that might be present，including microbial contamination．These may arise from a change in the source of material or from a change in the processing，or may be introduced from extraneous sources． Tests suitable for detecting such occurrences，the presence of which is inconsistent with applicable good manufacturing practice or good pharmaceutical practice，should be employed in addition to the tests provided in the individual monograph．

Other Impurities－Official substances may be obtained from more than one process，and thus may contain impurities not con－ sidered during preparation of monograph assays or tests．Wherever a monograph includes a chromatographic assay or purity test based on chromatography，other than a test for erganic volatile impuri－ ties，
■residual solvents $_{\text {пn }_{2 S}}$（USP27）
and that monograph does not detect such an impurity，solvents ex－ cepted，the impurity shall have its amount and identity，where both are known，stated under the heading Other Impurity（ies）by the la－ beling（certificate of analysis）of the official substance．

The presence of any unlabeled impurity in an official substance is a variance from the standard if the content is $0.1 \%$ or greater． Tests suitable for detection and quantitating unlabeled impurities， when present as the result of process change or other identifiable， consistent occurrence，shall be submitted to the USP for inclusion in the individual monograph．Otherwise，the impurity shall be identified，preferably by name，and the amount listed under the heading Other Impurity（ies）in the labeling（certificate of analysis） of the official substance．The sum of all Other Impurities combined with the monograph－detected impurities does not exceed $2.0 \%$（see Ordinary Impurities $\langle 466\rangle$ ），unless otherwise stated in the mono－ graph．

Categories of drug substances excluded from Other Impurities requirements are fermentation products and semi－synthetics de－ rived therefrom，radiopharmaceuticals，biologics，biotechnology－ derived products，peptides，herbals，and crude products of animal or plant origin．Any substance known to be toxic must not be listed under Other Impurities．

■Residual Solvents－The requirements are stated in Or － ganic Volatile Impurities $\langle 467\rangle$ together with information in Impurities in Official Articles $\langle 1086\rangle$ ．Thus all drug sub－ stances，excipients，and products are subject to relevant con－ trol of residual solvents，even when no test is specified in the individual monograph．The requirements have been aligned with the ICH guideline on this topic．If solvents are used during production，they are of suitable quality．In addition， the toxicity and residual level of each solvent are taken into consideration，and the solvents are limited according to the
principles defined and the requirements specified in Organic Volatile Impurities $\langle 467\rangle$, using the general methods presented therein or other suitable methods.m2S (USP27)

Procedures-Assay and test procedures are provided for determining compliance with the Pharmacopeial standards of identity, strength, quality, and purity.

In performing the assay or test procedures in this Pharmacopeia, it is expected that safe laboratory practices will be followed. This includes the utilization of precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures utilized. Prior to undertaking any assay or procedure described in this Pharmacopeia, the individual should be aware of the hazards associated with the chemicals and the procedures and means of protecting against them. This Pharmacopeia is not designed to describe such hazards or protective measures.

Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing process validation studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards.

Automated procedures employing the same basic chemistry as those assay and test procedures given in the monograph are recognized as being equivalent in their suitability for determining compliance. Conversely, where an automated procedure is given in the monograph, manual procedures employing the same basic chemistry are recognized as being equivalent in their suitability for determining compliance. Compliance may be determined also by the use of alternative methods, chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances. Such alternative or automated procedures or methods shall be validated. However, Pharmacopeial standards and procedures are interrelated; therefore, where a difference appears or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

In the performance of assay or test procedures, not fewer than the specified number of dosage units should be taken for analysis. Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards may be taken, provided the measurement is made with at least equivalent accuracy and provided that any subsequent steps, such as dilutions, are adjusted accordingly to yield concentrations equivalent to those specified and are made in such manner as to provide at least equivalent accuracy. To minimize environmental impact or contact with hazardous materials, apparatus and chemicals specified in Pharmacopeial procedures also may be proportionally changed.

Where it is directed in an assay or a test that a certain quantity of substance or a counted number of dosage units is to be examined, the specified quantity or number is a minimal figure (the singlet determination) chosen only for convenience of analytical manipulation; it is not intended to restrict the total quantity of substance or number of units that may be subjected to the assay or test or that should be tested in accordance with good manufacturing practices.

Where it is directed in the assay of Tablets to "weigh and finely powder not fewer than" a given number, usually 20, of the Tablets, it is intended that a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered tablets taken for assay is representative of the whole Tablets and is, in turn,
weighed accurately. The result of the assay is then related to the amount of active ingredient per Tablet by multiplying this result by the average Tablet weight and dividing by the weight of the portion taken for the assay.
Similarly, where it is directed in the assay of Capsules to remove, as completely as possible, the contents of not fewer than a given number, usually 20 , of the Capsules, it is intended that a counted number of Capsules should be carefully opened and the contents quantitatively removed, combined, mixed, and weighed accurately. The portion of mixed Capsules contents taken for the assay is representative of the contents of the Capsules and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Capsule by multiplying this result by the average weight of Capsule content and dividing by the weight of the portion taken for the assay.

Where the definition in a monograph states the tolerances as being "calculated on the dried (or anhydrous or ignited) basis," the directions for drying or igniting the sample prior to assaying are generally omitted from the Assay procedure. Assay and test procedures may be performed on the undried or unignited substance and the results calculated on the dried, anhydrous, or ignited basis, provided a test for Loss on drying, or Water, or Loss on ignition, respectively, is given in the monograph. Where the presence of moisture or other volatile material may interfere with the procedure, previous drying of the substance is specified in the individual monograph and is obligatory.

Throughout a monograph that includes a test for Loss on drying or Water, the expression "previously dried" without qualification signifies that the substance is to be dried as directed under Loss on drying or Water (gravimetric determination).

Unless otherwise directed in the test or assay in the individual monograph or in a general chapter, USP Reference Standards are to be dried before use, or used without prior drying, specifically in accordance with the instructions given in the chapter USP Reference Standards $\langle 11\rangle$, and on the label of the Reference Standard. Where the label instructions differ in detail from those in the chapter, the label text is determinative.

In stating the appropriate quantities to be taken for assays and tests, the use of the word "about" indicates a quantity within $10 \%$ of the specified weight or volume. However, the weight or volume taken is accurately determined and the calculated result is based upon the exact amount taken. The same tolerance applies to specified dimensions.

Where the use of a pipet is directed for measuring a specimen or an aliquot in conducting a test or an assay, the pipet conforms to the standards set forth under Volumetric Apparatus $\langle 31\rangle$, and is to be used in such manner that the error does not exceed the limit stated for a pipet of its size. Where a pipet is specified, a suitable buret, conforming to the standards set forth under Volumetric Apparatus $\langle 31\rangle$, may be substituted. Where a "to contain" pipet is specified, a suitable volumetric flask may be substituted.

Expressions such as " 25.0 mL " and " 25.0 mg ," used with respect to volumetric or gravimetric measurements, indicate that the quantity is to be "accurately measured" or "accurately weighed" within the limits stated under Volumetric Apparatus $\langle 31\rangle$ or under Weights and Balances $\langle 41\rangle$.

The term "transfer" is used generally to specify a quantitative manipulation.

The term "concomitantly," used in such expressions as "concomitantly determine" or "concomitantly measured," in directions for assays and tests, is intended to denote that the determinations or measurements are to be performed in immediate succession. See also Use of Reference Standards under Spectrophotometry and Light-Scattering $\langle 851\rangle$.
Blank Determination-Where it is directed that "any necessary correction" be made by a blank determination, the determination is to be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test, but with the substance itself omitted.

Desiccator-The expression "in a desiccator" specifies the use of a tightly closed container of suitable size and design that maintains an atmosphere of low moisture content by means of silica gel or other suitable desiccant.

A "vacuum desiccator" is one that maintains the low-moisture atmosphere at a reduced pressure of not more than 20 mm of mercury or at the pressure designated in the individual monograph.

Dilution-Where it is directed that a solution be diluted "quantitatively and stepwise," an accurately measured portion is to be diluted by adding water or other solvent, in the proportion indicated, in one or more steps. The choice of apparatus to be used should take into account the relatively larger errors generally associated with using small-volume volumetric apparatus (see Volumetric Apparatus $\langle 31\rangle$ ).

Drying to Constant Weight-The specification "dried to constant weight" means that the drying shall be continued until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional hour of drying.

Filtration-Where it is directed to "filter," without further qualification, the intent is that the liquid be filtered through suitable filter paper or equivalent device until the filtrate is clear.

Identification Tests-The Pharmacopeial tests headed Identification are provided as an aid in verifying the identity of articles as they are purported to be, such as those taken from labeled containers. Such tests, however specific, are not necessarily sufficient to establish proof of identity; but failure of an article taken from a labeled container to meet the requirements of a prescribed identification test indicates that the article may be mislabeled. Other tests and specifications in the monograph often contribute to establishing or confirming the identity of the article under examination.

Ignition to Constant Weight-The specification "ignite to constant weight" means that the ignition shall be continued, at 800 $\pm 25^{\circ}$ unless otherwise indicated, until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional 15-minute ignition period.

Indicators-Where the use of a test solution ("TS") as an indicator is specified in a test or an assay, approximately 0.2 mL , or 3 drops, of the solution shall be added, unless otherwise directed.

Logarithms-Logarithms used in the assays are to the base 10.
Microbial Strains-Where a microbial strain is cited and identified by its ATCC catalog number, the specified strain shall be used directly or, if subcultured, shall be used not more than five passages removed from the original strain.

Negligible-This term indicates a quantity not exceeding 0.50 mg.

Odor-Terms such as "odorless," "practically odorless," "a faint characteristic odor," or variations thereof, apply to examination, after exposure to the air for 15 minutes, of either a freshly opened package of the article (for packages containing not more than 25 g ) or (for larger packages) of a portion of about 25 g of the article that has been removed from its package to an open evaporating dish of about $100-\mathrm{mL}$ capacity. An odor designation is descriptive only and is not to be regarded as a standard of purity for a particular lot of an article.

Pressure Measurements-The term "mm of mercury" used with respect to measurements of blood pressure, pressure within an apparatus, or atmospheric pressure refers to the use of a suitable manometer or barometer calibrated in terms of the pressure exerted by a column of mercury of the stated height.

Solutions-Unless otherwise specified in the individual monograph, all solutions called for in tests and assays are prepared with Purified Water.

An expression such as " $(1$ in 10$)$ " means that 1 part by volume of a liquid is to be diluted with, or 1 part by weight of a solid is to be dissolved in, sufficient of the diluent or solvent to make the volume of the finished solution 10 parts by volume.

An expression such as "(20:5:2)" means that the respective numbers of parts, by volume, of the designated liquids are to be mixed, unless otherwise indicated.

The notation "VS" after a specified volumetric solution indicates that such solution is standardized in accordance with directions given in the individual monograph or under Volumetric Solutions in the section Reagents, Indicators, and Solutions, and is thus differentiated from solutions of approximate normality or molarity.

Where a standardized solution of a specific concentration is called for in a test or an assay, a solution of other normality or molarity may be used, provided allowance is made for the difference in concentration and provided the error of measurement is not increased thereby.

Specific Gravity-Unless otherwise stated, the specific gravity basis is $25^{\circ} / 25^{\circ}$, i.e., the ratio of the weight of a substance in air at $25^{\circ}$ to the weight of an equal volume of water at the same temperature.

Temperatures-Unless otherwise specified, all temperatures in this Pharmacopeia are expressed in centigrade (Celsius) degrees, and all measurements are made at $25^{\circ}$. Where moderate heat is specified, any temperature not higher than $45^{\circ}\left(113^{\circ} \mathrm{F}\right)$ is indicated. See Storage Temperature under Preservation, Packaging, Storage, and Labeling for other definitions.

Time Limit-In the conduct of tests and assays, 5 minutes shall be allowed for the reaction to take place unless otherwise specified.

Vacuum-The term "in vacuum" denotes exposure to a pressure of less than 20 mm of mercury unless otherwise indicated.

Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used.

Water-Where water is called for in tests and assays, Purified Water is to be used unless otherwise specified. For special kinds of water such as "carbon dioxide-free water," see the introduction to the section Reagents, Indicators, and Solutions. For High-purity Water see Containers $\langle 661\rangle$.

Water and Loss on Drying - Where the water of hydration or adsorbed water of a Pharmacopeial article is determined by the titrimetric method, the test is generally given under the heading Water. Monograph limits expressed as a percentage are figured on a weight/weight basis unless otherwise specified. Where the determination is made by drying under specified conditions, the test is generally given under the heading Loss on drying. However, Loss on drying is most often given as the heading where the loss in weight is known to represent residual volatile constituents including organic solvents as well as water.

Test Results, Statistics, and Standards-Interpretation of results from official tests and assays requires an understanding of the nature and style of compendial standards, in addition to an understanding of the scientific and mathematical aspects of laboratory analysis and quality assurance for analytical laboratories.

Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs. Compendial standards define what is an acceptable article and give test procedures that demonstrate that the article is in compliance. These standards apply at any time in the life of the article from production to consumption. The manufacturer's release specifications, and compliance with good manufacturing practices generally, are developed and followed to assure that the article will indeed comply with compendial standards until its expiration date, when stored as directed. Thus, when tested from the viewpoint of commercial or regulatory compliance, any specimen tested as directed in the monograph for that article shall comply.

Tests and assays in this Pharmacopeia prescribe operation on a single specimen, that is, the singlet determination, which is the minimum sample on which the attributes of a compendial article should be measured. Some tests, such as those for Dissolution and Uniformity of dosage units, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen. These procedures should not be confused with statistical sampling plans. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations are neither specified nor proscribed by
the compendia; such decisions are dependent on the objectives of the testing. Commercial or regulatory compliance testing, or manufacturer's release testing, may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies. Treatments of data handling are available from organizations such as ISO, IUPAC, and AOAC.
-Where the Content Uniformity determinations have been made using the same procedure specified in the Assay, the average of all of the individual Content Uniformity determi-
nations may be used as the Assay value. 1 1s (USP27)
Description-Information on the "description" pertaining to an article, which is relatively general in nature, is provided in the reference table Description and Relative Solubility of USP and NF Articles in this Pharmacopeia for those who use, prepare, and dispense drugs and/or related articles, solely to indicate properties of an article complying with monograph standards. The properties are not in themselves standards or tests for purity even though they may indirectly assist in the preliminary evaluation of an article.

Solubility-The statements concerning solubilities given in the reference table Description and Relative Solubility of USP and NF Articles for Pharmacopeial articles are not standards or tests for purity but are provided primarily as information for those who use, prepare, and dispense drugs and/or related articles. Only where a quantitative solubility test is given, and is designated as such, is it a test for purity.

The approximate solubilities of Pharmacopeial substances are indicated by the descriptive terms in the accompanying table. Soluble Pharmacopeial articles, when brought into solution, may show traces of physical impurities, such as minute fragments of filter paper, fibers, and other particulate matter, unless limited or excluded by definite tests or other specifications in the individual monographs.

|  | Parts of Solvent <br> Required for <br> Descriptive |
| :--- | :--- |
| 1 Part of Solute |  |
| Term | Less than 1 |
| Very soluble | From 1 to 10 |
| Freely soluble | From 10 to 30 |
| Soluble | From 30 to 100 |
| Sparingly soluble | From 100 to 1000 |
| Slightly soluble <br> Very slightly soluble <br> Practically insoluble, <br> or Insoluble | From 1000 to 10,000 |

## Change to read:

## PRESERVATION, PACKAGING, STORAGE, AND LABELING

Containers-The container is that which holds the article and is or may be in direct contact with the article. The immediate container is that which is in direct contact with the article at all times. The closure is a part of the container.

Prior to its being filled, the container should be clean. Special precautions and cleaning procedures may be necessary to ensure that each container is clean and that extraneous matter is not introduced into or onto the article.

The container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements.

The Pharmacopeial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph.

Tamper-Evident Packaging - The container or individual carton of a sterile article intended for ophthalmic or otic use, except where extemporaneously compounded for immediate dispensing on prescription, shall be so sealed that the contents cannot be used without obvious destruction of the seal.

Articles intended for sale without prescription are also required to comply with the tamper-evident packaging and labeling requirements of the FDA where applicable.

Preferably, the immediate container and/or the outer container or protective packaging utilized by a manufacturer or distributor for all dosage forms that are not specifically exempt is designed so as to show evidence of any tampering with the contents.

Light-Resistant Container (see Light Transmission under Containers $\langle 661\rangle$ )-A light-resistant container protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. Alternatively, a clear and colorless or a translucent container may be made light-resistant by means of an opaque covering, in which case the label of the container bears a statement that the opaque covering is needed until the contents are to be used or administered. Where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended.

Where an article is required to be packaged in a light-resistant container, and if the container is made light-resistant by means of an opaque covering, a single-use, unit-dose container or mnemonic pack for dispensing may not be removed from the outer opaque covering prior to dispensing.

Well-Closed Container-A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Tight Container-A tight container protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight re-closure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article.

A gas cylinder is a metallic container designed to hold a gas under pressure. As a safety measure, for carbon dioxide, cyclopropane, helium, nitrous oxide, and oxygen, the Pin-index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

NOTE-Where packaging and storage in a tight container or a well-closed container is specified in the individual monograph, the container utilized for an article when dispensed on prescription meets the requirements under Containers-Permeation $\langle 671\rangle$.

Hermetic Container-A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Single-Unit Container-A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

Single-Dose Container (see also Containers for Injections under Injections $\langle 1\rangle$ )—A single-dose container is a single-unit container for articles intended for parenteral administration only. A singledose container is labeled as such. Examples of single-dose containers include pre-filled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

Unit-Dose Container-A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container.

Unit-of-Use Container-A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. A unit-of-use container is labeled as such.

Multiple-Unit Container-A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

Multiple-Dose Container (see also Containers for Injections under Injections $\langle 1\rangle$ )-A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only.

Storage Temperature and Humidity-Specific directions are stated in some monographs with respect to the temperatures and humidity at which Pharmacopeial articles shall be stored and distributed (including the shipment of articles to the consumer) when stability data indicate that storage and distribution at a lower or a higher temperature and a higher humidity produce undesirable results. Such directions apply except where the label on an article states a different storage temperature on the basis of stability studies of that particular formulation. Where no specific storage directions or limitations are provided in the individual monograph, but the label of an article states a storage temperature that is based on stability studies of that particular formulation, such labeled storage directions apply (see also Stability under Pharmaceutical Dosage Forms $\langle 1151\rangle$ ). The conditions are defined by the following terms.

Freezer-A place in which the temperature is maintained thermostatically between $-25^{\circ}$ and $-10^{\circ}\left(-13^{\circ}\right.$ and $\left.14^{\circ} \mathrm{F}\right)$.

Cold-Any temperature not exceeding $8^{\circ}\left(46^{\circ} \mathrm{F}\right)$. A refrigerator is a cold place in which the temperature is maintained thermostatically between $2^{\circ}$ and $8^{\circ}\left(36^{\circ}\right.$ and $\left.46^{\circ} \mathrm{F}\right)$.

Cool-Any temperature between $8^{\circ}$ and $15^{\circ}\left(46^{\circ}\right.$ and $\left.59^{\circ} \mathrm{F}\right)$. An article for which storage in a cool place is directed may, alternatively, be stored and distributed in a refrigerator, unless otherwise specified by the individual monograph.

Room Temperature-The temperature prevailing in a working area.

Controlled Room Temperature-A temperature maintained thermostatically that encompasses the usual and customary working environment of $20^{\circ}$ to $25^{\circ}\left(68^{\circ}\right.$ to $\left.77^{\circ} \mathrm{F}\right)$; that results in a mean kinetic temperature calculated to be not more than $25^{\circ}$; and that allows for excursions between $15^{\circ}$ and $30^{\circ}\left(59^{\circ}\right.$ and $\left.86^{\circ} \mathrm{F}\right)$ that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to $40^{\circ}$ are permitted as long as they do not exceed 24 hours. Spikes above $40^{\circ}$ may be permitted if the manufacturer so instructs. Articles may be labeled for storage at "controlled room temperature" or at "up to $25^{\circ}$ ", or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage tem-
perature that simulates the nonisothermal effects of storage temperature variations. (See also Stability under Pharmaceutical Dosage Forms $\langle 1151\rangle$.)

An article for which storage at Controlled room temperature is directed may, alternatively, be stored and distributed in a cool place, unless otherwise specified in the individual monograph or on the label.

Warm-Any temperature between $30^{\circ}$ and $40^{\circ}\left(86^{\circ}\right.$ and $\left.104^{\circ} \mathrm{F}\right)$.
Excessive Heat-Any temperature above $40^{\circ}\left(104{ }^{\circ} \mathrm{F}\right)$.
Protection from Freezing-Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

Dry Place-The term "dry place" denotes a place that does not exceed $40 \%$ average relative humidity at Controlled Room Temperature or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place or may be based on reported climatic conditions. Determination is based on not less than 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to $45 \%$ relative humidity provided that the average value is $40 \%$ relative humidity.
Storage in a container validated to protect the article from moisture vapor, including storage in bulk, is considered a dry place.
${ }^{\triangle}$ Storage under Nonspecific Conditions-Where no specific directions or limitations are provided in the packaging and storage section of individual monographs or in the article's labeling, the conditions of storage shall include storage at controlled room temperature, protection from moisture, and, where necessary, protection from light. Articles shall be protected from moisture, freezing, and excessive heat, and, where necessary, from light during shipping and distribution. Active pharmaceutical ingredients are exempt from this requirement. $\Delta U S P 27$

■Repackaging Instructions-Except where a drug product is packaged in a container intended to be dispensed directly to the patient, such as a unit-of-use or unit-dose container, the labeling shall contain directions specifying the types of containers suitable for repackaging the drug product so as to maintain its identity, strength, quality, and purity. Such directions shall be sufficient to allow a repackager or dispenser to select an adequate container and shall include a description of the composition of the container(s), e.g., glass, polyethylene, polyvinyl chloride, and any moisture vapor transmission rate characteristics required. The labeling shall also indicate whether or not the container is to afford light protection, and shall include any storage or shipping temperature restrictions to which the drug as repackaged shall be limited (see 21 CFR 201.100). $\quad$ 2S (USP27)

Labeling-The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

A shipping container containing a single article, unless such container is also essentially the immediate container or the outside of the consumer package, is labeled with a minimum of product identification (except for controlled articles), lot number, expiration date, and conditions for storage and distribution.

Articles in this Pharmacopeia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the Pharmacopeial requirements set forth for the articles.

Amount of Ingredient per Dosage Unit-The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

Pharmacopeial articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each such unit; except that, in the case of unit-dose oral solutions or suspensions, whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon addition of a designated volume of a specific diluent, the label shall express the quantity of each active ingredient or recognized nutrient delivered under the conditions prescribed in Deliverable Volume $\langle 698\rangle$. Pharmacopeial drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient (see Percentage Measurements), except that oral liquids or solids intended to be constituted to yield oral liquids may, alternatively, be labeled in terms of each $5-\mathrm{mL}$ portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, such declarations of strength or quantity shall be stated only in metric units (see also Units of Potency in these General Notices).

Use of Leading and Terminal Zeros-In order to help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg$]$ ). The quantity of active ingredient when expressed as a decimal number smaller than one shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg ]).

Labeling of Salts of Drugs-It is an established principle that Pharmacopeial articles shall have only one official name. For purposes of saving space on labels, and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners as synonymous with the written forms, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and $K$ for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids; but these symbols are not used where the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not to be written).

Labeling Vitamin-Containing Products-The vitamin content of an official drug product shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.
${ }^{\Delta}$ Labeling Botanical-Containing Products-The label of an herb or other botanical intended for use as a dietary supplement bears the statement, "If you are pregnant or nursing a baby, seek the advice of a health professional before using this product." ${ }_{\triangle U S P 28}$

Labeling Parenteral and Topical Preparations-The label of a preparation intended for parenteral or topical use states the names of all added substances (see Added Substances in these General Notices and Requirements, and see Labeling under Injections $\langle 1\rangle$ ), and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

Labeling Electrolytes-The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

Labeling Alcohol-The content of alcohol in a liquid preparation shall be stated on the label as a percentage $(\mathrm{v} / \mathrm{v})$ of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Special Capsules and Tablets-The label of any form of Capsule or Tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it is to be used.

Expiration Date and Beyond-Use Date-The label of an official drug product, nutritional or dietary supplement product shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., "EXP 6/89," "Exp. June 89," or "Expires 6/89"). [NOTE-For additional information and guidance, refer to the Nonprescription Drug Manufacturers Association's Voluntary Codes and Guidelines of the OTC Medicines Industry.]

The monographs for some preparations state how the expiration date that shall appear on the label is to be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the article, with the following exception: the label need not show an expiration date in the case of a drug product or nutritional supplement packaged in a container that is intended for sale without prescription and the labeling of which states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions.

Where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article may be expected to meet the requirements of the Pharmacopeial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. Where an expiration date is stated only in terms of the month and the year, it is a representation that the intended expiration date is the last day of the stated month. The beyond-use date is the date after which an article must not be used. The dispenser shall place on the label of the prescription container a suitable beyond-use date to limit the patient's use of the article based on any information supplied by the manufacturer and the General Notices and Requirements of this Pharmacopeia. The be-yond-use date placed on the label shall not be later than the expiration date on the manufacturer's container.

For articles requiring constitution prior to use, a suitable be-yond-use date for the constituted product shall be identified in the labeling.

For all other dosage forms, in determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; any unusual storage conditions to which the article may be exposed; and the
expected length of time of the course of therapy. The dispenser shall, on taking into account the foregoing, place on the label of a multiple-unit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, or in the absence of stability data to the contrary, such beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) one year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be one year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturers container, whichever is earlier, unless stability data or the manufacturers labeling indicates otherwise.

The dispenser must maintain the facility where the dosage forms are packaged and stored, at a temperature such that the mean kinetic temperature is not greater than $25^{\circ}$. The plastic material used in packaging the dosage forms must afford better protection than polyvinyl chloride, which does not provide adequate protection against moisture permeation. Records must be kept of the temperature of the facility where the dosage forms are stored, and of the plastic materials used in packaging.

Pharmaceutical Compounding-The label on the container or package of an official compounded preparation shall bear a be-yond-use date. The beyond-use date is the date after which a compounded preparation is not to be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

The monograph for an official compounded preparation typically includes a beyond-use requirement that states the time period following the date of compounding during which the preparation, properly stored, is to be used. In the absence of stability information that is applicable to a specific drug and preparation, recommendations for maximum beyond-use dates have been devised for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated (see Stability Criteria and Beyond-Use Dating under Stability of Compounded Preparations in the general tests chapter ${ }^{4}$ Pharmaceutical Compounding-Nonsterile Preparations $\left.\mathbf{A U S P 2 7}^{\langle 795\rangle}\right\rangle$ ).

## MONOGRAPHS (USP)

BRIEFING

Acyclovir, USP 27 page 47 and page 1833 of $P F 29$ (6) [Nov.Dec. 2003]; Acyclovir Capsules, USP 27 page 48 and page 602 of PF 29(3) [May-June 2003]; Acyclovir Oral Suspension, USP 27 page 49 and page 1833 of PF 29(6) [Nov.-Dec. 2003]; Acyclovir Tablets, $U S P 27$ page 50 and page 604 of $P F$ 29(3) [May-June 2003]. Some lots of USP Acyclovir RS may contain a small amount of guanine. Therefore, it is proposed to prepare a separate guanine standard solution to avoid interference from a potential guanine impurity in the Reference Standard. System suitability solutions have also been added to evaluate the resolution and precision requirements. In the absence of any significant adverse
comment, it is proposed to implement this revision via the Fourth Interim Revision Announcement pertaining to USP 27-NF 22, with an official date of August 1, 2004.
(PA7b: B. Davani) RTS-40740-1

## Change to read:

Packaging and storage-Preserve in tight containers. Store-between $15^{\circ}$ and $25^{\circ}$. Protect from light and moisture.
-Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$. - $\mathbf{n}_{2 S}$ (USP27)

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. $\quad$ 2S (USP27)

Change to read:
USP Reference standards $\langle 11\rangle-U S P$ Acyclovir $R S$.

- USP Endotoxin RS.■2S (USP27)


## Add the following:

-Other requirements-Where the label states that Acyclovir is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Acyclovir for Injection. Where the label states that Acyclovir must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Acy-
clovir for Injection.■2S (USP27)

## Change to read:

## Assay and limit for guanine-

Mobile phase-Prepare a filtered and degassed solution of glacial acetic acid in water (1 in 1000). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

- System suitability preparation 1—Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having known concentrations of about 0.1 mg of each per mL .

System suitability preparation 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about $0.7 \mu \mathrm{~g}$ per $\mathrm{mL} . \bullet 4$

Guanine standard preparation-Transfer about 8.75 mg of guanine, accurately weighed, to a $500-\mathrm{mL}$ volumetric flask. Dissolve in 50 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix.
${ }^{\bullet}$ Transfer 2.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix to obtain a solution having a known concentration of about $0.7 \mu \mathrm{~g}$ per mL .4

Standard preparation-Dissolve about 25 mg of USP Acyclovir RS, accurately weighed, in 5 mL of 0.1 N sodium hydroxide in a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution 2.0 mL of the G twan
$\bullet \bullet$
to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix to obtain a solution having knowneeneentrations of aben 0.1 mg of USP Acyelovir RS per mL and $0.7 \mu \mathrm{~g}$ of guanine per mL.
-a known concentration of about 0.1 mg of USP Acyclovir

## RS per mL. $\bullet 4$

Assay preparation-Dissolve about 100 mg of Acyclovir, accurately weighed, in 20 mL of 0.1 N sodium hydroxide in a $200-$ mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.2-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph
${ }^{\bullet}$ System suitability solution $1, \bullet$
and record the peak responses as directed for Procedure: the resolution, $R$, between acyclovir and guanine is not less than 2.0 ; the tailing factor for the analyte peak is not more than 2 ; and the relative standard deviation for replicate injections
${ }^{\bullet}$ for the acyclovir peak ${ }_{\bullet 4}$ is not more than $2.0 \%$.
${ }^{\bullet}$ Chromatograph System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$. 4
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Stal
${ }^{\bullet}$ Guanine standard preparation. 4
and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in $\mu \mathrm{g}$, of guanine in the portion of Acyclovir taken by the formula:

$$
1000 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of guanine in the Stand prention

- Guanine standard preparation; 4
and $r_{U}$ and $r_{S}$ are the peak responses due to guanine in the Assay preparation and the st,
- Guanine standard preparation, $\bullet 4$
respectively: not more than $0.7 \%$ of guanine is found. Calculate the quantity, in mg , of $\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}$ in the portion of Acyclovir taken by the formula:

$$
1000 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses due to acyclovir in the Assay preparation and the Standard preparation, respectively.

Briefing
Acyclovir Capsules, USP 27 page 48 and page 602 of PF 29(3) [May-June 2003]-See briefing under Acyclovir.
(PA7b: B. Davani) RTS-40742-1

## Change to read:

Packaging and storage-Preserve in tight containers.
, and store at controlled room temperature, - Store between
$15^{\circ}$ and $25^{\circ}$. Protect from light and moisture. $\quad 1$ (USP27)

## Change to read:

Assay-
Mobile phase-Prepare a filtered and degassed solution of 0.02 M acetic acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
-System suitability preparation 1-Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.1 mg of each per mL .

System suitability preparation 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about $2.0 \mu \mathrm{~g}$ per $\mathrm{mL} . \bullet 4$

Standard preparation-Dissolve an accurately weighed quantity of USP Acyclovir RS and guanine
$\bullet$
in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.1 mg per mL . and 2.0 нes per mL , respective女.
$\bullet 4$
Assay preparation-Remove, as completely as possible, the contents of not fewer than 10 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 10 mg of acyclovir, to a $100-\mathrm{mL}$ volumetric flask, dissolve in 10 mL of 0.1 N sodium hydroxide, dilute with water to volume, mix, and filter.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.2-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the fation,
-System suitability preparation 1,•4 and record the peak responses
${ }^{\bullet}$ for acyclovir ${ }^{4}$
as directed for Procedure: the relative retention times are about 0.6 for guanine and 1.0 for acyclovir; the resolution, $R$, between guanine and acyclovir is not less than 2.0; and the relative standard deviation for replicate injections
${ }^{\bullet}$ of acyclovir ${ }_{\bullet 4}$
is not more than $2.0 \%$.
${ }^{\bullet}$ Chromatograph the System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg , of $\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}$ in the portion of Capsules taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Acyclovir for Injection, USP 27 page 48 and page 602 of $P F$ 29(3) [May-June 2003]-See briefing under Acyclovir.
(PA7b: B. Davani) RTS-40743-1

## Change to read:

Packaging and storage-Preserve in tight containers.
, and store at controlled room temperature- ${ }^{-1}$ Store between
$15^{\circ}$ and $25^{\circ}$. Protect from light. $\mathbf{L S S}_{\text {(USP27) }}$

## Change to read:

## Chromatographic purity-

Solution A-Prepare a filtered and degassed mixture of 0.17 M acetic acid and methanol (125:8). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Solution B: methanol, filtered and degassed.
Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments to either solution as necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
System suitability solution-Dissolve suitable quantities of purine and USP Acyclovir RS in Solution $A$ to obtain a solution containing about $0.5 \mu \mathrm{~g}$ of each per mL .
©Acyclovir standard solution-Dissolve an accurately weighed quantity of USP Acyclovir RS in Solution $A$, and dilute quantitatively, and stepwise if necessary, with Solution $A$ to obtain a solution having a known concentration of about $5 \mu \mathrm{~g}$ per mL .

Guanine solution-Dissolve about 25 mg of guanine, accurately weighed, in 50 mL of 0.1 N sodium hydroxide in a $500-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Standerd solution
-Standard solution $1 \bullet 4$
-Transfer 5.0 mL of Acyclovir standard solution me 5.0 mL of Gtanine solution

- 4
to a $50-\mathrm{mL}$ volumetric flask, dilute with Solution $A$ to volume, and mix. $\triangle$ USP27
- Standard solution 2-Transfer 5.0 mL of Guanine solu-
tion to a $50-\mathrm{mL}$ volumetric flask, dilute with Solution $A$ to volume, and mix. 4
Test solution-Constitute and combine not less than 10 vials of Acyclovir for Injection. Transfer an accurately measured quantity, equivalent to about 100 mg of acyclovir, to a $200-\mathrm{mL}$ volumetric flask, dilute with Solution $A$ to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L 1 . The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-15$ | 100 | 0 | isocratic |
| $15-45$ | $100 \rightarrow 65$ | $0 \rightarrow 35$ | linear gradient |
| $45-46$ | $65 \rightarrow 100$ | $35 \rightarrow 0$ | linear gradient |
| $46-56$ | 100 | 0 | re-equilibration |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between purine and acyclovir is not less than 2.0. Chromatograph the Standard solution,
-Standard solution 1 and Standard solution $2 \bullet 4$ and record the peak responses as directed for Procedure: the rela tive
${ }^{\bullet}$ typicale4
retention times for guanine and acyclovir are about ${ }^{\boldsymbol{\Delta}} \boldsymbol{\theta}_{4_{\Delta U S P 27}}$ and 1.0 ,
$\bullet 5.8$ minutes and 14 minutes, $\bullet 4$
respectively; and the relative standard deviation $\boldsymbol{\Delta}$ of the acyclovir peak area and the guanine peak area $\mathbf{\Delta U S P 2 7}$ for replicate injections is not more than $1 \%$. $\mathbf{\Delta}$ USP27

Procedure Injeet a volume

(about $50 \mu \mathrm{~L}$ ) of $\mathbf{\Delta}^{\boldsymbol{\Delta}}$ the Standard solution and $\mathbf{\Delta U S P 2 7}$ the Test solution into the chromatograph, record the chromatogram, and measure the peak ${ }^{\mathbf{\wedge}}$ area $_{\mathbf{U S P}, 27}$ responses. ${ }^{\mathbf{\Delta}}$ Calculate the percentage of guanine in the Acyclovir for Injection by the formula:

$$
20,000(C / W)\left(r_{g} / r_{s g}\right)
$$

in which $C$ is the concentration, in $m g$ per mL , of guanine in the Standard solution; $W$ is the total weight, in mg , of acyclovir in the Test solution based on the label claim; $r_{g}$ is the peak response for guanine, if present, in the Test solution; and $r_{s g}$ is the peak response of guanine in the Standard solution: not more than $1.0 \%$ is
 rity in the $\mathbf{\Delta U S P 2 7}$ Acyclovir for Injection $\mathbf{\Delta u S P}^{\mathbf{\Delta}}$ by the formula:

$$
20,000(C / W)\left(r_{i} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Acyclovir RS in the Standard solution; $W$ is the $\mathbf{~ t o t a l} \mathbf{D}_{U S P} Z_{z}$ weight, $\mathbf{\Delta}_{\text {in }}$ $\mathrm{mg},_{\triangle U S P 27}$ of acyclovir $\Delta \triangle U S P 27$ in the Test solution based on the label claim; ${ }_{U S P 27} r_{i}$ is the peak response for each impurity; and $r_{S}$ is the peak response of acyclovir in the Standard solution: ${ }^{\mathbf{4}} \mathbf{\Delta}$ USP27 not more than $0.15 \%$ for any peak having a relative retention time
 more than $0.5 \%$ of any other individual impurity is found; and the total of all other impurities is not more than $1.0 \%$.

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed solution of 0.02 $M$ acetic acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

- System suitability preparation 1—Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having known concentrations of about 0.1 mg of each per mL .

System suitability preparation 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having a known concentration of about $2.0 \mu \mathrm{~g}$ per mL . $\bullet 4$

Standard preparation-Dissolve accurately weighed quantities of USP Acyclovir RS granine

## $\bullet \bullet 4$

in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having a known concentration of about 0.1 mg per mL . and $2.0 \mu \mathrm{~g}$ per mL , respectively.
${ }^{\bullet} \cdot 4$
Assay preparation-Constitute, with water, one vial of Acyclovir for Injection. Transfer an accurately weighed amount of this solution, equivalent to about 10 mg of acyclovir, to a $100-\mathrm{mL}$ volumetric flask, and dilute with water to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )——The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.2-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the fation,
-System suitability preparation 1, $\bullet 4$
and record the peak responses

- for acyclovir ${ }_{P 4}$
as directed for Procedure: the relative retention times are about 0.6 for guanine and 1.0 for acyclovir; for the resolution, $R$, between guanine and acyclovir is not less than 2.0; and the relative standard deviation for replicate injections
${ }^{\bullet}$ for the acyclovir peak ${ }^{\bullet 4}$
is not more than $2.0 \%$.
${ }^{\bullet}$ Chromatograph the System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$. $\bullet 4$

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg , of $\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}$ in the portion of Acyclovir for Injection taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Acyclovir Ointment, USP 27 page 49 and page 604 of $P F$ 29(3) [May-June 2003]-See briefing under Acyclovir.
(PA7b: B. Davani) RTS-40744-1

## Change to read:

Packaging and storage-Preserve in tight containers.
, and-store at controlled room temperature- ${ }^{-}$Store between
$15^{\circ}$ and $25^{\circ}$ in a dry place. $\quad 1$ (USP27)

## Change to read:

Assay-

Mobile phase-Prepare a filtered and degassed solution of 0.02 M acetic acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve accurately weighed quantities of USP Acyclovir RS gunine
$\bullet 4$
in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having known concentrations of about 0.1 mg per mL . ad $2.0 \mathrm{\mu g}$ per mb, respectively.

## $\bullet$

-System suitability preparation 1-Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having known concentration of about 0.1 mg of each per mL.

System suitability preparation 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having a known concentration of about $2.0 \mu \mathrm{~g}$ per $\mathrm{mL} . \bullet 4$

Assay preparation-Transfer an accurately weighed quantity of Ointment, equivalent to about 10 mg of acyclovir, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with 0.1 N sodium hydroxide to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph the st tion,

- System suitability preparation 1,04
and record the peak responses as directed for Procedure: the relative retention times are about 0.6 for guanine and 1.0 for acyclovir; the resolution, $R$, between guanine and acyclovir is not less than 2.0; and the relative standard deviation for replicate injections
${ }^{-}$for acyclovir ${ }^{4}$
is not more than $2.0 \%$.
${ }^{\bullet}$ Chromatograph the System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$. $\bullet 4$

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of $\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}$ in the portion of Ointment taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Acyclovir Oral Suspension, USP 27 page 49 and page 1833 of PF 29(6) [Nov.-Dec. 2003]-See briefing under Acyclovir.
(PA7b: B. Davani) RTS-40745-1

## Change to read:

Packaging and storage-Preserve in tight containers.

$15^{\circ}$ and $25^{\circ}$. Protect from light. $\quad$ 1S (USP27)

## Add the following:

-Uniformity of dosage units $\langle 905\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements.m2S (USP27)

## Add the following:

-Deliverable volume $\langle 698\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements.m2S (USP27)

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed solution of 0.02 M acetic acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard preparation-Dissolve acemfaly weighed quantities of USP Acyelowir RS and guanine
-an accurately weighed quantity of USP Acyclovir RS ${ }_{\bullet 4}$ in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having know coneentration 0.1 mg per mL and 2.0 ug per mL, respectively.

- a known concentration of 0.1 mg per mL .

System suitability preparation 1-Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and step-
wise if necessary, with 0.1 N sodium hydroxide to obtain a solution having known concentrations of about 0.1 mg of each per mL.

System suitability preparation 2-Dissolve an accurately
weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with
0.1 N sodium hydroxide to obtain a solution having a
known concentration of about $2.0 \mu \mathrm{~g}$ per $\mathrm{mL} . \bullet 4$
Assay preparation-Transfer an accurately measured quantity of well-shaken Oral Suspension, equivalent to about 200 mg of acyclovir, to a $200-\mathrm{mL}$ volumetric flask, add 100 mL of 0.1 N sodium hydroxide, shake by mechanical means for 15 minutes, and sonicate, if necessary, to dissolve the Oral Suspension completely. Dilute with 0.1 N sodium hydroxide to volume, and mix. Transfer 10.0 mL of the solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, mix, and filter.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph the stan ,
-System suitability preparation 1,04
and record the peak responses as directed for Procedure: the relative retention times are about 0.6 for guanine and 1.0 for acyclovir; the resolution, $R$, between guanine and acyclovir is not less than 2.0; and the relative standard deviation for replicate injections
${ }^{-}$for the acyclovir ${ }_{6}$
is not more than $2.0 \%$.
${ }^{\bullet}$ Chromatograph the System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$. $\bullet 4$

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of acyclovir $\left(\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}\right)$ in the portion of Oral Suspension taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Acyclovir Tablets, USP 27 page 50 and page 604 of $P F$ 29(3) [May-June 2003]-See briefing under Acyclovir.
(PA7b: B. Davani) RTS-40741-1

## Change to read:

Packaging and storage-Preserve in tight containers.
, and store at contrelled room temperature- ${ }^{-1}$ Store between
$15^{\circ}$ and $25^{\circ}$. Protect from light and moisture. $\quad 15$ (USP27)

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed solution of 0.02 M acetic acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
-System suitability preparation 1-Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.1 mg of each per mL .
System suitability preparation 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration
of about $2.0 \mu \mathrm{~g}$ per $\mathrm{mL} . \bullet 4$
Standard preparation-Dissolve an accurately weighed ties
${ }^{-}$quantity ${ }^{4}$
of USP Acyclovir RS
$\bullet$
in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known centrations
${ }^{-}$concentration ${ }^{4}$
of about 0.1 mg per mL . and 2.0 .

- 4

Assay preparation-Weigh and finely powder not fewer than 10 Tablets. Transfer an accurately weighed quantity of powder, equivalent to about 10 mg of acyclovir, to a $100-\mathrm{mL}$ volumetric flask, dissolve in 10 mL of 0.1 N sodium hydroxide, dilute with water to volume, mix, and filter.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The column temperature is maintained at $40^{\circ}$. The flow rate is about 1.5 mL per minute. Chromatograph the stan,

- System suitability preparation 1, 4 and record the peak responses
${ }^{-}$for acyclovir ${ }^{4}$
as directed for Procedure: the relative retention times are about 0.6 for guanine and 1.0 for acyclovir; the resolution, $R$, between guanine and acyclovir is not less than 2.0 ; and the relative standard deviation for replicate injections
${ }^{\bullet}$ for the acyclovir peak ${ }_{\bullet 4}$
is not more than $2.0 \%$.
${ }^{\bullet}$ Chromatograph the System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$. 4

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg , of $\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}$ in the portion of Tablets taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Alendronate Sodium, page 737 of $P F 28$ (3) [May-June 2002]. On the basis of comments received, it is proposed to make a change in the Definition, to specify that the Assay limits apply on the dried basis. Some modifications are also being proposed in the Assay and Chromatographic purity tests. It is also proposed to add storage conditions to the Packaging and storage section.
(PA4: E. Gonikberg) RTS—39881-1; 40567-1

## Add the following:

## ©Alendronate Sodium


$\mathrm{C}_{4} \mathrm{H}_{12} \mathrm{NNaO}_{7} \mathrm{P}_{2} \cdot 3 \mathrm{H}_{2} \mathrm{O} \quad 325.13325 .12$
Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate.

Sodium trihydrogen (4-amino-1-hydroxybutylidene)diphosphonate, trihydrate [121268-17-5].

## » Alendronate Sodium contains not less than 99.0

 98.0 percent and not more than 101.0102 .0 percent of $\mathrm{C}_{4} \mathrm{H}_{12} \mathrm{NNaO}_{7} \mathrm{P}_{2}, \cdots 3 \mathrm{H}_{2} \mathrm{O}$, calculated on the dried basis.Packaging and storage-Preserve in well-closed containers. Store between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Alendronate Sodium $R S$.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$.
B: It meets the requirements of the flame test for So-
dium $\langle 191\rangle$.
Loss on drying $\langle 731\rangle$ —Dry it at a pressure not exceeding 5 mm of mercury at $140^{\circ}$ to constant weight: it loses not less than $16.1 \%$ and not more than $17.1 \%$ of its weight.

Heavy metals, Method III $\langle 231\rangle$ : 0.001\%.

## Chromatographic purity-

Buffer solution-Transfer 5.88 g of sodium citrate dihydrate and 2.84 g of anhydrous dibasic sodium phosphate to a 2-L volumetric flask, dilute with water to volume, and mix. Adjust with phosphoric acid to a pH of 8.0 , and pass the solution through a filter having a $0.5-\mu \mathrm{m}$ or finer porosity.

[^47]mL. Prepare a solution in acetonitrile containing about 4 mg of 9-fluorenylmethyl chloroformate per mL. Prepare this solution fresh just prior to use.
Berate solution Dissolve 19.1 g of sodium berate in water in a 1 - liter volumetric flask, dilute with water to vol ume, and mix.

Biltent Dissolve 29.4 g of soditm citrate dihydrate in Water in a 1 liter volumetric flack, dilute with water to vol the, and mix.

Solution A-Prepare a filtered and degassed mixture ining 1700 mL of Buffer solution and 300 mL of acetonitrile (17:3).

Solution B-Prepare a filtered and degassed mixture aning 300 mL of Buffer solution and 700 mL of acetonitrile (3:7).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard stock solution-Transer 30 mg of USP
Alendrenate Soditm RS, aceurately weighed, to a 50 mL velumetric flask, dissolve in and dilute with Diluent to vol the, Prepare a solution of USP Alendronate Sodium RS in Diluent having a known concentration of about 0.6 mg per mL .

Standard solution-Transfer 5.0 mL of the Standard stock solution to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube containing 5 mL of Borate solution. and Add 5 mL of acetonitrile-Add and 5 mL of 9-Fluorenylmethyl chloroformate solution, and shake for 45 seconds. Allow to stand at room temperature for 30 minutes. Add 20 mL of methylene chloride, and shake vigorously for 1 minute. Centrifuge for 5 to 10 minutes, and use a portion of the clear upper aqueous layer.

Diluted standard solution-Dilute a portion of Standard stock solution with Diluent to obtain a solution having a known concentration of about $0.6 \mu \mathrm{~g}$ per mL . Using 5 mL of this solution, proceed as directed for Standard solution, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."

Reagent blank-Using a $5.0-\mathrm{mL}$ portion of Diluent, proceed as directed for Standard solution, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."

Test solution-Transfer about 30 mg of Alendronate Sodium, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix. Using a $5.0-\mathrm{mL}$ volume of this solution, proceed as directed for Standard solution, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $266-\mathrm{nm}$ detector and a $4.1-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $10-\mu \mathrm{m}$ packing L21. The flow rate is about $z 1.8 \mathrm{~mL}$ per minute. The column temperature is maintained at about $45^{\circ}$. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-15$ | $100 \rightarrow 50$ | $0 \rightarrow 50$ | linear gradient |
| $15-25$ | $50 \rightarrow 0$ | $50 \rightarrow 100$ | linear gradient |
| $25-27$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $27-32$ | 100 | 0 | isocratic |

Chromatograph the Standard solution and the Diluted standard solution, and record the peak responses as directed for Procedure: the tailing factor for the principal peak in the chromatogram of the Standard solution is not more than 2.0; and the peak at that locus in the chromatogram of the Diluted standard solution is detectable with a signal-tonoise ratio of not less than 3 .

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L})$ of the Test solution and the Reagent blank into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Disregard any peak corresponding to those obtained from the Reagent blank. Calculate the percentage of each impurity in the portion of Alendronate Sodium taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the area of each impurity peak, ether than the principal peak and peaks correspending in retention time to any observed in the chromategramobtained from the Reand and $r_{s}$ is the sum of all impurity peaks and the principal peak: not more than $0.1 \%$ of any individual impurity is found; and not more than $0.5 \%$ total impurities is found.

## Assay-

Buffer solution-Transfer 14.7 g of sodium citrate dihydrate and 7.05 g of anhydrous dibasic sodium phosphate to a 1-L volumetric flask, dilute with water to volume, mix, and adjust with phosphoric acid to a pH of 8.日.
Diluent-Dissolve 29.4 g of sodium citrate dihydrate in water in a 1-L volumetric flask, dilute with water to volume, and mix.
Borate solution-Dissolve 19.1 g of sodium borate in water in a 1-L volumetric flask, dilute with water to volume, and mix.

9-Fluorenylmethyl chloroformate solution-Transfer 25 me of 9 fluorenylmethyl chloreformate to a 50 mL volumetric flask, dilute with acetonitrile to volume, and mix. Prepare fresh just prior to use. [NOTE-This solution contains abeut 0.5 mg of 9 -flurenylmethyl chloroformate per mL. . Prepare a solution in acetonitrile containing about 0.5 mg of 9-fluorenylmethyl chloroformate per mL . Prepare this solution fresh just prior to use.

Mobile phase—Prepare a filtered and degassed mixture of Buffer solution, acetonitrile, and methanol (70:25:5). Make adjustments if necessary (see System Suitability under Chromatography (621〉).

Standard stock preparation-Transer 25 me of USP Alendronate Sodimm RS, aceurately weighed, to a 250 mL velumetric flask, dissolve in and dilute with Piltuent velume, and mix. Prepare a solution of USP Alendronate Sodium RS in Diluent having a known concentration of about 0.1 mg per mL . Calculate the concentration, $C_{S}$, of anhydrous alendronate sodium in this solution.
Standard preparation-Transfer 5.0 mL of this solution the Standard stock preparation to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube containing $5 . \theta \mathrm{mL}$ of Borate solution. Add 5.0 mL of 9-Fluorenylmethyl chloroformate solution, and shake for 30 seconds. Allow to stand at room temperature for 25 minutes. Add 25 mL of methylene chloride, and shake vigorously for 1 minute. Centrifuge for 5 to 10 minutes. Use a portion of the clear upper aqueous layer.

Reagent blank—Using 55.0 mL of Diluent, proceed as directed for Standard preparation, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."
Assay stock preparation - Using Transfer about 25 mg of Alendronate Sodium, accurately weighed, for Stane to a $250-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.
Assay preparation-Using 5.0 mL of the Assay stock preparation, proceed as directed for the Standard preparation, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $266-\mathrm{nm}$ detector and a $4.1-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $10-\mathrm{mm}$ packing L21. The flow rate is about +1.2 mL per minute. The column temperature is maintained at about $35^{\circ}$. Chromatograph the Standard preparation, and record the peak
responses as directed for Procedure: the column efficiency is not less than 1500 theoretical plates; the tailing factor is not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $1.0 \% 2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation, Assay preparation, and Reagent blank into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{4} \mathrm{H}_{12} \mathrm{NNaO}_{7} \mathrm{P}_{2} \cdots-3 \mathrm{H}_{2} \mathrm{\theta}$ in the portion of Alendronate Sodium taken by the formula:

$$
\#\left(r_{5}+r_{s}\right),
$$

$$
D C_{S}\left(r_{U} / r_{S}\right)
$$

in whieh Wis the weight, in mis, of USP Alendrenate-Sodium RS taken to prepare the Standard preparation in which $D$ is the Dilution factor for the Assay stock preparation; $C_{S}$ is as defined under the Standard stock preparation; and $r_{U}$ and $r_{S}$ are the peak area responses for alendronic acid obtained from the Assay preparation and the Standard preparation, respectively. $\Delta$ USP28

## Briefing

Alendronic Acid Tablets, page 997 of PF 29(4) [July-Aug. 2003]. Comments were received that the HPLC method proposed in PF 28(3) lacked the sensitivity required to perform the Dissolution test for the $5-\mathrm{mg}$ Tablets. It was also reported that normal stability conditions for the product do not require monitoring phosphate. On the basis of these comments, the revision to the tests for Dissolution and Assay, and the new test for Limit of phosphate that were proposed in $P F$ 28(3) and the change to the USP designation of the chromatograpic reagent proposed in $P F$ 29(4) have been cancelled. The original proposal, previously published in $P F$ 28(1), is now presented with several changes. Also, tolerances
for weekly dosing tablets are being added to the Dissolution test. A labeling section is added accordingly.
(PA4: E. Gonikberg; BPC: M. Marques) RTS—39906-1; 39470-1; 40567-2

## Add the following:

## AAlendronate Sodium Tablets Alendronic Acid Tablets

## » Alendronate Sodizm Tablets contain Alendronic

 Acid Tablets contain an amount of Alendronate Sodium, equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of alendronatesodiam $\left(\mathrm{C}_{4} \mathrm{H}_{12}\right.$ $\left.\mathrm{NNaO}_{7} \mathrm{P}_{z} \cdot 3 \mathrm{H}_{z} \mathrm{O}\right)$. alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{13}\right.$ $\mathrm{NO}_{7} \mathrm{P}_{2}$ ).Packaging and storage-Preserve in tight containers. Store at between $15^{\circ}$ and $30^{\circ}$.

Labeling-The labeling indicates weekly dosing where appropriate.

USP Reference standards $\langle 11\rangle$ —USP Alendronate Sodium RS.

Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Dissolution $\langle 711\rangle$ -
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 15 minutes.
Determine the amount of $\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}$ dissolved by employing the following method.

Buffer solution and Mobile phase-Prepare as directed in the Assay.
$0.05 \%$ 9-Fluorenylmethyl chloroformate solutionTransfer 100 mg of 9-fluorenylmethyl chloroformate to a $200-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix. This solution must be freshly prepared.

Borate buffer-Dissolve 6.2 g of boric acid in approximately 950 mL of water, adjust with 1 N sodium hydroxide to a pH of 9.0 , and dilute with water to 1 L .

Diluent-Transfer 176.4 g of sodium citrate dihydrate to a 1000-mL volumetric flask, dissolve in and dilute with Dissolution Medium to volume, and mix.

Standard stock solution-Dissolve an accurately weighed quantity of USP Alendronate Sodium RS in Dissolution Medium, and dilute quantitatively and stepwise, with the same solvent to obtain a solution having a known concentration corresponding to the concentration that would be obtained by dissolving 1 Tablet in 900 mL of the same Medium. Calculate the concentration, $C$, in mg per mL , of anhydrous alendronate sodium in this solution.

Standard solution-Transfer 5.0 mL of the Standard stock solution to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube containing 1.0 mL of Diluent and 5.0 mL of Borate buffer, and mix for about 3 minutes. Add 4.0 mL of 0.05\% 9-Fluorenylmethyl chloroformate solution, and agitate for about 30 seconds. Allow the solution to stand at room temperature for 25 minutes. Add 25 mL of methylene chloride, and agitate for about 40 seconds. Centrifuge the mixture for 5 minutes. Use a portion of the clear upper aqueous layer.

Reagent blank-Using 5 mL of water, proceed as directed for Standard solution, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."

Test solution-After 15 minutes, withdraw a portion of the solution under test, and centrifuge immediately. Using 5.0 mL of the clear supernatant, proceed as directed for Standard solution, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."

Chromatographic system (see Chromatography $\langle 621\rangle$ )— Proceed as directed in the Assay. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solution, the Test solution, and the Reagent blank into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right)$ dissolved by the formula:

$$
827.1 C\left(r_{U} / r_{S}\right),
$$

in which $C$ is defined under the Standard stock solution; and $r_{U}$ and $r_{S}$ are the peak areas obtained from the Test solution and the Standard solution, respectively. [NOTE- 827.1 is the molecular weight conversion factor $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right.$ / $\mathrm{C}_{4} \mathrm{H}_{12} \mathrm{NNaO}_{7} \mathrm{P}_{2}$ ) multiplied by the volume of the Medium $(900 \mathrm{~mL})$ ]
Tolerances-Not less than $80 \%(Q)$ of the labeled amount of alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right)$ is dissolved in 15 minutes. Tablets labeled for weekly dosing: not less than $75 \%(Q)$ of the labeled amount of alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right)$ is dissolved in 15 minutes

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.


System suitability solution Prepare a-solution-of USP Alendrenate Sodium PS and sodium biphesphate in HPLC grade water containing 0.2 mg per mL and 0.1 mg per mL , respectively.

Standard preparation Prepare a solution of USP Alen drenate-Soditm PS in HPLC grade water having a known eoneentration of about 0.52 mg of alendronate sodium trihy drate per mL .
Assay preparation Weigh and finely powder not fewer than 20 - Tablets. Transfer an aceurately weighed pertion of the powder, equivalent to about 100 mg of alendronic acid, to a 250 mL volumetric flask, dissolve in HPLC grade water, senieate for 30 minttes, and shake for 10 minttes. Pilute with HPLC grade water to volume, and mix. Pass a pertion of this selution threugh a filter having a 0.45 -mmer finer porosity, and use the filtrate.

Chrematographic system (see Chromatography $\langle 624\rangle$ ) -
The liquid chromatograph is equipped with a 240 -nm detec for and a $4.1 \mathrm{~mm} \times 25-\mathrm{mm}$ columm that contains packing E53. L\#\# (see Chromatography $\langle 624\rangle$ ). The flow rate is about 1.6 mL per minte. Chremategraph the-System suit ability solution, and record the peak responses as-directed for Procedure: the resolution, $R$, between alendronate and phesphate is not less than 2.0; the tailing factor is net mere than 1.5 ; and the relative standard deviation for replieate in jections is net mere than $2.0 \%$.

Procedure Separately inject equal-volumes (about 100 HL) of the Standard preparation and the Assay preparation inte the chrematograph, record the ehromatograms, and meastre the respenses for the major peaks. Caleutate the quantity, in mg, of alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right)$ in the per tion of Tablets taken by the formala:

$$
250(249.10 / 325.12) C\left(F_{t}+r_{s}\right)
$$

in which 249.10 and 325.12 are the molecular weights of alendrenic acid and alendrenate-sedium trihydrate, respectively; $C$ is the concentration, in mg per mL , of alendrenate sedium trihydrate in the Standard preparation; and $r_{\text {t }}$ and $r_{s}$ are the peak respenses obtained from the - sssay preparation and the Standard preparation, respectively.

Diluent-Transfer 29.4 g of sodium citrate dihydrate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix.

Buffer solution-Transfer 14.7 g of sodium citrate dihydrate and 7.05 g of anhydrous dibasic sodium phosphate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in about 900 mL of water, adjust with phosphoric acid to a pH of 8.0 , dilute with water to volume, and mix.
$0.1 \%$ 9-Fluorenylmethyl chloroformate solution-Transfer 250 mg of 9-fluorenylmethyl chloroformate to a 250mL volumetric flask, dilute with acetonitrile to volume, and mix. Prepare this solution fresh just prior to use.

Borate solution-Transfer 38.1 g of sodium borate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix.

Mobile phase_Prepare a filtered and degassed mixture of Buffer solution, acetonitrile, and methanol (75:20:5). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard stock preparation-Prepare a solution of USP
Alendronate Sodium RS in diluent containing 0.03 mg of anhydrous alendronate sodium per mL .

Standard preparation-Transfer 5.0 mL of the Standard stock preparation to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube containing 5 mL of Borate solution, and mix for about 3 minutes. Add 4 mL of $0.1 \%$ 9-Fluorenylmethyl chloroformate solution, and agitate for about 30 seconds. Allow the solution to stand at room temperature for $25 \mathrm{~min}-$
utes. Add 25 mL of methylene chloride, and agitate for about 40 seconds. Centrifuge the mixture for 10 minutes. Use the clear upper aqueous layer.

Assay stock preparation-Transfer not fewer than 10 Tablets to a $1000-\mathrm{mL}$ volumetric flask. Add 500 mL of Diluent, shake by mechanical means for 30 minutes, and sonicate for 5 minutes. Dilute with Diluent to volume, mix, and centrifuge a portion of this solution. Quantitatively dilute a portion of the clear supernatant to a concentration in a range of 0.02 to 0.03 mg per mL .

Assay preparation-Using 5.0 mL of the Assay stock preparation, proceed as directed for Standard preparation, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."

Reagent blank-Using 5 mL of Diluent, proceed as directed for Standard preparation, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $266-\mathrm{nm}$ detector and a $4.1-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L21. The column is maintained at a constant temperature of about $35^{\circ}$. The flow rate is about 1 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard preparation, Assay preparation, and the Reagent blank into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right)$ in the portion of Tablets taken by the formula:

$$
0.919 D C\left(r_{U} / r_{S}\right)
$$

in which $D$ is the dilution factor for the Assay stock preparation; $C$ is the concentration, in mg per mL , of anhydrous USP Alendronate Sodium RS in the Standard stock preparation; and $r_{U}$ and $r_{S}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively. [NOTE- 0.919 is the molecular weight conversion factor $\left.\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2} / \mathrm{C}_{4} \mathrm{H}_{12} \mathrm{NNaO}_{7} \mathrm{P}_{2}\right) \cdot\right]_{\Delta U S P 28}$

## BRIEFING


#### Abstract

Amphetamine Sulfate, USP 27 page 143; Dextroamphetamine Sulfate, USP 27 page 576. It is proposed to revise the concentration of triethylamine used to prepare the Buffer solution in the test for Chromatographic purity. This correction reflects the actual concentration used in the validation of the method.


(PA3: S. Salado) RTS-40699-1

## Change to read:

## Chromatographic purity-

Diluent-Dilute 3.12 mL of phosphoric acid with water to 1000 mL .
Buffer solution-Dissolve 2.16 g of sodium 1-octanesulfonate in 1000 mL of water, and add 1.0 mL of $0.1 \%$ triethylame (
${ }^{\Delta}$ triethylamine. $\triangle$ USP28
Mix, and adjust with phosphoric acid to a pH of 2.5 .
Mobile phase -Prepare a filtered and degassed mixture of Buffer solution, acetonitrile, and methanol (144:37:19). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).
Standard stock solution-Dissolve an accurately weighed quantity of USP Dextroamphetamine Sulfate RS in Diluent to obtain a solution having a known concentration of about 0.3 mg per mL .
Standard solution-Dilute an accurately measured volume of Standard stock solution in Diluent to obtain a solution having a known concentration of about 0.003 mg per mL .
Test solution-Transfer about 30 mg of Amphetamine Sulfate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in 50 mL of Diluent, sonicate for 5 minutes, dilute with Diluent to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard stock solution, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$. Chromatograph the Test solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the amphetamine peak and any adjacent peak, if any, is not less than 1.5 .

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Amphetamine Sulfate taken by the formula:

$$
10,000(C / W)\left(r_{i} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Dextroamphetamine Sulfate RS in the Standard solution; $W$ is the weight, in mg , of Amphetamine Sulfate taken to prepare the Test solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the peak response for amphetamine obtained from the Standard solution: not more than $0.1 \%$ of any individual impurity is found; and not more than $0.5 \%$ of total impurities is found.

## BRIEFING

Amphotericin B Lotion, USP 27 page 146. It is proposed to change the title of this monograph to Amphotericin B Topical Emulsion. Revisions are proposed by the Expert Committee on Nomenclature and Labeling to change the titles of twenty-two USP monographs from [DRUG] Lotion to [DRUG] Topical Emulsion or [DRUG] Topical Suspension, as appropriate. The change of terminology proposed for these older Lotion monograph titles is consistent with the nomenclature that has been applied over the past several years for terminology for new preparations that are administered externally, such as Topical Solution, Topical Aerosol, and Topical Powder. It follows the policy established by a former USP Drug Nomenclature Committee and continued in effect by the present Expert Committee on Nomenclature and Labeling, whereby these topical preparations are to be named in the general form [DRUG NAME][ROUTE OF ADMINISTRATION] [DOSAGE FORM], e.g., [Clindamycin Phosphate][Topical][Suspension]. The decision to move away from traditional Lotion terminology came about because the term Lotion does not have the meaning and is not as informative as the descriptive Topical Emulsion and Topical Suspension terminology.

Revisions are proposed for eleven USP monographs on other dosage forms in which references, currently made to Lotion monographs, would necessarily be changed concomitantly to ensure that reference is made to the correctly titled topical liquid dosage forms.

Revisions of the following monographs are proposed for publication in USP 28-NF 23, which is to become official January 1, 2005, but with July 1, 2007, designated as the official date for the name changes. Use of the revised names would be permitted as of January 1, 2005, the official date of $U S P 28-N F 23$, but use of the revised names would not become mandatory until July

1, 2007. The 30 -month postponement of the official date for the name changes is intended to allow for product label changes to be made and for health practitioners and consumers to become familiar with the revised terminology.

Benzoyl Peroxide Lotion
Benzyl Benzoate Lotion
Betamethasone Dipropionate Lotion
Betamethasone Valerate Lotion
Calamine Lotion
Phenolated Calamine Lotion
Clotrimazole Lotion
Flurandrenolide Lotion
Hydrocortisone Lotion
Hydrocortisone Acetate Lotion
Hydrocortisone Acetate Ointment
Lindane Lotion
Malathion Lotion
Methylbenzethonium Chloride Lotion
Methylbenzethonium Chloride Topical Powder
Neomycin Sulfate and Flurandrenolide Lotion
Neomycin Sulfate and Hydrocortisone Acetate Cream
Neomycin Sulfate and Hydrocortisone Acetate Lotion
Neomycin Sulfate and Hydrocortisone Acetate Ointment
Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment
Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment
Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment
Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment
Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream
Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream
Nystatin Lotion
Padimate O Lotion
Penicillin G Procaine, Neomycin and Polymyxin B Sulfates, and Hydrocortisone Acetate Topical Suspension
Resorcinol and Sulfur Lotion
Selenium Sulfide Lotion
Triamcinolone Acetonide Lotion
White Lotion
(NL: C. Barnstein) RTS-40776-1

## Amphotericin B Lotion

(Current title—not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Amphotericin B Topical Emulsion

> Amphotericin B Topical Emulsion-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40776-1

## Add the following:

## AAmphotericin B Topical Emulsion <br> (Monograph under this new title-to become official July 1, 2007) <br> (Current monograph title is Amphotericin B Lotion)

» Amphotericin B Topical Emulsion contains not less than 90.0 percent and not more than 125.0 percent of the labeled amount of amphotericin $B$.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle$ —USP Amphotericin B RS.
Minimum fill $\langle 755\rangle$ : meets the requirements.
$\mathbf{p H}\langle 791\rangle$ : between 5.0 and 7.0.
Assay-Proceed as directed for amphotericin B under Anti-biotics-Microbial Assays $\langle 81\rangle$, dissolving a suitable accurately measured volume of Topical Emulsion quantitatively in sufficient dimethyl sulfoxide to give a convenient concentration. Dilute an accurately measured volume of this solution quantitatively with dimethyl sulfoxide to obtain a stock solution having a concentration of about $20 \mu \mathrm{~g}$ of amphotericin B per mL . Dilute an accurately measured volume of this stock solution quantitatively with Buffer No. 10 to obtain a Test Dilution having a concentration assumed to be equal to the median dose level of the Standard. $\Delta$ USP28
(Official July 1, 2007)

Anecortave Acetate; Anecortave Acetate Injectable Suspension. Because there are no existing USP monographs for this drug substance and drug product, new monographs are being proposed. The drug product has been granted Fast-Track Designation by the FDA as a treatment for Age-Related Macular Degeneration (AMD), the common cause of vision loss in elderly people. USP has given these monographs special consideration to ensure that quality public standards are available so that appropriate treatment is provided for persons affected by AMD. The drug product has not been approved by the FDA, therefore neither the API or product monographs will become official until approval has been granted by the agency. The liquid chromatographic procedure in the test for Related compounds and in the Assay is based on analyses performed with the Phenomenex Spherisorb brand of L1 column. The typical retention time for anecortave acetate is about 10.5 minutes.
(PA6: L. Evans) RTS-40612-1

## Add the following:

## ©Anecortave Acetate


$\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{O}_{5} \quad 386.48$
21-(Acetyloxy)-17-hydroxypregna-4,9(11)-diene-3,20dione.

17,21-Dihydroxypregna-4,9(11)-diene-3,20-dione 21-acetate. [7753-60-8].
» Anecortave Acetate contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{O}_{5}$, calculated on the dried basis.

Packaging and storage-Preserve in well-closed containers at controlled room temperature.

USP Reference standards $\langle 11\rangle-U S P$ Anecortave Acetate RS. USP Anecortave Acetate Related Compound A RS. USP Hydrocortisone Acetate RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $+120.0^{\circ}$ and $+128.0^{\circ}$.
Test solution: 10 mg per mL , in chloroform.
Bacterial endotoxins $\langle 85\rangle$ : [To come.]
Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 4 hours: it loses not more than $0.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : 0.002\%.

## Related compounds-

Buffer, Mobile phase, System suitability, and Chromatographic system-Proceed as directed in the Assay.
Test solution-Proceed as directed under Assay preparation in the Assay.

Procedure-Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Anecortave Acetate taken by the formula:

$$
100 F\left(r_{i} / r_{s}\right),
$$

in which $F$ is the relative response factor; $r_{i}$ is the peak response for each individual impurity; and $r_{s}$ is the sum of the responses of all the peaks.

Table 1

| Relative Retention |  | Response Relative | Limit |
| :---: | :---: | :---: | :---: |
| Time | Name | Factor (F) | (\%) |
| about 0.39 | 9(11)-Dehydrocortisol (anecortave acetate related | 0.91 | 0.2 |
|  | compound A) | 1.15 |  |
| about 0.49 <br> about 0.75 | Hydrocortisone acetate | 1.15 | 0.2 |
|  | 21-Acetyloxy-17 $\alpha$-hydroxypregna-1,4,9(11)-triene- | 1.00 | 0.2 |
|  | 3,20-dione |  |  |
| - | Any other individual impurity | - | 0.1 |
| - | Total Impurities | - | 0.7 |

## Assay-

Buffer—Add 1.0 mL of concentrated phosphoric acid to 1.0 L of water. Adjust with sodium hydroxide to a pH of 3.0 .

Mobile phase-Prepare a filtered and degassed mixture of Buffer and acetonitrile (57:43). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve about 5 mg of USP Anecortave Acetate RS, 4 mg of USP Hydrocortisone Acetate RS, and 3 mg of USP Anecortave Acetate Related Compound A RS into a $5.0-\mathrm{mL}$ volumetric flask, dilute with ethyl acetate to volume, and mix. Transfer 2.0 mL of this solution to a $25-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Standard preparation-Transfer about 25 mg of USP Anecortave Acetate RS, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask. Add 9 mL of ethyl acetate, sonicate for 5 minutes, and cool to room temperature. Dilute with ethyl acetate to volume, and mix. Transfer 2.0 mL into a $25-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to obtain a concentration of about 0.2 mg per mL .

Assay preparation-Prepare as directed for Standard preparation using anecortave acetate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $242-\mathrm{nm}$ detector and $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between hydrocortisone acetate and anecortave acetate is not less than 10 ; the resolution, $R$, between hydrocortisone acetate and anecortave acetate related compound A is not less than 2; the column efficiency determined for the anecortave acetate peak is not less than 3000 theoretical plates; the tailing factor for anecortave acetate is not more than 2.0 ; and the relative standard deviation for replicate injections of the Standard preparation is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{O}_{5}$ in the portion of Anecortave Acetate taken by the formula:

$$
125 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Anecortave Acetate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively._USP28

## Briefing

Anecortave Acetate Injectable Suspension-See briefing under Anecortave Acetate.
(PA6: L. Evans) RTS-40612-2

## Add the following:

## -Anecortave Acetate Injectable Suspension

## » Anecortave Acetate Injectable Suspension is a

 sterile suspension of Anecortave Acetate in a suitable aqueous medium. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of anecortave acetate $\left(\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{O}_{5}\right)$.Packaging and storage-Preserve in single dose-containers preferably of Type I glass. Avoid freezing.

Labeling-Label it to indicate that it is not recommended for intravenous use and that it is to be well shaken before use.

USP Reference standards $\langle 11\rangle — U S P$ Anecortave Acetate RS. USP Anecortave Acetate Related Compound A RS. USP Hydrocortisone Acetate RS.

## Identification-

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

B: Thin-Layer Chromatographic Identification Test〈201〉—
Adsorbent: a $0.20-\mathrm{mm}$ layer of chromatographic silica gel mixture containing fluorescent indicator.

Test solution-Transfer a quantity of the Injectable Suspension, equivalent to about 10 mg of anecortave acetate, to a suitable flask, and extract with one $2.0-\mathrm{mL}$ portion of ethyl acetate. Use the extract as the Test solution.

Standard solution-Prepare a solution in chloroform containing 5.0 mg of USP Anecortave Acetate RS per mL.

Application volume: $2 \mu \mathrm{~L}$.
Developing solvent system: a mixture of chloroform and methanol (12:1).

Sterility $\langle 71\rangle$ — To come.]
Bacterial endotoxins $\langle 85\rangle$ - [To come.]
$\mathbf{p H}\langle 791\rangle$ : between 6.8 and 7.8.

## Particle size-

Carrier fluid-Heat Purified Water to $40^{\circ}$ to $50^{\circ}$, add 100 mg anecortave acetate per L while stirring, cool to room temperature while stirring, filter through a $0.2-\mu \mathrm{m}$ filter, and store in a clean, covered container.
Test preparation-Dilute several $\mu \mathrm{L}$ of Injectable Suspension with Carrier fluid to 25 mL .

Procedure-(see the Light Obscuration Particle Count Test under Particulate Matter in Injections $\langle 788\rangle$ )—Analyze the Test preparation using an electronic, liquid-borne particle counting system that employs a light obsuration sensor with a suitable sample feeding device. Not less than $95.0 \%$ of the particles are $\leq 10 \mu \mathrm{~m}$, not less than $99.50 \%$ are $\leq 25 \mu \mathrm{~m}$, not less than $99.95 \%$ are $\leq 50 \mu \mathrm{~m}$, and not less than $99.995 \%$ are $\leq 100 \mu \mathrm{~m}$.

## Related compounds-

Buffer, Mobile phase, System suitability solution and Chromatographic system-Proceed as directed in the Assay under Anecortave Acetate.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Procedure-[NOTE-Use peak areas where peak responses are indicated.] Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph. Measure the areas of the analyte peaks. Allow the elution to continue for about 10 to 15 min utes after the elution time of the anecortave acetate. Calculate the quantity, in mg , of the degradation products in each mL of the Injectable Suspension taken by the formula:

$$
50 \mathrm{C}\left(r_{U} / r_{S}\right) F
$$

in which $C$ is the concentration, in mg per mL , of anecortave acetate in the Standard solution; $r_{U}$ and $r_{S}$ are the degradation product peak responses obtained from the Test solution and the anecortave acetate peak response obtained from the Standard solution, respectively; and $F$ is the relative response factor for each individual degradation product ( 0.91 for $9(11)$-dehydrocortisol, and 1.00 for all other degradation products): not more than $0.7 \%$ of 9(11)-dehydrocortisol of the labeled amount of anecortave acetate is found; no other single impurity is more than $0.2 \%$; and the sum of all impurities found is not more than $1.5 \%$.

## Assay-

Buffer, Mobile phase, Standard preparation, System suitability solution, and Chromatographic system—Proceed as directed in the Assay under Anecortave Acetate.

Assay preparation-Transfer an accurately measured volume of Injectable Suspension, equivalent to about 10 mg of anecortave acetate, to a $50-\mathrm{mL}$ volumetric flask. Add 4.0 mL of ethyl acetate, followed by 40.0 mL of Mobile phase, sonicate for 5 minutes, cool to room temperature, dilute with Mobile phase to volume, and mix.

Procedure-Proceed as directed for Procedure in the $A s$ say under Anecortave Acetate. Calculate the quantity, in mg, of anecortave acetate $\left(\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{O}_{5}\right)$ in each mL of the Injectable Suspension taken by the formula:

$$
50(C / V)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of anecortave acetate in the Standard preparation; $V$ is the volume, in mL , of Injectable Suspension taken; and $r_{U}$ and $r_{S}$ are the anecortave acetate peak responses obtained from the Assay preparation and the Standard preparation, respectively._USP28

## BRIEFING

Arginine Hydrochloride, USP 27 page 167. It is proposed to add units of volume to clarify the concentration of the System suitability solution in the test for Chromatographic purity.
(PA6: L. Evans) RTS-40897-1

## Change to read:

Chromatographic purity-
Adsorbent: $0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture.

Test solution-Dissolve an accurately weighed quantity of Arginine Hydrochloride in water to obtain a solution having a concentration of 10 mg per mL .

Standard solution-Dissolve an accurately weighed quantity of USP Arginine Hydrochloride RS in water to obtain a solution having a known concentration of about 0.05 mg per mL . [NOTE-This solution has a concentration equivalent to about $0.5 \%$ of that of the Test solution.]

System suitability solution-Prepare a solution in water containing 0.4 mg each of USP Arginine Hydrochloride RS and USP LLysine Hydrochloride RS

## ©per mL. $\quad$ USP28

Spray reagent-Dissolve 0.2 g of ninhydrin in 100 mL of a mixture of butyl alcohol and 2 N acetic acid (95:5).
Application volume: $5 \mu \mathrm{~L}$.
Developing solvent system-Prepare a mixture of isopropyl alcohol and ammonium hydroxide (70:30).

Procedure-Proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$. Dry the plate between $100^{\circ}$ and $105^{\circ}$ until the ammonia disappears completely. Spray with Spray reagent, and heat between $100^{\circ}$ and $105^{\circ}$ for about $15 \mathrm{~min}-$ utes. Examine the plate under white light. The chromatogram obtained from the System suitability solution exhibits two clearly separated spots. Any secondary spot in the chromatogram obtained
from the Test solution is not larger or more intense than the principal spot in the chromatogram obtained from the Standard solution: not more than $0.5 \%$ of any individual impurity is found; and not more than $2.0 \%$ of total impurities is found.

## Briefing

Atovaquone Oral Suspension, USP 27 page 187 and page 1846 of PF 29(6) [Nov.-Dec. 2003]. It is proposed to revise the test for Sedimentation to specify that the test applies only to oral suspension packaged in multiple-unit containers.
(PA7b: B. Davani) RTS-40504-1

## Add the following:

- Uniformity of dosage units $\langle 905\rangle$ -

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements.■2S (USP27)
Change to read:
Deliverable volume $\langle 698\rangle$ -

- FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-

TAINERS: $\mathbf{n}_{2 S}$ (USP27)
meets the requirements.

## Change to read:

## Sedimentation-

© FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS- $\quad$ USP28
Transfer 50 mL of well-mixed Oral Suspension to a glass-stoppered graduated cylinder, and allow to stand for 16 hours. Measure the volume, if any, of clear liquid observed in the cylinder: not more than 1 mL of clear liquid is found.

## Briefing

Atracurium Besylate Injection, USP 27 page 189 and page 1008 of PF 29(4) [July-Aug. 2003]. It is proposed to revise the Assay to correct the formula in the Procedure.
(PA3: S. Salado) RTS-40861-1

## Change to read:

Related compounds-
Buffer solution, Solution A, Solution B, Mobile phase, and Standard preparation-Proceed as directed in the Assay under Atracurium Besylate.

System suitability solution-Heat a portion of the Standard preparation at $90^{\circ}$ for 30 minutes, and chill immediately to about $5^{\circ}$.

Diluted standard preparation-Dilute a portion of the Standard preparation quantitatively, and stepwise if necessary, with Solution $A$ to obtain a solution having a known concentration of about 0.02 mg per mL .

Test preparation-Use the Assay preparation.
Chromatographic system-Prepare as directed for Chromatographic system in the Assay. Chromatograph the System suitability solution and the Diluted standard preparation, record the chromatograms, and measure the responses for the degradation products by comparing the peak responses of the System suitability solution to those of the Diluted standard preparation as directed for Procedure: the retention times relative to the atracurium besylate cis-cisisomer are about 0.22 for the acidic compound, 0.29 for laudanosine, 0.44 and 0.50 for the trans- and cis-isomers, respectively, of the hydroxy compound, and about 1.28 and 1.33 for the trans- and cis-isomers, respectively, of the monoacrylate.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Diluted standard preparation and the Test preparation into the chromatograph, record the chromatograms, and measure the peak responses, except the peak due to benzenesulfonic acid occurring at a retention time of about 0.08 relative to the atracurium besylate cis-cis-isomer. Calculate the percentage of each impurity in the portion of Test preparation taken by the formula:

$$
100(C / M)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Atracurium Besylate RS in the Diluted standard preparation; $M$ is the concentration of atracurium besylate, in mg per mL , in the Test preparation; $r_{i}$ is the peak response for each impurity obtained from the Test preparation; and $r_{s}$ is the sum of the responses of all the peaks obtained from the Diluted standard preparation: not more than $6.0 \%$ of the acidic compound, not more than $6.0 \%$ of the combined cis- and trans-isomers of the hydroxy compound, not more than $3.0 \%$ of laudanosine, and not more than $3.0 \%$ of the combined cis- and trans-isomers of the monoacrylate, tand not mere than $0.5 \%$ of other known impurities
$\Delta^{4}$ and not more than $2.0 \%$ of other known impurities ${ }_{\triangle U S P 28}$ is found; not more than $0.1 \%$ of any other impurity is found; and not more than $15.0 \%$ of total impurities is found.
*(Postpened Indefinitely)
4 $\mathbf{\Delta S P 2 8}$

## Change to read:

Assay-
Buffer solution, Solution A, Solution B, Mobile phase, and Standard preparation-Proceed as directed in the Assay under Atracurium Besylate.

Assay preparation-Transfer an accurately measured volume of Injection, equivalent to about 50 mg of atracurium besylate, to a $50-\mathrm{mL}$ volumetric flask, dilute with Solution $A$ to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains base-deactivated packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 80 | 20 | equilibration |
| $0-5$ | 80 | 20 | isocratic |
| $5-15$ | $80 \rightarrow 40$ | $20 \rightarrow 60$ | linear gradient |
| $15-25$ | 40 | 60 | isocratic |
| $25-30$ | $40 \rightarrow 0$ | $60 \rightarrow 100$ | linear gradient |

Chromatograph replicate injections of the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.8 for the atracurium besylate trans-trans-isomer, 0.9 for the cis-trans-isomer, and 1.0 for the cis-cisisomer; the resolution, $R$, between the atracurium besylate trans-trans-isomer and the cis-trans-isomer and between the atracurium besylate cis-trans-isomer and the cis-cis-isomer is not less than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the three atracurium besylate isomer peaks. Calculate the quantity, in mg, of atracurium besylate $\left(\mathrm{C}_{65} \mathrm{H}_{82} \mathrm{~N}_{2} \mathrm{O}_{18} \mathrm{~S}_{2}\right)$ in each mL of the Injection taken by the formula:

$$
50(C / V) 10 C\left(+_{t}+r_{s}\right)
$$

$$
\Delta_{50}(\mathrm{C} / \mathrm{V})\left(r_{U} / r_{S}\right)_{, \mathbf{\Delta S P 2 8}}
$$

in which $C$ is the concentration, in mg per mL , of USP Atracurium Besylate RS in the Standard preparation; $V$ is the volume, in mL , of Injection taken for the Assay preparation; and $r_{U}$ and $r_{S}$ are the sums of the peak responses of the atracurium besylate trans-trans, trans-cis, and cis-cis-isomers obtained from the Assay preparation and the Standard preparation, respectively.

Briefing

Azithromycin, USP 27 page 198 and page 1417 of $P F$ 29(5) [Sept.-Oct. 2003]. On the basis of comments and data received, modification of the proposed test for Loss on drying of Azithromycin monohydrate is proposed. One comment noted that the proposed temperature range of $80^{\circ}$ to $130^{\circ}$ for the release of the monohydrate water is arbitrary, and that different thermogravimetric apparatuses could give different results. It is now proposed to define the temperature range based on a plot of the first derivatives of the thermogram, that is, the percent weight loss per minute of heating. The range is identified by observing the inflection points of the first derivative curve at about $70^{\circ}$ and $130^{\circ}$. The flow rate of nitrogen is changed from 100 mL per minute to a constant
rate of about 35 mL per minute. The lower flow rate is to assure better equilibrium of the sample and volatiles during heating and to yield better precision of results.
(PA7: W. Wright) RTS-40858-1

## Change to read:



```
\(\mathrm{E}_{38} H_{72} \mathrm{~N}_{2} \theta_{12}-2 H_{2} \theta\)
\({ }_{785.02}^{\Delta} \mathrm{C}_{38} \mathrm{H}_{72} \mathrm{~N}_{2} \mathrm{O}_{12} \cdot x \mathrm{H}_{2} \mathrm{O}_{\Delta U S P 28}\)
785.02
```


1-Oxa-6-azacyclopentadecan-15-one, 13 -[(2,6-dideoxy-3-C-meth-yl-3-O-methyl- $\alpha-\mathrm{L}$-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-tri-deoxy-3-(dimethylamino)- $\beta$-D-xylo-hexopyranosyl] $]$ xy]-, dihydrate, $\left[2 R\left(2 R^{*}, 3 S^{*}, 4 R^{*}, 5 R^{*}, 8 R^{*}, 10 R^{*}, 11 R^{*}, 12 S^{*}\right.\right.$, $\left.\left.13 S^{*}, 14 R^{*}\right)\right]$.
$(2 R, 3 S, 4 R, 5 R, 8 R, 10 R, 11 R, 12 S, 13 S, 14 R)$-13-[(2,6-Dideoxy-3-C-methyl-3-O-methyl- $\alpha$-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)- $\beta$-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. dihydrate.
9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A.
${ }^{\boldsymbol{\Delta}}$ Monohydrate 767.02 [121479-24-4] $\mathbf{\Delta U S P 2 8}$
Dihydrate
$\triangle 785.02$ AUSP28
[117772-70-0]
Anhydreas 749.00-83005-015
${ }^{\boldsymbol{\Delta}} \mathbf{U S P} 28$

## Change to read:

» Azithromycin contains
$\Delta_{\text {one or }}$ or two molecules of water of hydration. It contains $_{\triangle U S P 28}$
the equivalent of not less than $945 \mu \mathrm{~g}$ and not more than $1030 \mu \mathrm{~g}$ of azithromycin $\left(\mathrm{C}_{38} \mathrm{H}_{72} \mathrm{~N}_{2} \mathrm{O}_{12}\right)$ per mg , calculated on the anhydrous basis.

## Add the following:

${ }^{\boldsymbol{\Delta}}$ Labeling-Label it to indicate whether it is the monohydrate or the dihydrate. Where the quantity of azithromycin is indicated in the labeling of any preparation containing Azithromycin, this shall be understood to be in terms of anhydrous azithromycin $\left(\mathrm{C}_{28} \mathrm{H}_{72} \mathrm{~N}_{2} \mathrm{O}_{12}\right)$. $\mathbf{\Delta U S P 2 8}$

## Change to read:

Water, Method $I\langle 921\rangle$ : between $4.0 \%$ and $5.0 \%$
© where it is labeled as the dihydrate; between $1.8 \%$ and $4.0 \%$ where it is labeled as the monohydrate, except that it may be between $4.0 \%$ and $6.5 \%$ when the requirements of the Loss on drying test are met. IUSP28 $^{\text {U }}$

## Add the following:

${ }^{\Delta}$ Loss on drying (where it is labeled as Azithromycin monohydrate and has a Water content of between $4.0 \%$ and 6.5\%) (see Thermal Analysis $\langle 891\rangle$ )-[NOTE-The quantity taken for the determination may be adjusted, if necessary, for instrument sensitivity.] Determine the percentage of volatile substances by thermogravimetric analysis in an appropriately calibrated instrument, using about 10 mg of Azithromycin, accurately weighed. Heat the specimen at the rate of $10^{\circ}$ per minute between ambient temperature and $150^{\circ}$ in an atmosphere of nitrogen at a 100 mL per minnte. From the thermegram determine the aeet mulated loss in weight between ambient temperature and about $80^{\circ}$ on the plateat, and from $80^{\circ}$ to $130^{\circ}$ : it loses not more than $4.5 \%$ of its weight between ambient temperature and about $80^{\circ}$, and between 1.8\% and 2.6\% between $80^{\circ}$ and $130^{\circ}$. constant flow rate of about 35 mL per minute. From the thermogram plot the derivatives of the loss on drying (percent loss per minute), identify the inflection points of the two weight loss steps at about $70^{\circ}$ and $130^{\circ}$ : it loses not more than $4.5 \%$ of its weight between ambient temperature and the inflection point at about $70^{\circ}$, and between $1.8 \%$ and $2.6 \%$ between the inflection point at about $70^{\circ}$ and the inflection point at about $130^{\circ} \cdot \mathbf{\Delta U S P 2 8}$

BCG Live, page 1419 of $P F 29$ (5) [Sept.-Oct. 2003]. This proposed new monograph is being presented again with changes recommended by the monograph sponsor. It is proposed to revise the Definition to specify that the vaccine is to be used intravesically for immunotherapy. In the Packaging and storage section it is proposed to delete the specification for a particular type of container. Also, to be more inclusive of all marketed products, it is proposed to revise the tests for Identification, Virulent mycobacteria, Skin reactivity, and Potency.
(VVI: T. Morris) RTS-40859-1

## Add the following:

## $\triangle$ BCG Live

» BCG Live (intravesical) for immunotherapy is a freeze-dried preparation of attenuated live bacteria derived from a culture of Bacillus Calmette-Guérin (Mycobacterium bovis, var. BCG) and used intravesically in the treatment of carcinoma in situ and papilloma tumors of the urinary bladder. The bacteria are grown in a medium that does not contain substances known to cause toxic or allergic reactions in human beings or to cause the bacteria to become virulent for guinea pigs. The culture is harvested and formulated to contain one or more excipients. The freeze-dried preparation is reconstituted and further diluted aseptically with a sterile diluent for use. A reconstituted dose contains $1.0-19.2 \times 10^{8}$ colony-forming units (cfu). BCG Live does not contain a preservative.

Packaging and storage-Preserve in single-dose hermetic Type I glass eontainers and store at a temperature between $z^{\circ}$ and $8^{\circ}$ away from direet sumlight. Do not freeze. BCG

Live is sensitive to light and therefore must be preserved and stored where it is protected from direct light at a temperature between $2^{\circ}$ and $8^{\circ}$.

Expiration date-The product is stable for 1 year 3 years when stored between $2^{\circ}$ and $8^{\circ}$.

Labeling-Label it to indicate the dry weight of bacteria in a vial, cfu per dose, the storage conditions, the expiration date, and that it is not to be used after the expiration date given on the package. Label it to state that it should be protected from direct sunlight light and that it should be used immediately after reconstitution/dilution. Label it to indicate that it is "for intravesical use". "Renly."

## Identification-

Garbol fuchsin solution Transfer 10 g of basic fuchsim powder and 100 mL of aleohol to a $100-\mathrm{mL}$ bettle. Mix using a magnetic stir bar and a magnetic stirrer to dissolve. Transfer the solution to a 1-E Erlenmeyer flask. Adt 50 mE Of Liqueffed Phenel and 850 mL of water. Mix, and fiter. Stere at reom temperature. [NOTE The-solution is stable up to 3-menths when stored at ambient temperature. $]$

Aeid atcoltol solution Transfer 970 mL of alceheltoat 1-L bettle, adt 30 mL of hydrochtoric acid, and mix. Stere at reom temperature. [NOTE The solution is stable up-to-3 fonths when stered at ambient temperature.]

Methylene blut solution Transfer 4.5 g of methylene blue-ta 2 E Erlemmeyer flack, and add-450 mL aleohel. Add 150 mg of potassium hydroxide and 1500 mL of water to the flask. Mix until the solutes dissolve and filter. Store-at ambient temperature. [NOTE The-solution is-stable tp to 4 year when stered at ambient temperature.]

Standard suspension Use approved U.S. Reference
BCG Live.
Fest suppension Reconstitute the freez-dried BCG Live according to the manufacturer's instructions for human use with the diluent recommended by the manufacturer.

Negative control Use the dilthent recemmended by the manufacturer for reconstitution of BCG Live.

Procedtre Prepare a suitable bacteriologieal loop and flame it where it joins the handle until it is red hot. Allow the loop to cool down to room temperature without touching anything. Transfer a loep-full of each of the Standtard suts pension, Test suspension, and Negative eontrol on-separate slides. Wash the loop in a stream of water, flame it, and at low it to cooldown as described above in between the transfers. [NOTE-Altematively separate loops may be used for the transfer of different solutions.] Heat fix each-slide by passing it over a flame four times. [NOTE-Too much heat may cause the slide to break.] Flood the slides with the Catbol fuehsin solution, and heat them over a steam bath for about 5 minttes. [NOTE-Make-sure that the entire-slide-is eovered with the Carbol fuchsin solution throughout the staining procedtre.] Rinse the slides with water. Flood the slides with the Aeid aleohol selution until no more-coler eomes out and the stides are clear of stain visible to the naked eye (about 30 -secends). Rinse the slides theroughly with water and drain any exeess water frem the slides. Flood the slides with the Methylene blue solution for about 30 sec ends to 1 minute, and rinse them-with-water. Examine the slides under a mieroscope. Bacteria in the Standerd suspensign and the Test suspension stain red, and the negative contrel is celorless. The merphelegical chatacteristies of the stains from the Test suspension are similar to these from the Standard suspension.

BCG Live is identified by microscopic examination of the bacilli in stained smears demonstrating their acid-fast property. Alternatively, validated molecular biology techniques may be used.

General Safety—It meets the requirements as set forth for Safety Tests-Biologicals under Biological Reactivity Tests, In Vivo $\langle 88\rangle$, modified as follows. Guinea pigs are injected intraperitoneally with 3.0 mL of the reconstituted product.

Sterility $\langle 71\rangle$ —It meets the requirements when tested as directed for Direct Inoculation of the Culture Medium under Test for Sterility of the Product to be Examined.

## Virulent mycobacteria-

Test suspension-Reconstitute the freeze-dried BCG Live arding to as per the manufacturer's instructions for human use with the diluent recommended by the manufacturer, and dilute aseptically to about 5 ms per mL with sterile $0.9 \%$ chlimeride 2 mg per mL with sterile BCG diluent.

Procedure-Randomly select not fewer than six guinea pigs (male or female), of the same sex, each weighing 250 to 300 g . fijecech mimal with 1.0 mL of the Test suspen sion intramuseularly in the rear left internal thigh, and observe them for a period of 6 weeks. Note the number of animals that strvive at the end of the observation period, and then saerifice them. Perform autopsies of all animats post mortem to examine them for mieroseopic tubereutous infections, particularly at the popliteal and inguinal lymph nodes, limgs, as well as at the injection site. If the results are not conelusive, perform a histologieal-mamination for fowing the procedure described in Identification, except for the following: suitable tissue sections are used insted of the Fest suspension, no Standerd suspension is required, and the tubereulous infections are demenstrated by red stains in a blue background. [NOTE The blue color is due to the staining of the nenacid fast cells by methylene blue.] At the end of the observation period, not less than the thirds of the an imals survive, ho sign of tubereulosis is detected in animals that survive, as well as these that died; and the animals that surving. Inject each animal with a total of at
least 4 mg of the Test suspension intramuscularly or subcutaneously in the rear left internal thigh, and observe them for a period of 6 weeks. Note the number of animals that survive at the end of the observation period, and then sacrifice them. Perform autopsies of all animals postmortem to examine them for evidence of tuberculous infections, particularly at the popliteal and inguinal lymph nodes, liver, spleen, pancreas, and lungs as well as at the injection site. If any abnormalities are found, perform a histological examination using standard and Acid-Fast staining techniques to detect Acid-Fast organisms. The product complies with the test if none of the animals show signs of tuberculosis and not more than one-third of the animals die during the observation period.

## Skin reactivity-

## Test suspensions - Reenstitute the freezedried BCG

 Live according to the manufacturer's instruetions for human we with the diluent reeommended by the manufacturer. Dilute the solution further $1: 10,1: 100$, and $1: 1000$ aseptically using the diluent. Using the same diluent and the Test suspension prepared as directed for the test for Virulent mycobacteria, further dilute aseptically by making three serial tenfold dilutions.Procedure-Randomly select two guinea pigs (male or female), each weighing 250 to 300 g . Inject 0.1 mL of each of the four suspensions intradermally at different sites on the back of each animal. After 4 weeks, the animals are shaved so that the injection sites and any reactions are made clearly visible. The diameters of the reactions are measured, and the presence of necrosis or nodules noted. The reaction for the largest dose is between 4 and 10 mm and the smallest dose induces a nodule less than or equal to 4 mm . Each animal gains weight during the observation period.

## Tuberculin sensitivity-

Tuberculin solution-Use tuberculin, purified protein derivative, to prepare a solution containing 25 U.S. Tuberculin Units per 0.1 mL . Dilute aseptically, if necessary, with sterile $0.9 \%$ sodium chloride solution.

Procedure-Use the same animals on which the Skin reactivity test is performed. After the Skin reactivity test is completed, inject each animal intradermally on the back with 0.1 mL of the Tuberculin solution, and observe after 18 to 24 hours. An erythematous reaction of not less than 10 mm in diameter is measured on each animal.

Residual moisture: Meth $\mathrm{Ie}\langle(924\rangle \div$ Net more than $2.5 \%$. Not greater than the limit approved for the particular product, determined by a suitable validated method. Limits vary in accordance with the method.

Viability-Determine the potencies of BCG Live using not less than 5 containers before freeze-drying and an equal number of containers after freeze-drying, following the procedure described under Potency, except use the suspension before freeze-drying as is. The loss in viability due to freeze-drying is not more than $90 \%$.

## Potency-

Culture medium-Prepare the eulture medium as de-
seribed below: Dissolve, adjust the pH to 7.0 with a sodium hydroxide solution, and sterilize by filtration.

| Compenents | Weight |
| :---: | :---: |
|  | $5.0-\mathrm{g}$ |
| Asparagine | 5.0 - |
| Monobasic petassitm phosphate |  |
| Potassimm sulfate | 0.5-g |
|  | 1.5 F |
| Magnesitmm eitrate | 19.0-5 |
| Monesodium glatamate | 20.0 mL |
| Glycerin |  |


| Gempenents | Weight |
| :--- | :---: |
| Weter | $900.0-\mathrm{mL}$ |
| $5 \%$ aqueous solution | 100.0 mL |
| of albumin bovine-serum |  |

## Agar solution Transfer 1.5-g of agar to an- Erlenmeyer

flask and add 100 mL of water. Close the meuth airtight with a suitable cotton plug and attoclave at $120^{\circ}$ for 15 to 30 minutes. With the mouth tightly closed by the cotton plus, eool the solution to $-42^{\circ}$ and maintain in a water bath at $42^{\circ}$ untiluse.

Fest suspensions-Recenstitute net less than 5-entainers of the freeze dried BCG Live according to the manufac turer's instructions for human use with the diluent reeommended by the manufacturer.

Procedtre [NOTE-Work in a laminar flow biologieat safety cabinet under aseptic conditions.] Transfer 4.5 mL of the-Culture meditun to each of a series of $16 \mathrm{~mm}-*$ 125 mm serew eapped test tubes. Arrange the tubes in rows such that each row eontains 10 tubes. Mark the tubes from 1 t-10. Add $0.5-\mathrm{mL}$ of thoroughly mixed Test suspension from one container to the first test tube (Tube number 1) ef arow, mix, and transfer 0.5 mL to the next test tube (Tube number 2). Mix thereughly and transfer 0.5 mL to the next test tube (Tube number 3). Repent the procescof mixing and serially transferring to each consecutive tube and diseard 0.5 mL from the last test tube. Repeat the same process to serially dilute reconstituted vaceine from the-other containers sueh that the reconstituted vaccine from each container ean be diluted serially along separate rows. From-each row select the test tube that is expected to contain 10 to 50 efu, and the test tubes that have immediately higher and-immediately lower efu, and ineubate them-in a water bath at $42^{\circ}$ for about 10 mintutes. Add 0.5 mL of $A$ gat solt
tion to each test tube, mix thoroughly, transfer on a sterile $0.5 \%$ agar gel plate, and immediately spread the solution taiformly on the plate. Ineubate the plates at $35^{\circ}$ to $37^{\circ}$ for 3 to 4 weeks. For each container, count the number of eolenies on the plates that contain between 10 to 50-0f them and caleulate the-eftrin each-container.

Determine the number of viable units per mL by viable count on solid medium using a method suitable for the product to be examined. Alternatively, a validated biochemical method may be used. $\triangle U S P 28$

## BRIEFING

Benzoyl Peroxide Gel, USP 27 page 224. On the basis of numerous comments received, in the Chromatographic system under Related compounds, it is proposed to change the acceptance criteria for the resolution between methylparaben and benzoic acid in the chromatogram of the System suitability solution. The column dimensions and the gradient are also being modified to enhance this resolution.
(PA7b: B. Davani) RTS-40462-2

## Change to read:

## Related compounds-

Solution $A$-Prepare a filtered and degassed mixture of acetonitrile and glacial acetic acid (1000:1).

Solution B-Prepare a filtered and degassed mixture of water and glacial acetic acid (1000:1).

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Prepare a solution in acetonitrile containing $100 \mu \mathrm{~g}$ of benzoic acid and $60 \mu \mathrm{~g}$ of methylparaben per mL.

Test preparation-Transfer an accurately weighed quantity of Gel, equivalent to about 100 mg of benzoyl peroxide, to a $50-$ mL volumetric flask, add 25 mL of acetonitrile, shake vigorously to disperse the specimen, sonicate for 5 minutes, dilute with acetonitrile to volume, mix, and filter.
Standard preparation A-Prepare a solution of benzoic acid in acetonitrile containing $500 \mu \mathrm{~g}$ per mL .

Standard preparation B-Prepare a solution of ethyl benzoate in acetonitrile containing $20 \mu \mathrm{~g}$ per mL .

Standard preparation $C$-Prepare a solution of benzaldehyde in acetonitrile containing $20 \mu \mathrm{~g}$ per mL .

Standard preparation D-Prepare a solution of hydrous benzoyl peroxide, previously subjected to the Assay under Hydrous Benzoyl Peroxide, in acetonitrile containing the equivalent of $40 \mu \mathrm{~g}$ of anhydrous benzoyl peroxide per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $235-\mathrm{nm}$ detector and a $3.9 \mathrm{~mm} \times 15 \mathrm{em}$
${ }^{\Delta} 4.6-\mathrm{mm} \times 25-\mathrm{cm}_{\Delta U S P 28}$
column containing packing L1. The flow rate is about 1.2 mL per minute. The chromatograph is programmed as follows.

| $\begin{gathered} \text { Time } \\ \text { (minutes) } \end{gathered}$ | Solution A (\%) | $\begin{gathered} \text { Solution B } \\ (\%) \\ \hline \end{gathered}$ | Elution |
| :---: | :---: | :---: | :---: |
| 0 | 18 | 82 | equilibration |
| -10 | $18 \rightarrow 60$ | $82 \rightarrow 40$ | linear gradient |
| $\begin{gathered} \Delta_{0}-20 \hat{\wedge}^{U S P} 28 \\ 10-22 \end{gathered}$ | 60 | 40 | isocratic |
| ${ }^{\mathbf{4}} \mathbf{2 0 - 3 0}{ }_{\text {^USP28 }}$ |  |  |  |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between benzoic acid and methylparaben is not less than 3.0 ;

## ${ }^{\Delta} 2.0 ;_{\mathbf{\Delta U S P 2 8}}$

and the tailing factors for the benzoic acid and methylparaben peaks are not more than 2.0.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparations and the Test preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. The responses of any peaks obtained from the Test preparation corresponding to benzoic acid, ethyl benzoate, and benzaldehyde are not greater than those of the main peaks obtained from Standard preparation $A$ (25\%), Standard preparation B (1\%), and Standard preparation C (1\%), respectively; the response of any other impurity peak obtained from the Test preparation, other than the main benzoyl peroxide peak, any benzoic acid, ethyl benzoate, benzaldehyde, methylparaben, or propylparaben peak, and any solvent peak, is not more than that obtained from Standard preparation $D(2 \%)$; and the sum of the responses of all the impurity peaks, other than those of benzoic acid, ethyl benzoate, and benzaldehyde is not more than that obtained from Standard preparation $D(2 \%)$.

## BRIEFING

Benzoyl Peroxide Lotion, USP 27 page 225. It is proposed to change the title of this monograph to Benzoyl Peroxide Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40777-1

## Benzoyl Peroxide Lotion

(Current title—not to change until July 1, 2007) Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Benzoyl Peroxide Topical Emulsion

## Briefing

Benzoyl Peroxide Topical Emulsion-See briefing under Amphotericin $B$ Lotion.
(NL: C. Barnstein) RTS-40777-1

## Add the following:

## ©Benzoyl Peroxide Topical Emulsion

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Benzoyl Peroxide Lotion)
» Benzoyl Peroxide Topical Emulsion contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\mathrm{C}_{14} \mathrm{H}_{10} \mathrm{O}_{4}$.

Packaging and storage-Preserve in tight containers.

## Identification-

A: Dilute a quantity of Topical Emulsion with acetone to obtain a solution having a concentration of benzoyl peroxide equivalent to 10 mg per mL , and proceed with the solution so obtained as directed in the Identification test $A$ under Hydrous Benzoyl Peroxide, beginning with "Apply 5 $\mu \mathrm{L}$ of this solution." The solution responds to the test.

B: It responds to the Identification test under Benzoyl
Peroxide Gel.
$\mathbf{p H}\langle 791\rangle$ : between 2.8 and 6.6.

## Related compounds-

Solution A, Solution B, Mobile phase, Standard preparation A, Standard preparation B, Standard preparation C, Standard preparation D, Resolution solution, and Chromatographic system - Proceed as directed in the test for Related compounds under Benzoyl Peroxide Gel.

Test preparation-Transfer an accurately weighed quantity of Topical Emulsion, equivalent to about 100 mg of benzoyl peroxide, to a $50-\mathrm{mL}$ volumetric flask, add 25 mL of acetonitrile, shake vigorously to disperse the specimen, sonicate for 5 minutes, dilute with acetonitrile to volume, mix, and filter.

Procedure-Proceed with Topical Emulsion as directed for Procedure in the test for Related compounds under Benzoyl Peroxide Gel: it meets the limits stated.

## Assay-

Mobile phase, Internal standard solution, Standard preparation, and Chromatographic system-Proceed as directed in the Assay under Benzoyl Peroxide Gel.

Assay preparation-Prepare as directed for Assay preparation in the Assay under Benzoyl Peroxide Gel, using Topical Emulsion.

Procedure-Proceed as directed for Procedure in the Assay under Benzoyl Peroxide Gel. Calculate the quantity, in mg , of $\mathrm{C}_{14} \mathrm{H}_{10} \mathrm{O}_{4}$ in the portion of Topical Emulsion taken by the formula:

$$
125 C\left(R_{U} / R_{S}\right),
$$

in which $C$ is the concentration, in mg per mL , of benzoyl peroxide in the Standard preparation, and $R_{U}$ and $R_{S}$ are the ratios of benzoyl peroxide peak response to ethyl benzoate peak response obtained from the Assay preparation and the Standard preparation, respectively. $\Delta$ USP28
(Official July 1, 2007)

## Briefing

Benzyl Benzoate Lotion, USP 27 page 227. It is proposed to change the title of this monograph to Benzyl Benzoate Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40778-1

## Benzyl Benzoate Lotion

(Current title—not to change until July 1, 2007) Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Benzyl Benzoate Topical Emulsion

BRIEFING

Benzyl Benzoate Topical Emulsion-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40778-1

## Add the following:

## ©Benzyl Benzoate Topical Emulsion

## (Monograph under this new title-to become official July 1, 2007) <br> (Current monograph title is Benzyl Benzoate Lotion)

» Benzyl Benzoate Topical Emulsion contains not less than 26.0 percent and not more than 30.0 percent (w/w) of $\mathrm{C}_{14} \mathrm{H}_{12} \mathrm{O}_{2}$.

|  |  |
| :---: | :---: |
| Benzyl Benzoate . . . . . . . . . | 250 mL |
| Triethanolamine . . . . . . . . . | 5 g |
| Oleic Acid. . . . . . . . . . . . . | 20 g |
| Purified Water | 750 mL |
| To make about. . . . . . . . . . | 1000 mL |

Mix the Triethanolamine with the Oleic Acid, add the Benzyl Benzoate, and mix. Transfer the mixture to a suitable container of about 2000mL capacity, add 250 mL of Purified Water, and shake the mixture thoroughly. Finally add the remaining Purified Water, and again shake thoroughly.

Packaging and storage-Preserve in tight containers.
$\mathbf{p H}\langle 791\rangle$ : between 8.5 and 9.2.
Assay—Place about 5 g of Topical Emulsion, accurately weighed, in a conical flask. Add 25 mL of alcohol and 2 drops of phenolphthalein TS. Cool the solution to about $15^{\circ}$, and titrate quickly with 0.1 N sodium hydroxide to a slight pink color. Add 50.0 mL of 0.5 N alcoholic potassium hydroxide VS, connect the flask to a reflux condenser, and boil gently for 1 hour. Cool, promptly add phenolphthalein TS, and titrate with 0.5 N hydrochloric acid VS. Perform a blank determination (see Residual Titrations under Titrime$\operatorname{try}\langle 541\rangle$ ). Each mL of 0.5 N alcoholic potassium hydroxide is equivalent to 106.1 mg of $\mathrm{C}_{14} \mathrm{H}_{12} \mathrm{O}_{2 \cdot} \cdot \mathbf{\Delta S P P 2 8}$
(Official July 1, 2007)

Betamethasone Dipropionate Lotion, USP 27 page 236 and page 1430 of $P F 29(5)$ [Sept.-Oct. 2003]. It is proposed to change the title of this monograph to Betamethasone Dipropionate Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40779-1

## Betamethasone Dipropionate Lotion

(Current title—not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007
(see Official Title Changes on the first page of InProcess Revision):
See Betamethasone Dipropionate Topical Emulsion

## Change to read:

Packaging and storage-Preserve in tight containers.
-Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$. Protect from light and freezing. $\mathbf{w 2 S}_{\text {(USP27) }}$

## Change to read:

## Identifiention-

-Thin-layer chromatographic identification test〈201〉-■2S (USP27)
Transfer a quantity of Lotion, equivalent to about 0.6 mg of beta methasene dipropienate, to a 50 mL vial. Ade 10 mL of 0.1 N hy drechloric acid, then ade 4 mL of chloroform. Disperse on a vortex miver for about 1 minute, then shake vigoreusly for 10 minutes, and centrifuge at 2000 rpm for about 5 mimutes. Transfer the ehlereferm layer to a suitablevial. Proceed as directed in the Ident fification test under Betamethasone Dipropionate Gream, beginfimg with "Apply $40-\mu \mathrm{of}$ this solation."
-Test solution-Transfer a quantity of Lotion, equivalent to about 0.6 mg of betamethasone dipropionate, to a $50-\mathrm{mL}$ vial. Add 10 mL of 0.1 N hydrochloric acid, then add 4 mL of chloroform. Disperse on a vortex mixer for about 1 minute, then shake vigorously for 10 minutes, and centrifuge at 2000 rpm for about 5 minutes. Transfer the chloroform layer to a suitable vial.

Standard solution: USP Betamethasone Dipropionate RS in chloroform containing $150 \mu \mathrm{~g}$ per mL .

Application volume: $40 \mu \mathrm{~L}$.
Developing solvent system: a mixture of chloroform and acetone (7:1).

Procedure-Proceed as directed in the chapter.■2S (USP27)

Briefing
Betamethasone Dipropionate Topical Emulsion-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40779-1

## Add the following:

## -Betamethasone Dipropionate Topical Emulsion

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Betamethasone Dipropionate Lotion)
» Betamethasone Dipropionate Topical Emulsion contains an amount of betamethasone dipropionate $\left(\mathrm{C}_{28} \mathrm{H}_{37} \mathrm{FO}_{7}\right)$ equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of betamethasone $\left(\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{FO}_{5}\right)$.

Packaging and storage-Preserve in tight containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$. Protect from light and freezing.

USP Reference standards $\langle 11\rangle$ —USP Beclomethasone Dipropionate RS. USP Betamethasone Dipropionate RS.

Thin-layer chromatographic identification test $\langle 201\rangle$ -
Test solution-Transfer a quantity of Topical Emulsion, equivalent to about 0.6 mg of betamethasone dipropionate, to a $50-\mathrm{mL}$ vial. Add 10 mL of 0.1 N hydrochloric acid, then add 4 mL of chloroform. Disperse on a vortex mixer for about 1 minute, then shake vigorously for 10 minutes, and centrifuge at 2000 rpm for about 5 minutes. Transfer the chloroform layer to a suitable vial.

Standard solution: USP Betamethasone Dipropionate RS in chloroform containing $150 \mu \mathrm{~g}$ per mL .

Application volume: $40 \mu \mathrm{~L}$.

Developing solvent system: a mixture of chloroform and acetone (7:1).
Procedure-Proceed as directed in the chapter.
Minimum fill $\langle 755\rangle$ : meets the requirements.
Assay-
Mobile phase and Chromatographic system—Prepare as directed in the Assay under Betamethasone Dipropionate.
Internal standard solution-Prepare as directed in the Assay under Betamethasone Dipropionate, except to use chloroform as the solvent.

Standard preparation-Prepare as directed in the Assay under Betamethasone Dipropionate, except to use chloroform as the solvent. To 10.0 mL of 0.1 N hydrochloric acid in a capped $5-\mathrm{mL}$ centrifuge tube add 4.0 mL of the prepared solution, and treat this solution as follows. Cap, and shake vigorously for about 2 minutes, or disperse on a vortex mixer for about 1 minute. Centrifuge at 2500 rpm for about 3 minutes. Transfer the chloroform phase to a suitable vial. Evaporate the chloroform under a stream of nitrogen at a slightly elevated temperature to dryness. Cool the vial to room temperature, add 4.0 mL of methanol, and swirl to dissolve the residue.

Assay preparation-Transfer an accurately weighed quantity of Topical Emulsion, equivalent to about 1.2 mg of betamethasone dipropionate, to a capped $50-\mathrm{mL}$ centrifuge tube. Add 10.0 mL of 0.1 N hydrochloric acid, shake to disperse, then add 2.0 mL of Internal standard solution and 2.0 mL of chloroform. Proceed as directed under Standard preparation beginning with "Cap, and shake."

Procedure-Proceed as directed for Procedure in the $A s$ say under Betamethasone Dipropionate. Calculate the quantity, in mg , of betamethasone $\left(\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{FO}_{5}\right)$ in the portion of Topical Emulsion taken by the formula:
$(392.46 / 504.60)(4 C)\left(R_{U} / R_{S}\right)$,
in which 392.46 and 504.60 are the molecular weights of betamethasone and betamethasone dipropionate, respective$\mathrm{ly}, C$ is the concentration, in mg per mL , of USP Betamethasone Dipropionate RS in the Standard preparation; and $R_{U}$ and $R_{S}$ are the peak height ratios of the betamethasone dipropionate peak and the internal standard peak obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{U S P 2 8}$
(Official July 1, 2007)

## BRIEFING

Betamethasone Oral Solution, USP 27 page 231 and page 1009 of $P F$ 29(4) [July-Aug. 2003]; Betamethasone Syrup, USP 27 page 231 and page 1010 of $P F 29(4)$ [July-Aug. 2003]. On the basis of comments received concerning the revisions proposed in PF 29(4), it is proposed to make further revisions to the storage statement in the Packaging and storage section.

## (PA1: C. Anthony) RTS-40544-1

## Betamethasone Oral Solution

(Monograph under this new title-to become official June 1, 2005)
(Current monograph title is Betamethasone Syrup)

## Change to read:

Packaging and storage - Preserve in well elosed containers.
${ }^{\triangle}$ Store between $2^{\circ}$ and $25^{\circ}$, excursions permitted been
$15^{\circ}$ and up to $30^{\circ}$, protected from light. Preserve in a tight
container. Protect from freezing. $\triangle$ USP28

## Delete the following:

-Identifieation Evaperate 25 mL of the Assay preparation, prepared as direeted in the Assety, on a steam bath just to drymess, and dissolve the residte in 0.5 mL of aleohel. Proeed as direeted for Itentifican test $B$ under Betane, beginning with " $A p p l y$ $10 \mu \mathrm{~L}$ of this selution." ${ }^{1}$ 2S (USP27)

## Add the following:

-Thin-Layer Chromatographic Identification Test〈201〉—

Test solution-Evaporate 25 mL of the Assay preparation, prepared as directed in the Assay, on a steam bath just to dryness, and dissolve the residue in 0.5 mL of alcohol.

Developing solvent system: a mixture of chloroform and diethylamine (2:1).
Procedure-Proceed as directed in the chapter. Locate the spots by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots ap-

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pear.■2S (USP27)
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## BRIEFING

Betamethasone Syrup, USP 27 page 231 and page 1010 of $P F$ 29(4) [July-Aug. 2003]-See briefing under Betamethasone Oral Solution.

$$
\text { (PA1: C. Anthony) } \quad \text { RTS }-40544-1
$$

## Betamethasone Syrup

(Current title-not to change until June 1, 2005)
Monograph title change-to become official June 1, 2005
See Betamethasone Oral Solution

## Change to read:

Packaging and storage-Preservinell clores.
${ }^{4}$ Store between $2^{\circ}$ and $25^{\circ}$, excursions permitted $15^{\circ}$ up to $30^{\circ}$, protected from light. Preserve in a tight container. Protect from freezing. $\Delta U S P 28$

## Delete the following:

■Identifieation-Evaperate 25-mL of the Assay preparation, prepared as direeted in the $4 s$ scty on a steam bath-just to dryness, and dissolve the residue in 0.5 mb of alcohol. Proceed as directed for Itentificutest Bunder Betanethasone, begimning with " $A p p l y$ $10 \mu \mathrm{~L}$ of this solution." ${ }^{12 S}$ (USP27)

## Add the following:

-Thin-Layer Chromatographic Identification Test〈201〉—

Test solution-Evaporate 25 mL of the Assay preparation, prepared as directed in the Assay, on a steam bath just to dryness, and dissolve the residue in 0.5 mL of alcohol.

Developing solvent system: a mixture of chloroform and diethylamine (2:1).
Procedure-Proceed as directed in the chapter. Locate the spots by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear.■2S (USP27)

## BRIEFING

Betamethasone Valerate Lotion, USP 27 page 240. It is proposed to change the title of this monograph to Betamethasone Valerate Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40780-1

## Betamethasone Valerate Lotion

(Current title-not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Betamethasone Valerate Topical Emulsion

## Briefing

Betamethasone Valerate Topical Emulsion-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40780-1

## Add the following:

## $\triangle$ Betamethasone Valerate Topical Emulsion

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Betamethasone Valerate Lotion)
» Betamethasone Valerate Topical Emulsion contains an amount of Betamethasone Valerate $\left(\mathrm{C}_{27} \mathrm{H}_{37} \mathrm{FO}_{6}\right)$ equivalent to not less than 95.0 percent and not more than 115.0 percent of the labeled amount of betamethasone $\left(\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{FO}_{5}\right)$.

Packaging and storage-Preserve in tight, light-resistant containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Betamethasone Valerate $R S$.

Identification-Mix an amount of Topical Emulsion, equivalent to about 5 mg of betamethasone, with a mixture of methanol and chloroform (2:1) to make 10 mL . Apply 20 $\mu \mathrm{L}$ of this solution and $20 \mu \mathrm{~L}$ of a Standard solution of USP Betamethasone Valerate RS in a mixture of methanol and chloroform (2:1) containing 0.6 mg per mL to a suitable thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ) coated with a $0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of chloroform and ethyl acetate (1:1), until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. View the spots under UV light: the $R_{F}$ value of the principal spot obtained from the test solution corresponds to that obtained from the Standard solution.

Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.

Minimum fill $\langle 755\rangle$ : meets the requirements.
$\mathbf{p H}\langle 791\rangle$ : between 4.0 and 6.0.

## Assay-

Mobile phase and Chromatographic system-Proceed as directed in the Assay under Betamethasone Valerate.

Internal standard solution-Transfer about 50 mg of beclomethasone dipropionate to a $25-\mathrm{mL}$ volumetric flask, add chloroform to volume, and mix.

Standard preparation-Transfer about 40 mg of USP Betamethasone Valerate RS, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, add chloroform to volume, and mix. Pipet 2 mL of this solution into a $50-\mathrm{mL}$ centrifuge tube, add 10 mL of 0.1 N hydrochloric acid, then add 2.0 mL of Internal standard solution. Insert the stopper into the tube, shake vigorously for about 2 minutes, and centrifuge to separate the phases. Using a syringe, transfer the lower, chloroform phase to a small stoppered vial. Evaporate the chloroform on a steam bath, at low heat, with the aid of a stream of nitrogen. Add 4.0 mL of a 1 in 1000 solution of glacial acetic acid in methanol, and swirl to dissolve the residue.

Assay preparation-Transfer an accurately weighed portion of Topical Emulsion, equivalent to about 2.5 mg of betamethasone, to a stoppered, $50-\mathrm{mL}$ centrifuge tube. Add 10.0 mL of 0.1 N hydrochloric acid, insert the stopper, and shake to disperse the specimen. Add 2.0 mL of chloroform and 2.0 mL of Internal standard solution, insert the stopper, and proceed as directed for Standard preparation, beginning with "shake vigorously for about 2 minutes."

Procedure-Proceed as directed for Procedure in the Assay under Betamethasone Valerate. Calculate the quantity, in mg , of betamethasone $\left(\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{FO}_{5}\right)$ in the portion of Topical Emulsion taken by the formula:

$$
(392.46 / 476.59)(4 C)\left(R_{U} / R_{S}\right),
$$

in which 392.46 and 476.59 are the molecular weights of betamethasone and betamethasone valerate, respectively; $C$ is the concentration, in mg per mL, of USP Betamethasone Valerate RS in the Standard preparation; and $R_{U}$ and $R_{S}$ are the peak response ratios obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{U S P P 2 8}$
(Official July 1, 2007)

## BRIEFING

Caffeine Injection, page 1992 of $P F$ 28(6) [Nov.-Dec. 2002]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded with changes to In-Process Revision. It is proposed to change the name to Caffeine Citrate Injection to reflect the name of the registered product, to revise the Definition to specify that the solution is prepared with Water for Injection and does not contain any preservative, and to add a test for Color and clarity.
(PA3: S. Salado; NL: C. Barnstein) RTS-39923-4

## Add the following:

## -Caffeine Citrate Injection

## » Caffeine Citrate Injection is a sterile solution containing Citric Acid and an amount of Caffeine equivalent to Caffeine and citric acid in Water for Injection. It contains not less than 90.0 percent

and not more than 110.0 percent of the labeled amount of caffeine $\left(\mathrm{C}_{8} \mathrm{H}_{10} \mathrm{~N}_{4} \mathrm{O}_{2}\right)$. It contains no bacteriostat or other preservative.

Packaging and storage-Preserve in single-dose, tight containers of Type I glass, and store at a temperature between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle —$ USP Caffeine RS. USP
Endotoxin RS.

## Identification-

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

B: It meets the requirements of the test for Citrate $\langle 191\rangle$.

C: Transfer about 4 g of potassium iodide to a $100-\mathrm{mL}$ volumetric flask. Add 10 mL of water, and shake until the potassium iodide is dissolved. Transfer 2 g of iodine to the volumetric flask, and shake until dissolved. Dilute with water to volume, and mix. Transfer 5 drops of the solution so obtained to a $25-\mathrm{mL}$ centrifuge tube containing 5.0 mL of the Injection, and mix. Add 0.5 mL of 2.0 M hydrochloric acid solution, and mix: a brown precipitate is produced that dissolves on neutralization with 0.5 mL of sodium hydroxide TS.

Color and clarity-Transfer a suitable portion of the Injection to a clear glass test tube, and visually examine the solution in a well-lighted area: the solution is colorless and free of haze, obvious turbidity, and precipitate.

Bacterial endotoxins $\langle 85\rangle$ : not more than 0.25 USP Endotoxin Unit per mg of caffeine.

Sterility $\langle 71\rangle$-It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.
$\mathbf{p H}\langle 791\rangle$ : between 4.2 and 5.2.
Particulate matter $\langle 788\rangle$ : not more than 150 particles are equal to or greater than $10 \mu \mathrm{~m}$ and not more than 25 particles are equal to or greater than $25 \mu \mathrm{~m}$.

## Related compounds-

Mobile phase and Theophylline solution-Proceed as directed in the Assay.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.
System sensitivity solution-Transfer 2.5 mL of the Standard solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay. Chromatograph the System sensitivity solution, and record the peak responses as directed for Procedure: the theophylline peak produces a discernible peak response at its retention time.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of any related compound in the portion of Injection taken by the formula:

$$
100 F\left(C_{S} / C_{W}\right)\left(r_{i} / r_{S}\right)
$$

in which $F$ is the relative response factor and is equal to 0.878 for theobromine at a relative retention time of about 0.4 , equal to 1.10 for paraxanthine at a relative retention time of about 0.6 , equal to 0.905 for theophylline at a relative retention time of about 0.7 , and equal to 1.0 for any other related compound; $C_{S}$ is the concentration, in mg per mL , of USP Caffeine RS in the Standard solution; $C_{W}$ is the caffeine concentration, in mg per mL , in the Test solution, as obtained in the Assay; $r_{i}$ is the individual peak response for each related compound obtained from the Test solution; and
$r_{S}$ is the caffeine peak response obtained from the Standard solution: not more than $0.10 \%$ of any individual related compound is found; and not more than $0.1 \%$ of total impurities is found.

Other requirements-It meets the requirements under Injections $\langle 1\rangle$.

## Assay-

Mobile phase-Prepare a mixture of 0.01 M sodium acetate, acetonitrile, and tetrahydrofuran (191:5:4). Adjust with glacial acetic acid to a pH of 4.5 , filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Theophylline solution-Dissolve an accurately weighed quantity of theophylline in water, and dilute quantitatively, and stepwise if necessary, with water, to obtain a solution having a concentration of about 0.02 mg per mL .

Standard preparation-Transfer about 5 mg of USP Caffeine RS, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask. Add 5 mL of the Theophylline solution, dissolve in and dilute with water to volume, and mix.

Assay preparation-Transfer an accurately measured volume of Injection, equivalent to about 50 mg of caffeine, to a $250-\mathrm{mL}$ volumetric flask. Dilute with water to volume, mix, and filter through a polyvinylidene difluoride or equivalent membrane having a porosity of $0.45 \mu \mathrm{~m}$.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $275-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 150-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for theophylline and 1.0 for caffeine; the resolution, $R$, between theophylline and caffeine is not less than 6.0 ; the tailing factor, determined from the theo-
phylline and caffeine peaks, is not more than 2.0 ; and the relative standard deviation for replicate injections, determined from the caffeine peaks, is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the caffeine peak responses. Calculate the quantity, in mg , of caffeine $\left(\mathrm{C}_{8} \mathrm{H}_{10} \mathrm{~N}_{4} \mathrm{O}_{2}\right)$ in the volume of Injection taken by the formula:

$$
250 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Caffeine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. USP28 $^{\text {U }}$

## Briefing

Caffeine Oral Solution, page 1994 of $P F 28(6)$ [Nov.-Dec. 2002]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded with changes to In-Process Revision. It is proposed to change the name to Caffeine Citrate Oral Solution to reflect the name of the registered product. It is also proposed to revise the Definition to specify that the solution does not contain any preservative.
(PA3: S. Salado; NL: C. Barnstein) RTS—39923-5

## Add the following:

## ${ }^{\Delta}$ Caffeine Citrate Oral Solution

## » Caffeine Citrate Oral Solution is a sterile aque-

 ous solution containing Citric Acid and an amount of Caffeine equivalent to Caffeine and citric acid. It contains not less than 90.0 percent and not morethan 110.0 percent of the labeled amount of caffeine $\left(\mathrm{C}_{8} \mathrm{H}_{10} \mathrm{~N}_{4} \mathrm{O}_{2}\right)$. It contains no bacteriostat or other preservative.

Packaging and storage-Preserve in single-dose, tight containers of Туpe I glass, and store at a temperature between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Caffeine RS.

## Identification-

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

B: It meets the requirements of the test for Citrate $\langle 191\rangle$.

C: Transfer about 4 g of potassium iodide to a $100-\mathrm{mL}$ volumetric flask. Add 10 mL of water, and shake until the potassium iodide is dissolved. Transfer 2 g of iodine to the volumetric flask, and shake until dissolved. Dilute with water to volume, and mix. Transfer 5 drops of the solution so obtained to a $25-\mathrm{mL}$ centrifuge tube containing 5.0 mL of the Oral Solution, and mix. Add 0.5 mL of 2.0 M hydrochloric acid solution, and mix: a brown precipitate is produced that dissolves on neutralization with 0.5 mL of sodium hydroxide TS.

Sterility $\langle 71\rangle$-It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.
$\mathbf{p H}\langle 791\rangle$ : between 4.2 and 5.2.

## Related compounds-

Mobile phase and Theophylline solution-Proceed as directed in the Assay.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

System sensitivity solution-Transfer 2.5 mL of the Standard solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay. Chromatograph the System sensitivity solution, and record the peak responses as directed for Procedure: the theophylline peak produces a discernible peak response at its retention time.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of any related compound in the portion of Oral Solution taken by the formula:

$$
100 F\left(C_{S} / C_{W}\right)\left(r_{i} / r_{S}\right)
$$

in which $F$ is the relative response factor and is equal to 0.878 for theobromine at a relative retention time of about 0.4 , equal to 1.10 for paraxanthine at a relative retention time of about 0.6 , equal to 0.905 for theophylline at a relative retention time of about 0.7 , and equal to 1.0 for any other related compound; $C_{S}$ is the concentration, in mg per mL , of USP Caffeine RS in the Standard solution; $C_{W}$ is the caffeine concentration, in mg per mL , in the Test solution, as obtained in the Assay; $r_{i}$ is the individual peak response for each related compound obtained from the Test solution; and $r_{S}$ is the caffeine peak response obtained from the Standard solution: not more than $0.10 \%$ of any individual related compound is found; and not more than $0.1 \%$ of total impurities is found.

Assay-
Mobile phase-Prepare a mixture of 0.01 M sodium acetate, acetonitrile, and tetrahydrofuran (191:5:4). Adjust with glacial acetic acid to a pH of 4.5 , filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Theophylline solution-Dissolve an accurately weighed quantity of theophylline in water, and dilute quantitatively, and stepwise if necessary, with water, to obtain a solution having a concentration of about 0.02 mg per mL .

Standard preparation-Transfer about 5 mg of USP Caffeine RS, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask. Add 5 mL of the Theophylline solution, dissolve in and dilute with water to volume, and mix.

Assay preparation-Transfer an accurately measured volume of Oral Solution, equivalent to about 50 mg of caffeine, to a $250-\mathrm{mL}$ volumetric flask. Dilute with water to volume, mix, and filter through a polyvinylidene difluoride or equivalent membrane having a porosity of $0.45 \mu \mathrm{~m}$.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a $275-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 150-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for theophylline and 1.0 for caffeine; the resolution, $R$, between theophylline and caffeine is not less than 6.0 ; the tailing factor, determined from the theophylline and caffeine peaks, is not more than 2.0 ; and the relative standard deviation for replicate injections, determined from the caffeine peaks, is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and
measure the caffeine peak responses. Calculate the quantity, in mg, of caffeine $\left(\mathrm{C}_{8} \mathrm{H}_{10} \mathrm{~N}_{4} \mathrm{O}_{2}\right)$ in the volume of Oral Solution taken by the formula:

$$
250 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Caffeine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta}$ USP28

## BRIEFING

Calamine Lotion, USP 27 page 296. It is proposed to change the title of this monograph to Calamine Topical Suspension. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40781-1

## Calamine Lotion

(Current title-not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Calamine Topical Suspension

## BRIEFING

Phenolated Calamine Lotion, USP 27 page 296. It is proposed to change the title of this monograph to Phenolated Calamine Topical Suspension. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40782-1

## Phenolated Calamine Lotion

(Current title-not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007
(see Official Title Changes on the first page of InProcess Revision): See Phenolated Calamine Topical Suspension

## BRIEFING

Calamine Topical Suspension-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40781-1

## Add the following:

## ${ }^{\Delta}$ Calamine Topical Suspension

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Calamine Lotion)
» Prepare Calamine Topical Suspension as follows.

$$
\begin{aligned}
& \text { Calamine. . . . . . . . . . . . . . . . . . } 80 \mathrm{~g} \\
& \text { Zinc Oxide . . . . . . . . . . . . . . . . . } \quad 80 \mathrm{~g} \\
& \text { Glycerin . . . . . . . . . . . . . . . . . . . } 20 \mathrm{~mL} \\
& \text { Bentonite Magma . . . . . . . . . . . . } 250 \mathrm{~mL} \\
& \text { Calcium Hydroxide Topical Solu- } \\
& \text { tion, a sufficient quantity, to make } 1000 \mathrm{~mL}
\end{aligned}
$$

Dilute the Bentonite Magma with an equal volume of Calcium Hydroxide Topical Solution. Mix the powders intimately with the Glycerin and about 100 mL of the diluted magma, triturating until a smooth, uniform paste is formed. Gradu-
ally incorporate the remainder of the diluted magma. Finally add enough Calcium Hydroxide Topical Solution to make 1000 mL , and shake.

If a more viscous consistency in the Calamine Topical Suspension is desired, the quantity of Bentonite Magma may be increased to not more than 400 mL .

NOTE-Shake the Calamine Topical Suspension before dispensing.

Packaging and storage-Preserve in tight containers.
Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa. $\mathbf{\Delta S P P 2 8}$
(Official July 1, 2007)

BriEfing

Phenolated Calamine Topical Suspension-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40782-1

## Add the following:

## ©Phenolated Calamine Topical Suspension

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Phenolated Calamine Lotion)
» Prepare Phenolated Calamine Topical Suspen-sion as follows:
Liquefied Phenol ..... 10 mL
Calamine Topical Suspension ..... 990 mL
To make. . . . . . . . . . . . . . . . 1000 mL
Mix the ingredients.

## NOTE-Shake Phenolated Calamine Topical

## Suspension before dispensing.

Packaging and storage-Preserve in tight containers. $\triangle$ USP28
(Official July 1, 2007)

## BRIEFING

Methionine C 11 Injection, USP 27 page 332. It is proposed to revise the Definition to allow for alternative chemistry labeling.
(RMI: A. Wilk) RTS-40885-1

## Methionine C 11 Injection

## Delete the following:



## Briefing

Cephapirin Benzathine, USP 27 page 397; Cephapirin Benzathine Intramammary Infusion, USP 27 page 398; Cephapirin Sodium, USP 27 page 398; Cephapirin for Injection, USP 27 page 398; Cephapirin Sodium Intramammary Infusion, USP 27 page 399. It is proposed to replace the microbial-based Assay specified in the Cephapirin Benzathine, Cephapirin Benzathine Intramammary Infusion, and Cephapirin Sodium Intramammary Infusion, monographs with a new HPLC-based method. It is proposed to replace the official HPLC-based Assay specified in the Cephapirin Sodium monograph with this new HPLC-based method in the interest of consistency. The liquid chromatographic procedure in the Assay is based on analyses performed with the Perkin-Elmers RP-18 Newguard, 7- $\mu \mathrm{m} \mathrm{L1}$ brand guard column, and a Waters Novapak C18, 4- $\mu \mathrm{m}$ L1 brand analytical column. Because USP has not received validation data that indicate this new HPLC method is suitable for Cephapirin for Injection, it is proposed to revise the Assay of the monograph to specify the details for performing the Assay and removing the linkage to the Cephapirin Sodium monograph. Interested parties are encouraged to submit comments and to perform validation studies that would indicate whether the new HPLC method is suitable for Cephapirin for Injection.
(VET: I. DeVeau) RTS—39799-1; 40505-1

## Change to read:

Assay - Proe das direeted for Cephapirin mader Antibioties Mi erobial Asseays- $\langle 84\rangle$, preparing the Test Dilution as follows. Tramsfer about 150 mg of Cephapirin Benzathine, aceurately weighed, to a 100 mL volumetric flask, add 20 mL of 0.1 N hydrechloric acid, and swirl to dissolve. Dilute with Buffer No. 1 to volume, and mix. Pilute an aceurately measured volume of this stock solution with Buffer No. 1 to obtain a Test Dilution having an estimated concentration of $1.3 \mu \mathrm{~g}$ of eephapirin benzathine $(1.0 \mu \mathrm{~g}$ of cephapirin $)$ per mL.
${ }^{4}$ Solution A-Transfer about 26.2 mL of acetic acid and about 99.12 g of potassium acetate to a 4-L volumetric flask. Add 2000 mL of water, and mix to dissolve. Dilute with water to volume, and pass through a $0.45-\mu \mathrm{m}$ nylon filter.
Solution B: acetonitrile.
Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments, if necessary (see System Suitability under Chromatography (621〉).

Extraction solution: a mixture of 400 mL of acetic acid and 600 mL of water.

Dilution buffer-Dissolve about 205 g of potassium acetate in about 800 mL of water. Adjust with acetic acid to a pH of 7.5 to 8.2. Dilute with water to 1000 mL , and pass through a $0.45-\mu \mathrm{m}$ nylon filter.
$10 \%$ Acetic acid solution-Add about 10.0 mL of acetic acid to a $100-\mathrm{mL}$ volumetric flask. Mix, and dilute with water to volume.

System suitability solution-Dissolve an accurately weighed quantity of USP Cephapirin Sodium RS in $10 \%$ Acetic acid solution to prepare a solution containing a known concentration of about 2.0 mg per mL . Heat the solution at $50^{\circ}$ for 12 to 18 hours.

Standard preparation-In duplicate, accurately weigh about 50 mg of USP Cephapirin Sodium RS, and transfer into a $25-\mathrm{mL}$ volumetric flask. Add about 2.5 mL of Extraction solution and about 15.0 mL of Dilution buffer, and agitate to dissolve. Add 7.0 mL of acetonitrile, and mix well. Allow the solution to return to room temperature, and dilute with water to volume.

Assay preparation-In duplicate, weigh about 60 mg of Cephapirin Benzathine, and transfer into a $25-\mathrm{mL}$ volumetric flask. Add about 2.5 mL of Extraction solution and 15.0 mL of Dilution buffer, and mix to dissolve. Add 7.0 mL of acetonitrile, and mix. Allow the flask to return to room temperature, and dilute with water to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $260-\mathrm{nm}$ detector, a $3.2-\mathrm{mm} \times 15-\mathrm{mm}$ guard column that contains $7-\mu \mathrm{m}$ packing L 1 and a $3.9-\mathrm{mm} \times 15-\mathrm{cm}$ analytical column that contains $4-\mu \mathrm{m}$ packing L 1 . The flow rate is about 2.0 mL per minute, and the columns are heated to $40^{\circ}$. The chromatograph is programmed as follows.

| Time | Solution A |  |  |
| :---: | :---: | :---: | :--- |
| (minutes) | $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| $0-6$ | 91.5 | 8.5 | isocratic |
| $6-10$ | $91.5 \rightarrow 80.0$ | $8.5 \rightarrow 20.0$ | linear |
| $10-12$ | 80.0 | 20.0 | isocratic |
| 12 | $80.0 \rightarrow 91.5$ | $20.0 \rightarrow 8.5$ | return to initial |
| $12-21$ | 91.5 | 8.5 | re-equilibration |

Chromatograph the System suitability solution and the Standard preparation, and record the peak heights and valleys as directed for Procedure. Using the results from the System suitability solution, calculate the percentage of the height of the valley taken by the formula:

$$
100\left(r_{V} / r_{i}\right)
$$

in which $r_{V}$ is the height of the valley between cephapirin and any impurity; and $r_{i}$ is the impurity peak height. The percentage of the height of the valley is not more than $25 \%$ for the impurity peaks adjacent to the cephapirin peak. [NOTE-The System suitability solution is acceptable as long as the cephapirin peak is larger than the two peaks on either side of the cephapirin peak. ] The relative standard deviation for replicate injections of the Standard preparation is not more than $3.0 \%$.

Procedure-Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of the duplicate Standard preparation and the duplicate Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in $\mu \mathrm{g}$, of $\mathrm{C}_{17} \mathrm{H}_{17} \mathrm{~N}_{3} \mathrm{O}_{6} \mathrm{~S}_{2}$ in each mg of Cephapirin Benzathine taken by the formula:

$$
P\left(W_{S} / W_{U}\right)\left(V_{U} / V_{S}\right)\left(r_{U} / r_{S}\right)
$$

in which $P$ is the assigned potency, in $\mu \mathrm{g}$ of cephapirin per mg , of USP Cephapirin Sodium RS; $W_{S}$ and $W_{U}$ are the quantities of USP Cephapirin Sodium RS and Cephapirin Benzathine, in mg, used to prepare the Standard prepara-
tion and Assay preparation, respectively; $V_{S}$ and $V_{U}$ are the final volumes, in mL, of the Standard preparation and Assay preparation, respectively; and $r_{U}$ and $r_{S}$ are the average peak areas of the cephapirin peaks obtained from the Assay preparation, and the Standard preparation, respectively. $\Delta$ USP28

## Briefing

Cephapirin Benzathine Intramammary Infusion, USP 27 page 398-See briefing under Cephapirin Benzathine.
(VET: I. DeVeau) RTS—39799-2; 40505-2

## Change to read:

Assay Proceed as directed for Cephapirin under Antibiotics_Mi erobial Assayis $\langle 84$, preparing the Test Dilution as follows. Weigh 1 syringe of Intramammary Infusion. Expel the content of the sy ringe into a large blender jar containing. 1 mL of polysorbate 80 and sufficient 0.1 N hydrechloric acid to yield a volume of 500.0 mL , and blend at low speed for about 5 minntes. Weigh the empy sy ringe, and determine the weight of the Intramammary Infusion added to the blender jar. Allow the blended suspension to stand for about 5 -minutes to degas, then-dilute an aceurately measured velume of this solution quantitatively with Buffer No. 1 to obtain a Test Dildtion having an estimated concentration assumed to be equal to the median dose level of the Standard.
$\triangle$ Solution A, Solution B, Mobile phase, Extraction solution, Dilution buffer, 10\% Acetic acid solution, System suitability solution, Standard preparation, and Chromatographic system-Proceed as directed in the Assay under Cephapirin Benzathine.

Assay preparation-Express the entire contents of a syringe of the Intramammary Infusion into a centrifuge tube. For each mL of Intramammary Infusion, add $1.0 n$-heptane and 1.5 mL of Extraction solution, cap, and vortex at high speed for 5 minutes. Centrifuge for 5 minutes at a sufficient speed to break the emulsion. Remove the aqueous layer, and pass through a $0.45-\mu \mathrm{m}$ nylon filter, discarding the first 0.5
mL . Transfer 2.5 mL of the filtered aqueous phase into a $25-$ mL volumetric flask that contains a solution composed of 15.0 mL of Dilution buffer and 7.0 mL of acetonitrile. Add water to volume, and mix well to obtain a single phase.

Procedure-Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of the duplicate Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas of the major peaks. Calculate the quantity, in mg , of cephapirin $\left(\mathrm{C}_{17} \mathrm{H}_{17} \mathrm{~N}_{3} \mathrm{O}_{6} \mathrm{~S}_{2}\right)$ in each syringe of Intramammary Infusion taken by the formula:

$$
15 P W\left(V_{U} / V_{S}\right)\left(r_{U} / r_{S}\right),
$$

in which $P$ is the assigned potency, in $\mu \mathrm{g}$ cephapirin per mg , of USP Cephapirin Sodium RS; $W$ is the quantity of USP Cephapirin Sodium RS, in mg, used to prepare the Standard preparation; $V_{S}$ is the final volume, in mL , of the Standard preparation; $V_{U}$ is the entire volume of Intramammary Infusion, in mL , in one syringe; and $r_{U}$ and $r_{S}$ are the peak area and the average peak area of the cephapirin peaks obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta U S P 2 8}$

## BRIEFING

Cephapirin for Injection, USP 27 page 398—See briefing under Cephapirin Benzathine.
(VET: I. DeVeau) RTS-39942-1

## Change to read:

## Assay-

Mobile phase, Resolution solution, Standerd pre paration, and Chromatographic system- Prepare as direeted in the Assely under Gephapirin Sodinal.
${ }^{\Delta}$ Mobile phase-Prepare a filtered and degassed mixture of water, dimethylformamide, glacial acetic acid, and 11.7 N potassium hydroxide (1834:160:4:2). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ). Increase the proportion of dimethylformamide to decrease the retention time of cephapirin.

Resolution solution-Prepare a solution of Cephapirin Sodium in pH 2.0 hydrochloric acid buffer (see Buffer Solutions in the section Reagents, Indicators, and Solutions) containing about 1 mg per mL . Place 10 mL of this solution in a test tube and heat at $95^{\circ}$ for 10 minutes, accurately timed. Promptly cool the tube in an ice water bath. Dilute 5 mL of the cooled solution with Mobile phase to obtain

## 50 mL of Resolution solution.

Standard preparation-Transfer about 21 mg of USP Cephapirin Sodium RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. This solution contains about 0.2 mg of cephapirin per

## mL . $\triangle$ USP28

Assay preparation 1 (where it is packaged for dispensing and is represented as being in a single-dose container)-Constitute Cephapirin for Injection in a volume of water, accurately measured, corresponding to the volume of solvent specified in the labeling. Withdraw all of the withdrawable contents, using a suitable hypodermic needle and syringe, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution containing the equivalent of about 0.2 mg of cephapirin per mL .

Assay preparation 2 (where the label states the quantity of cephapirin in a given volume of constituted solution)-Constitute Cephapirin for Injection in a volume of water, accurately measured, corresponding to the volume of solvent specified in the labeling. Dilute an accurately measured volume of the constituted solution quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution containing the equivalent of about 0.2 mg of cephapirin per mL. [NOTE-Use the Standard preparation and the Assay preparation within 1 hour.]
©Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the cephapirin peak and the peak having a retention time of about 0.9 relative to that of cephapirin is not less

than 0.9. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for cephapirin lactone and 1.0 for cephapirin; the column efficiency determined from the cephapirin peak is not less than 1200 theoretical plates; the tailing factor for the cephapirin peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$. | USP28 |
| :--- |

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the appropriate Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of cephapirin $\left(\mathrm{C}_{17} \mathrm{H}_{17} \mathrm{~N}_{3} \mathrm{O}_{6} \mathrm{~S}_{2}\right)$ withdrawn from the container, or in the portion of constituted solution, taken by the formula:

$$
(L / D)(C P / 1000)\left(r_{U} / r_{S}\right),
$$

in which $L$ is the labeled quantity, in mg , of cephapirin in the sin-gle-dose container, or in the volume of constituted solution taken; $D$ is the concentration, in mg per mL , of cephapirin in Assay preparation 1 or in Assay preparation 2, on the basis of the labeled quantity in the container, or in the portion of constituted solution taken, respectively, and the extent of dilution; $C$ is the concentration, in mg per mL, of USP Cephapirin Sodium RS in the Standard preparation; $P$ is the potency, in $\mu \mathrm{g}$ of cephapirin per mg , of USP Cephapirin Sodium RS; and $r_{U}$ and $r_{S}$ are the cephapirin peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Briefing
Cephapirin Sodium, USP 27 page 398-See briefing under Cephapirin Benzathine.
(VET: I. DeVeau) RTS—39799-3; 40505-3

## Change to read:

## Assay-

Mobile phase Prepare a fltered and degassed mix dimethylformamide, glacial acetic acid, and 11.7 N petassitum hy droxide (1834:160:4:2). Make adjustments-if neeessary (see-Syis tem Suitability under Chromatography $\langle 621\rangle$ ). Inerease the propertion of dimethylformamide to decrease the retention time of eephapirim.

Resolution-solution Prepare- a solution-of Cephapirin Sodium in pH 2.0 hydrochloric acid buffer (see Buffer Solutions in the see tion Reagents, Indicators, and Selutions) containing about 1 mg per mL . Place 10 mL of this solution in a test tube and heat at $95^{\circ}$ for 10 minutes, aeeurately timed. Promptly cool the tube-in an-iee water bath. Dilute-5 mL of the cooled solution with Mobite phase to-obtain $50-\mathrm{mL}$ of Resolution selution.

Standard preparation Transfer about 21 mg of USP Cephapir in Sodium RS, aceurately weighed, to a 100 mL volumetric flask, dilute with Mobile phase to volume, and mix. This solution con tins about 0.2 mg of cephapirin per mL .

Assay preparation Transfer about 42 mg of Cephapirin So dium, aceurately weighed, to a 200 mL volumetric flack, dilute with Mobile phase to volume, and mix. [NOTE-Use the Stateded preparan and the Assay preparation within 1 hour.]

Chromatographic system (see Chromatography $\langle 621$ ) ) The tiquid chromatograph is equipped with a 254 nm detector and a $4 \mathrm{~mm} \times 30 \mathrm{~cm}$ columa that contains packing L 1 . The flow rate is abeut 2 mL per minte. Chremategraph the Resolution solution, and record the peak responses as directed under Proedtre: the resolution, $R$, between the eephapirin peak and the peak having a retention time of about 0 ., relative to that of eephapirin is not less than 0.9 . Chromatograph the Steded preparation, and record the peak respenses as directed under Procedure: the column efficiency determined from the cephapirin peak is not less than 1200 theore tieal plates, the tailing factor for the eephapirin peak is not more than 2.0 , and the relative standard deviation for replieate injections is net mere han $2.0 \%$.

Proedure- Separately inject equal volumes (about 20- $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation int the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0 . 9 for eephapirin lactone and 1.0 for eephapirin. Caleulate the quantity, in Hg, of eephapirin $\left(\mathrm{C}_{42} \mathrm{H}_{47} \mathrm{~N}_{3} \Theta_{6} \mathrm{~S}_{2}\right)$ per mg of the-Cephapirin So ditm taken by the formula:

$$
200(C P / H)\left(+_{4}+T_{s}\right)
$$

in which $C$ is the eoneentration, in me per mL, of USP Cephapirim Sodium PS in the Standard preparation, $P$ is the peteney, in 4 of of eephapirim per mo, of USP Cephapirin Sodium $P S$, Wis the quan tity, in mo of Cephapirin Sodium takento prepare the Assty prepatation, and $r_{5}$ and $r_{s}$ are the eephapirin peak respenses obtained from the Assay preparation and the Standard preparation, respec tively.
$\triangle$ Solution A, Solution B, Mobile phase, Extraction solution, Dilution buffer, 10\% Acetic acid solution, System suitability solution, Standard preparation, and Chromatographic system-Proceed as directed in the Assay under Cephapirin Benzathine.
Assay preparation-In duplicate, weigh about 50 mg of Cephapirin Sodium, and transfer into a $25-\mathrm{mL}$ volumetric flask. Add about 2.5 mL of Extraction solution and 15.0 mL of Dilution buffer, and mix to dissolve. Add 7.0 mL of acetonitrile, and mix. Allow the flask to return to room temperature, and dilute with water to volume.
Procedure-Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of the duplicate Standard preparation and the duplicate $A s$ say preparation into the chromatograph, record the chroma-
tograms, and measure the areas of the major peaks. Calculate the quantity, in $\mu \mathrm{g}$, of cephapirin $\left(\mathrm{C}_{17} \mathrm{H}_{17} \mathrm{~N}_{3} \mathrm{O}_{6} \mathrm{~S}_{2}\right)$ in each mg of Cephapirin Sodium taken by the formula:

$$
P\left(W_{S} / W_{U}\right)\left(V_{U} / V_{S}\right)\left(r_{U} / r_{S}\right)
$$

in which $P$ is the assigned potency, in $\mu \mathrm{g}$ of cephapirin per mg , of USP Cephapirin Sodium RS; $W_{S}$ and $W_{U}$ are the quantities of USP Cephapirin Sodium RS and Cephapirin Sodium, in mg, used to prepare the Standard preparation and the Assay preparation, respectively; $V_{U}$ and $V_{S}$ are the final volumes, in mL, of the Assay preparation and the Standard preparation, respectively; and $r_{U}$ and $r_{S}$ are the average peak areas of the cephapirin peaks obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{U S P 2 8}$

## BRIEFING

Cephapirin Sodium Intramammary Infusion, USP 27 page 399-See briefing under Cephapirin Benzathine.
(VET: I. DeVeau) RTS-39799-4; 40505-4

## Change to read:

Assay-Proe das direeted for Cephapirin under Antibioties Mi erobiah Assayis $\langle 81\rangle$, preparing the Test Dilution as follows. Weigh 4 syring of Intramammary Infusion. Expel the contents of the sy ringe into a large blender jar containing 1 mL of polysorbate 80 and sufficient 0.1 N hydrochloric acid to yield a volume of 500.0 mL , and blend at low speed for about 5 minutes. Weigh the empty sy ringe, and determine the weight of the Intramammary Infusion added to the blender jar. Allow the blended suspension to stand for about 5 minutes to degas, then dilute an aceurately measured velume of this solution quantitatively with Buffer No. 1 to obtain a- Test Dilution having an estimated eoncentration assumed to be equal to the median dose level of the Standard.
${ }^{\wedge}$ Solution A, Solution B, Mobile phase, Extraction solution, Dilution buffer, 10\% Acetic acid solution, System suitability solution, Standard preparation, and Chromatographic system—Proceed as directed in the Assay under Cephapirin Benzathine.

Assay preparation-Express the entire contents of a syringe of the Intramammary Infusion into a centrifuge tube. For each mL of Intramammary Infusion, add $1.0 n$-heptane and 1.0 mL of Extraction solution, cap, and vortex at high speed for 5 minutes. Centrifuge for 5 minutes at a sufficient speed to break the emulsion. Remove the aqueous layer, and pass through a $0.45-\mu \mathrm{m}$ nylon filter, discarding the first 0.5 mL . Transfer 2.5 mL of the filtered aqueous phase into a $25-$ mL volumetric flask that contains a solution composed of 15.0 mL of Dilution buffer and 7.0 mL of acetonitrile. Add water to volume, and mix well to obtain a single phase.

Procedure—Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of the duplicate Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas of the major peaks. Calculate the quantity, in mg , of cephapirin $\left(\mathrm{C}_{17} \mathrm{H}_{17} \mathrm{~N}_{3} \mathrm{O}_{6} \mathrm{~S}_{2}\right)$ in each syringe of Intramammary Infusion taken by the formula:

$$
10 P W\left(V_{U} / V_{S}\right)\left(r_{U} / r_{S}\right)
$$

in which $P$ is the assigned potency, in $\mu \mathrm{g}$ cephapirin per mg , of USP Cephapirin Sodium RS; $W$ is the quantity of USP Cephapirin Sodium RS, in mg, used to prepare the Standard preparation; $V_{S}$ is the final volume, in mL , of the Standard preparation; $V_{U}$ is the entire volume of Intramammary Infusion, in mL , in one syringe; and $r_{U}$ and $r_{S}$ are the peak area and the average peak area of the cephapirin peaks obtained from the Assay preparation and the Standard preparation, respectively. $\quad$ USP28

## Briefing

Ciprofloxacin Injection, USP 27 page 456. On the basis of information received, it is proposed to modify the Definition to accommodate potential equivalent formulations for this product.
(PA7b: B. Davani) RTS-40387-1; 40616-1

## Change to read:

» Ciprofloxacin Injection is a sterile solution of Ciprofloxacin
${ }^{\text {ºr }}$ Oiprofloxacin Hydrochloride ${ }_{\Delta U S P 28}$
in Sterile Water for Injection, in 5 percent Dextrose Injection, or in 0.9 percent Sodium Chloride Injection prepared with the aid of Lactic Acid. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ciprofloxacin $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{FN}_{3} \mathrm{O}_{3}\right)$.

## Briefing

Clotrimazole Lotion, USP 27 page 492. It is proposed to change the title of this monograph to Clotrimazole Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40783-1

## Clotrimazole Lotion

(Current title-not to change until July 1, 2007) Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Clotrimazole Topical Emulsion

Briefing
Clotrimazole Topical Emulsion-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40783-1

## Add the following:

## - Clotrimazole Topical Emulsion (Monograph under this new title-to become official July 1, 2007) <br> (Current monograph title is Clotrimazole Lotion)

» Clotrimazole Topical Emulsion contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of clotrimazole $\left(\mathrm{C}_{22} \mathrm{H}_{17} \mathrm{ClN}_{2}\right)$.

Packaging and storage-Preserve in tight containers, at a temperature between $2^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$-USP Clotrimazole RS.
USP Clotrimazole Related Compound A RS.
Identification-The retention time of the major peak for clotrimazole in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.
$\mathbf{p H}\langle 791\rangle$ : between 5.0 and 7.0.
Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.

Limit of clotrimazole related compound A-Using the chromatograms of the Assay preparation and the Standard preparation obtained as directed in the Assay, calculate the
percentage of clotrimazole related compound A in the portion of Topical Emulsion taken by the formula:

$$
2000(C / Q)\left(R_{U} / R_{S}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Clotrimazole Related Compound A RS in the Standard preparation; $Q$ is the quantity, in mg , of clotrimazole $\left(\mathrm{C}_{22} \mathrm{H}_{17} \mathrm{ClN}_{2}\right)$ in the portion of Topical Emulsion taken; and $R_{U}$ and $R_{S}$ are the peak response ratios of clotrimazole related compound A to testosterone propionate obtained from the Assay preparation and the Standard preparation, respectively: not more than $5 \%$ is found.

## Assay-

Dibasic potassium phosphate solution-Dissolve 4.35 g of dibasic potassium phosphate in water to make 1000 mL .

Mobile phase-Prepare a mixture of methanol and Dibasic potassium phosphate solution (3:1), pass through a membrane filter having a $0.5-\mu \mathrm{m}$ or finer porosity, and degas.

Internal standard solution-Prepare a solution of testosterone propionate in dehydrated alcohol having a concentration of about 0.07 mg per mL .

Clotrimazole standard stock solution-Transfer about 50 mg of USP Clotrimazole RS, accurately weighed, to a $25-$ mL volumetric flask, add dehydrated alcohol to volume, and mix.

Clotrimazole related compound A standard stock solu-tion-Prepare a solution of USP Clotrimazole Related Compound A RS in dehydrated alcohol having a known concentration of about 0.1 mg per mL .

Standard preparation-Mix 5.0 mL of Clotrimazole standard stock solution, 5.0 mL of Clotrimazole related compound A standard stock solution, and 10.0 mL of Internal standard solution.

Assay preparation-Accurately weigh a portion of freshly mixed Topical Emulsion, equivalent to about 10 mg of clotrimazole, and transfer to a screw-capped, $50-\mathrm{mL}$ centrifuge tube. Add 10.0 mL of Internal standard solution, place the cap on the tube, and heat at $50^{\circ}$ in a water bath for 5 minutes, with occasional shaking. Remove the tube from the bath, and shake vigorously for 5 minutes. Cool in a methanolice bath for 15 minutes, and promptly centrifuge. Transfer the supernatant to a test tube. Add 10.0 mL of dehydrated alcohol to the residue in the centrifuge tube, and repeat the extraction as directed above, beginning with "place the cap on the tube." Transfer the supernatant to the test tube containing the supernatant from the first extraction, mix, and use this solution as the Assay preparation.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $2.1-\mathrm{mm} \times 6-\mathrm{cm}$ guard column that contains $10-$ $\mu \mathrm{m}$ packing L 2 and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ analytical column that contains $10-\mu \mathrm{m}$ packing L 1 . The flow rate is about 1 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for clotrimazole related compound A, 1.0 for clotrimazole, and 1.5 for testosterone propionate; the resolution, $R$, between clotrimazole related compound A and clotrimazole is not less than 1.2; the resolution, $R$, between clotrimazole and testosterone propionate is not less than 1.9; and the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the
quantity, in mg, of clotrimazole $\left(\mathrm{C}_{22} \mathrm{H}_{17} \mathrm{ClN}_{2}\right)$ in each g of Topical Emulsion taken by the formula:

$$
20(C / W)\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Clotrimazole RS in the Standard preparation; $W$ is the weight, in g , of Topical Emulsion taken; and $R_{U}$ and $R_{S}$ are the peak response ratios of clotrimazole to testosterone propionate obtained from the Assay preparation and the Standard preparation, respectively. $\Delta U S P 28$
(Official July 1, 2007)

## BRIEFING

Demeclocycline Hydrochloride Tablets, USP 27 page 549 and page 625 of $P F 29(3)$ [May-June 2003]. It is proposed to revise the Loss on drying limit from not more than $2.0 \%$ to not more than $2 \%$. The $2 \%$ limit reflects the requirement specified consistently in the regulations of the U.S. Food and Drug Administration from its origin in 1974 ( 21 CFR 446.116a). This is a technical correction to reflect the original and longstanding specifications of the Food and Drug Administration.
(PA7: W. Wright) RTS-40827-1

## Change to read:

## Dissolution $\langle 711\rangle$ -

Medium: water; 900 mL .
Apparatus 2: 75 rpm .
Time: 45 minutes.
Procedure-Determine the amount of $\mathrm{C}_{21} \mathrm{H}_{21} \mathrm{ClN}_{2} \mathrm{O}_{8}$ dissolved from UV absorption at the wavelength of maximum absorbance at about 270
-274 ${ }^{1 S}$ (USP27)
nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Demeclocycline Hydrochloride RS in the same Medium.
Tolerances-Not less than $75 \%$ (Q) of the labeled amount of demeclocycline $\left(\mathrm{C}_{21} \mathrm{H}_{21} \mathrm{ClN}_{2} \mathrm{O}_{8}\right)$ is dissolved in 45 minutes.

## Change to read:

Loss on drying $\langle 731\rangle$ - Dry about 100 mg of finely ground Tablet powder, accurately weighed, in a capillary-stoppered bottle in vacuum at $60^{\circ}$ for 3 hours: it loses not more than $2.0 \%$

$$
\begin{aligned}
& \Delta_{2}^{2} \% \text { USP28 } \\
& \text { of its weight. }
\end{aligned}
$$

Dextroamphetamine Sulfate, USP 27 page 576-See briefing under Amphetamine Sulfate.
(PA3: S. Salado) RTS-40699-2

## Change to read:

Chromatographic purity-
Diluent-Dilute 3.12 mL of phosphoric acid with water to 1000 mL .

Buffer solution-Dissolve 2.16 g of sodium 1-octanesulfonate in 1000 mL of water, and add 1.0 mL of $0.1 \%$ triethylamine solution (w).
${ }^{\Delta}$ triethylamine.
Mix, and adjust with phosphoric acid to a pH of 2.5 .
Mobile phase-Prepare a filtered and degassed mixture of Buffer solution, acetonitrile, and methanol (144:37:19). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Standard stock solution-Dissolve an accurately weighed quantity of USP Dextroamphetamine Sulfate RS in Diluent to obtain a solution having a known concentration of about 0.3 mg per mL .

Standard solution-Dilute an accurately measured volume of Standard stock solution in Diluent to obtain a solution having a known concentration of about 0.003 mg per mL .

Test solution-Transfer about 30 mg of Dextroamphetamine Sulfate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in 50 mL of Diluent, sonicate for 5 minutes, dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard stock solution, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$. Chromatograph the Test solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the dextroamphetamine peak and any adjacent peak is not less than 1.5.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Dextroamphetamine Sulfate taken by the formula:

$$
10,000(C / W)\left(r_{i} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Dextroamphetamine Sulfate RS in the Standard solution; $W$ is the weight, in mg , of Dextroamphetamine Sulfate taken to prepare the Test solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the peak response for amphetamine obtained from the Standard solution: not more than $0.1 \%$ of any individual impurity is found; and not more than $0.5 \%$ of total impurities is found.

## BRIEFING

Diclofenac Sodium Extended-Release Tablets, page 319 of PF 29(1) [Jan.-Feb. 2003]. This proposed new monograph, which previously appeared in Pharmacopeial Previews, is now being forwarded to In-Process Revision with the addition of a new Drug release test.
(BPC: M. Marques) RTS-37957-2

## Add the following:

## ©Diclofenac Sodium Extended-Release Tablets

## » Diclofenac Sodium Extended-Release Tablets

 contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of diclofenac sodium $\left(\mathrm{C}_{14} \mathrm{H}_{10} \mathrm{Cl}_{2} \mathrm{NNaO}_{2}\right)$.Packaging and storage-Preserve in well-closed containers. Store at controlled room temperature, and protect from light.

USP Reference standards $\langle 11\rangle$ —USP Diclofenac Sodium
RS. USP Diclofenac Related Compound A RS.

## Identification-

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, as obtained in the Assay.

B: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -
Solvent system: methanol, toluene, glacial acetic acid (40:60:0.5).

Test solution-Finely powder not fewer than 10 Tablets. Accurately weigh a portion of the powder, equivalent to about 50 mg of diclofenac sodium, and transfer to a $25-$ mL volumetric flask. Add about 15 mL of methanol, sonicate for 10 minutes, shake by mechanical means for 10 min-
utes, dilute with methanol to volume, and mix. Centrifuge this solution, and use the clear supernatant as the Test solution.

Standard solution-Accurately weigh about 50 mg of USP Diclofenac Sodium RS into a $25-\mathrm{mL}$ volumetric flask. Add 10 mL of methanol, shake by mechanical means for 10 minutes, dilute with methanol to volume, and mix.

Drug release $\langle 724\rangle$ -
Medium: 0.05 M phosphate buffer, $\mathrm{pH} 7.5 ; 900 \mathrm{~mL}$
Apparatus 2: 50 rpm ; use wire sinkers.
Times: 1, 5, 10, 16, and 24 hours.
Procedure: Determine the amount of $\mathrm{C}_{14} \mathrm{H}_{10} \mathrm{Cl}_{2} \mathrm{NNaO}_{2}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Diclofenac Sodium RS in the same Medium.

Tolerances: The percentages of the labeled amount of $\mathrm{C}_{14} \mathrm{H}_{10} \mathrm{Cl}_{2} \mathrm{NNaO}_{2}$ dissolved at the times specified conform to Acceptance Table 1 under Drug release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $15 \%$ and $35 \%$ |
| 5 | between $45 \%$ and $65 \%$ |
| 10 | between $65 \%$ and $85 \%$ |
| 16 | between $75 \%$ and $95 \%$ |
| 24 | not less than $80 \%$ |

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.
Assay-[NOTE—Protect the Assay preparation, Standard preparation, and System suitability solution from light.]

Diluent: a mixture of acetonitrile and water (43:57).
0.05 M Monobasic potassium phosphate buffer-Dissolve 6.8 g of monobasic potassium phosphate in 950 mL of water, adjust with dilute phosphoric acid or dilute potassium hydroxide solution to a pH of $4.0 \pm 0.05$, dilute with water to 1 liter, and mix.

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile, 0.05 M Monobasic potassium phosphate buffer, and tetrahydrofuran (43:57:2). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diclofenac related compound A solution-Dissolve an accurately weighed quantity of USP Diclofenac Related Compound A RS in Diluent, and quantitatively dilute with Diluent to obtain a solution having a known concentration of about $200 \mu \mathrm{~g}$ per mL .
Standard preparation-Dissolve an accurately weighed quantity of USP Diclofenac Sodium RS in Diluent, and quantitatively dilute with Diluent to obtain a solution having a known concentration of about $200 \mu \mathrm{~g}$ per mL .

System suitability solution-Transfer 10 mL of the Standard preparation and 5 mL of Diclofenac related compound A solution to a $20-\mathrm{mL}$ volumetric flask. Dilute with Diluent to volume, and mix.

Assay preparation-Powder not fewer than 20 Tablets, and transfer an accurately weighed portion of the powder, equivalent to about 100 mg of diclofenac sodium, to a $100-\mathrm{mL}$ volumetric flask, add about 50 mL of Diluent, sonicate for about 15 minutes, then shake by mechanical means for 15 minutes. Add a few drops of methanol to remove the foam, dilute with Diluent to volume, and mix. Transfer 10.0 mL of the supernatant to a $50-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ ) The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. Inject $40 \mu \mathrm{~L}$ and chromatograph the System suitability solution,
and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for diclofenac related compound A and 1.0 for diclofenac; and the resolution, $R$, between the diclofenac peak and the diclofenac related compound A peak is not less than 2.0. Inject $20 \mu \mathrm{~L}$ and chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor of the diclofenac peak is not more than 2.0 ; and the relative standard deviation of the diclofenac peak for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg , of diclofenac sodium $\left(\mathrm{C}_{14} \mathrm{H}_{10}\right.$ $\mathrm{Cl}_{2} \mathrm{NNaO}_{2}$ ) in the portion of Tablets taken by the formula:

$$
500 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in $m g$ per $m L$, of USP Diclofenac Sodium RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the diclofenac peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\quad$ USP28

## Briefing

Diltiazem Hydrochloride Extended-Release Capsules, USP 27 page 625. It is proposed to add Drug Release Test 14 to this monograph because FDA recently approved an ANDA for this product. Because of difference in dissolution rates in vitro, the new product was approved with a Drug release test that differs from those currently official in the USP monograph.
(BPC: M. Marques) RTS-39543-1

## Change to read:

## Drug release $\langle 724\rangle$ -

FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS-
Test 1-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 1. Proceed as directed for Extended-Release Articles-General Drug Release Standard $\langle 724\rangle$.

Medium: water; 900 mL .
Apparatus 2: 100 rpm .
Times: 3, 9, and 12 hours.
Procedure-Determine the amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same Me dium.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2}$ $\mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to the Acceptance Table given.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 3 | between $10 \%$ and $25 \%$ |
| 9 | between $45 \%$ and $85 \%$ |
| 12 | not less than $70 \%$ |

## Acceptance Table

| Level | Number <br> Tested | Criteria |
| :---: | :---: | :---: | | No individual value lies outside each of |
| :--- |
| the stated ranges, and no individual value |
| is less than the stated amount at the final |
| test time. |

Test 4-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 4.

Medium, Apparatus, and Procedure-Proceed as directed under Test 1.

Times: 4, 8, 12, and 24 hours.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Ac ceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :---: |
| 4 | between $10 \%$ and $25 \%$ |
| 8 | between $35 \%$ and $60 \%$ |
| 12 | between $55 \%$ and $80 \%$ |
| 24 | not less than $80 \%$ |

Test 5-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 5.

Medium: 0.05 M phosphate buffer, $\mathrm{pH} 7.2 ; 900 \mathrm{~mL}$.
Apparatus 2: 50 rpm .
Procedure-Proceed as directed under Test 1.
Times: 1, 3, and 8 hours.
Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to $A c$ ceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | not more than $15 \%$ |
| 3 | between $45 \%$ and $70 \%$ |
| 8 | not less than $80 \%$ |

Test 10-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 10.

Medium: 0.05 M phosphate buffer, $\mathrm{pH} 6.5 ; 900 \mathrm{~mL}$. Prepare the buffer employing the following method. Dissolve 7.1 g of anhydrous dibasic sodium phosphate in 1000 mL of water, and adjust with phosphoric acid to a pH of 6.5 .

Apparatus 1: 100 rpm .
Procedure-Proceed as directed under Test 1.
Times: 1, 6, 9, and 24 hours.
Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26}$ $\mathrm{N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Acceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | not more than $10 \%$ |
| 6 | between $10 \%$ and $30 \%$ |
| 9 | between $34 \%$ and $60 \%$ |
| 24 | not less than $80 \%$ |

FOR PRODUCTS LABELED FOR DOSING EVERY 24 HOURS-
Test 2-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 2.

Test 1 Medium, Apparatus, and Procedure-Proceed as directed under.

Times: $1,4,10$, and 15 hours.
Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Ac ceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $5 \%$ and $20 \%$ |
| 4 | between $30 \%$ and $50 \%$ |
| 10 | between $70 \%$ and $90 \%$ |
| 15 | not less than $80 \%$ |

Test 3-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 3.

Medium: 0.1 N hydrochloric acid; 900 mL .
Apparatus 2: 100 rpm .
Times: 6, 12, 18, 24, and 30 hours.

Procedure—Determine the amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same Medium.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2}$ $\mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Acceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 6 | between $20 \%$ and $45 \%$ |
| 12 | between $25 \%$ and $50 \%$ |
| 18 | between $35 \%$ and $70 \%$ |
| 24 | not less than $70 \%$ |
| 30 | not less than $85 \%$ |

Test 6-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 6.

Medium and Procedure-Proceed as directed under Test 1.
Apparatus 1: 100 rpm .
Times: 2, 4, 8, 12, and 16 hours.
Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2}$ $\mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Acceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 2 | not more than $25 \%$ |
| 4 | between $25 \%$ and $50 \%$ |
| 8 | between $60 \%$ and $85 \%$ |
| 12 | not less than $70 \%$ |
| 16 | not less than $80 \%$ |

Test 7--If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 7.

Medium: pH 4.2 acetate buffer; 900 mL . Prepare the buffer by employing the following method. Transfer 115 mL of acetic acid to a 10 -liter volumetric flask, dilute with water to volume, and mix (Solution A). Transfer 165.4 g of anhydrous sodium acetate to a 10 -liter volumetric flask, dilute with water to volume, and mix (Solution B). Mix 4410 mL of Solution A with 1590 mL of Solution B. Adjust, if necessary, with the addition of Solution A or Solution B to a pH of $4.2 \pm 0.05$.

Apparatus 2: 100 rpm .
Times: 1, 4, 10, and 15 hours.
Procedure-Determine the amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration ofUSP Diltiazem Hydrochloride RS in the same Me dium.
Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2}$ $\mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Acceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | not more than $10 \%$ |
| 4 | between $15 \%$ and $35 \%$ |
| 10 | between $65 \%$ and $85 \%$ |
| 15 | not less than $80 \%$ |

Test 8-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 8.

Medium, Apparatus, and Procedure-Proceed as directed under Test 1.

Times: 1, 4, 10, and 15 hours.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Ac ceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $5 \%$ and $20 \%$ |
| 4 | between $30 \%$ and $50 \%$ |
| 10 | between $60 \%$ and $90 \%$ |
| 15 | not less than $80 \%$ |

Test 9-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 9.

NOTE-Perform the test separately in each of the two media.
Medium 1: 0.1 N hydrochloric acid; 900 mL .
Medium 2: simulated intestinal fluid TS, prepared without enzyme and adjusted to a pH of $7.5 \pm 0.1 ; 900 \mathrm{~mL}$.
Apparatus 2: 75 rpm .
Time for Medium 1: 2 hours.
Times for Medium 2: 2, 12, 18, and 24 hours.
Procedure-Determine the amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with the appropriate Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same Medium.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Ac ceptance Table 1.

| Time <br> (hours) | Amount dissolved <br> (Medium 1) | Amount dissolved <br> (Medium 2) |
| :---: | :---: | :--- |
| 2 | between $0 \%$ and $5 \%$ | between $20 \%$ and $45 \%$ |
| 12 |  | between $35 \%$ and $55 \%$ |
| 18 |  | not less than $60 \%$ |
| 24 |  | not less than $80 \%$ |

Test 11-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 11.

Medium, Apparatus, and Procedure-Proceed as directed under Test 3.

Times: 1, 6, 12, and 18 hours.
Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Ac ceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | not more than $10 \%$ |
| 6 | between $30 \%$ and $40 \%$ |
| 12 | between $36 \%$ and $58 \%$ |
| 18 | not less than $85 \%$ |

Test 12-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 12. Proceed as directed for Extended-Release Articles-General Drug Release Standard〈724〉.

Medium and Procedure-Proceed as directed under Test 1. Apparatus 1: 100 rpm .
Times: 2, 8, 14, and 24 hours.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to $A c$ ceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 2 | not more than $20 \%$ |
| 8 | between $30 \%$ and $55 \%$ |
| 14 | not less than $65 \%$ |
| 24 | not less than $80 \%$ |

Test 13-If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 13. Proceed as directed for Extended-Release Articles-General Drug Release Standard $\langle 724\rangle$.

Medium and Procedure-Proceed as directed under Test 1.
Apparatus 1: 100 rpm .
Times: 2, 8, 14, and 24 hours.
Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to $A c$ ceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 2 | not more than $20 \%$ |
| 8 | between $30 \%$ and $55 \%$ |
| 14 | between $60 \%$ and $80 \%$ |
| 24 | not less than $80 \%$ |

${ }^{\Delta}$ Test 14 -If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 14. Proceed as directed for Extended-Release Articles-General Drug Release Standard under the general chapter Drug Release $\langle 724\rangle$.

Medium, Apparatus, Times, and Procedure—Proceed as directed under Test 3.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Acceptance Table 1 under Drug Release $\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 6 | between $20 \%$ and $45 \%$ |
| 12 | between $25 \%$ and $50 \%$ |
| 18 | between $35 \%$ and $70 \%$ |
| 24 | not less than $70 \%$ |
| 30 | not less than $80 \%$ |

## Briefing

Dorzolamide Hydrochloride, USP 27 page 662 and page 99 of PF 30(1) [Jan.-Feb. 2004]. It is proposed to specify the sample weight to be used when performing the test for Water.
(PA6: L. Evans) RTS-40569-1

## Change to read:

Water, Method $I\langle 921\rangle$ : not more than $0.5 \%$,
${ }^{\Delta}$ using 0.4 g. ${ }^{\text {UUSP28 }}$

## Change to read:

Limit of dorzolamide hydrochloride related compound AMobile phase-Prepare a filtered and degassed mixture of tertbutyl methyl ether, chromatographic $n$-heptane, acetonitrile, and water (63:35:2:0.2). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Transfer about 18 mg of USP Dorzolamide Hydrochloride RS and 2 mg of USP Dorzolamide Hydrochloride Related Compound A RS, each accurately weighed, to a $15-\mathrm{mL}$ centrifuge tube, dissolve in 4 mL of 0.5 N ammonium hydroxide, add 4 mL of ethyl acetate, and mix. Separate the ethyl acetate layer, and transfer to a $15-\mathrm{mL}$ centrifuge tube. Add 4 mL of ethyl acetate to the aqueous layer, mix, separate the ethyl acetate layer, and combine it with the first extract. Evaporate the combined organic layers to dryness on a water bath maintained at $50^{\circ}$ under a stream of nitrogen. Dissolve the residue in 3 mL of acetonitrile, add 3 drops of (S)-(-)- $\alpha$-methylbenzyl isocyanate
${ }^{\boldsymbol{\Delta}}$ [NOTE-Discard the reagent if it is colored.],$_{\mathbf{A S P} 28}$ and allow to react for 5 minutes on a water bath maintained at $50^{\circ}$. under a stream of nitrogen. [NOTE-Diseard the solution if it is eotored.
AUSP28
Evaporate the mixture to dryness on a water bath maintained at $50^{\circ}$ under a stream of nitrogen. Dissolve the residue in 10 mL of a mixture of tert-butyl methyl ether, glacial acetic acid, and acetonitrile (87:10:3).

Test solution-Transfer about 20 mg of Dorzolamide Hydrochloride, accurately weighed, to a $15-\mathrm{mL}$ centrifuge tube, and proceed as directed for System suitability solution beginning with "dissolve in 4 mL ".

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L3. The flow rate is about 2 mL per minute. Chromatograph the System suitability solution, and record the peak respenses
$\Delta_{\operatorname{areas}_{\mathbf{A S P}}{ }^{28}}$
as directed for Procedure: the relative retention times are about 1.0 for dorzolamide and 1.5 for dorzolamide hydrochloride related compound A ; the resolution, $R$, between dorzolamide and dorzolamide hydrochloride related compound A is not less than 4.0 ; the column efficiency
${ }^{\mathbf{\Delta}}$ for the dorzolamide hydrochloride peak $\mathbf{A U S P 2 8}$ is not less than 600
${ }^{4} 4000 \mathbf{A U S P 2 8}^{\text {U }}$
theoretical plates; the tailing factor is not more than 1.4 ; and the relative standard deviation for replicate injections determined from the dorzolamide peak is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the System suitability solution and the Test solution into the chromatograph, record the chromatograms, and measure the respenses for
$\Delta_{\text {areas of }}^{\text {AUSP28 }}$
the major peaks. Calculate the percentage of dorzolamide hydrochloride related compound A in the portion of Dorzolamide Hydrochloride taken by the formula:

$$
\epsilon 100\left(r_{i}+x_{s}\right)
$$

in which $C$ is the coneentration, in mg per mL, of USP Dorzola mide Hydrochloride Related Compernd $A$ PS in the System suit ability solution; andr, andrs are the peak responses of dorzolamide hydrochloride relatedempeund $A$ obtained frem the Test solution and the System sutitability solution, respectively: not more than $0.5 \%$ is found.

$$
\mathbf{\Delta} 100 r_{I}\left(r_{I}+r_{S}\right)
$$

in which $r_{I}$ is the peak area of dorzolamide hydrochloride related compound A obtained from the Test solution; and $r_{S}$ is the peak area of dorzolamide hydrochloride obtained from the Test solution: not more than $0.5 \%$ is found. ${ }_{\triangle U S P 28}$

## Change to read:

Chromatographic purity-
${ }^{\Delta}$ Phosphate buffer, ${ }_{\mathbf{\Delta U S P 2 8}}$
Solution A, Solution B, Mobile phase, and Chromatographic sys-tem-Proceed as directed in the Assay.

Stand solution Use the Standeripreparion as preparedian the Assety.
© $\triangle U S P 28$
Test solution-Use the Assay preparation.
Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standerd solution and
${ }^{\mathbf{\Delta}}$ Inject a volume (about $10 \mu \mathrm{~L}$ ) of ${ }_{\Delta U S P 28}$
the Test solution into the chromatograph, record the chromatogram, and measure all of the peak respenses.
©areas. $\mathbf{\Delta}$ USP28
Calculate the percentage of each impurity in the portion of Dorzolamide Hydrochloride taken by the formula:

$$
10,000(C / 4)\left(+x_{5}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Dorzola mide Hydrechleride RS in the Standerd solution, Wis the weight, in me, of Dorzolamide Hydrochloride taken to prepare the Test solution; $T$; is the peak respense for each impurity obtained from the Test solution; and $\rightarrow$ s is the peak respense for dorzolamide obtained from the Statedrd solution: not more than $0.1 \%$ of any imt purity with a relative retention time of 0.92 is found; not more than $0.1 \%$ of any individual impurity is found; and not more than $0.3 \%$ of total impurities is found.
in which $r_{i}$ is the peak area of each individual impurity obtained from the Test solution; and $r_{s}$ is the sum of all the peak areas obtained from the Test solution: not more than $0.1 \%$ of any individual impurity is found; and not more than $0.5 \%$ of total impurities is found. $\triangle$ USP28

## Change to read:

Assay-
Solution - 4
${ }^{\mathbf{\Delta}}$ Phosphate buffer $_{\mathbf{\Delta} \text { USP? } 28}$
-Dissolve 3.7 g of potassium phosphate in 100 mL of a mixture
$\Delta_{1000} \mathrm{~mL}_{\mathbf{4} \text { USP28 }}$
of water. ade sp28 itrile (94:6).
${ }^{\Delta}$ Solution A-Prepare a filtered and degassed mixture of Phosphate buffer and acetonitrile (94:6). $\mathbf{U S S P 2 8}$ Solution $B$-Use acetonitrile.
Mobile phase-Use variable mixtures of Solution $A$ and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard preparation-Dissolve suitable quantities of USP Dorzolamide Hydrochloride RS in Solution $A$ to obtain a solution having a known concentration of about 0.6 mg per mL .
Assay preparation-Transfer about 60 mg of Dorzolamide Hydrochloride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Solution $A$ to volume, and mix.

Chromatographic system (see Chromatography $(621\rangle$ )-The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $35^{\circ}$. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0-15$ | 100 | 0 | isocratic |
| $15-30$ | $100 \rightarrow 50$ | $0 \rightarrow 50$ | linear gradient |
| $30-37$ | $50 \rightarrow 100$ | $50 \rightarrow 0$ | linear gradient |
| $37-44$ | 100 | 0 | isocratic |

Chromatograph the Standard preparation, and record the peak respenses
$\Delta^{4} \operatorname{areas}_{\triangle U S P 28}$
as directed for Procedure: the column efficiency is not less than 6500 theoretical plates; the tailing factor is not less than 0.6 and not more than 1.2; and the relative standard deviation for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the respenses
$\Delta_{\text {areas }}^{\triangle U S P 28}{ }^{\text {. }}$
for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{10} \mathrm{H}_{16} \mathrm{~N}_{2} \mathrm{O}_{4} \mathrm{~S}_{3} \cdot \mathrm{HCl}$ in the portion of Dorzolamide Hydrochloride taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Dorzolamide Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Ephedrine Sulfate Oral Solution, USP 27 page 709. It is proposed to revise the Identification test to eliminate an obsolete crossreference. The procedure and acceptance criterion are added to the monograph.
(PA1: K. Russo) RTS-40737-1

## Ephedrine Sulfate Oral Solution

## (Monograph under this new title-to become official June 1, 2005) <br> (Current monograph title is Ephedrine Sulfate Syrup)

## Change to read:

## Identification,

©Angular rotation $\langle 781 \mathrm{~A}\rangle$ -
Use $_{\mathbf{A}}{ }^{\text {USP } 28}$
the 0.1 N sulfuric acid extract of the chloroform solution obtained as directed for Assay preparation: tifieation Cest $C$ under Ephedrine Sullate Injection
the angular rotation is levorotatory. $\triangle$ USP28

## Briefing

Felodipine Extended-Release Tablets, USP 27 page 778. It is proposed to make several modifications to the Drug release test, in accordance with validated procedures.
(BPC: M. Marques) RTS-40772-1

## Change to read:

## Drug release $\langle 724\rangle$ -

Mediun: $\mathrm{pH} 6.5,0.1 \mathrm{M}$ pherphate buffer with $1 \%$ of sodium tauryl sulfate; 500 mL . (Transfer 206 mL of 1 M sodium phesphate, 196 mL of 0.5 M sodium phosphate, and 50.0 g of sodium latryl sulfate to a 5000 ml volumetrie flack. Add approximately 4000 mL of water, and mix. If neeessary, adjust with $1-\mathrm{N}$ sodium hydroxide to a pH of 6.5 . Dilute with water to volume, and mix). Appatas 2: 50 fpm .
Finnes: 2, 6, and 10 hours.
Fest preparation Place each Tablet in a specially made quad rangular baske of stainless steel wire gatze, soldered in one of its upper, narrow sides to the end of a steel rod (see Figure 1). Place the tablet cover (C) in the horizental diagenal of the basket. Put the rod assembly up through the cover of the dissolution vessel, and fix it by mens of two teflon nuts, 3.2 cm from the eenter of the vessel. Adjust he lower edge of the bottom of the baske to approximately

1 cm above the top of the paddle blade (see Figtre 2). Orient the targe side of the basket angentially to the flow stream with the tablet standing on its edge. Filter a 10 mL portion of the solution under test, obtained at each time interval, threugh a suitable filter.

Proedtre Determine the amount of $\mathrm{C}_{18} \mathrm{H}_{49} \mathrm{Cl}_{2} \mathrm{NO}_{4}$ dissolved as directed in the Assem, making any neeessary modifieations.
${ }^{\Delta}$ Medium: pH 6.5 phosphate buffer with $1 \%$ of sodium lauryl sulfate (Transfer 206 mL of 1 M monobasic sodium phosphate monohydrate, 196 mL of 0.5 M dibasic sodium phosphate anhydrous, and 50.0 g of sodium lauryl sulfate to a $5000-\mathrm{mL}$ volumetric flask. Add approximately 4000 mL of water, and mix well. If necessary, adjust with 1 N sodium hydroxide to a pH of 6.5 . Dilute with water to volume, and mix well.); 500 mL .

Apparatus 2: 50 rpm .
Times: 2, 6, and 10 hours.
Buffer solution-Prepare as directed in the Assay.
Mobile phase-Prepare a filtered and degassed mixture of Buffer solution, acetonitrile, and methanol (2:2.5:1). Make adjustments if necessary (see System suitability under Chromatography $\langle 621\rangle$ ).

Standard stock solution-Dissolve an accurately weighed quantity of USP Felodipine RS in alcohol to obtain a solution having a known concentration of 0.25 mg per mL .

Standard solution-Dilute an accurately measured volume of the Standard stock solution, quantitatively and stepwise, if necessary, with Medium to obtain a solution having a known concentration of USP Felodipine RS equivalent to the concentration that would result from about $60 \%$ dissolution of a single Tablet in 500 mL of Medium.

Test solution-Place each Tablet in a specially made quadrangular basket of stainless steel wire gauze, soldered in one of its upper, narrow sides to the end of a steel rod (see Figure 1). Place the tablet cover in the horizontal diagonal
of the basket. Put the rod assembly up through the cover of the dissolution vessel, and fix it by means of two teflon nuts, 3.2 cm from the center of the vessel, or by any other appropriate means. Adjust the lower edge of the bottom of the basket to approximately 1 cm above the top of the paddle blade (see Figure 2). Orient the large side of the basket tangentially to the flow stream with the Tablet standing on its edge. Pass a $10-\mathrm{mL}$ portion of the solution under test, obtained at each time interval, through a suitable filter.

Chromatographic system-Proceed as directed in the Assay.
Procedure-Separately inject equal volumes ( $100 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg , of felodipine $\left(\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{Cl}_{2} \mathrm{NO}_{4}\right)$ dissolved in the Medium by the formula:

$$
C D\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Felodipine RS in the Standard solution; $D$ is the dilution factor used in preparing the Test solution; and $r_{U}$ and $\mathrm{r}_{S}$ are the felodipine peak areas obtained from the Test solution and the Standard solution, respectively. $\triangle$ USP28
Tolerances-The percentages of the labeled amount of $\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{ClNO}_{4}$ dissolved at the times specified conform to Acceptance Table 1
$\mathbf{\Delta u n d e r}^{\text {Drug Release }}\langle 724\rangle_{\cdot \mathbf{\Delta U S P 2 8}}$

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 2 | between $10 \%$ and $30 \%$ |
| 6 | between $42 \%$ and $68 \%$ |
| 10 | not less than $75 \%$ |




## NOTES

1. Rod and Basket with a Tablet cover placed in the horizontal diagonal of the basket.
2. Basket and Tablet cover material; stainless steel.
3. Basket gauze wire size: 8 mesh.

Figure 1. Stationary Tablet Basket ${ }_{\mathbf{\Delta} \text { USP28 }}$


Figure 2. Drug Release Stationary Tablet Basket Configuration Diagram

## BRIEFING

Fluorodopa F 18 Injection, $U S P 27$ page 817. It is proposed to specify the method to be used for determining Specific activity, add a new Reference Standard for unlabeled L-fluorodopa, revise the test for Radionuclidic identification, and change the upper limit for $p H$. It is also proposed to add a new HPLC method in the test for Radiochemical purity and a new test for Limit of organotin as a new alternative synthetic route for determining Chemical purity. In addition, editorial changes have been made in the test for Enantiomeric purity.
(RMI: A. Wilk) RTS-40877-1

## Change to read:

» Fluorodopa F 18 Injection is a sterile, isie
${ }^{\wedge}$ ⓊSP28
aqueous solution, suitable for intravenous administration of $6-\left[{ }^{18} \mathrm{~F}\right] f l u o r o l e v o d o p a ~ i n ~ w h i c h ~ a ~ p o r t i o n ~ o f ~ t h e ~$ molecules are labeled with radioactive ${ }^{18} \mathrm{~F}$ (see Radiopharmaceuticals for Positron Emission TomographyCompounding $\langle 823\rangle$ ). It contains not less than 90.0
percent and not more than 110.0 percent of the labeled amount of ${ }^{18} \mathrm{~F}$ expressed in MBq (or mCi ) per mL at the time indicated in the labeling. It may contain suitable preservatives and/or stabilizing agents.

## Change to read:

Specific activity mos lhan $3.7 \times 10^{3} \mathrm{MBq}(100$ mCi) per mmol.
${ }^{\Delta}$ Mobile phase, Standard solution, Test solution, and Chromatographic system-Proceed as directed in the test for Radiochemical purity.
Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the concentration of L-fluorodopa found, in mg per mL , in the Injection by the formula:

$$
C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration of the Standard solution; and $r_{U}$ and $r_{S}$ are the peak responses of the Test solution and the Standard solution, respectively. Determine the concentration of fluorodopa F 18, in mCi per mL , as directed in the Assay for radioactivity. Calculate the Specific activity by dividing the result from the Assay (in mCi per mL ) by the concentration (in mg per mL ): it is not less than 0.463 mCi per mg of L-fluorodopa $\left(3.7 \times 10^{3} \mathrm{MBq}[100 \mathrm{mCi}]\right.$ per mmol). $\mathbf{\Delta U S P 2 8}$

Change to read:
USP Reference standards $\langle 11\rangle$-USP Endotoxin RS.
${ }^{\mathbf{\Delta}}$ USP L-Fluorodopa RS. ${ }^{\text {USP28 }}$
Change to read:
Radionuclidic identification (see Radioactivity $\langle 821\rangle$ )-
A: Its half-life, determined using a suitable detector system, is between 105 and 115 minutes.

B: Its gramma ray speetrum is identiealto that of a specimen of ${ }^{18} \mathrm{~F}$ in that it exhibits a majer photepeak at 0.511 MeV and pessibly a sum peak of 1.022 MeV dependent on geometry and detector ef fieieney.
${ }^{4}$ B: Radiochemical identity-The retention time of the major peak in the chromatogram of the Test solution corresponds to that in the chromatogram of the Standard solution, as obtained in the test for Radiochemical purity. $\triangle$ USP28

## Change to read:

$\mathbf{p H}\langle 791\rangle$ : between 4.0 and 5.0
${ }^{\Delta} 5.5$. $\quad$ USP28

## Change to read:

Radiochemical purity-[nOTE—This article may be synthesized by different methods and processes and may, therefore, contain dif ferent impurities. It may be neeessary to use additional validated limit tests relevant to the symthetic procedure used to ensure radioehemieal purity of the final product.]

Mobile phase. Prepare a filtered and degassed mixture-of $83.5 \%$ of a solution containing 100 mM soditm phosphate, 2.6 mM - sodium $1-0 c t a n e s u l f o n a t e$, and 0.1 mM -detatedisodium and $16.5 \%$ of methanol. Careftlly adjust with phosphoric acid to apH of $3.3-0.2$. Retention times will valy drastically with sol vent pH . At pH 3.5 , the observed retention time is about 6.0 mmin utes. Make adjustments if necessary (see System Suitability under Chromatography (624)).

Fest preparation Use-Injection appropriately diluted with water, such that it provides a count rate of about $5 \times 10^{5}$ eounts per mintle.

Chromegran sistem (see-Chrematograhy $\langle 624\rangle$ ). The liquid chromatograph is equipped with a radioactivity detector and $a-4.6 \mathrm{~mm} \times 25 \mathrm{em}$ column that contains $5 \mathrm{\mu m}$ packing L4. The flow rate is about 1 mL per minute.

Procedure Inject about $50 \mu \mathrm{~L}$ of the Test preparation into the chromatograph, record the chromatogram, and measure the areas for all radionctivity peaks. The radionctivity recorded for the main peak at a retention time of about 6 minutes is not less than $95 \%$ of the radiactivity injected. Fer simultaneous analysis of chemienl purity, a variable wavelength UV detector, operating in the range of 260 to 290 nm , is coupled to the system.
${ }^{\Delta}$ Mobile phase-Prepare a filtered and degassed mixture of $0.1 \%$ acetic acid and methanol (97:3).

Standard solution-Dissolve an accurately weighed quantity of USP L-Fluorodopa RS in 10 mmol of pH 4.5 sodium acetate buffer and dilute quantitatively, and stepwise if necessary, with the same buffer to obtain a solution having a known concentration of about 0.1 mg per mL .
Test solution-Use the Injection diluted with water such that it provides a count rate of about $5 \times 10^{5}$ counts per minute.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $4.6-\mathrm{mm} \times 30$ cm column that contains packing L1, a radioactivity detector, and a variable wavelength UV detector operating in the range of 260 to 290 nm . The flow rate is about 0.8 mL per minute. Chromatograph the Test solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Prepare a mixture of the Test solution and the Standard solution and inject it (about $50 \mu \mathrm{~L}$ ) into the chromatograph, record the chromatograms, and measure the areas for both the radioactive and nonradioactive peaks. The ratio and injected volume may be adjusted to obtain suitable detection system sensitivity. The radioactivity of the major peak is not less than $90 \%$ of the total radioactivity measured, and no individual radiochemical impurity is more than $2 \%$. The retention time of the major peak in the chromatogram of the Test solution corresponds to that in the chromatogram of the Standard solution. [NOTE-The typical retention time for fluorodopa is about 6 minutes. Retention times are very sensitive to the pH of the solvent. $]_{\text {USP28 }}$

## Change to read:

Chemical purity-This article may be synthesized by different metheds and processes and, therefore, contains different impurities. It is neeessay to demenstrate the absence or lack of physio logienl effect of any umlabeled starting ingredients or by products formed during the reaction and reagent chemieats employed in the synthetic process that may be present, by the use of one or more validated limit tests using known analytical teehniques (see Proee dure in the test for Radiochemieal purity).
${ }^{\Delta}$ The methods and limits described in this section relate to potential impurities associated with commonly used methods of synthesis for Fluorodopa F 18 Injection. If methods of synthesis are used that may result in different impurities, the presence of unlabeled ingredients, reagents, and by-products specific to the process must be controlled and then potential for physiological or pharmacological effects must be considered.

LIMIT OF ORGANOTIN (to be determined if tin-containing starting materials or reagents are used in the synthesis)-

Mobile phase—Prepare a filtered and degassed $5 \mu \mathrm{~mol}$ solution of morin in a mixture of acetic acid, methanol, acetonitrile, and toluene (5:2:2:91).

Standard solution-Prepare a mixture of 10 mmol each of dimethyltin dibromide and trimethyltin bromide in alcohol.

## Test solution-Use the Injection.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a fluorescence detector (excitation at 420 nm and detection at 500 nm ) and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L32. The flow rate is about 1 mL per minute.

Procedure—Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. The volume of Injection in the Standard solution and the Test solution may be adjusted to obtain suitable detection system sensitivity. Calculate the concentration, in $\mu \mathrm{g}$ per mL , of dimethyltin and trimethyltin in the portion of Injection taken by the formula:

$$
C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of the relevant organotin compound in the Standard solution; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Test solution and the Standard solution, respectively: not more than 0.5
$\mu \mathrm{g}$ per mL of dimethyltin and trimethyltin is found. $\triangle$ USP28 LIMIT OF MERCURY (to be determined if mercury-containing starting materials or reagents are used in the synthesis)-[Cau-tion-Because of the toxic nature of mercury vapor, great care must be taken to avoid inhaling it. A bypass has been included in the system, therefore, either to vent the mercury vapor into an exhaust hood or pass the vapor through some absorbing media such as a solution containing equal volumes of 0.1 M potassium permanganate and dilute sulfuric acid (1 in 10).]

Apparatus-Use a flameless atomic absorption spectrophotometer for measuring radiation at 253.7 nm emitted by mercury vapor.
Stannous chloride suspension-Add 25 g of stannous chloride to 250 mL of 0.5 N sulfuric acid. This mixture is a suspension and is to be stirred continuously during use.

Sodium chloride-hydroxylamine hydrochloride solution-Dissolve 12 g of sodium chloride and 12 g of hydroxylamine hydrochloride in water, dilute with water to 100 mL , and mix.

Mercury stock solution-Dissolve 135.4 mg of mercuric chloride, accurately weighed, in 75 mL of water. Add 10 mL of nitric acid, dilute with water to 100.0 mL , and mix. Each mL of this solution contains 1 mg of mercury.

Mercury standard solution-Before using, make successive dilutions of the Mercury stock solution with water to obtain a Mercury standard solution containing $0.1 \mu \mathrm{~g}$ per mL .

Calibration-To six $300-\mathrm{mL}$, glass-stoppered bottles transfer, respectively, $0-$, $0.5-, 1.0-, 2.0-, 5.0-$, and $10.0-\mathrm{mL}$ aliquots of the Mercury standard solution containing $0 \mu \mathrm{~g}$ to $1.0 \mu \mathrm{~g}$ of mercury. To each bottle add water to make 100 mL , mix, and add 5 mL of sulfuric acid and 2.5 mL of nitric acid. Add 15 mL of potassium permanganate solution (1 in 20). Allow to stand for 15 minutes. Add 8 mL of potassium persulfate solution ( 1 in 20 ), and heat in a water bath at $95^{\circ}$ for 2 hours. Cool, and add 6 mL of Sodium chloride-hydroxylamine hydrochloride solution to reduce the excess permanganate. When the solution has been decolorized, wait for 30 seconds and add 5 mL of Stannous chloride suspension. Immediately attach the flask to the aeration apparatus to form a closed system. Allow the sample to stand without manual agitation. The circulating pump, previously adjusted to a rate of 1 L per minute, is allowed to run continuously. The absorbance will increase and reach a maximum within 30 seconds. As soon as the recorder pen levels off, in about 1 minute, open the bypass valve and continue the aeration until the absorbance returns to its minimum value. Close the bypass valve, remove the stopper and frit from the bottle, and continue the aeration. Plot a standard curve of the peak height versus micrograms of mercury.
Test preparation-Transfer 1.0 mL of Injection to a $300-\mathrm{mL}$, glass-stoppered bottle, and proceed as directed under Calibration, beginning with "To each bottle add water". Measure the absorbance of the solution, and determine the quantity, in $\mu \mathrm{g}$, of mercury in the Test preparation from the standard curve: not more than 0.5 $\mu \mathrm{g}$ is found.

## Change to read:

Enantiomeric purity-Inject a suitable volume of Injection into a high pressure liquid chromatograph equipped with a chiral ligand exehange $-4.6 \mathrm{~mm} \times 25 \mathrm{~cm}$ column that contains packing L32. The Mobile phase is a mixtare of 100 mM menebasic petassitum phesphate and 2 mM eupric sulfate ( $1: 1$ ) adjusted to a pH of 4.6 . The flow rate is abeut 1 mL per mintte. The eapacity facters, $k$, are 2.1 and 7.3 for the - and t isemers, respectively. The radionetivity of the-Lisomer is not less than-95\% of the total radiactivity mea stred.
${ }^{\Delta}$ Mobile phase-Prepare a filtered and degassed mixture of 100 mmol of monobasic potassium phosphate and 2 mmol of cupric sulfate (1:1). Adjust to a pH of 4.6. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Use the Standard solution as directed under Radiochemical purity.

Test solution-Use the Injection.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph as directed under Radiochemical purity is equipped with a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L32. The flow rate is about 1 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the capacity factors, $k^{\prime}$, for the D- and L-isomers are not less than 2.1 and 7.3, respectively.

Procedure-Prepare a mixture of the Test solution and the Standard solution, and inject it (about $50 \mu \mathrm{~L}$ ) into the chromatograph, record the chromatograms, and measure the areas for both the radioactive and nonradioactive peaks. The ratio and injected volume may be adjusted to obtain suitable detection system sensitivity. The radioactivity of the L-isomer is not less than $95 \%$. USPP28

## Briefing

Flurandrenolide Lotion, USP 27 page 832. It is proposed to change the title of this monograph to Flurandrenolide Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40784-1

## Flurandrenolide Lotion

(Current title—not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007
(see Official Title Changes on the first page of InProcess Revision):
See Flurandrenolide Topical Emulsion

## BRIEFING

Flurandrenolide Topical Emulsion-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40784-1

## Add the following:

## ©Flurandrenolide Topical Emulsion <br> (Monograph under this new title-to become official July 1, 2007) <br> (Current monograph title is Flurandrenolide Lotion)

» Flurandrenolide Topical Emulsion contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\mathrm{C}_{24} \mathrm{H}_{33} \mathrm{FO}_{6}$.

Packaging and storage-Preserve in tight containers, protected from heat, light, and freezing.

USP Reference standards $\langle 11\rangle-U S P$ Flurandrenolide $R S$.

Identification-It responds to the Identification test under Flurandrenolide Cream.

Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.

Minimum fill $\langle 755\rangle$ : meets the requirements.
$\mathbf{p H}\langle 791\rangle$ : between 3.5 and 6.0, determined in a 1 in 10 dilution of the Topical Emulsion in water containing 0.30 mL of saturated potassium chloride solution per 100 mL .

Assay-
Methanolic sodium chloride, Mobile phase, Internal standard solution, Standard preparation, and Chromatographic system-Prepare as directed in the Assay under Flurandrenolide Cream.

Assay preparation-Transfer an accurately weighed portion of Topical Emulsion, calculated from the density to contain about $500 \mu \mathrm{~g}$ of flurandrenolide, to a separator. (Determine the density by taring a $100-\mathrm{mL}$ volumetric flask containing 50.0 mL of water, adding approximately 25 g of well-shaken Topical Emulsion, and again weighing, then carefully adjusting the contents of the volumetric flask with water from a buret to volume, and finally calculating the density taken by the formula:

$$
A / B
$$

in which $A$ is the weight, in g , of the Topical Emulsion taken; and $B$ is 50.0 mL minus the volume, in mL , of water necessary to adjust the contents of the volumetric flask to volume.) Proceed as directed for Assay preparation in the Assay under Flurandrenolide Cream, beginning with "Add 50 mL of hexane and 25 mL of Methanolic sodium chloride."

Procedure-Proceed as directed in the Assay under Flurandrenolide Cream. Calculate the quantity, in mg, of $\mathrm{C}_{24} \mathrm{H}_{33} \mathrm{FO}_{6}$ in each mL of the Topical Emulsion taken by the formula:
in which $C$ is the concentration, in mg per mL , of USP Flurandrenolide RS in the Standard preparation; $D$ is the density of the Topical Emulsion; $W$ is the weight, in g , of Topical Emulsion taken; and $R_{U}$ and $R_{S}$ are the peak response ratios obtained from the Assay preparation and the Standard preparation, respectively._USP28
(Official July 1, 2007)

## BRIEFING

Flurazepam Hydrochloride, USP 27 page 833. It is proposed to correct the Definition of the monograph to specify that the Assay limits apply on the anhydrous basis, not the dried basis.
(PA3: S. Salado) RTS-40839-1

## Change to read:

» Flurazepam Hydrochloride contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{21} \mathrm{H}_{23} \mathrm{ClFN}_{3} \mathrm{O} \cdot 2 \mathrm{HCl}$, calculated on the dried
${ }^{\boldsymbol{\Delta}} \mathrm{anhydrous}_{\Delta U S P 28}$
basis.

## BRIEFING

Graftskin, page 1804 of PF 28(6) [Nov.-Dec. 2002]. On the basis of comments received, this proposed new monograph is being revised to clarify the use of the USP Graftskin Reference Photomicrographs in performing the test for Histological characterization. Furthermore, the system suitability requirements of the Gene expression profile test are being revised to be more descriptive. Comments on this proposed monograph are encouraged and should be directed to the attention of the USP Expert Committee on Gene Therapy, Cell Therapy, and Tissue Engineering.
(GCT: I. DeVeau) RTS-40842-1

$$
10 C(D / W)\left(R_{U} / R_{S}\right)
$$

## Add the following:

## ${ }^{\Delta}$ Graftskin

» Graftskin ${ }^{1}$ is a living, bilayered skin substitute derived from neonatal foreskins manufactured under Class 100 sterile conditions. The upper, epidermal layer is formed by human keratinocytes and has a well-differentiated stratum corneum. The inner, dermal layer is composed of human fibroblasts in a bovine Type I collagen lattice. Graftskin does not contain Langerhans cells, melanocytes, macrophages, lymphocytes, blood vessels, hair follicles, or any other epidermallyderived components. The fibroblast and keratinocyte cell banks from which Graftskin is derived test negative for human and animal viruses, retroviruses, bacteria, fungi, yeast, mycoplasma, and tumorigenicity. The cell banks are also tested for normal human karyology and isoenzymes. The fi-

[^48]nal product is tested for morphology, cell viability, and physical container integrity. Used tissue culture media are tested for mycoplasma and sterility. All materials derived from bovine sources originate from countries free of bovine spongiform encephalopathy.

Packaging and storage-Graftskin is aseptically packaged in a Class 100 environment in single-use containers that preserve cell viability and product integrity. Store at controlled room temperature for no longer than 5 days, and do not subject to freezing temperatures. The atmosphere within the package contains air enriched with $10 \%$ carbon dioxide. The device is translucent and off-white in color. The upper, or epidermal surface, is dull with small irregularities resulting from the cornification of keratinocytes, while the bottom surface is smooth and shiny in appearance. The device is packaged so that the dermal (glossy layer) is closest to the agarose-based nutrient medium. The packaging permits easy observation of the medium and provides ready access to the Graftskin when needed. The medium contains all of the required nutrients for the living cell components of Graftskin, plus an appropriate, nontoxic, pH -sensitive dye to indicate package breaches or microbial contamination. The medium should appear pink ( $\mathrm{pH} 6.8-7.7$ ) when compared to the enclosed pH color chart.

Labeling-Label it to indicate the dimensions of the enclosed Graftskin, the expiry date, required storage conditions, and the lot number. The label indicates that the enclosed Graftskin and surrounding medium are to be examined for signs of contamination or deterioration. The label also contains a pH color code to be used for determination of the acceptability of the pH of the Graftskin medium. The label cautions that Graftskin is not to be used if the package shows signs of damage or microbial contam-
ination. Label it to indicate that sterile techniques are to be used in handling Graftskin and that cytotoxic agents are not to be used. Label it to indicate the time frame for use after package opening.

USP Referenee-standards- $\langle H\rangle$-USP Graftskin Photomi erographs RS.

USP Authentic Visual References $\langle 11\rangle$ —USP Graftskin Reference Photomicrographs. [NOTE-These 10 photomicrographs represent examples of both passing and failing Graftskin units. They are specified to assist in ascertaining histological quality.]

## Histological characterization-

## SOLUTION PREPARATIONS-

2.0 M Monobasic potassium phosphate—Dissolve 13.61 g of anhydrous monobasic potassium phosphate in 50 mL of water.
2.0 M Dibasic potassium phosphate—Dissolve 17.42 g of anhydrous dibasic potassium phosphate in 50 mL of water.

Phosphate-buffered saline solution (pH 7.1-7.5)—Combine 3.6 mL of 2.0 M Monobasic potassium phosphate, 16.4 mL of 2.0 M Dibasic potassium phosphate, 8 g of sodium chloride, and 1 L of water. Mix thoroughly.
$0.3 \%$ Acid alcohol-To 100 mL of $70 \%$ alcohol, add 0.3 mL of hydrochloric acid, and mix.

Hematoxylin-alcohol solution-Dissolve 2.5 g of hematoxylin in 25.0 mL of dehydrated alcohol, with heating.

Potassium alum solution-Dissolve 50.0 g of potassium alum in 500 mL of water, with heating.

Hematoxylin staining solution-Mix Hematoxylin-alco-
hol solution and Potassium alum solution, and heat to boiling as rapidly as possible with constant stirring. Do not heat for more than 1 minute. Slowly add 0.185 g of sodium iodate, and reheat to a simmer until the solution becomes a deep purple. Remove from the heat, and quickly cool. Filter daily before use.

Bluing agent-Dissolve 200 mg of sodium bicarbonate and 40 mg of lithium carbonate in 63 mL of water and 37 mL of methanol, and mix.

Eosin solution-Dissolve 1 g of eosin Y in 100 mL of alcohol. Filter daily before use.
TISSUE PREPARATION-Remove three $2-\mathrm{cm}$ diameter circular sections from every $30 \mathrm{~cm}^{2}$ section of Graftskin (not less than $30 \%$ of the total unit area), using the appropriate size biopsy punch. Cut with a circular rocking motion to prevent crushing the tissue. Immerse the sections in 3.7\% dimethoxymethane for 30 minutes, using a gentle rocking motion. Remove the sections, and lay on a cutting surface, dermal side (glossy side) down. Cut an approximately 3 -mm wide strip through the center of the specimen, using a new, single-edged, razor blade. Place the strips in a histological microwave cassette, using suitable biopsy pads pre-moistened with Phosphate-buffered saline solution (pH 7.17.5) to hold the strips in place. Insert the cassette into a histological microwave processing rack, place the rack inside a suitable microwave container, and add sufficient Phosphatebuffered saline solution ( $\mathrm{pH} 7.1-7.5$ ) to completely cover the rack. Place the container in a microwave oven suitable for histological work ${ }^{2}$, and heat for 4 minutes at $55^{\circ}$. Remove the Phosphate-buffered saline solution ( $\mathrm{pH} 7.1-$ 7.5), and add enough dehydrated alcohol to completely cover the rack. Return the container to the microwave oven, and heat for 4 minutes at $67^{\circ}$. Remove the alcohol, and add enough dehydrated isopropyl alcohol to completely cover the rack. Return the container to the microwave oven, and heat for 4 minutes at $74^{\circ}$. Remove the isopropyl alcohol, and add enough suitable grade paraffin ${ }^{3}$ that has been melted and held at $84^{\circ}$ prior to use, to completely cover the rack. Return

[^49]the container to the microwave oven, and heat for 7 minutes at $84^{\circ}$. Remove the histological microwave cassette from the container and rack while the paraffin is still melted, and disassemble, discarding the biopsy pads. Fill preheated embedding molds with molten paraffin ${ }^{4}$ heated to $60^{\circ}$, and place on top of a preheated warming platform that is designed for histological work. Using forceps, remove the Graftskin specimens from the cassette, and place the specimens in individual molds. Orient the specimens in the molds to enable cutting of a cross or longitudinal section. Cool the paraffin by sliding the mold down the platform to its cool side until the paraffin has solidified. Maintain the specimen orientation with forceps during cooling, removing the forceps when the paraffin becomes translucent. Slide the paraffin block onto a histological cold plate to rapidly cool the block. Trim the paraffin block with a new single-edged razor blade to form a rectangle or slight trapezoid to within 5 mm of the tissue mass, if necessary. Cool the block at $4^{\circ}$ for 15 to 30 minutes, and clamp the paraffin block into the block holder of the microtome. Fill a histological tissue-flotation water bath with fresh water, add an appropriate amount of a suitable histological adhesive ${ }^{5}$, and heat to a temperature $5^{\circ}$ lower than the melting point of the paraffin. Properly mount the paraffin block into a microtome, adjusting as necessary. Set the microtome to make $5-\mu \mathrm{m}$ thick cuts with a blade angle of $5 \pm 2^{\circ}$. Insert into the knife holder a sharp stainless steel microtome knife that has been properly honed or a new disposable microtome knife, and cut a ribbon that contains 6 to 10 sections of Graftskin. Pick up the ribbon with forceps, and stretch it across the tissue-flotation water bath. Separate 2 to 3 adjacent sections from the ribbon on the water bath.

[^50]The selected sections should not be compressed, wrinkled, or scratched. Pick up the selected sections by dipping a microscope slide into the water bath under the floating sections, and gently lift the slide out of the water. Allow the mounted sections to air-dry completely, or dry the slide in a $60^{\circ}$ oven for 1 hour. The microscope slide with affixed tissue is sequentially immersed in 3 changes of a suitable histological, aliphatic xylene substitute ${ }^{6}$, 5 minutes per step, followed by two changes of dehydrated alcohol, 3 minutes per step. Sequentially immerse the slide in alcohol (for 3 minutes), running water rinse ( 3 minutes), Hematoxylin staining solution ( 6 minutes), running water rinse ( 7 min utes), $0.3 \%$ Acid alcohol ( 6 seconds), running water rinse ( 5 minutes), Bluing agent ( 1 second), running water rinse ( 5 minutes), Eosin solution ( 2 minutes), 2 changes of alcohol ( 3 minutes each step), 4 changes of dehydrated alcohol ( 3 minutes each step), and 4 changes of a suitable histological xylene substitute ( 3 minutes each step). Adjust the above immersion times as needed to suitably stain the tissue. Remove the slide from the last histological xylene substitute wash, and blot dry the back of the slide. Do not allow the tissue to dry. Affix a coverslip over the tissue, using a suitable coverslip mountant.
MICROSCOPIC SPECIFICATIONS-A light microscope with $4 \times, 10 \times, 20 \times$, and $40 \times$ objectives installed in a revolving nosepiece; a $10 \times$ widefield ocular with 19 to 10 mm per 100 microdisk reticle installed; and a $10 \times$ widefield ocular with grid reticle installed.

MICROSCOPIC AND MORPHOLOGICAL CHARACTERISTICSScore the 3 Graftskin sections for epidermal and dermal aspects using the light microscope. Slides from each of the sections taken should be evaluated. The aspect values for each section should be averaged $(n=3)$ to determine the

[^51]overall aspect score for the Graftskin unit. When examined microscopically, Graftskin shows a bilayered construct resembling the epidermal and dermal layers of human skin. Graftskin meets the following requirements for epidermat and dermal aspects of the deviee, using USP Graftskin Photomierographs RS of passing and failing articles for eomparisen. Using USP Graftskin Reference Photomicrographs of passing and failing articles for comparison, Graftskin meets the requirements for epidermal aspects, including epidermal coverage, epidermal development, and keratinocyte aspect, and meets the requirements for dermal aspects, including dermal matrix thickness, fibroblast density, and matrix aspect, as described below.

Epidermal aspects (see USP Graftskin Reference Photomicrograph 1 for an example of a passing unit)-

Epidermal coverage-Ninety-five percent or more of the dermal matrix present on the slide is covered with epidermal keratinocytes.

Epidermal development-Seventy percent or more of the Graftskin epithelium is composed of 3 distinct cell layers (see USP Graftskin Reference Photomicrograph 2 for an example of a failing unit). The basal cell layer of the epithelium is at least 1-cell thick, consisting of keratinocytes with a cuboidal-columnar shape (see USP Graftskin Reference Photomicrograph 3 for an example of a failing unit). The suprabasal layer is composed of stratified cells and is at least 5-cells thick. Suprabasal cells closest to the basal layer are cuboidal in shape; cells become progressively stratified the closer they are to the uppermost, squamous cell layer. The squamous cell layer on the apical surface is cornified and at least 1-cell thick (see USP Graftskin Reference Photomicrograph 4 for an example of a failing unit). The uppermost cell layer of the epithelium is analogous to the stratum corneum
of human skin and is composed of one or more rows of flat, scaly cells that are nonliving and keratinized (see USP Graftskin Reference Photomicrograph 5 for an example of a failing unit).

Keratinocyte aspect-Ninety-five percent or more of the basal keratinocytes have basophilic cytoplasm that have neither distinct vacuoles nor are necrotic (see USP Graftskin Reference Photomicrograph 6 for an example of a failing unit). Eighty percent or more of suprabasal cells (excluding those in the upper $20 \%$ of the cell layer closest to the squamous layer) have basophilic cytoplasm. Furthermore, these basophilic suprabasal cells do not have distinct vacuoles and are neither necrotic nor keratinized (see USP Graftskin Reference Photomicrographs 7 and 8 for examples of failing units).

Dermal Aspects (see USP Graftskin Reference Photomicrograph 1 for an example of a passing unit)-Five randomly selected fields per slide will be evaluated for dermal matrix thickness and fibroblast density. The 5 fields will be averaged to obtain the final value for each section.

Dermal matrix thickness-The Graftskin dermal layer is not less than $40-\mu \mathrm{m}$ thick and is composed of several rows of flat dermal cells.

Fibroblast density-The dermal matrix contains an average of at least 4 nonpyknotic nuclei present per microscopic field (field $=20$ grid squares of reticle when using the $10 \times$ widefield ocular and $40 \times$ objective).

Matrix aspect-At least $95 \%$ of the dermal matrix collagen stain uniformly with no large holes or inclusions present (see USP Graftskin Reference Photomicrographs 9 and 10 for examples of failing units).

## Gene expression profile-

RNA extraction solution-Use an aqueous phenol and guanidine isothiocyanate solution suitable for RNA extraction. ${ }^{7}$

DEPC-treated water-Add 0.2 mL of diethylpyrocarbonate (DEPC) to 100 mL of sterile purified water, shake vigorously, and allow to stand for at least 12 hours. Autoclave the resulting solution for 15 minutes, using the liquid cycle, to inactivate residual DEPC. Prepare fresh as needed.

5X Reaction buffer-Prepare a solution of potassium chloride, magnesium chloride, and tris(hydroxymethyl)aminomethane hydrochloride having concentrations of 375 $\mathrm{mM}, 15 \mathrm{mM}$, and 250 mM , respectively. Adjust to a pH of 8.3.

10X Reaction buffer-Prepare a solution of potassium chloride and tris(hydroxymethyl)aminomethane hydrochloride having concentrations of 500 mM and 100 mM , respectively. Adjust to a pH of 8.3.

Oligo-deoxythymidine solution-Prepare a 20 mM oligodeoxythymidine (primer length: 18) solution using a suitable buffer. ${ }^{8}$
$d N T P$ solution $I$-Using a suitable buffer ${ }^{8}$, prepare a solution of deoxyadenosine triphosphate, deoxyguanosine triphosphate, deoxycytidine triphosphate, and deoxythymidine triphosphate in which the concentration of each component is 10 mM .
$d N T P$ solution II-Prepare a solution, in water, of deoxyadenosine triphosphate, deoxyguanosine triphosphate, deoxycytidine triphosphate, and deoxythymidine triphosphate, in which the concentration of each component is 10 mM .

[^52]Ribonuclease inhibitor solution-Prepare a solution containing 40 units of ribonuclease inhibitor per mL of a suitable buffer. ${ }^{8}$

Reverse transcriptase solution-Prepare a solution containing 200 units of reverse transcriptase per $\mu \mathrm{L}$ of a solution of sodium chloride, edetate disodium, dithiothreitol, nonylphenol polyoxyethylene ether, glycerin, and tris(hydroxymethyl)aminomethane hydrochloride having concentrations of $0.1 \mathrm{M}, 0.1 \mathrm{M}, 1.0 \mathrm{M}, 0.01 \%, 50 \%$, and 200 mM , respectively. Adjust to a pH of 7.5 .

DNA primer pairs-Prepare individual $20 \mu \mathrm{M}$ solutions of the following DNA primer pairs ${ }^{9}$ using deoxyribonu-clease- and ribonuclease-free water.

## Transforming growth factor $\beta$ -

TGF $\beta$ 1-3' agg ctc caa atg tag ggg cag g
TGF $\beta$ 1-5' $\quad$ gcc ctg gac acc aac tat tgc t

## Interleukin-1 $\alpha-$

| IL1 $\alpha-3^{\prime}$ | tag tge cgt gag ttt ccc aga aga <br> aga gga gg |
| :--- | :--- |
| IL1 $\alpha-5^{\prime}$ | caa gga gag cat ggt ggt agt <br>  |

## Interleukin-4-

| IL4-3' | acg tac tct ggt tgg ctt cct tca |
| :--- | :--- |
|  | cag gac ag |
| IL4-5' | cgg caa ctt tga cca cgg aca <br>  |
|  | caa gtg cga ta |

[^53]Platelet-derived growth factor $\mathbf{A}-$

\[\)|  PDGF-A-3'  |  |
| :---: | :--- |
|  |  ttg ctt cac cga gtg cta caa tac  |
|  PDGF-A-5'  |  aga agt cca ggt gag gtt aga  |
|  |  gga gca $t$ |

\]

## Glyceraldehyde-3-phosphate dehydrogenase-

| G3PDH-3' | cat gtg ggc cat gag gtc cac |
| :--- | :--- |
| G3PDH-5' | cac |
|  | tga agg tcg gag tca acg gat |
|  | ttg gt |

DNA polymerase solution-Prepare a solution containing 5 units of deoxyribonucleic acid polymerase per mL of a solution of potassium chloride, edetate disodium, dithiothreitol, polyoxyethylene(20) sorbitan monolaurate, nonylphenol polyoxyethylene ether, glycerin, and tris(hydroxymethyl)aminomethane hydrochloride, having concentrations of $100 \mathrm{mM}, 0.1 \mathrm{mM}, 1 \mathrm{mM}, 0.5 \%, 0.5 \%$, $50 \%$, and 20 mM , respectively. Adjust to a pH of 8.0 .

RNA Extraction Procedure-Remove three 2-cm diameter circular sections from every $30 \mathrm{~cm}^{2}$ of Graftskin (not less than $30 \%$ of the total unit area), using the appropriate size biopsy punch. Transfer each piece of tissue to individual polypropylene microcentrifuge tubes. Add 1.0 mL of $R N A$ extraction solution to each tube, homogenize by repetitive pipetting, and incubate the samples for 5 minutes at room temperature. To each tube add 0.2 mL of chloroform, mix on a vortex mixer, and centrifuge at $12,000 \mathrm{~g}$ for 15 minutes at $2^{\circ}$ to $8^{\circ}$. Transfer the upper, aqueous phase to a second tube, add 0.5 mL of isopropanol, and incubate for 30 minutes to overnight at $-20^{\circ}$. Centrifuge at $12,000 \mathrm{~g}$ for 15 minutes, discard the supernatants by aspiration, and add $75 \%$ alcohol to each pellet. Mix the sample on a vortex mixer , centrifuge at $12,000 \mathrm{~g}$ for 2 minutes, and discard the
supernatants by aspiration without disturbing the RNA pellets. Recentrifuge at $12,000 \mathrm{~g}$ for 2 minutes, and remove the remaining supernatants with a small-volume $(20 \mu \mathrm{~L}$ or smaller capacity) micropipette. Air-dry the pellets for $5 \mathrm{~min}-$ utes at room temperature by keeping the microcentrifuge cap off, and resuspend each pellet in $50 \mu \mathrm{~L}$ of DEPC-treated water. Bring absorbance into linear range by diluting $5 \mu \mathrm{~L}$ of each suspension with $195 \mu \mathrm{~L}$ of DEPC-treated water. Transfer the samples to suitable quartz microplates or cuvettes and determine the absorbance of the RNA solution at wavelengths of 260 and 280 nm , using a spectrophotometer and DEPC-treated water as the blank. The ratio of the absorbance at 260 versus 280 nm should be greater than or equal to 1.65 . If this ratio is less than 1.65 , then mix the resuspended pellet by repetitive pipetting, and repeat the dilution step and absorbance measurement. If this fails to raise the absorbance ratio, then repeat the RNA extraction for that sample by adding 1 mL of $R N A$ extraction solution, and proceed as above beginning with "incubate the sample for 5 minutes at room temperature". Determine the concentration of RNA in $\mu \mathrm{g}$ per mL using the following equation:

## $40 A D$,

in which $A$ is the absorbance at 260 nm ; and $D$ is the dilution factor. Adjust the volume of the RNA solutions with additional DEPC-treated water to bring the concentration of RNA to about $80 \mu \mathrm{~g}$ per mL . If the absorbance at 260 nm is less than 0.05 , discard the sample, and repeat the RNA extraction on a fresh sample.

Synthesis of $c D N A-T o$ separate, individual thin-walled polymerase chain reaction (PCR) tubes add $12.5 \mu \mathrm{~L}$ of the RNA solution from samples 1, 2, and 3 (3 reaction tubes total). Add $1 \mu \mathrm{~L}$ of Oligo-deoxythymidine solution to each tube, and incubate at $72^{\circ}$ for 2 minutes to anneal the oligodeoxythymidine to the mRNA. Place the tubes in an ice
bath, and to each tube add $4 \mu \mathrm{~L}$ of $5 X$ Reaction buffer, $1 \mu \mathrm{~L}$ of $d N T P$ solution I, $0.5 \mu \mathrm{~L}$ of Ribonuclease inhibitor solution, and $1 \mu \mathrm{~L}$ of Reverse transcriptase solution. Incubate at $42^{\circ}$ for 1 hour to synthesize cDNA, and then incubate at $94^{\circ}$ for 5 minutes to inactivate the reverse transcriptase. To each tube add $80 \mu \mathrm{~L}$ of DEPC-treated water, and mix.

Polymerase chain reaction amplification of cDNA-For each of the five DNA primer pairs, label five individual centrifuge tubes ( 5 tubes total). Add the following to each centrifuge tube: $D E P C$-treated water, $135.8 \mu \mathrm{~L} ; d N T P$ solution II, $10.5 \mu \mathrm{~L}$; $10 X$ Reaction buffer, $21 \mu \mathrm{~L}$; the appropriate $5^{\prime}$ primer, $3.5 \mu \mathrm{~L}$; the appropriate $3^{\prime}$ primer, $3.5 \mu \mathrm{~L}$; and 25 mM magnesium chloride, $12.6 \mu \mathrm{~L}$. Close, mix on a vortex mixer, and pulse spin in a microcentrifuge. Add $2.1 \mu \mathrm{~L}$ of DNA polymerase solution to each centrifuge tube, and mix by repetitive pipetting. For each primer pair, transfer $27 \mu \mathrm{~L}$ of the resulting solution to five, thin-walled PCR tubes. There should be a total of 25 PCR tubes. Add the following to the PCR tubes of each primer set:

|  | PCR tube number |
| :--- | :--- |
| 1. | $3 \mu \mathrm{~L}$ Graftskin sample 1 cDNA |
| 2. | $3 \mu \mathrm{~L}$ Graftskin sample 2 cDNA |
| 3. | $3 \mu \mathrm{~L}$ Graftskin sample 3 cDNA |
| 4. | $3 \mu \mathrm{~L}$ cDNA positive control ${ }^{10}$ |
| 5. Negative | $3 \mu \mathrm{~L}$ DEPC-treated water |
| $\quad$ control |  |

${ }^{10}$ A suitable cDNA positive control can be obtained from BD Biosciences Clontech, 1020 East Meadow Circle, Palo Alto, CA 94303-4230.

Repeat for the remaining primer pairs. The positive control contains authentic cDNA of Transforming growth factor $\beta$, Interleukin- $1 \alpha$, Interleukin-4, Platelet-derived growth factor A, and Glyceraldehyde-3-phosphate dehydrogenase,
as appropriate for each primer set. Pulse spin the PCR tubes in a microcentrifuge to mix, and place the tubes in a single PCR thermal cycler. Cycling conditions are as follows.

| Melting temperature: | 94 degrees |
| :--- | :--- |
| Melting time: | 45 seconds |
| Anneal temperature: | 58 degrees |
| Anneal time: | 45 seconds |
| Elongation temperature: | 72 degrees |
| Elongation time: | 2 minutes |
| Number of cycles: | 30 |
| Final elongation <br> $\quad$ temperature: | 72 degrees |
| Final elongation time: | 2 minutes |

Terminate the PCR amplification by heating each tube to
$72^{\circ}$ for 7 minutes.

## ELECTROPHORESIS IDENTIFICATION-

Tris-boric acid buffer-Prepare a solution containing 89 mmoles of tris(hydroxymethyl) aminomethane, 89 mmoles of boric acid, and 2 mmoles of edetate disodium per L .

6X Loading buffer—Prepare a solution containing $15 \%$ of a branched polymeric sucrose ( 400 kDa ), $0.25 \%$ bromophenol blue, and $0.25 \%$ xylene cyanole FF.

Ethidium bromide solution-Prepare a solution of ethidium bromide in Tris-boric acid buffer having a concentration of 10 mg per mL .

Agarose gel-Prepare a horizontal $2 \%$ agarose ${ }^{11}$ gel in Tris-boric acid buffer. Once the gel is set, remove the comb, and place the gel into the electrophoresis chamber with the comb end of the gel situated closest to the cathode terminal. Fill the electrophoresis chamber with Tris-boric acid buffer until the buffer reaches 3 to 5 mm over the surface of the gel.

[^54]100-bp DNA ladder markers-Prepare a solution containing 10 DNA fragments covering the range of 100 to 1000 base pairs (bp) in 100-bp increments, with a total DNA content of approximately 100 ng per $\mu \mathrm{L}$ ( $15-20 \mathrm{ng}$ of DNA per band) in an appropriate buffer. ${ }^{12}$

Procedure-Dilute the 25 PCR samples prepared in the Polymerase chain reaction amplification of $c D N A$ with $6 X$ Loading buffer such that the final concentration of the buffer is one-sixth of its original concentration. Load $5 \mu \mathrm{~L}$ of the 100-bp DNA ladder markers in the first lane of the agarose gel. Load $10 \mu \mathrm{~L}$ of each PCR sample into each gel well, and attach the cathode to the terminal close to the loaded wells. Attach the anode to the terminal farthest from the loaded wells, and apply 120 V to the gel. Run the gel until the bromophenol blue is about two-thirds the length of the gel. Remove the gel from the electrophoresis apparatus, and place it in a tray containing enough Ethidium bromide solution to cover the gel. Slowly agitate the gel on a shaker table for 30 minutes. Completely remove the Ethidium bromide solution from the tray, add an equal amount of Tris-boric acid buffer, and slowly agitate the gel on a shaker table for 60 minutes. Place the gel on a 312 -nm UV light source, photograph the gel, and imspeet the image for bands. The analysis is censidered valid if the pesitive contrels show the apprepriately sized eDNA PCR products, and no-PCR produet bands appear in the negative controls. inspect the image for bands that have migrated from each individual well. If a band appears, it is verified for size in base pairs by comparing it to the lane for the $100-\mathrm{bp}$ DNA ladder marker. If a band appears and it is of the appropriate size, it is considered positive. The analysis is considered valid if the positive controls show the appropriately sized cDNA-PCR products, no PCR product bands appear in the negative controls, and all

[^55]bands are observed to be visually discrete. The lanes of the agarose gel that correspond to Graftskin show cDNA bands for Interleukin- $1 \alpha$ (expected PCR product band size of 491 base pairs, limit of detection not less than $9.6 \times 10^{-21}$ moles); Platelet-derived growth factor (expected PCR product band size of 304 base pairs, limit of detection not less than $1.5 \times 10^{-20}$ moles); Transforming growth factor- $\beta 1$ (expected PCR product band size of 161 base pairs, limit of detection not less than $1.5 \times 10^{-20}$ ) moles; and Glyceraldehyde-3-phosphate dehydrogenase (expected PCR product band size of 983 base pairs); but not Interleu-kin-4 (expected PCR product band size of 344 base pairs, limit of detection not less than $1.5 \times 10^{-22}$ moles). If one of the replicates tested yields results discordant with the other two replicates, repeat the assay, and accept only if all 3 replicates are concordant.

## Barrier integrity assessment-

Ham's F-12 tissue culture medium-Prepare a solution that contains the following:

| Component | mg per mL |
| :--- | :---: |
| L-Alanine | 8.91 |
| L-Arginine hydrochloride | 210.7 |
| L-Asparagine monohydrate | 15.01 |
| L-Aspartic acid | 13.30 |
| L-Cysteine hydrochloride |  |
| $\quad$ monohydrate | 35.12 |
| L-Glutamic acid | 14.70 |
| L-Glutamine | 46.2146 .2 |
| Aminoacetic Acid | 7.51 |
| L-Histidine hydrochloride | 20.96 |
| monohydrate | 3.94 |
| L-Isoleucine | 13.12 |
| L-Leucine | 36.54 |
| L-Lysine hydrochloride | 4.48 |


| Component | mg per mL |
| :--- | :---: |
| L-Phenylalanine | 4.96 |
| L-Proline | 34.53 |
| L-Serine | 10.51 |
| L-Threonine | 11.91 |
| L-Tryptophan | 2.04 |
| L-Tyrosine disodium | 6.71 |
| L-Valine | 11.71 |
| Calcium chloride | 44.00 |
| Cupric sulfate, pentahydrate | 0.0025 |
| Ferric sulfate, heptahydrate | 0.834 |
| Potassium chloride | 223.7 |
| Magnesium chloride | 57.22 |
| Sodium chloride | 7599.0 |
| Sodium phosphate, dibasic | 142.0 |
| Zinc sulfate, heptahydrate | 0.863 |
| D-Biotin | 0.0073 |
| D-Calcium pantothenate | 1801.6 |
| Choline chloride | 0.338 |
| Fodium pyruvate | 110.0 |
| Hexic acid | 13.96 |
| Hypoxanthine | 1.30 |
| Inositol | 4.04 |
| Niacinamide | 18.02 |
| Pyridoxine hydrochloride | 0.0366 |
| Riboflavin | 0.0617 |
| Thiamine hydrochloride | 0.0376 |
| Thymidine | 0.337 |
|  | 0.727 |


| Component | mg per mL |
| :--- | :---: |
| Putrescine dihydrochloride | 0.161 |
| Sodium bicarbonate | 1176.0 |

Tritiated water: $2.0 \mu \mathrm{Ci} / \mathrm{mL}$ (see Radioactivity $\langle 821\rangle$ ).
Percutaneous absorption apparatus-Prepare the apparatus as described below. ${ }^{13}$

Six-well cell culture plate-The dimensions are inner diameter, about 35 mm ; depth, about 18 mm .

Cell culture well insert-Each well is a plastic cylinder with inner length, about 15 mm ; inner diameter, about 24 mm ; outer diameter, about 27 mm , with a flanged end extending about 4 mm from the outer diameter. The inner diameter opposite the flanged end is covered by a taut polycarbonate membrane having a porosity of $3 \mu \mathrm{~m}$. The flange should allow the Cell culture well insert to be suspended in the well of a Six-well cell culture plate, leaving a $3-\mathrm{mm}$ space between the bottom of the Cell culture well insert and the inner bottom surface of the Six-well cell culture plate.
Percutaneous absorption insert-Use a polytetrafluoroethylene cylinder having the following dimensions: length, about 20 mm ; inner diameter, about 20 mm ; outer diameter, about 23 mm with a flanged end extending about 3 mm from the outer diameter. Ten mm from the flanged end of the cylinder, the inner diameter begins to funnel such that the inner diameter at about 10 mm from the flanged end is about 20 mm , and the inner diameter at about 15 mm from the flanged end is about 8 mm . From about 15 mm to about 20 mm from the flanged end, the inner diameter remains at 8 mm . The

[^56]outer diameter of the cylinder remains constant at about 23 mm . The flanged end is considered to be the top of the component.

Silicon grease-Use high-vacuum silicon grease suitable for glass. ${ }^{14}$
Procedure-Fill each well of the Six-well cell culture plate with 1.5 mL of Ham's F-12 tissue culture medium. Remove two $2-\mathrm{cm}$ circular sections from every $30 \mathrm{~cm}^{2}$ of Graftskin (not less than $20 \%$ of the total unit area), using the appropriate size biopsy punch. Transfer each excised section to a separate Cell culture well insert, dermal side down on the polycarbonate membrane. Using forceps, gently smooth out the section to remove any wrinkles. Apply a narrow ring of Silicon grease to the underside of the Percutaneous absorption insert, and place the insert into the Cell culture well insert, grease side down, onto the epidermal surface of the Graftskin biopsy, with slight pressure to form a tight seal. Do not allow any grease to enter the $8-\mathrm{mm}$ diameter exposed area of the Graftskin surface. Place the Cell culture well insert containing the Percutaneous absorption insert into one of the wells of the Six-well cell culture plate containing 1.5 mL of Ham's F-12 tissue culture medium. Apply 1.0 mL of Tritiated water to the exposed surface of the Graftskin unit in the Percutaneous absorption insert, and incubate at ambient temperature for 6 hours. At the end of each hour, transfer the Cell culture well insert containing the Percutaneous absorption insert to a new well within the Six-well cell culture plate containing 1.5 mL of fresh Ham's F-12 tissue culture medium. After the 6-hour incubation, remove the Cell culture well insert. Remove a $0.5-\mathrm{mL}$ aliquot of Ham's F-12 tissue culture medium from each well of the Six-well cell culture plate, and transfer into individual scintillation vials. Dispense 0.5 mL of Tritiated

[^57]water to a separate scintillation vial as a control, to each scintillation vial add 4.5 mL of a suitable scintillation cocktail ${ }^{15}$, and gently mix. Place the scintillation vials into a liquid scintillation counter, and count the emissions in the tritium spectrum for 60 seconds. Average the counts for each of the six time points (punch average) and duplicate sections (unit average). Determine the percent penetration per hour by the formula:
$$
150\left(C_{S} / C_{C}\right)
$$
in which $C_{S}$ are the counts per minute of the $0.5-\mathrm{mL}$ aliquot of the Ham's F-12 tissue culture medium taken at the end of the incubation period; and $C_{C}$ are the counts per minute in the $0.5-\mathrm{mL}$ aliquot of Tritiated water. Not more than $1.97 \%$ penetration is found.

## Metabolic activity assessment-

Dulbecco's modified Eagle's tissue culture medium -Prepare a solution that contains the following components.

| Component | mg per L |
| :--- | :---: |
| Calcium chloride | 264.9 |
| Ferric nitrate, nonahydrate | 0.10 |
| Potassium chloride | 400.0 |
| Magnesium sulfate, heptahydrate | 200.0 |
| Sodium chloride | $6,400.0$ |
| Sodium bicarbonate | $3,700.0$ |
| Sodium phosphate, monobasic |  |
| $\quad$ (monohydrate) | 125.0 |
| Dextrose | $4,500.0$ |
| Phenol red | 15.0 |
| Sodium pyruvate | 110.0 |
| L-Arginine hydrochloride | 84.0 |
| L-Cystine | 48.0 |
| Aminoacetic acid | 30.0 |

${ }^{15}$ A suitable scintillation cocktail is Optiphase ${ }^{\circledR}$, Supermix ${ }^{\circledR}$, Perkin-Elmer Life Sciences, Inc., 549 Albany St., Boston, MA 02118.

| Component | mg per L |
| :--- | :---: |
| L-Histidine hydrochloride monohydrate | 42.0 |
| L-Isoleucine | 104.8 |
| L-Leucine | 104.8 |
| L-Lysine hydrochloride | 146.2 |
| L-Methionine | 30.0 |
| L-Phenylalanine | 66.0 |
| L-Serine | 42.0 |
| L-Threonine | 95.2 |
| L-Tryptophan | 16.0 |
| L-Tyrosine | 72.0 |
| L-Valine | 93.6 |
| D-Calcium pantothenate | 4.0 |
| Choline chloride | 4.0 |
| Folic acid | 4.0 |
| Inositol | 7.0 |
| Nicotinamide | 4.0 |
| Pyridoxine hydrochloride | 4.0 |
| Riboflavin | 0.40 |
| Thiamine hydrochloride | 4.0 |

MTT solution-Dissolve 0.33 g of (3-(4,5-dimethylthia-zol-2yl)-2,5-diphenyl tetrazolium bromide in 1 L of Dulbecco's modified Eagle's tissue culture medium, with constant stirring. Pass the solution through a suitable size filter having a $0.2-\mu \mathrm{m}$ porosity.
0.04 N Acidified isopropyl alcohol-Add 3.45 mL of hydrochloric acid to 1 L of isopropyl alcohol, and mix thoroughly. Store at room temperature no longer than 6 months.

Procedure-Immerse the Graftskin in separate, $40.0-\mathrm{mL}$ portions of MTT solution, making sure that about 20 mL of MTT solution is under the test article, and 20 mL of MTT solution is on the surface. Take care not to produce any bubbles. Incubate for 3 hours at $37^{\circ}$, in an environment of air enriched with $10 \%$ carbon dioxide. After incubation, remove from the $37^{\circ}, 10 \%$ carbon dioxide-enriched air environment. Transfer the Graftskin to a suitable cutting surface, and, using an appropriate biopsy punch, remove three 8 -mm diameter circular sections from every $30 \mathrm{~cm}^{2}$ of Graftskin ( $5 \%$ of unit area). Transfer each punch to individual snap-top test tubes. Add 0.9 mL of 0.04 N Acidified isopropyl alcohol to each tube, making sure that the tissue is completely submerged. If not submerged, use forceps to place the sample into the 0.04 N Acidified isopropyl alcohol. Cap each tube tightly, place on an orbital shaker, and shake for 1 hour at a moderate setting. After 1 hour, remove the tubes from the orbital shaker, and mix each tube on a vortex mixer. Inspect the tubes to make sure that the tissue samples continue to be submerged. If not, use forceps or other device to resubmerge the tissues. Return the tubes to the orbital shaker, and continue to shake for an additional 1 hour. Remove the tubes from the orbital shaker, mix the tubes on a vortex mixer, and transfer a $0.2-\mathrm{mL}$ aliquot to a suitable 96 well flat bottom plate. Read the absorbance of each sample at 570 nm , using 0.2 mL of 0.04 N Acidified isopropyl alcohol as the blank. The average absorbance value is $\geq 0.237$. $\Delta U S P 28$

## Briefing

Helium, USP 27 page 903 and page 1121 of $P F$ 28(4) [JulyAug. 2002]. It is proposed to add a new USP Reference Standard and to revise the Assay to incorporate the new standard.
(AER: K. Zaidi) RTS-40629-4

## Add the following:

${ }^{\mathbf{4}}$ USP Reference standards $\langle 11\rangle —$ USP Air-Helium $R S_{.}{ }_{\text {USSP28 }}$

## Change to read:

Assay-Introduce a specimen of Helium into a gas chromatograph by means of a gas sampling valve. Select the operating conditions of the gas chromatograph such that the standard peak signal resulting from the following procedure corresponds to not less than 70\% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 6 m in length and 4 mm in inside diameter and is packed with porous polymer beads, which permits complete separation of nitrogen and oxygen from Helium, although the nitrogen and oxygen may not be separated from each other. Use industrial grade helium (99.99\%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by an air helium certified standard (see under Reagents in the sec tion Reagents, Indicators, and Solutions),
${ }^{\boldsymbol{4}}$ USP Air-Helium RS,
and indicates not more than $1.0 \%$ of air when compared to the peak response of the air helimmertified standare,
${ }^{\boldsymbol{\Delta}}$ USP Air-Helium RS,,$_{\text {aSP28 }}$
and not less than $99.0 \%$, by volume, of He.

## BRIEFING

Homatropine Hydrobomide, USP 27 page 911. It is proposed to replace the test for Melting range with a more specific test for Chromatographic purity. The Melting range information is being placed under Description and Solubility in the Reference Tables. The stability-indicating liquid chromatographic procedure in the test for Chromatographic purity is based on analyses performed with the GL Sciences Inertsil ODS-3 brand of L1 column. The typical retention time for homatropine is about 6.8 minutes. The thinlayer chromatographic procedure in the test for Limit of tropine is intended to quantify the tropine impurity not detected by the HPLC procedure and is based on analyses performed with the high performance silica gel $60 \mathrm{~F}_{254}$ plates. The $R_{F}$ values for homatropine and tropine are about 0.47 and 0.21 , respectively. It is also proposed to replace the titration procedure in the Assay with a more selective liquid chromatographic procedure, and to change the acceptance criteria in the Definition from "not less than 98.5 percent
and not more than 100.5 percent" to "not less than 98.0 percent and not more than 102.0 percent," which are typical for chromatographic procedures.
(PA4: E. Gonikberg) RTS-37240-1

## Change to read:

») Homatropine Hydrobromide contains net less than 98.5 pereent and not mere than 100.5 pereent

Anot less than 98.0 percent and not more than
102.0 percent $_{{ }_{\Delta S P 28}}$
of $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{NO}_{3} \cdot \mathrm{HBr}$, calculated on the dried basis.

## Change to read:

USP Reference standards $\langle 11\rangle —$ USP Homatropine Hydrobromide $R S$.
${ }^{\mathbf{\Delta}}$ USP Scopolamine Hydrobromide $R S . \_$USP28

## Delete the following:

${ }^{4}$ Melting range $\langle 744\rangle \div$ been $214^{\circ}$ and $217^{\circ}$, with slight deem perition._USP28

## Add the following:

## ${ }^{\Delta}$ Limit of tropine-

Adsorbent: $0.2-\mathrm{mm}$ layer of chromatographic silica gel mixture.

Diluent-Prepare a mixture of methanol and water (9:1).
Test solution-Transfer about 0.2 g of Homatropine Hydrobromide to a $5-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.
Standard solution-Dilute 0.5 mL of the Test solution
with Diluent to 100.0 mL .
Tropine reference solution-Prepare a solution of tropine having a concentration of about 0.4 mg per mL .
Application volume: $1 \mu \mathrm{~L}$.
Developing solvent system: a mixture of ethyl acetate, anhydrous formic acid, and water (67:16.5:16.5).

Procedure—Proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$, applying the Test solution, the Standard solution, and the Tropine reference solution. Spray the plate with Dragendorff's reagent, followed by hydrogen peroxide TS, and immediately cover
with a glass plate of the same size. Examine the plate no later than 5 to 10 minutes after spraying. In the chromatogram obtained from the Test solution, identify the spot corresponding to the principal spot in the chromatogram of the Tropine reference solution: this spot is not more intense than the spot obtained from the Standard solution: not more than $0.5 \%$ of tropine is found. $\triangle$ USP28

## Add the following:

${ }^{\Delta}$ Chromatographic purity-
Buffer solution, Mobile phase, System suitability solution, and Chromatographic system-Proceed as directed in the Assay.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Procedure-Separately inject a volume (about $7 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the responses for the major peaks. Continue the elution for 2.2 times the retention time of the homatropine peak. Disregard the peak for the bromide ion, which appears close to the solvent peak. Calculate the percentage of each impurity in the portion of Homatropine Hydrobromide taken by the formula:

$$
100\left(r_{i} / r_{s}\right),
$$

in which $r_{i}$ and $r_{s}$ are the peak response for each impurity and the sum of all peak responses, respectively, obtained from the Test solution. In addition to not exceeding the lim-
its for each impurity in Table 1, not more than $0.1 \%$ of any other individual impurity is found; and not more than $1.0 \%$ of total impurities is found.

Table 1.

|  | Relative <br> Retention | Limit |
| :--- | :---: | :---: |
| Impurity | Time | $(\%)$ |
| Mandelic acid | 0.3 | 0.1 |
| Dihydrohomatropine | 0.9 | 0.5 |
| Scopolamine | 1.1 | 0.1 |
| Atropine | 1.9 | 0.1 |

## Change to read:

Assay-Dissolve about 400 mg of Hematropine Hydrebromide, aceurately weighed, im water to make 50.0 mL , and mix. Transfer 10.0 mL of this solution to a beaker, add 5 mL of 1 N sodium hy droxide, and heat the solution just to beiling. Add 10 mL of 1 N nitrie acid, add water to make 50 mL , and cool im an iee bath. Con emitantly add 5 mL of 1 N nitrie acid to seend 10.0 mL pertion of the solution of Hematropine Hydrobremide, add water to make 50 mL , and cool in an ice bath. Add 1 drop of nitrophenanthroline TS to each solution, and, while keeping the solutions cold, titrate with 0.05 N -eric ammonium nitrate $V S$ until the pink color is dis eharged. Each mL of the difference in volumes of 0.05 N ceric am monium nitrate required is equivalent to 8.907 mg of $\mathrm{G}_{16} \mathrm{H}_{24} \mathrm{NO}_{3}-\mathrm{HBr}$.
${ }^{\boldsymbol{4}}$ Buffer solution-Dissolve 6.8 g of monobasic potassium phosphate and 7.0 g of sodium 1-heptanesulfonate monohydrate in 1000 mL of water, adjust with 3 M phosphoric acid to a pH of 2.7 , and mix.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and methanol (67:33).

Standard preparation-Dissolve an accurately weighed quantity of USP Homatropine Hydrobromide RS in Mobile phase to obtain a solution having a concentration of about 2 mg per mL .
System suitability solution-Prepare a solution of USP Scopolamine Hydrobromide RS having a concentration of about 0.1 mg per mL . Transfer 10 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, add 0.5 mL of the Standard preparation, and dilute with Mobile phase to volume.

Test preparation-Transfer about 100 mg of Homatropine Hydrobromide, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ column that contains $3-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $1.0 \%$. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution between homatropine and scopolamine peaks is not less than 1.5 .

Procedure-Separately inject equal volumes (about $7 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{NO}_{3} \cdot \mathrm{HBr}$ in the portion of Homatropine Hydrobromide taken by the formula:

$$
50 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Homatropine Hydrobromide RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta S P 2 8}$

BRIEFING
Hydrocortisone Acetate Lotion, USP 27 page 926. It is proposed to change the title of this monograph to Hydrocortisone Acetate Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40786-1

## Hydrocortisone Acetate Lotion

(Current title-not to change until July 1, 2007) Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Hydrocortisone Acetate Topical Emulsion

## BRIEFING

Hydrocortisone Acetate Ointment, USP 27 page 927. An editorial revision is indicated to conform with the title change proposed for Hydrocortisone Acetate Lotion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40787-1

## Change to read:

Assay-Proceed with Ointment as directed in the Assay under Hydrocortisone Acetate Lotion
${ }^{\boldsymbol{4}}$ (Hydrocortisone Acetate Topical Emulsion, Official July 1, 2007). $\mathbf{\Delta S S P 2 8}$

## BRIEFING

Hydrocortisone Acetate Topical Emulsion-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40786-1

Add the following:

## ©Hydrocortisone Acetate Topical Emulsion

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Hydrocortisone Acetate Lotion)

## » Hydrocortisone Acetate Topical Emulsion is

 Hydrocortisone Acetate in a suitable aqueous vehicle. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\mathrm{C}_{23} \mathrm{H}_{32} \mathrm{O}_{6}$.Packaging and storage-Preserve in tight containers.
USP Reference standards $\langle 11\rangle$-USP Hydrocortisone Acetate RS.

Identification-It responds to the Identification test under Hydrocortisone Acetate Ointment.

Minimum fill $\langle 755\rangle$ : meets the requirements.
Assay-
Mobile phase-Prepare a filtered and degassed solution containing butyl chloride, water-saturated butyl chloride, tetrahydrofuran, methanol, and glacial acetic acid (475:475:70:35:30). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Hydrocortisone Acetate RS in water-saturated chloroform to obtain a solution having a known concentration of about 0.10 mg per mL .

Assay preparation-Transfer an accurately weighed quantity of Topical Emulsion, equivalent to about 2.5 mg of hydrocortisone acetate, to a closable container. Add 25.0 mL of water-saturated chloroform and about 10 glass
beads. Securely close the container, and shake vigorously for approximately 15 minutes. Centrifuge, and use the clear, lower chloroform layer.

Procedure-Introduce equal volumes of the Assay preparation and the Standard preparation into a high-pressure liquid chromatograph fitted with a $254-\mathrm{nm}$ detector. Typically the apparatus is fitted with a $4-\mathrm{mm} \times 30-\mathrm{cm}$ column containing packing L3 and operated at room temperature. Six replicate injections of the Standard preparation show a relative standard deviation of not more than $2.0 \%$. Calculate the quantity, in mg , of $\mathrm{C}_{23} \mathrm{H}_{32} \mathrm{O}_{6}$ in the portion of Topical Emulsion taken by the formula:

$$
25 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Hydrocortisone Acetate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the hydrocortisone acetate peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\triangle$ USP28
(Official July 1, 2007)

## BRIEFING

Hydrocortisone Lotion, USP 27 page 923. It is proposed to change the title of this monograph to Hydrocortisone Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40785-1

## Hydrocortisone Lotion

(Current title-not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision): See Hydrocortisone Topical Emulsion

## Briefing

Hydrocortisone Topical Emulsion-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40785-1

## Add the following:

## ©Hydrocortisone Topical Emulsion

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Hydrocortisone Lotion)
» Hydrocortisone Topical Emulsion is Hydrocortisone in a suitable aqueous vehicle. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\mathrm{C}_{21} \mathrm{H}_{30} \mathrm{O}_{5}$.

Packaging and storage-Preserve in tight containers.
USP Reference standards $\langle 11\rangle$-USP Hydrocortisone RS. Identification-Transfer a quantity of Topical Emulsion, equivalent to about 5 mg of hydrocortisone, to a separator containing 10 mL of methylene chloride, shake for 1 min ute, and allow the layers to separate. Filter the methylene chloride extract onto a suitable chromatographic column that has been packed with 2 g of activated magnesium silicate. Wash the column with 25 mL of methylene chloride with the aid of slight air pressure, discarding the washings, and elute the hydrocortisone with 10 mL of methanol. Using USP Hydrocortisone RS to prepare a Standard solution having a concentration of $500 \mu \mathrm{~g}$ per mL , and using as the solvent system a mixture of 180 volumes of chloroform, 15 volumes of methanol, and 1 volume of water, proceed as directed under Thin-layer Chromatographic Identification Test $\langle 201\rangle$.

Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.

Minimum fill $\langle 755\rangle$ : meets the requirements.

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of water, acetonitrile, and methanol (58:21:21). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Hydrocortisone RS in alcohol and dilute quantitatively, and stepwise if necessary, with alcohol to obtain a solution having a known concentration of about 0.1 mg per mL . Quantitatively dilute a known volume of the final solution with an equal volume of water to obtain the Standard preparation.

System suitability preparation-Dissolve about 5 mg of propylparaben in 100 mL of alcohol. Dilute 1 mL of this solution with the Standard preparation to 10 mL , and mix.
Assay preparation-In a tared, $100-\mathrm{mL}$ volumetric flask, weigh 100 mL of Topical Emulsion that previously has been shaken to ensure homogeneity, allow to stand until the entrapped air rises, and finally invert carefully just prior to transfer to the volumetric flask. Transfer an accurately weighed quantity of Topical Emulsion, freshly mixed but free from air bubbles, equivalent to about 10 mg of hydrocortisone, to a $40-\mathrm{mL}$ beaker, and add about 30 mL of alcohol. Warm gently until the Topical Emulsion is dispersed, and cool to room temperature. Quantitatively transfer the mixture, filter through a pledget of cotton previously moistened with alcohol to a $100-\mathrm{mL}$ volumetric flask, rinse the beaker with two $20-\mathrm{mL}$ portions of alcohol, and collect the washings in the same volumetric flask. Dilute with alcohol
to volume, and mix. Quantitatively dilute a known volume of this solution with an equal volume of water to obtain the Assay preparation.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard preparation and the System suitability preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between the propylparaben and hydrocortisone peaks is not less than 2.0; the column efficiency determined from the analyte peak is not less than 1000 theoretical plates; the tailing factor for the analyte peak is not more than 1.2; and the relative standard deviation for replicate injections of the Standard preparation is not more than $3.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{21} \mathrm{H}_{30} \mathrm{O}_{5}$ in the portion of Topical Emulsion taken by the formula:

$$
200 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Hydrocortisone RS in the Standard preparation; and $r_{U}$ and the $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. From the observed weight of 100 mL of the Topical Emulsion, calculate the quantity of $\mathrm{C}_{21} \mathrm{H}_{30} \mathrm{O}_{5}$ in each 100 mL . $\mathbf{\Delta S P 2 8}$
(Official July 1, 2007)

## Briefing

Hydroxyzine Hydrochloride Tablets, USP 27 page 945 and page 1903 of $P F 29(6)$ [Nov.-Dec. 2003]. It is proposed to reverse the order of the Dissolution tests: Test 1 will become Test 2, and Test 2 will become Test 1 . This modification is being proposed because the product that generated Dissolution Test 1 is discontinued in the U.S. market. Therefore, it is intended to eliminate the need for modifying the labeling for all generic products.
(BPC: M. Marques) RTS-40874-1

## Add the following:

${ }^{\boldsymbol{4}}$ Labeling-When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used. $\Delta$ USP28

## Change to read:

Dissolution $\langle 711\rangle$ -
Meditum: water; 800 mL
Apparatus Proceed as directed for Uncouted Tablets under Disintegration- $\langle 701$ ) beginning with "Place 1. Tablet in each of the six tubec of the basket", with these exceptions: (a) the disks are net used; (b) the apparatus is adjustedso that the bettem of the basket rack assembly descendsto $1.0 \pm 0.1 \mathrm{em}$ frem the inside bettom-surface of the vessel on the downward stroke; (e) the 10 mesh, stainless steel cleth in the basket rack is replaced with 40 mesh, stainless steel cleth; and (d) 40 mesh, stainless steeleloth-is flted to the top of the basket rack assembly if necessary to prevent any desage unit from fleating out of the tubes of the assembly.

Tinne: 45 minutes.
Proecture Determine the ameunt of $\mathrm{C}_{24} \mathrm{H}_{27} \mathrm{ClN}_{2} \Theta_{2}-2 \mathrm{HCldis}$ selved by employing UV abserption at the wavelength of maximam abserbance at about 230 mm on fitered pertions of the solution under test, suitably diluted with Dissolution Mediunt, if neeessary, in comparisen with a-Standard solution having a known eoncentration of USP Hydroxyzine Hydrochloride RS in the same Mediun. Caleulate the ameunt of $\mathrm{C}_{24} \mathrm{H}_{27} \mathrm{ClN}_{2} \Theta_{2} \cdot 2 \mathrm{HCl}$ dissolved in each Tablet.

Toleranees Not less than 75\% of the-labeled ameant of $\mathrm{C}_{24} \mathrm{H}_{27} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot 2 \mathrm{HCl}$ is dissolved in 45 mintites.

TEST 2 -If the product complies with this test, the labeling
indientes that it meets USP Dissolution Test 2.
$\Delta_{\text {TEST }}$ 1-
Medium: water, 900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-Determine the amount of $\mathrm{C}_{21} \mathrm{H}_{27}$
$\mathrm{ClN}_{2} \mathrm{O}_{2} \cdot 2 \mathrm{HCl}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 230 nm on filtered portions of the solution under test, suitably di-
luted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Hydroxyzine Hydrochloride RS in the same Medium. Calculate the amount of $\mathrm{C}_{21} \mathrm{H}_{27} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot 2 \mathrm{HCl}$ dissolved per Tablet.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{21} \mathrm{H}_{27} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot 2 \mathrm{HCl}$ is dissolved in 45 minutes.

TEST 1—TEST 2—
If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium: water, 250 mL .
Apparatus 3 (see Drug Release $\langle 724\rangle$ ): 30 dips per minute.

Time: 45 minutes.
Procedure-Determine the amount of $\mathrm{C}_{21} \mathrm{H}_{27}$ $\mathrm{ClN}_{2} \mathrm{O}_{2} \cdot 2 \mathrm{HCl}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 230 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Hydroxyzine Hydrochloride RS in the same Medium. Calculate the amount of $\mathrm{C}_{21} \mathrm{H}_{27} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot 2 \mathrm{HCl}$ dissolved per Tablet.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{21} \mathrm{H}_{27} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot 2 \mathrm{HCl}$ is dissolved in 45 minutes. $\triangle$ USP28

## BRIEFING

Indinavir Sulfate Capsules. This proposed new monograph replaces the one previously published in Pharmacopeial Previews (see page 1641 of PF 26(6) [Nov.-Dec. 2000]). On the basis of comments received, the specifications in the Definition and in the sections on Packaging and storage and Dissolution have been revised to reflect those in the NDA submission. Also, it is proposed
to employ an IR method in the test for Identification. The test for Chromatography purity and the Assay have also been revised for further clarification.
(PA7b: B. Davani) RTS-40598-1

## Add the following:

## ©Indinavir Sulfate Capsules

» Indinavir Sulfate Capsules contain an amount of Indinavir Sulfate equivalent to not less than 93.0 percent and not more than 105.0 percent of the labeled amount of $\mathrm{C}_{36} \mathrm{H}_{47} \mathrm{~N}_{5} \mathrm{O}_{4}$.

Packaging and storage-Preserve in tight containers at $15^{\circ}$ to $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Indinavir $R S$.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$-The spectrum exhibits maxima at about $3.0-3.1,5.9,6.2$, and $13.6 \mu \mathrm{~m}$.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Dissolution $\langle 711\rangle$ -
pH 3.8 Citrate buffer-Transfer 21.0 g of citric acid to a $1000-\mathrm{mL}$ volumetric flask, and dissolve in about 980 mL of water. Adjust with $50 \%$ sodium hydroxide solution to a pH of $3.8 \pm 0.1$, and dilute with water to volume.

Medium: pH 3.8 Citrate buffer; 900 mL .
Apparatus 2: 50 rpm .
Time: 20 minutes.
Procedure-Determine the amount of indinavir $\left(\mathrm{C}_{36} \mathrm{H}_{47} \mathrm{~N}_{5} \mathrm{O}_{4}\right)$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 260 nm on filtered portions of the solution under test, suitably di-
luted with Dissolution Medium, in comparison with a Standard solution having a known concentration of USP Indinavir RS in the same Medium.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{36} \mathrm{H}_{47} \mathrm{~N}_{5} \mathrm{O}_{4}$ is dissolved in 20 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements for Weight Variation.

## Chromatographic purity-

Mobile phase and Resolution solution-Proceed as directed in the Assay.
Standard solution-Prepare as directed for Standard preparation in the Assay.

Dilute standard solution-Dilute an accurately measured volume of the Standard solution with Mobile phase to obtain a solution having a known concentration of about 0.3 $\mu \mathrm{g}$ per mL .

Test solution-Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay. Chromatograph the Dilute standard solution, and record the peak responses as directed for Procedure: the signal-to-noise ratio of the major peak is not less than 10 .

Procedure-Inject a volume (about $50 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Capsules taken by the formula:

$$
100 F\left(C_{S} / C_{J}\right)\left(r_{i} / r_{S}\right)
$$

in which $F$ is a response factor, and is equal to 0.93 for a peak, if present, at a retention time of 1.6 relative to indinavir, and equal to 1 for all other peaks; $C_{S}$ is the concentration, in mg per mL , of USP Indinavir RS in the Standard solution; $C_{I}$ is the concentration, in mg per mL , of indinavir in the Test solution; $r_{i}$ is the peak area for each impurity obtained from the Test solution; and $r_{S}$ is the peak area for
indinavir obtained from the Standard solution: not more than $1.5 \%$ of any individual impurity with a relative retention time of about 1.6 with respect to indinavir is found, not more than $0.1 \%$ of any other individual impurity is found, and not more than $2.5 \%$ of total impurities is found.

## Assay-

Citrate buffer-Transfer about 3.7 g of sodium citrate dihydrate and 1.6 g of citric acid to a $1000-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with water to volume. If necessary, adjust the resulting solution with 1 N sodium hydroxide or with phosphoric acid to a pH of $5.0 \pm 0.1$.

Mobile phase—Prepare a filtered and degassed mixture of Citrate buffer and acetonitrile (6:4).

Resolution solution-Transfer about 6 mg of USP Indinavir RS to a $20-\mathrm{mL}$ volumetric flask, and add 1 drop of 2 N hydrochloric acid to dissolve. Allow the solution to stand at room temperature for 1 hour, and then dilute with Mobile phase to volume.
Standard preparation-Dissolve an accurately weighed quantity of USP Indinavir RS in Mobile phase to obtain a solution having a concentration of about 0.3 mg per mL .
Assay preparation-Transfer not fewer than 10 Capsules, accurately counted, to a suitable volumetric flask. [NOTEThe target concentration is about 2 mg per mL .] Add a sufficient quantity of Mobile phase, and sonicate for 10 min utes with occasional shaking or until the capsule contents and shell are dispersed into small particles. Mix on a magnetic stirrer for 30 minutes or until dissolved. Cool the solution to room temperature, dilute with Mobile phase to volume, and mix. Quantitatively dilute a portion of this solution with Mobile phase to obtain a solution having a concentration of about 0.3 mg of indinavir per mL , and centrifuge.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $260-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L7. The flow rate is about 1.0 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Standard preparation, and record the peak response as directed for Procedure: the capacity factor, $k^{\prime}$, for the major peak is not less than 2.0 ; the tailing factor is less than 1.4 ; and the relative standard deviation for 5 replicate injections is not more than $1.0 \%$. Chromatograph the Resolution solution, and record the peak response as directed for Procedure: the resolution, $R$, between the major peak and the peak at a relative retention time of about 1.6 is not less than 2 .

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of indinavir $\left(\mathrm{C}_{36} \mathrm{H}_{47} \mathrm{~N}_{5} \mathrm{O}_{4}\right)$ in the portion of Capsules taken by the formula:

$$
D C\left(r_{U} / r_{S}\right)
$$

in which $D$ is the dilution factor for the Assay preparation; $C$ is the concentration, in mg per mL , of USP Indinavir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta}$ USP28

## Briefing

Isoproterenol Hydrochloride Injection, USP 27 page 1040. It is proposed to add storage conditions to the Packaging and storage section, in accordance with the current policies of the USP Packaging, Storage, and Distribution (PSD) Expert Committee.
(PA1: K. Russo; PSD: C. Okeke) RTS-40853-1

## Change to read:

Packaging and storage-Preserve in single-dose containers, preferably of Type I glass, protected from light.
${ }^{\boldsymbol{4}}$ Store at controlled room temperature. $\Delta$ USP28

## BRIEFING

Isradipine Capsules, page 1037 of $P F$ 29(4) [July-Aug. 2003]. It is proposed to add a Dissolution test to this monograph. Also the limit of total impurities in the Chrmatographic purity test is corrected.
(PA5: A. Wilk; BPC: M. Marques)
RTS-40548-1 ; 40820-1

## Add the following:

## ©Isradipine Capsules

» Isradipine Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of isradipine $\left(\mathrm{C}_{19} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{5}\right)$.

Packaging and storage-Store in a tight container at controlled room temperature. Protect from light.

USP Reference standards $\langle 11\rangle$ —USP Isradipine RS. USP Isradipine Related Compound A RS.

## Identification-

A: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle-$
Medium: methanol.

Solution-Transfer the contents of 1 Capsule into a suitable volumetric flask, dissolve the contents in the Medium by mechanical shaking for 15 minutes, and dilute with Me dium to obtain a solution containing $25 \mu \mathrm{~g}$ of isradipine per mL .

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, as obtained in the Assay.

Dissolution $\langle 711\rangle$ -
Medium: $0.1 \%$ aqueous solution of lauryl dimethyl amine oxide (prepared by transfering 500 mL of deaerated water into the dissolution vessel, adding 1.65 mL of $30 \%$ lauryl dimethyl amine oxide, and mixing); 500 mL .

Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-Determine the amount of $\mathrm{C}_{19} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{5}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 328 nm on filtered portions of the solution under test, suitably diluted with Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Isradipine RS in the same $M e$ dium.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{19} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{5}$ is dissolved in 45 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements. NOTE-Isradipine is light sensitive. Throughout the following procedures, protect test or assay specimens, the Reference Standards, and solutions containing them from unnecessary exposure to light. Use low-actinic glassware, unless otherwise directed.

## Chromatographic purity-

Mobile phase, Resolution solution, and Chromatographic system-Proceed as directed in the test for Chromatographic purity under Isradipine.

Standard solution-Dissolve an accurately weighed quantity of USP Isradipine RS in Mobile phase, with the aid of sonication if necessary, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $1 \mu \mathrm{~g}$ per mL . [NOTE-If necessary, use 1 mL of methanol per 20 mL of Mobile phase to dissolve the Reference Standard prior to diluting with Mobile phase.]

Test solution-Use the Assay preparation.
Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for all the peaks: the sum of all peak responses, other than that of isradipine, from the Test solution is not more than three four times the isradipine response obtained from the Standard solution (1.5\%); (2.0\%); and no single peak response is greater than that of the isradipine peak response obtained from the Standard solution ( $0.5 \%$ ).

## Assay-

Mobile phase, Standard preparation, and Chromatographic system-Proceed as directed in the Assay under Isradipine.

Assay preparation-Remove, as completely as possible, the contents of not fewer than 20 Capsules, and mix the combined contents. Transfer an accurately weighed quantity, equivalent to about 25 mg of isradipine, to a $100-\mathrm{mL}$ volumetric flask. Add 5.0 mL of methanol and 5.0 mL of Mobile phase, and sonicate at room temperature for 15 min utes. Shake for 15 minutes in a mechanical shaker. Dilute with Mobile phase to volume, mix, and filter, discarding the first 5 mL of the filtrate.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and
measure the responses for the major peaks. Calculate the quantity, in mg , of isradipine $\left(\mathrm{C}_{19} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{5}\right)$ in the portion of Capsules taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Isradipine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the isradipine peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\Delta$ USP28

## Briefing

Lindane Lotion, USP 27 page 1094 and page 635 of PF 29(3) [May-June 2003]. It is proposed to change the title of this mongraph to Lindane Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40788-1

## Lindane Lotion

(Current title-not to change until July 1, 2007) Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Lindane Topical Emulsion

## Change to read:

» Lindane Lotion is Lindane in a suitable aqueous vehicle. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\mathrm{E}_{6} \mathrm{H}_{6} \mathrm{Cl}_{6}$.
-the gamma isomer of lindane $\left(\mathrm{C}_{6} \mathrm{H}_{6} \mathrm{Cl}_{6}\right)$.ens (USP27)

## Briefing

Lindane Topical Emulsion—See briefing under Amphotericin $B$ Lotion.
(NL: C. Barnstein) RTS-40788-1

## Add the following:

## ©Lindane Topical Emulsion

## (Monograph under this new title-to become official July 1, 2007) <br> (Current monograph title is Lindane Lotion)

» Lindane Topical Emulsion is Lindane in a suitable aqueous vehicle. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of the gamma isomer of lindane $\left(\mathrm{C}_{6} \mathrm{H}_{6} \mathrm{Cl}_{6}\right)$.

Packaging and storage-Preserve in tight containers.
USP Reference standards $\langle 11\rangle$ —USP Lindane RS.
Identification-It responds to the Identification test under
Lindane Cream.
$\mathbf{p H}\langle 791\rangle$ : between 6.5 and 8.5.
Assay-Proceed as directed in the Assay under Lindane Cream, substituting "Topical Emulsion" for "Cream" throughout. $\triangle$ USP28
(Official July 1, 2007)

Briefing
Malathion Lotion, USP 27 page 1131. It is proposed to change the title of this monograph to Malathion Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40789-1

## Malathion Lotion

(Current title-not to change until July 1, 2007) Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Malathion Topical Emulsion

## BRIEFING

Malathion Topical Emulsion-See briefing under Amphoteri$\operatorname{cin} B$ Lotion.
(NL: C. Barnstein) RTS-40789-1

## Add the following:

## ©Malathion Topical Emulsion

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Malathion Lotion)
» Malathion Topical Emulsion is Malathion in a suitable isopropyl alcohol vehicle. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\mathrm{C}_{10} \mathrm{H}_{19} \mathrm{O}_{6} \mathrm{PS}_{2}$.

Packaging and storage-Preserve in tight, glass containers.

Labeling-The labeling states the percentage ( $\mathrm{v} / \mathrm{v}$ ) of isopropyl alcohol in the Topical Emulsion.

USP Reference standards $\langle 11\rangle$ —USP Malathion $R S$.
Identification-The chromatogram of the Assay preparation obtained as directed in the Assay exhibits a major peak for malathion, the retention time of which corresponds to that exhibited in the chromatogram of the Standard preparation, both relative to the internal standard, obtained as directed in the Assay.

## Isopropyl alcohol content-

Internal standard solution-Mix 4 volumes of ethyl acetate and 1 volume of dehydrated alcohol.

Standard preparation-Transfer 2.0 mL of isopropyl alcohol and 5.0 mL of Internal standard solution to a 200mL volumetric flask, dilute with ethyl acetate to volume, and mix.

Test preparation-Transfer an accurately measured volume of Malathion Topical Emulsion, equivalent to about 2.0 mL of isopropyl alcohol, to a $200-\mathrm{mL}$ volumetric flask. Add 5.0 mL of Internal standard solution, dilute with ethyl acetate to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and contains a $2-\mathrm{mm} \times 1.8-\mathrm{m}$ glass column packed with 110- to 120 -mesh support S 2 . Maintain the temperature of the column, the injector port, and the detector block at $130^{\circ}, 200^{\circ}$, and $220^{\circ}$, respectively. Use dry nitrogen as the carrier gas at a flow rate of about 7 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation of the ratio of the isopropyl alcohol peak response to the internal standard peak response for replicate injections is not more than $2.0 \%$.

Procedure-[NOTE-Use peak areas where peak responses are indicated.] Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard preparation and the Test preparation into the gas chromatograph, record the chromato-
grams, and measure the responses for the major peaks. Calculate the percentage of isopropyl alcohol $\left(\mathrm{C}_{3} \mathrm{H}_{8} \mathrm{O}\right)$ in the Topical Emulsion by the formula:

$$
(200 / V)\left(R_{U} / R_{S}\right)
$$

in which $V$ is the volume, in mL , of Topical Emulsion taken; and $R_{U}$ and $R_{S}$ are the ratios of the peak responses of isopropyl alcohol to internal standard obtained from the Test preparation and the Standard preparation, respectively: between $90 \%$ and $110 \%$ of the labeled amount of $\mathrm{C}_{3} \mathrm{H}_{8} \mathrm{O}$ is found.

## Assay-

Solvent mixture-Mix 4 volumes of methyl ethyl ketone and 1 volume of $n$-hexane.

Internal standard solution-Prepare a solution of parathion in Solvent mixture containing about 2 mg per mL .

Standard preparation-Dissolve an accurately weighed quantity of USP Malathion RS in Solvent mixture to obtain a solution having a known concentration of about 2 mg per mL . Transfer 5.0 mL of this solution to a $25-\mathrm{mL}$ volumetric flask, add 5.0 mL of Internal standard solution, dilute with Solvent mixture to volume, and mix.

Assay preparation-Transfer an accurately measured volume of Topical Emulsion, equivalent to about 10 mg of malathion, to a $25-\mathrm{mL}$ volumetric flask, add 5.0 mL of Internal standard solution, dilute with Solvent mixture to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and contains a $2-\mathrm{mm} \times 1.8-\mathrm{m}$ glass column packed with $5 \%$ G6 liquid phase on 110 - to 120 -mesh support S1A. Maintain the temperature of the column, the injector port, and the detector block at $190^{\circ}, 230^{\circ}$, and $250^{\circ}$, respectively. Use dry nitrogen as the carrier gas at a flow rate of about 15 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure:
the relative retention times are 1.0 for malathion and about 1.3 for parathion; the resolution, $R$, between the malathion and parathion peaks is not less than 3.0 ; and the relative standard deviation for replicate injections is not more than 2.0\%.

Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses of the major peaks. Calculate the quantity, in mg , of malathion $\left(\mathrm{C}_{10} \mathrm{H}_{19} \mathrm{O}_{6} \mathrm{PS}_{2}\right)$ in each mL of the Topical Emulsion taken by the formula:

$$
25(C / V)\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Malathion RS in the Standard preparation; $V$ is the volume, in mL , of Topical Emulsion taken; and $R_{U}$ and $R_{S}$ are the ratios of the peak responses of malathion to parathion obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta U S P 2 8}$
(Official July 1, 2007)

## BRIEFING

Mephobarbital Tablets, USP 27 page 1163. It is proposed to add a Dissolution test.
(BPC: M. Marques) RTS-40370-1

## Add the following:

${ }^{4}$ Dissolution $\langle 711\rangle$ -
Medium: a 1\% solution of 3-(dodecyldimethylammonio)propanesulfonate in pH 8.0 phosphate buffer (prepared by dissolving 10.0 g of 3-(dodecyldimethylammonio)propanesulfonate in 400 mL of warm water, and adding 250 mL of
0.2 M monobasic potassium phosphate and about 220 mL of 0.2 M sodium hydroxide; the solution is then cooled to room temperature, and adjusted with 0.2 M sodium hydroxide to a pH of 8.0 , followed by diluting with water to 1000 mL , mixing, and degassing.); 900 mL .

Apparatus 2: 75 rpm .
Time: 75 minutes.
Procedure-Determine the amount of $\mathrm{C}_{13} \mathrm{H}_{14} \mathrm{~N}_{2} \mathrm{O}_{3}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 244 nm on portions of the solution under test passed through $0.45-\mu \mathrm{m}$ nylon filters, suitably diluted with Dissolution Medium, if necessary in comparison with a Standard solution having a known concentration of USP Mephobarbital RS in the same Medium.

Tolerances: not less than $70 \%(Q)$ of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{14} \mathrm{~N}_{2} \mathrm{O}_{3}$ is dissolved in 75 minutes. $\triangle$ USP28

## BRIEFING

Methylbenzethonium Chloride Lotion, USP 27 page 1207. It is proposed to change the title of this monograph to Methylbenzethonium Chloride Topical Emulsion. See briefing under Amphotericin $B$ Lotion.
(NL: C. Barnstein) RTS-40790-1

## Methylbenzethonium Chloride Lotion

(Current title—not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Methylbenzethonium Chloride Topical Emulsion

## Briefing

Methylbenzethonium Chloride Topical Emulsion-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40790-1

## Add the following:

## ©Methylbenzethonium Chloride Topical Emulsion

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Methylbenzethonium Chloride Lotion)
» Methylbenzethonium Chloride Topical Emulsion contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\mathrm{C}_{28} \mathrm{H}_{44} \mathrm{ClNO}_{2} \cdot \mathrm{H}_{2} \mathrm{O}$.

Packaging and storage—Preserve in tight containers.
USP Reference standards $\langle 11\rangle$ —USP Docusate Sodium RS.

Identification-Suspend about 0.5 mL of Topical Emulsion in 20 mL of water, add 0.1 g of sodium carbonate, 1 mL of bromophenol blue TS, and 10 mL of chloroform, and shake the mixture: the chloroform layer is blue.
$\mathbf{p H}\langle 791\rangle$ : between 5.2 and 6.0.
Assay-
0.0001 N Docusate sodium—Dissolve an accurately weighed quantity of USP Docusate Sodium RS in isopropyl alcohol, and dilute quantitatively with isopropyl alcohol to obtain a solution having a concentration of 4.446 mg of anhydrous docusate sodium per mL. Store this solution in a tightly stoppered glass container. On the day of use, pipet 10 mL of this solution into a $1000-\mathrm{mL}$ volumetric flask, add water to volume, and mix to obtain a 0.0001 N solution.

Procedure-Transfer an accurately weighed portion of Topical Emulsion, equivalent to about 0.5 mg of methylbenzethonium chloride, to a glass-stoppered, $50-\mathrm{mL}$ cylinder. Add 5 mL of chloroform (freshly purified by shaking 100 mL with 10 g of silica gel, allowing to settle, and withdrawing the supernatant), 5 mL of phosphoric acid solution ( 1 in 10), and 1 mL of safranin $O$ solution ( $1 \mathrm{in} 20,000$ ). Titrate with 0.0001 N Docusate sodium until about 1 mL from the endpoint, then shake the stoppered tube vigorously for about 2 minutes, and continue the titration in $0.1-\mathrm{mL}$ increments, shaking vigorously after each addition, until a pink color appears in the chloroform layer. Perform a blank determination, and make any necessary correction. Each mL of 0.0001 N Docusate sodium is equivalent to $48.01 \mu \mathrm{~g}$ of $\mathrm{C}_{28} \mathrm{H}_{44} \mathrm{ClNO}_{2} \cdot \mathrm{H}_{2} \mathrm{O} \cdot \mathbf{\Delta U S P 2 8}$
(Official July 1, 2007)

Methylbenzethonium Chloride Topical Powder, USP 27 page 1207. An editorial revision is indicated to conform with the title change proposed for Methylbenzethonium Chloride Lotion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40791-1

## Change to read:

Assay-
0.0001 N Docusate sodium-Prepare as directed for 0.0001 N Docusate sodium in the Assay under Methylbenzethonium Chloride Lotion
© (Methylbenzethonium Chloride Topical Emulsion, Official

July 1, 2007). $\mathbf{A}$ USP28
Procedure- Transfer an accurately weighed portion of Topical Powder, equivalent to about 0.5 mg of methylbenzethonium chloride, to a glass-stoppered, $50-\mathrm{mL}$ cylinder, and proceed as directed in the Assay under Methylbenzethonium Chloride Lotion
©(Methylbenzethonium Chloride Topical Emulsion, Official

## Briefing

Neomycin Sulfate and Flurandrenolide Lotion, USP 27 page 1292. It is proposed to change the title of this monograph to Neomycin Sulfate and Flurandrenolide Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40792-1

## Neomycin Sulfate and Flurandrenolide Lotion

(Current title-not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Neomycin Sulfate and Flurandrenolide Topical Emulsion

## BRIEFING

Neomycin Sulfate and Flurandrenolide Topical EmulsionSee briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40792-1

## Add the following:

## ©Neomycin Sulfate and Flurandrenolide Topical Emulsion

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Neomycin Sulfate and Flurandrenolide Lotion)
» Neomycin Sulfate and Flurandrenolide Topical Emulsion contains the equivalent of not less than 90.0 percent and not more than 130.0 percent of the labeled amount of neomycin, and not less than

July 1, 2007), $\mathbf{\Delta S S P 2 8}$
beginning with "Add 5 mL of chloroform."
90.0 percent and not more than 110.0 percent of the labeled amount of flurandrenolide $\left(\mathrm{C}_{24} \mathrm{H}_{33} \mathrm{FO}_{6}\right)$.

Packaging and storage-Preserve in tight containers, protected from light.

USP Reference standards $\langle 11\rangle$ —USP Flurandrenolide
RS. USP Neomycin Sulfate RS.

## Identification-

A: It meets the requirements for neomycin under ThinLayer Chromatographic Identification Test $\langle 201 \mathrm{BNP}\rangle$.

B: It meets the requirements for the Identification test under Flurandrenolide Cream.

Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.

Minimum fill $\langle 755\rangle$ : meets the requirements.
Assay for neomycin-Proceed as directed for neomycin under Antibiotics-Microbial Assays $\langle 81\rangle$, using an accurately weighed portion of Topical Emulsion, equivalent to about 3.5 mg of neomycin, blended for 3 to 5 minutes in a high-speed glass blender jar containing an accurately measured volume of Buffer No. 3 sufficient to obtain a stock solution having a convenient concentration of neomycin. Dilute an accurately measured volume of this stock solution quantitatively with Buffer No. 3 to obtain a Test Dilution having a concentration of neomycin assumed to be equal to the median dose level of the Standard.

Assay for flurandrenolide-Proceed with Neomycin Sulfate and Flurandrenolide Topical Emulsion as directed in the Assay under Flurandrenolide Cream. Calculate the quantity, in mg, of $\mathrm{C}_{24} \mathrm{H}_{33} \mathrm{FO}_{6}$ in the portion of Topical Emulsion taken by the formula:

$$
10 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Flurandrenolide RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{\Delta U S P 2 8 ~}^{\text {. }}$
(Official July 1, 2007)

## Briefing

Neomycin Sulfate and Hydrocortisone Acetate Cream, USP 27 page 1294. An editorial revision is indicated to conform with the title change proposed for Hydrocortisone Acetate Lotion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40793-1

## Change to read:

Assay for hydrocortisone acetate-Proceed with Cream as directed in the Assay under Hydrocortisone Acetate Lotion
© (Hydrocortisone Acetate Topical Emulsion, Official July 1, 2007). $\triangle U S P 28$

## BRIEFING

Neomycin Sulfate and Hydrocortisone Acetate Lotion, USP 27 page 1294. It is proposed to change the title of this monograph to Neomycin Sulfate and Hydrocortisone Acetate Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40794-1

Neomycin Sulfate and Hydrocortisone Acetate Ointment, USP 27 page 1294. An editorial revision is indicated to conform with the title change proposed for Hydrocortisone Acetate Lotion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40795-1

## Change to read:

Assay for hydrocortisone acetate-Proceed with the Ointment as directed in the Assay under Hydrocortisone Acetate Lotion
© (Hydrocortisone Acetate Topical Emulsion, Official July 1, 2007). $\triangle U S P 28$

## BRIEFING

Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment, USP 27 page 1295. An editorial revision is indicated to conform with the title change proposed for Hydrocortisone Acetate Lotion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40796-1

## Change to read:

Assay for hydrocortisone acetate-Proceed with Ophthalmic Ointment as directed in the Assay under Hydrocortisone Acetate Lotion
(Hydrocortisone Acetate Topical Emulsion, Official July 1,
2007). $\triangle U S P 28$

Neomycin Sulfate and Hydrocortisone Acetate Topical Emulsion-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40794-1

Add the following:

## ©Neomycin Sulfate and Hydrocortisone Acetate Topical Emulsion <br> (Monograph under this new title-to become official July 1, 2007) <br> (Current monograph title is Neomycin Sulfate and Hydrocortisone Acetate Lotion)

» Neomycin Sulfate and Hydrocortisone Acetate Topical Emulsion contains the equivalent of not less than 90.0 percent and not more than 130.0 percent of the labeled amount of neomycin, and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of hydrocortisone acetate $\left(\mathrm{C}_{23} \mathrm{H}_{32} \mathrm{O}_{6}\right)$.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle — U S P$ Hydrocortisone Acetate RS. USP Neomycin Sulfate RS.

## Identification-

A: It meets the requirements for neomycin under Thin-
Layer Chromatographic Identification Test $\langle 201 \mathrm{BNP}\rangle$.
B: The retention time of the major peak for hydrocortisone acetate in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay for hydrocortisone acetate.

Minimum fill $\langle 755\rangle$ : meets the requirements.

Assay for neomycin-Proceed as directed for neomycin under Antibiotics-Microbial Assays $\langle 81\rangle$, blending an accurately measured volume of Topical Emulsion for 3 to 5 minutes in a high-speed glass blender jar containing an accurately measured volume of Buffer No. 3. Dilute an accurately measured volume of the solution so obtained quantitatively and stepwise with Buffer No. 3 to obtain a Test Dilution having a concentration of neomycin assumed to be equal to the median dose level of the Standard.

Assay for hydrocortisone acetate-Proceed with Topical Emulsion as directed in the Assay under Hydrocortisone Acetate Topical Emulsion. $\mathbf{\Delta S P P 2 8}$
(Official July 1, 2007)

## Briefing

Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment, USP 27 page 1299. An editorial revision is indicated to conform with the title change proposed for Hydrocortisone Acetate Lotion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40797-1

## Change to read:

Assay for hydrocortisone acetate-Proceed with Ointment as directed in the Assay under Hydrocortisone Acetate Lotion
(Hydrocortisone Acetate Topical Emulsion, Official July 1, 2007). $\triangle$ USP28

## Briefing

Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment, USP 27 page 1299. An editorial revision is indicated to conform with the title change proposed for Hydrocortisone Acetate Lotion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40799-1

## Change to read:

Assay for hydrocortisone acetate-Proceed with Ophthalmic Ointment as directed in the Assay under Hydrocortisone Acetate Lotion
${ }^{\boldsymbol{\Delta}}$ (Hydrocortisone Acetate Topical Emulsion, Official July 1, 2007). $\mathbf{\Delta U S P 2 8}$

## Briefing

Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment, USP 27 page 1301. An editorial revision is indicated to conform with the title change proposed for Hydrocortisone Acetate Lotion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40800-1

## Change to read:

Assay for hydrocortisone acetate-Proceed with Ophthalmic Ointment as directed in the Assay under Hydrocortisone Acetate Lotion
${ }^{\boldsymbol{\Delta}}$ (Hydrocortisone Acetate Topical Emulsion, Official July 1, 2007). $\triangle U S P 28$

Briefing
Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream, USP 27 page 1304. An editorial revision is indicated to conform with the title change proposed for Hydrocortisone Acetate Lotion. See briefing under Amphotericin $B$ Lotion.
(NL: C. Barnstein) RTS-40801-1

## Change to read:

Assay for hydrocortisone acetate-Proceed with Cream as directed in the Assay under Hydrocortisone Acetate Lotion
(Hydrocortisone Acetate Topical Emulsion, Official July 1, 2007). $\triangle U S P 28$

## Briefing

Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream, USP 27 page 1305. An editorial revision is indicated to conform with the title change proposed for Hydrocortisone Acetate Lotion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40802-1

## Change to read:

Assay for hydrocortisone acetate-Proceed with Cream as directed in the Assay under Hydrocortisone Acetate Lotion
${ }^{\Delta}$ (Hydrocortisone Acetate Topical Emulsion, Official July 1, 2007). $\triangle$ USP28

## Briefing

Nitrofurantoin Oral Suspension, USP 27 page 1325. In accordance with the implemented name change, it is proposed to change USP $N$-(aminocarbonyl)- $N$-[([5-nitro-2-furanyl]methylene)ami-
no]glycine RS to USP Nitrofurantoin Related Compound A RS. The limit test, which has been editorially restyled, is also affected by this revision.
(PA7b: B. Davani) RTS-40896-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Nitrofurantoin RS. USP N (amineatrbomy) N [([5-nitro-2 furanyl]methylene)amino]glyeine RS.
${ }^{\mathbf{\Delta}}$ USP Nitrofurantoin Related Compound A RS. $\quad$ USP28

## Add the following:

- Uniformity of dosage units $\langle 905\rangle$ -

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements.■2S (USP27)

## Add the following:

■Deliverable volume $\langle 698\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements.n2S (USP27)

## Change to read:

Limit of $N$-(aminocarbonyl)- $N$-[([5-nitro-2-furanyl]methylene)aminolglycine (NF 250) and Assay-
pH 7.0 Phosphate buffer and Mobile phase-Prepare as directed in the Assay under Nitrofurantoin.

Internal standard solution-Dissolve about 13 mg of acetanilide in Mobile phase, dilute with Mobile phase to 200 mL , and mix.
Standard NF 250 preparation-Prepare a solution of USP N (amineearbenyl) $N[([5$ - nitre 2 ftranyl]methylene)amine $]$ glyeine RS-
${ }^{\boldsymbol{A}}$ USP Nitrofurantoin Related Compound $\mathrm{A} \mathrm{RS}_{\mathbf{\Delta U S P 2 8}}$ in Mobile phase to contain $125 \mu \mathrm{~g}$ per mL .

${ }^{\boldsymbol{\Delta}}$ [NOTE-USP Nitrofurantoin Related Compound A RS is $N$-(aminocarbonyl)- $N$-[([5-nitro-2-furanyl]methylene)amino]glycine.] |  |
| :---: |
| DSP28 |

Dilute 2.0 mL of this solution with Mobile phase to 100.0 mL , and mix.

Standard nitrofurantoin preparation-Transfer about 25 mg of USP Nitrofurantoin RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask with the aid of about 50 mL of dimethylformamide. Add 20 mL of water, cool to room temperature, and dilute with dimethylformamide to volume to obtain a Standard solution. Transfer a $4.0-\mathrm{mL}$ aliquot of this Standard solution to a glass-stoppered flask, add 15.0 mL of Internal standard solution, and mix.
Assay preparation-Transfer an accurately measured volume of freshly mixed Oral Suspension, equivalent to about 25 mg of nitrofurantoin, to a $100-\mathrm{mL}$ volumetric flask, add 20 mL of water to the flask, and mix. Add about 50 mL of dimethylformamide, and shake the flask for about 20 minutes. Cool to room temperature, and dilute with dimethylformamide to volume. Centrifuge a portion of the solution, and transfer a $4.0-\mathrm{mL}$ aliquot of the supernatant liquid to a glass-stoppered flask. Add 15.0 mL of Internal standard, and mix. Filter a portion of the solution through a $5-\mu \mathrm{m}$ pore size polytef filter, discarding the first few mL of the filtrate.

Test preparation-Transfer an accurately measured volume of the freshly mixed Oral Suspension, equivalent to 5 mg of nitrofurantoin, to a $100-\mathrm{mL}$ volumetric flask. Dilute with Mobile phase to volume, and mix. Centrifuge a portion of this solution. Filter a portion of the supernatant through a $5-\mu \mathrm{m}$ pore size polytef filter, discarding the first few mL of the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )——The liquid chromatograph is equipped with both a $254-\mathrm{nm}$ detector and a $375-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. For the Assay, chromatograph the Standard nitrofurantoin preparation, adjusting the operating parameters so that the retention time of the nitrofurantoin peak is about 8 minutes and its peak height is about half full-scale: the relative standard deviation of the ratio of the peak responses in replicate injections is not more than $2.0 \%$, and the resolution, $R$, of the acetanilide and nitrofurantoin peaks is not less than 3.5. The flow rate is about 1.2 mL per minute. For the NF 250 test, adjust the operating parameters so that the NF 250 peak has a retention time of between 3 and 6 minutes and its height is about 0.1 full-scale. The flow rate is about 1.2 mL per minute.
Procedure for limit of $N$-(aminocarbonyl)-N-[([5-nitro-2-furanyl]methylene) amino]glycine-Inject separately equal volumes $(30 \mu \mathrm{~L}$ to $60 \mu \mathrm{~L})$ of Standard NF 250 preparation and the Test preparation into the chromatograph, and record the peak responses with the $375-\mathrm{nm}$ detector: the height of any peak appearing in the chromatogram of the Test preparation at a retention time corresponding to that of the main peak in the Standard NF 250 preparation is not greater than the height of the latter (5.0\%).

Procedure for assay-Inject equal volumes (about $15 \mu \mathrm{~L}$ ) of Standard nitrofurantoin preparation and the Assay preparation separately into the chromatograph, and record the peak responses with the $254-\mathrm{nm}$ detector. Calculate the quantity, in mg , of $\mathrm{C}_{8} \mathrm{H}_{6} \mathrm{~N}_{4} \mathrm{O}_{5}$ in each mL of the Oral Suspension taken by the formula:

$$
0.1(C / V)\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Nitrofurantoin RS in the Standard solution; $V$ is the volume, in mL , of Oral Suspension taken; and $R_{U}$ and $R_{S}$ are the ratios of the peak responses of the nitrofurantoin to the internal standard obtained from the Assay preparation and the Standard nitrofurantoin preparation, respectively.

## Briefing

Nitrous Oxide, USP 27 page 1331. It is proposed to add new USP Reference Standards, which will affect the tests for Identification and the Assay.
(AER: K. Zaidi) RTS-40629-3

## Add the following:

${ }^{\wedge}$ USP Reference standards-USP Air-Helium RS. USP
Nitrous Oxide $R S_{\triangle U S P 28}$

## Change to read:

## Identification-

A: With the container temperatures the same and maintained between $15^{\circ}$ and $25^{\circ}$, concomitantly read the pressure of the Ni trous Oxide container and of a container of nitrous oxideentiffed standard (see under Reagents in the section Reagents, Indieaters, and Solutions).
${ }^{\Delta}$ USP Nitrous Oxide RS. $\qquad$
[NOTE-Do not use the nitrous-oxide entified sadad
${ }^{\boldsymbol{\Delta}}$ USP Nitrous Oxide RS ${ }_{\mathbf{\Delta U S P 2 8}}$
if it has been depleted to less than half of its full capacity.] The pressure of the Nitrous Oxide container is within 50 psi of that of the nitrous oxide certified standard.
${ }^{\triangle}$ USP Nitrous Oxide RS. $\triangle$ USP28
B: Pass $100 \pm 5 \mathrm{~mL}$ released from the vapor phase of the contents of the Nitrous Oxide container through a carbon dioxide detector tube at the rate specified for the tube: no color change is observed (distinction from carbon dioxide).

C: Collect about 100 mL of the gas under test in a $100-\mathrm{mL}$ tube fitted at the top with a stopcock. Open the stopcock, and quickly add a freshly prepared solution of 500 mg of pyrogallol in 2 mL of water and a freshly prepared solution of 12 g of potassium hydroxide in 8 mL of water. Immediately close the stopcock, and mix: the gas is not absorbed, and the solution does not become brown (distinction from oxygen).
${ }^{\mathbf{4}} \mathbf{D}$ : Prepare a gas chromatograph as directed in the $A s$ say, and inject USP Nitrous Oxide RS and a sample of Ni trous Oxide into the gas chromatograph. The retention time of the major peak in the chromatogram of the Nitrous Oxide sample corresponds to that of the chromatogram of the USP

Nitrous Oxide RS. _USP28 $^{\text {U }}$

## Change to read:

Assay-Introduce a specimen of Nitrous Oxide taken from the liquid phase, as directed in the test for Nitrogen dioxide, into a gas chromatograph by means of a gas-sampling valve. Select the operating conditions of the gas chromatograph such that the peak response resulting from the following procedure corresponds to not less than $70 \%$ of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 6 m in length and 4 mm in inside diameter and is packed with porous polymer beads, which permits complete separation of $\mathrm{N}_{2}$ and $\mathrm{O}_{2}$ from $\mathrm{N}_{2} \mathrm{O}$, although the $\mathrm{N}_{2}$ and $\mathrm{O}_{2}$ may not be separated from each other. Use industrial grade helium ( $99.99 \%$ ) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by annir helimmeer tified standard (see under Reagents in the section Reagents, Indieators, and Solutions),
${ }^{\Delta}$ USP Air-Helium RS, ${ }_{\text {aUSP28 }}$
and is equivalent to not more than $1.0 \%$ of air when compared to the peak response of the air helium certified standard,
${ }^{\boldsymbol{\Delta}}$ USP Air-Helium RS, ${ }_{\mathbf{A}}^{\boldsymbol{A} U S P 28}$
indicating not less than $99.0 \%$, by volume, of $\mathrm{N}_{2} \mathrm{O}$.

Briefing
Nystatin Lotion, USP 27 page 1350. It is proposed to change the title of this monograph to Nystatin Topical Emulsion. See briefing under Amphotericin B Lotion.

## (NL: C. Barnstein) RTS-40803-1

## Nystatin Lotion

(Current title—not to change until July 1, 2007) Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Nystatin Topical Emulsion

BRIEFING

Nystatin Topical Emulsion-See briefing under Amphotericin $B$ Lotion.
(NL: C. Barnstein) RTS-40803-1

## Add the following:

## ©Nystatin Topical Emulsion

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Nystatin Lotion)
» Nystatin Topical Emulsion contains not less than 90.0 percent and not more than 140.0 percent of the labeled amount of USP Nystatin Units.

Packaging and storage-Preserve in tight containers, at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Nystatin $R S$.
$\mathbf{p H}\langle 791\rangle$ : between 5.5 and 7.5.
Assay-Proceed with Topical Emulsion as directed in the Assay under Nystatin Cream. $\mathbf{\Delta U S P 2 8}$
(Official July 1, 2007)

## Briefing

Omeprazole, USP 27 page 1358. Based on the comments received, it is proposed to clarify that the pH of the Phosphate buffer under Assay should be adjusted, if necessary, to 7.6.
(PA4: E. Gonikberg) RTS-40863-1

## Change to read:

## Assay-

Phosphate buffer-Dissolve 0.725 g of monobasic sodium phosphate and 4.472 g of anhydrous dibasic sodium phosphate in 300 mL of water, dilute with water to 1000 mL , and mix. Dilute 250 mL of this solution with water to 1000 mL .
${ }^{4}$ If necessary, adjust the pH with phosphoric acid to

### 7.6. USP28

Mobile phase-Prepare a filtered and degassed mixture of Phosphate buffer and acetonitrile (3:1). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare a mixture of 0.01 M sodium borate and acetonitrile ( $3: 1$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Omeprazole RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 0.2 mg per mL .

Assay preparation-Transfer about 100 mg of Omeprazole, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix. Transfer 5.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.

System suitability solution-Dilute a volume of Standard preparation with Diluent to obtain a solution containing about 0.1 mg of USP Omeprazole RS per mL.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The flow rate is about 0.8 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 6.0; the column efficiency is not less than 3000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than $1.0 \%$.

Procedure—Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}$ in the portion of Omeprazole taken by the formula:

$$
500 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Omeprazole RS in theStandard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparationand the Standard preparation, respectively.

## BRIEFING

Orphenadrine Citrate, USP 27 page 1362 and page 1944 of PF 29(6) [Nov.-Dec. 2003]. The proposed change is made to identify the compounds described by relative retention time in the test for Related compounds.
(PA3: S. Salado) RTS-40860-1

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers.
${ }^{■}$ Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ} \cdot$ ■2S (USP27)

## Add the following:

-Labeling-Where it is intended for use in preparing inject-
able dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of in-
jectable dosage forms. $\quad$ 2S (USP27)

## Change to read:

USP Reference standards $\langle 11\rangle$ -
-USP Endotoxin RS. ■2S (USP27)
USP Orphenadrine Citrate RS.

## Change to read:

## ${ }^{\Delta}$ Related compounds-

0.05 M Ammonium phosphate buffer, Mobile phase, System sensitivity solution, and Chromatographic system-Prepare as directed in the Assay.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.
Test solution-Use the Assay preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Test solution and the Standard solution into the chromatograph, record the chromatogram for at least 2.5 times the retention time of orphenadrine citrate, and measure all of the peak areas. Calculate the percentage of each impurity in the portion of Orphenadrine Ci trate taken by the formula:

$$
5000 F(C / W)\left(r_{i} / r_{S}\right)
$$

in which $C$ is the concentration, in me per mL , of USP Orphent drine Citrate RS in the Standerd solution; Wis the weight, in me, of Orphenadrine Citrate taken to prepare the Test solution; $F$ is the relative respense factor and is equal to 0.75 for any peak at a retative retention time of about $0.25,0.41$ for any peak at a relative retention time of about $0.51,0.52$ for any peak at a relative reten tion time of about 1.54, and 1.0 for any other peak; in $_{i}$ is the peak area for each impurity in the Test solution; and $r_{s}$ is the peak areaf erphenadrine citrate in the Stenderd solution: not more than $0.5 \%$ of total impurities is found. $\Delta U S P 27$
${ }^{\boldsymbol{\Delta}}$ in which $C$ is the concentration, in mg per mL , of USP Orphenadrine Citrate RS in the Standard solution; $W$ is the weight in mg , of the sample taken to prepare the Test solution; $F$ is the relative response factor described in the table below; $r_{i}$ is the peak area for each impurity in the Test solution; and $r_{S}$ is the peak area of Orphenadrine Citrate in the Standard solution: not more than $0.5 \%$ of total impurities is found.

|  | Relative Retention | Relative Response |
| :--- | :---: | :---: |
| Compound name | Time | Factor |
| Ethyldimethyl [2-(2-methylbenzhydryloxy)ethyl] ammonium |  |  |
| chloride 0.25 <br> 2-Methylbenzhydrol 0.51 <br> Orphenadrine Citrate 1.0 <br> $N$ N-Dimethyl-2-(o-tolyl-o-xylyloxy)ethylamine 1.54 <br> Others - | 0.75 |  |

## Add the following:

-Other requirements-Where the label states that Orphenadrine Citrate is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Orphenadrine Citrate Injection. Where the label states that Orphenadrine Citrate must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Orphenadrine Citrate Injec-

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tion.п2S (USP27)
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## BRIEFING

Orphenadrine Citrate Injection, USP 27 page 1363-See briefing under Orphenadrine Citrate.
(PA3: S. Salado) RTS-40860-2

## Change to read:

${ }^{4}$ Related compounds-
0.05 M Ammonium phosphate buffer, Mobile phase, System sensitivity solution, and Chromatographic system-Prepare as directed in the Assay.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Test solution and the Standard solution into the chromatograph, record the chromatogram for at least 2.5 times the retention time of orphenadrine citrate, and measure all of the peak areas. Calculate the percentage of each impurity in the portion of Injection taken by the formula:

$$
(10,000 F)(C / V)(1 / D)\left(r_{i} / r_{S}\right),
$$

in which $C$ is the eoncentration, in me per mL , of USP Orphenndrine Citrate RS in the Standard solution; $V$ is the volume, in mL , of the Injection taken to prepare the Test solution; $D$ is the labeled dose of the Injection; $F$ is the relative respense factor and is equal to 0.75 for any peak at relative retention time of about $0.25,0.44$ for any peak at a relative retention time of about $0.51,0.52$ for any peak at a relative retention time of about 1.54 , and 1.0 for any other peak; $i_{i}$ is the peak aren for each impurity in the Test solution; and $r_{s}$ is the peak area of orphenadrine citrate in the Standerd solution: not more than- $4.0 \%$ of total impurities is found. [NOTE-The relative retention time for orphenadrine citrate in the Test solution is equal to 1.0.子 $\Delta U S P 27$
$\boldsymbol{\Delta}_{\text {in }}$ which $F$ is the relative response factor as found in the table below; $C$ is the concentration, in mg per mL , of USP Orphenadrine Citrate RS in the Standard solution; $V$ is the volume, in mL, of the injection taken to prepare the Test solution; $D$ is the labeled dose of the injection; $r_{i}$ is the peak area for each impurity in the Test solution; and $r_{S}$ is the peak area of Orphenadrine Citrate in the Standard solution: not more than $4.0 \%$ of total impurities is found.

| Compound name | Relative Retention <br> Time | Relative Response <br> Factor |
| :--- | :---: | :---: |
| Ethyldimethyl [2-(2-methylbenzhydryloxy)ethyl] |  |  |
| $\quad$ ammonium chloride | 0.25 | 0.75 |
| 2-Methylbenzhydrol | 0.51 | 0.41 |
| Orphenadrine Citrate | 1.0 | - |
| $N, N$-Dimethyl-2-(o-tolyl- $O$-xylyloxy)ethylamine | 1.54 | 0.52 |
| Others | - | 1.0 |

## Briefing

Oxybutynin Chloride Extended-Release Tablets. Because there is no existing USP monograph for this drug product, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedure in the test for Related compounds and in the Assay is based on analyses performed with the Inertsil Phenyl brand of L11 column. The typical retention time for the oxybutynin peak is about 5 minutes.
(PA4: E. Gonikberg) RTS-40034-1

## Add the following:

## ©Oxybutynin Chloride ExtendedRelease Tablets

» Oxybutynin Chloride Extended-Release Tablets contain not less than 90 percent and not more than 110 percent of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{31} \mathrm{NO}_{3} \cdot \mathrm{HCl}$.

Packaging and Storage-Preserve in tight containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Oxybutynin Chloride RS. USP Oxybutynin Related Compound A RS.

## Identification-

A: Infrared Absorption $\langle 197\rangle$ -
Test specimen-Add a quantity of finely powdered Tablets, equivalent to about 15 mg of oxybutynin chloride, to 5 mL of water per tablet. Mix for one minute. Adjust with 0.1 N sodium hydroxide to a pH between 7 and 8 . Extract the solution twice with 10 mL of ether. Combine and evaporate the ether extract, and dry under vacuum over silica gel for at least 30 minutes. Redissolve the dried residue in a small amount of acetone, transfer the solution to an IR salt plate, and evaporate to cast a thin film.
Standard specimen-Dissolve 15 mg of USP Oxybutynin chloride RS in 5 mL of water. Proceed as directed for the Test specimen, beginning with "Adjust with".

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, as obtained in the Assay.

Uniformity of dosage units $\langle 905\rangle$-meet the requirements.

## Related compounds-

Mobile phase, Diluent, Preparation medium, Impurity stock solution and System suitability solution-Proceed as directed in the Assay.
Impurity standard solution-Dilute the Impurity stock solution with Diluent to obtain a solution having a known concentration of about $1 \mu \mathrm{~g}$ of phenylcyclohexylglycolic acid (Oxybutynin related compound A) per mL.

Test solution- Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L11. The flow rate is about 1.5 mL per minute. Chromatograph the Impurity standard solution, and record the peak responses as directed for Procedure: the tailing factor is greater than 0.75 and not more than 2.5 for the phenylcyclohexylglycolic acid peak. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.0 for oxybutynin and about 1.6 for phenylcyclohexylglycolic acid; the resolution, $R$, between oxybutynin and phenylcyclohexylglycolic acid is not less than 1.5 ; and the relative standard deviation of peak area responses for six replicate injections of System suitability solution is not more than $3 \%$ for each compound.
Procedure-Separately injects equal volumes (about 50 $\mu \mathrm{L}$ ) of the Impurity standard solution and the Test solution into the chromatograph, record the chromatograms and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$
C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of phenylcyclohexylglycolic acid in the Impurity standard solution, and $r_{U}$ and $r_{S}$ are the peak responses for each impurity obtained from the Test solution and the Impurity standard solution, respectively. Disregard any peak less than $0.1 \%$ : not more than $1 \%$ of phenylcyclohexylglycolic acid is found, and not more than $2 \%$ of total impurities is found.

## Assay-

Mobile phase-Prepare a mixture of water, acetonitrile, and triethylamine (65:35:0.15). Adjust with phosphoric acid to a pH of 3.9 , degas, and filter.
Diluent-Use water adjusted with phosphoric acid to a pH of 3.5 .

Preparation medium-Prepare a solution of methanol and acetonitrile (1:1).

Impurity stock solution-Dissolve an accurately weighed quantity of USP Oxybutynin Related compound $A R S$ in acetonitrile, to obtain a solution having a known concentration of about 0.11 mg of phenylcyclohexylglycolic acid per mL . [NOTE-Oxybutynin related compound A is phenylcyclohexylglycolic acid.]
System suitability solution-Transfer 10 mL of the Standard stock solution and 1 mL of the Impurity stock solution into a $100-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.
Standard stock preparation-Dissolve an accurately weighed quantity of USP Oxybutynin Chloride $R S$ in acetonitrile, to obtain a solution having a known concentration of about 0.37 mg per mL .
Standard preparation-Dilute the Standard stock preparation with Diluent to obtain a solution having a known concentration of about 0.1 mg per mL .

FOR TABLETS THAT CONTAIN 5 MG OF OXYBUTYNIN CHLO-RIDE-Place 10 tablets in a $500-\mathrm{mL}$ volumetric flask, add 150 mL of Preparation medium, and stir overnight or until dissolved. Dilute with Diluent to volume. Mix thoroughly, centrifuge, and use the clear supernatant.

FOR TABLETS THAT CONTAIN 10 MG OF OXYBUTYNIN CHLORIDE OR MORE-Place 10 tablets in a $1000-\mathrm{mL}$ volumetric flask, add 300 mL of Preparation medium, and stir overnight or until dissolved. Dilute with Diluent to volume. If necessary, make a further dilution with Diluent to obtain a solution with a final concentration equivalent to 0.1 mg per mL of oxybutynin chloride. Mix thoroughly, centrifuge, and use the clear supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ ) The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L11. The flow rate is about 1.5 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor is greater than 0.75 and not more than 2.5. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.0 for oxybutynin and about 1.6 for phenylcyclohexylglycolic acid; the resolution, $R$, between oxybutynin and phenylcyclohexylglycolic acid is not less than 1.5 ; and the relative standard deviation of peak area responses for six replicate injections of System suitability solution is not more than $3 \%$ for each compound.
Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard Preparation and Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of oxybutynin chloride $\left(\mathrm{C}_{22} \mathrm{H}_{31} \mathrm{NO}_{3} \cdot \mathrm{HCl}\right)$ in the portion of Tablets taken by the formula

$$
C \times V \times D\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of oxybutynin chloride in the Standard preparation; $V$ is the volume, in mL , of the Assay preparation; $D$ is the dilution factor; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Drug release $\langle 724\rangle$-[To come $]_{\Delta U S P 28}$

## Briefing

Padimate O Lotion, USP 27 page 1397. It is proposed to change the title of this monograph to Padimate O Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40804-1

## Padimate $\mathbf{O}$ Lotion

(Current title—not to change until July 1, 2007) Monograph title change—to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Padimate O Topical Emulsion

BRIEFING
Padimate O Topical Emulsion-See briefing under Amphotericin $B$ Lotion.
(NL: C. Barnstein) RTS-40804-1

## Add the following:

## - Padimate O Topical Emulsion

(Monograph under this new title—to become official July 1, 2007)
(Current monograph title is Padimate $O$ Lotion)
» Padimate O Topical Emulsion contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{27} \mathrm{NO}_{2}$.

Packaging and storage-Preserve in tight, light-resistant containers.

USP Reference standards $\langle 11\rangle —$ USP Padimate $O R S$.
Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

## Assay-

Mobile phase-Prepare a suitable filtered and degassed solution containing methanol, water, and glacial acetic acid (85:15:0.5).

Standard preparation-Dissolve an accurately weighed quantity of USP Padimate O RS in isopropyl alcohol, and dilute quantitatively, and stepwise if necessary, with isopropyl alcohol to obtain a solution having a known concentration of about $100 \mu \mathrm{~g}$ per mL .

Assay preparation-Transfer an accurately weighed quantity of Topical Emulsion, equivalent to about 100 mg of padimate O , to a $100-\mathrm{mL}$ volumetric flask, and add about 75 mL of isopropyl alcohol. Heat gently with swirling until the specimen is dispersed. Cool to room temperature, dilute with isopropyl alcohol to volume, and mix. Pipet 10.0 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, dilute with isopropyl alcohol to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $308-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ basedeactivated packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and re-
cord the peak responses as directed for Procedure: the tailing factor is not more than 2.5 , and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{17} \mathrm{H}_{27} \mathrm{NO}_{2}$ in the portion of Topical Emulsion taken by the formula:

$$
C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Padimate O RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses for padimate O obtained from the Assay preparation and the Standard preparation, respectively. $\triangle$ USP28
(Official July 1, 2007)

## BriEfing

Penicillin G Procaine, Neomycin and Polymyxin B Sulfates, and Hydrocortisone Acetate Topical Suspension, USP 27 page 1427. An editorial revision is indicated to conform with the title change proposed for Hydrocortisone Acetate Lotion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40805-1

## Change to read:

Assay for hydrocortisone acetate-Using an accurately measured volume of Topical Suspension, proceed as directed in the $A s$ say under Hydrocortisone Acetate Lotion
(Hydrocortisone Acetate Topical Emulsion, Official July 1, 2007). $\triangle U S P 28$

## Briefing

Phenytoin Oral Suspension, USP 27 page 1479 and page 1965 of PF 29(6) [Nov.-Dec. 2003]. In the test for Dissolution it is proposed to add instructions for the introduction of the sample into the dissolution vessel because the procedure used to introduce the sample has a great impact on the dissolution results.
(BPC: M. Marques) RTS-40811-1

## Change to read:

Dissolution $\langle 711\rangle$ -
0.05 M Tris buffer-Dissolve 36.3 g of tris(hydroxymethyl)aminomethane and 60 g of sodium lauryl sulfate in 6 L of water, adjust with hydrochloric acid to a pH of $7.5 \pm 0.05$, and degas.

Medium: 0.05 M Tris buffer; 900 mL .
Apparatus 2: 35 rpm .
Time: 60 minutes.
${ }^{\triangle}$ Dissolution procedure-Shake the sample suspension well, about 100 shakes. Using a $5-\mathrm{mL}$ syringe, collect approximately 5 mL of suspension, and record the weight. With the paddles lowered, gently empty the contents of each syringe into the bottom of each vessel containing the Dissolution Medium. Start rotating the paddles. Reweigh each syringe, and determine the amount of suspension delivered into each vessel. At the end of 60 minutes, remove 4 mL from each vessel, and pass through a $0.45-\mu \mathrm{m}$ nylon filter presaturated with Dissolution Medium. $\mathbf{A}$ USP28
Determine the amount of $\mathrm{C}_{15} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{2}$ dissolved by employing the following method.
0.02 M Sodium phosphate buffer-Dissolve 2.76 g of monobasic sodium phosphate in 1 L of water.
Mobile phase-Prepare a filtered and degassed mixture of 0.02 M Sodium phosphate buffer, methanol, and acetonitrile (50:27:23), and mix. Adjust with phosphoric acid to a pH of 3.0 . Make adjustments if necessary (see System Suitability under Chromatography〈621〉).
Standard solution-Transfer about 70 mg of USP Phenytoin RS, accurately weighed, to a $500-\mathrm{mL}$ volumetric flask. Dissolve in 15 mL of methanol, dilute with Dissolution Medium to volume, and mix.

Fest pension, aeeurately weighed, into each dissolution vessel. Withdraw the sample after 60 minutes, and filter.
${ }^{\Delta}$ USP28
Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $240-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard solution, and record the responses as directed for Procedure: the column efficiency is not less than 5400 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard solution and the Fest solution
$\Delta_{\text {solution under test }}^{\mathbf{A}_{\text {USP28 }}}{ }^{\text {S }}$
into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{15} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{2}$ dissolved. [NOTE-The density of Oral Suspension must be determined and used in calculating the quantity, in mg , of phenytoin dissolved.]

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{15} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{2}$ is dissolved in 60 minutes.

## Add the following:

- Uniformity of dosage units $\langle 905\rangle$ -

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT
CONTAINERS: meets the requirements.■2S (USP27)

## Add the following:

-Deliverable volume $\langle 698\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements.■2S (USP27)

## BRIEFING

Propoxyphene Hydrochloride, USP 27 page 1578 and page 660 of PF 29(3) [May-June 2003]. It is proposed to revise the USP Reference standards section to change the name of USP $\alpha$ -$d$-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane RS to USP Propoxyphene Related Compound B RS. It is also proposed to revise the test for Related compounds and the Assay to incorporate the name change.
(PA2: C. Anthony) RTS-40681-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Propoxyphene Hydrochloride RS. USP -d-4 Aevy-4 dimethylamine-1,2 diphemy 3 methylbutane RS.
${ }^{\star}$ USP Propoxyphene Related Compound B RS. $\quad$ USP28 USP Propoxyphene Related Compound A RS.

## Change to read:

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~S}\rangle$ -
Solution: 1 in 20.
Medium: chloroform.
B: It respends to the tests for Chtorite $\langle 194\rangle$ :

- Dissolve 0.25 g of Propoxyphene Hydrochloride in 15 mL of Purified Water, and treat 3 mL of this solution with 1 mL of 6 N ammonium hydroxide to precipitate the propoxy-
phene base. Filter to remove the precipitate, acidify the filtrate with 2 mL of nitric acid, and add 1 mL of silver nitrate TS: a white, curdy precipitate that is soluble in an excess of 6 N ammonium hydroxide confirms the presence of silver chloride. ${ }^{2 S}$ (USP27)


## Change to read:

Related compounds-
Mobile phase and Chromatographic system-Proceed as directed in the Assay.

Standard solution- Proceed as directed for the Standard prep-

## aration in the Assay.

Relatempards stated
${ }^{\mathbf{\Delta}}$ Standard stock $\mathbf{\Delta U S P 2 8 ~}$ solution- Pissolve
${ }^{\wedge}$ Accurately weigh
about 10 mg each of USP Propoxyphene Related Compound A RS and USP a d 2 acetoxy - 4 dimethylamine 1,2 diphenyl 3 -methyl butane RS
${ }^{\mathbf{\Delta}}$ USP Propoxyphene Related Compound B RS $\mathbf{A U S P 2 8}$
in 20 mL of methanol in
$\Delta_{\text {into }}$ USP28
a $50-\mathrm{mL}$ volumetric flask,
${ }^{\boldsymbol{\Delta}}$ dissolve using 2 mL of methanol,,$_{\mathbf{\Delta S P 2 8}}$
dilute with Mobile phase to volume, and mix.
${ }^{\wedge}$ Standard solution-Transfer 5.0 mL of the Standard stock solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Mo-
bile phase to volume, and mix. $\triangle$ USP28
Test solution-Use the Assay preparation.
System suitability solution Combine 1.0 mL of the Related compounds. Standend stock solution containing about 0.2 mg per mL of each related compernd with 10.0 mL of the Standerd Test solution, and mix.
${ }^{\mathbf{\Delta}}$ Transfer 1.0 mL of the Standard stock solution to a 10.0 mL volumetric flask, dilute with Mobile phase to volume, and mix. $\Delta$ USP28

Chromatographic system (see Chromatography $\langle 621\rangle$ )-Proceed as directed in the Assay. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.63 for propoxyphene related compound A, 0.78 for $x-d 2$ aeetoxy 4 -dimethylamine-1,2 diphe-nyl-3 methylbutane,
${ }^{\Delta}$ propoxyphene related compound $\mathrm{B},{ }_{\mathbf{\Delta S P} 28}$
and 1.0 for propoxyphene hydrochloride; the resolution, $R$, between $\alpha$ d 2 acetoxy 4 -dimethylamino-1,2 diphenyl-3 methylbut路,
${ }^{\text {4 }}$ propoxyphene related compound $\mathrm{B}, \mathbf{\Delta U S P 2 8}$ and propoxyphene
$\boldsymbol{\Delta}_{\text {related compound }} \mathrm{A}_{\mathbf{\Delta} U S P 28}$
is not less than 1.4 ;
${ }^{\Delta} 2.0 ;_{\mathbf{\Delta S P 2 8}}$
and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-
${ }^{\Delta}$ Separately ${ }_{\mathbf{A S P} \text { U }}$
inject a
${ }^{4}$ equal ${ }_{\text {aUSP28 }}$
volumes (about $50 \mu \mathrm{~L}$ ) of the Test solution
$\boldsymbol{\Delta}_{\text {and }}$ the Standard solution ${ }_{\mathbf{A S P 2 8}}$
into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the perenge
${ }^{4}$ quantity, in $\mathrm{mg},{ }_{\text {USP2 }}$
of propoxyphene related compound A in the portion of Propoxyphene Hydrochloride taken by the formula:

$$
\begin{aligned}
& 100\left(r_{i}+\Psi_{4}\right) \text {, } \\
& { }^{\Delta} 50 C\left(r_{U} / r_{S}\right)_{, \mathbf{\Delta S P 2 8}}
\end{aligned}
$$

in which $F_{i}$ is the individual peak respense of propexyphene related eompound $A$ in the Test solution; and ${ }_{s}$ is the sum of the respenses for all of the peaks:
${ }^{\Delta} C$ is the concentration, in mg per mL , of USP Propoxyphene Related Compound A RS in the Standard solution; and $r_{U}$ and $r_{S}$ are the propoxyphene related compound A peak responses obtained from the Test solution and Stan-
dard solution, respectively. $\Delta$ USP28
Not more than $0.5 \%$ of propoxyphene related compound $A$ as the hydrochloride
A UUSP28
is found. Calculate the percenge
${ }^{\Delta}$ quantity, in mg , $\triangle U S P 28$
of $\alpha d-2$ aeetoxy 4 dimethylamine-1,2 diphenyl 3-methylbutane,
${ }^{\Delta}$ propoxyphene related compound B as the ${ }_{\Delta U S P 28}$
hydrochloride in the portion of Propoxyphene Hydrochloride taken by the formula:

$$
\begin{gathered}
100(1.112)\left(r_{t} \not+r_{t}\right), \\
\triangle 50 C(361.93 / 325.45)\left(r_{U} / r_{S}\right),_{\Delta U S P 28}
\end{gathered}
$$

in which 1.112 is the ratio of the molecular weight of $\alpha d 2$ ace exy 4 dimethylamine 1,2 diphenyl 3 methylbutane hydrechleride to that of $\alpha d 2$ acetoxy - 4 dimethylamine 1,2 diphenyl 3 methyl butane free base; $;$ is the individual penk respense of $\alpha-d / 2$ acet oxy 4 dimethylamine-1,2 diphenyl-3 methylbutane in the Test solution; and $T_{s}$, is the sum of the respenses for all of the peaks:
${ }^{\Delta} C$ is the concentration, in mg per mL , of USP $\alpha-d-$ Acet exy 4-dimethylamine-1,2 diphenyl 3-methylbutane RS USP Propoxyphene Related Compound B RS in the Standard solution; 361.93 and 325.45 are the molecular weights of $\alpha-d$-2 acetoxy-4-dimethylamine-1,2-diphenyl-3-methyl butane, propoxyphene related compound $B$ as the hydrochloride and $\alpha$ 2 2 eny-4 dimethylamino-1,2 diphenyl-3-methylbutane, propoxyphene related compound B , respectively; and $r_{U}$ and $r_{S}$ are the $\alpha-2$-acetoxy-4-di methylamine 1,2 diphenyl 3 methylbutane, propoxyphene related compound B peak responses obtained from the Test
solution and the Standard solution, respectively. $\triangle$ USP28.
Not more than $0.6 \%$ of $* d-2$ acetoxy - 4 dimethylamine-1,2 diphenyl 3 methylbutane,
${ }^{4}$ propoxyphene related compound B as the ${ }_{\Delta U S P 28}$ hydrochloride is found.

## Change to read:

## Assay-

${ }^{\mathbf{4}} 0.1 M_{\mathbf{4} U S P 28}$
Monobasic ammonium phosphate buffer, pH 6.3-Dissolve 11.5 g of monobasic ammonium phosphate and 1.0 mL of triethylamine in 1000 mL of water, adjust with $10 \%$ sodium hydroxide to a pH of $6.3 \pm 0.05$, and mix.

Mobile phase-Prepare a filtered and degassed mixture of methanol and 6.01-M
$\Delta_{0.1} M_{\Delta U S P 28}$
Monobasic ammonium phosphate buffer, pH 6.3 (67:33). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard preparation-Dissolve an accurately weighed quantity of USP Propoxyphene Hydrochloride RS in Mobile phase to obtain a solution having a known concentration of about 5.0 mg per mL .
Assay preparation-Transfer about 250 mg of Propoxyphene Hydrochloride, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the retention time of propoxyphene hydrochloride is about 9 minutes; the resolution, $R$, between $\alpha-d 2$ acetoxy 4 dimethylamine 1,2 diphenyl 3 methylbutane and propoxyphene is not less than 1.4;
$\Delta_{\text {the tailing factor for the propoxyphene hydrochloride peak }}$ is not more than $3.5 ;_{\mathbf{\Delta S P}}$ IS
and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ in the portion of Propoxyphene Hydrochloride taken by the formula:

$$
100 \mathrm{C}\left(+_{t}+\Psi_{s}\right)
$$

$$
{ }^{\mathbf{\Delta}} 50 C\left(r_{U} / r_{S}\right)_{, \mathbf{\Delta U S P 2 8}}
$$

in which $C$ is the concentration, in mg per mL , of USP Propoxyphene Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Quazepam Tablets, USP 27 page 1614. It is proposed to revise the test for Related compounds to correct the composition of Standard solution C. The reference to USP Quazepam Related Compound A RS was inadvertently replaced with USP Quazepam RS.

[^58]
## Change to read:

Related compounds-
Test solution-Grind 10 Tablets to a fine powder. Dissolve an accurately weighed portion of the powder in methylene chloride to obtain a solution having a concentration of 10 mg of quazepam per mL . Mix for 30 minutes, and centrifuge.

Standard solution $A$-Dissolve an accurately weighed quantity of USP Quazepam RS in methylene chloride to obtain a solution having a known concentration of about 10 mg per mL .

Standard solution B-Dissolve an accurately weighed quantity of USP Quazepam RS in methylene chloride to obtain a solution having a known concentration of about 0.04 mg per $\mathrm{mL}(0.2 \%)$.

Standard solution C-Dissolve an accurately weighed quantity of USP Quazepam RS
${ }^{\Delta}$ USP Quazepam Related Compound A RS ${ }_{\Delta U S P 28}$
in methylene chloride to obtain a solution having a known concentration of about 0.3 mg per $\mathrm{mL}(1.5 \%)$.

Procedure-Separately apply $10 \mu \mathrm{~L}$ each of the Test Solution and Standard solution $A$ and $5 \mu \mathrm{~L}$ each of Standard solutions $B$ and $C$ to a thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ) coated with a $0.25-\mathrm{mm}$ layer of chromatographic silica gel. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of cyclohexane, ethyl acetate, and ether (170:40:25) in a paper-lined tank until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, allow to air-dry, and examine the plate under short-wavelength UV light. Compare the intensity of the secondary spot in the chromatogram
of the Test solution having the same $R_{F}$ value as the principal spot in the chromatogram of Standard solution $C$. The spot is not larger or more intense than the principal spot obtained from Standard solution C. Compare the intensities of any additional secondary spots observed in the chromatogram of the Test solution with that of the principal spot in the chromatogram of Standard solution B: no additional secondary spot from the chromatogram of the Test solution is larger or more intense than the principal spot obtained from Standard solution B, and the sum of the intensities of the additional secondary spots obtained from the Test solution is not more than $0.6 \%$.

## BRIEFING

Resorcinol and Sulfur Lotion, USP 27 page 1643. It is proposed to change the title of this monograph to Resorcinol and Sulfur Topical Suspension. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40806-1

## Resorcinol and Sulfur Lotion

(Current title-not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Resorcinol and Sulfur Topical Suspension

BRIEFING
Resorcinol and Sulfur Topical Suspension-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40806-1

## Add the following:

## $\triangle$ Resorcinol and Sulfur Topical Suspension

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Resorcinol and Sulfur Lotion)
» Resorcinol and Sulfur Topical Suspension is Resorcinol and Sulfur in a suitable hydroalcoholic vehicle. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of resorcinol $\left(\mathrm{C}_{6} \mathrm{H}_{6} \mathrm{O}_{2}\right)$ and not less than 95.0 percent and not more than 110.0 percent of the labeled amount of sulfur (S).

Packaging and storage-Preserve in tight containers.
USP Reference standards $\langle 11\rangle-U S P$ Resorcinol $R S$.

## Identification-

A: Transfer a quantity of Topical Suspension, equivalent to about 20 mg of resorcinol, to a $15-\mathrm{mL}$ centrifuge tube, add 5 mL of 5 N sodium hydroxide, mix, and centrifuge the mixture for 5 minutes. Decant the supernatant into a test tube, and retain the residue for Identification test $B$. Add 0.5 mL of chloroform, mix, and heat on a steam bath: an intense crimson color is produced. Add a slight excess of hydrochloric acid: the color changes to pale yellow (presence of resorcinol).

B: Place a small portion of the residue from the centrifuge tube in Identification test $A$ on the tip of a spatula, and burn it: sulfur dioxide, which turns moistened starch-iodate paper blue, is formed (presence of sulfur).

Alcohol content $\langle 611\rangle$-Determine by the gas-liquid chromatographic method, acetone being used as the internal standard: it contains between $90.0 \%$ and $110.0 \%$ of the labeled amount of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

## Assay for resorcinol-

Mobile phase-Prepare a suitable degassed solution of water, acetonitrile, and methanol (about 55:7:6) such that the retention times of resorcinol and caffeine are about 3 minutes and 4 minutes, respectively.

Internal standard solution-Dissolve about 140 mg of caffeine in 2 mL of chloroform, add methanol to make 100 mL , and mix.

Standard preparation-Transfer 50 mg of USP Resorcinol RS, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dilute with methanol to volume, and mix. Transfer 10.0 mL of this solution and 5.0 mL of Internal standard solution to a $100-\mathrm{mL}$ volumetric flask, dilute with methanol to volume, and mix.

Assay preparation-Transfer an accurately weighed portion of Topical Suspension, equivalent to about 20 mg of resorcinol, to a $150-\mathrm{mL}$ beaker. Add 40 mL of methanol and 5.0 mL of Internal standard solution, and heat on a steam bath for 5 minutes. Cool the mixture to room temperature, and decant the liquid into a $100-\mathrm{mL}$ volumetric flask. Wash the residue in the beaker by adding 20 mL of methanol to the beaker. Heat on a steam bath for 5 minutes, cool the mixture to room temperature, and decant the liquid into the volumetric flask. Repeat the washing, heating, cooling, and decanting. Dilute the contents of the volumetric flask with methanol to volume, and mix.

Procedure-Introduce equal volumes (about $10 \mu \mathrm{~L}$ ) of the Assay preparation and the Standard preparation into a high-pressure liquid chromatograph (see Chromatography $\langle 621\rangle$ ), operated at room temperature, by means of a suitable microsyringe or sampling valve, adjusting the specimen size and other operating parameters such that the peak obtained from the Standard preparation is about 0.6 full scale. Typically, the apparatus is fitted with a $4-\mathrm{mm}$ $\times 30-\mathrm{cm}$ column containing packing L1 and is equipped with an UV detector capable of monitoring absorption at 280 nm , and a suitable recorder. In a suitable chromatogram the coefficient of variation for five replicate injections of the Standard preparation is not more than $3.0 \%$. Measure the peak responses at equivalent retention times, obtained from
the Assay preparation and the Standard preparation, and calculate the quantity, in mg , of $\mathrm{C}_{6} \mathrm{H}_{6} \mathrm{O}_{2}$ in the portion of Topical Suspension taken by the formula:

$$
(100 C)\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Resorcinol RS in the Standard preparation; and $R_{U}$ and $R_{S}$ are the ratios of the responses of the resorcinol and caffeine peaks obtained from the Assay preparation and the Standard preparation, respectively.

Assay for sulfur-Transfer an accurately weighed portion of Topical Suspension, equivalent to about 85 mg of sulfur, to a suitable flask, add 40 mL of sodium sulfite solution ( 1 in 20), a few drops of antifoam, and a few boiling chips, and boil under a reflux condenser for 1 hour. Cool to room temperature, add 10 mL of formaldehyde solution and 6 mL of 6 N acetic acid, and dilute with water to 150 mL . Add 3 mL of starch TS, and titrate with 0.1 N iodine VS until a permanent blue color is produced. Each mL of 0.1 N iodine is equivalent to 3.206 mg of $\mathrm{S}_{.}$USSP28
(Official July 1, 2007)

## BRIEFING

Rifampin and Isoniazid Capsules, USP 27 page 1651 and page 1862 of $P F$ 28(6) [Nov.-Dec. 2002]; Rifampin, Isoniazid, and Pyrazinamide Tablets, USP 27 page 1653 and page 1865 of $P F$ (28(6) [Nov.-Dec. 2002]; Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets, USP 27 page 1654. It is proposed to revise the Standard preparation in the Assay for rifampin and isoniazid under Rifampin and Isoniazid Capsules and in the Assay for rifampin, isoniazid, and pyrazinamide in the other two monographs. Because it has been observed that the rifampin component of the Standard preparation degrades rapidly with time, it is proposed to add a note to the Standard preparation stating that it is to be used within 10 minutes.
(PA7a: W. Wright) RTS-40695-1

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: 0.1 N hydrechloric acid;
$\Delta 10 \mathrm{mM} \mathrm{pH} 6.8$ sodium phosphate buffer, prepared by dissolving 7 g of anhydrous dibasic sodium phosphate in 5 L of water, and adjusting with phosphoric acid to a pH of
6.8 ; $_{\text {USP2 }}$

900 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Determine the amount of rifampin $\left(\mathrm{C}_{43} \mathrm{H}_{58} \mathrm{~N}_{4} \mathrm{O}_{12}\right)$ diselv by employing the following method.
© and isoniazid $\left(\mathrm{C}_{6} \mathrm{H}_{7} \mathrm{~N}_{3} \mathrm{O}\right)$ dissolved using filtered portions of the solution under test and by employing the procedure set forth in the Assay for rifampin and isoniazid. $\Delta U S P 28$

Phosphate buffer solution Dissolve 15.3- g of dibasic potas simm phesphate and 80.0 s of menobasie petassium phesphate inte a 1 liter volumetric flask, mix, dilute with water to volume, and mix.
 USP Iseniazid PS into a 100 mL volumetric flask. Pissolve in and dilute with 0.1 N hydrochloric acid to volume, and mix.

Stadad strek solution- Aceurately weigh about 66 mg of USP Rifampin PS inte 200 mL volumetric flack, dissolve in 10 mL of 0.1 N hydrochloric acid, and mix. Add 50.0 mL of Isonid stan dacd solution, dilute with 0.1 N hydrochlorie acid to volume, and mix. [Nөте- Prepare this solution immediately before the test is performed, and place in the dissolution bath at the start of the test.].

Stadedred solution At the end of the test rm, transfer a 5.0 mb aliquet of the Stand stock solution and 10.0 mL of Phosphate buffer solution to a 50 mL volumetric flack. Dilute with water to volume, and mix. [NOTE-Analyze the solution immediately, if possible, and if not, within 3 hours after final dilution.]

Fest solution At the end of the test rum, withdraw a 25 mL aliquet, and filter, disearding the first 10 mL of the filtrate. Allow to eool for abeut 10 minutes, and transfer 5.0 mL of the filtrate and 10.0 mL of the Phosphate buffer solution to a 50 mL volumetric flack. Dilute with water to volume, and mix. [NOTE-Analyze the solution immediately, if pessible, and if not, within 3 hours after final dilution.?
Betermine the ameunt of rifampin $\left(\mathrm{C}_{42} \mathrm{H}_{58} \mathrm{~N}_{4} \Theta_{42}\right)$ dissolved from absorbanees at the wavelength of maximum absorbance at about 475 nm of the Standard solution and the Test solution.
Petermine the mount of isoniazid $\left(\mathrm{C}_{6} \mathrm{H}_{7} \mathrm{~N}_{3} \mathrm{O}\right)$ dissolved by em ploying the following method.

Mobile phase Prepare a filtered and degassed mixare of water, Phosphate buffer solution, and methanol (850:100:50). Make ad justments if neeessay (see System Suitubility under Chromatog raphy-(624)).

Ehromatographie syistem (see-Chromatography $\langle 624$ ) (The tiquid chromategraph is equipped with a 254 nm detector and a $4.0 \mathrm{~mm} \times 30 \mathrm{~cm}$ column that contains $10-\mathrm{mm}$ packing L1. The flow rate is about 1.5 mL per minute.

Procedure Separately inject equal volumes (about $50-\mu \mathrm{L}$ ) of the Standed solution and the Test solution int the chremategraph, record the chromatograms, and meastre the respenses for the iso niazid peaks.
© $\Delta$ USP28
USP28 ${ }_{\text {Tolerances-N }}$ Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{43} \mathrm{H}_{58} \mathrm{~N}_{4} \mathrm{O}_{12}$ and not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{6} \mathrm{H}_{7} \mathrm{~N}_{3} \mathrm{O}$ are dissolved in 45 minutes.

## Change to read:

Assay for rifampin and isoniazid-
Buffer solution-Dissolve 1.4 g of dibasic sodium phosphate in 1 L of water, and adjust with phosphoric acid to a pH of 6.8 .

Solution A-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (96:4).

Solution B-Prepare a filtered and degassed mixture of acetonitrile and Buffer solution (55:45).

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve accurately weighed quantities of USP Rifampin RS and USP Isoniazid RS in a mixture of Buffer solution and methanol (96:4) to obtain a solution having known concentrations of about 0.16 mg per mL and 0.08 mg per mL , respectively.
${ }^{\boldsymbol{\Delta}}$ [NOTE-Use this solution within 10 minutes. $]_{\Delta U S P 28}$
Assay preparation-Weigh the contents of not fewer than 10 Capsules, mix, and transfer an accurately weighed portion of the powder, equivalent to about 8 mg of isoniazid, to a $100-\mathrm{mL}$ volumetric flask, and add about 90 mL of Buffer solution. Sonicate for about 10 minutes, allow to equilibrate to room temperature, dilute with Buffer solution to volume, and mix. [NOTE-Use this solution within 2 hours.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $238-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ base-deactivated packing L1. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-5$ | 100 | 0 | isocratic |
| $5-6$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| $6-15$ | 0 | 100 | isocratic |

Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 2.6 and 1.0 for rifampin and isoniazid, respectively; the column efficiency is not less than 50,000 and not less than 6,000 theoretical plates for rifampin and isoniazid, respectively; the tailing factors are not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg , of rifampin $\left(\mathrm{C}_{43} \mathrm{H}_{58} \mathrm{~N}_{4} \mathrm{O}_{12}\right)$ and isoniazid $\left(\mathrm{C}_{6} \mathrm{H}_{7} \mathrm{~N}_{3} \mathrm{O}\right)$ in the portion of Capsules taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Rifampin RS, calculated on the dried basis, or of USP Isoniazid RS, as appropriate, in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the corresponding analytes obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Rifampin, Isoniazid, and Pyrazinamide Tablets, $U S P 27$ page 1653 and page 1865 of $P F$ 28(6) [Nov.-Dec. 2002]-See briefing under Rifampin and Isoniazid Capsules.
(PA7a: W. Wright) RTS-40695-2

## Change to read:

## Dissolution $\langle 711\rangle$ -

Medium: simmated gastric fluid TS, witheut pepsin;
${ }^{\boldsymbol{\Delta}} 10 \mathrm{mM} \mathrm{pH} 6.8$ sodium phosphate buffer, prepared by dissolving 7 g of anhydrous dibasic sodium phosphate in 5 L of water, and adjusting with phosphoric acid to a pH of
6.8; UUSP28

900 mL .
Apparatus 1: 100 rpm .
Time: 30 minutes.
Standard stok solution Prepare a-solution in Dissolution Me dium having known concentrations of about 0.22 mg of USP Iso fiazid PS and 1.3 mg of USP Pyrazinamide RS per mL. Use this selution on the day prepared.

Imtermediate standtad solution-Transfer about 27 mg of USP Rifampin PS, aceurately weighed, to a 200 mL volumetric flask, add 50.0 mL of the Standed stock solution, and swinl to dissolve. Bilute with Dissolution Medium to volume, and mix. Place this flask into the dissolution bath immediately prier to stating the tabtet dissolution. Withdraw the flask from the dissolution bath at the same time that the solutions under test are withdrawn.

- $\Delta$ USP28

Determine the amount of $\mathrm{G}_{42} \mathrm{H}_{58} \mathrm{~N}_{4} \Theta_{42}$ dissolved by employing the following method.
$\Delta_{\text {rifampin }}\left(\mathrm{C}_{43} \mathrm{H}_{58} \mathrm{~N}_{4} \mathrm{O}_{12}\right)$, isoniazid $\left(\mathrm{C}_{6} \mathrm{H}_{7} \mathrm{~N}_{3} \mathrm{O}\right)$, and pyrazinamide $\left(\mathrm{C}_{5} \mathrm{H}_{5} \mathrm{~N}_{3} \mathrm{O}\right)$ dissolved using filtered portions of the solution under test and by employing the procedure set forth in the Assay for rifampin, isoniazid, and pyrazina-


Standard solution Transfer 10.0 mL of the Internediate stan Ated sum to -50 mL volumetrie flask, dilute with Dissolution Mediun to volume, and mix.
Preedure Transfer 10.0 mL of the filtered solution under test to a separate 50 mL volumetrie flask, dilute with Dissolution Me diun to volume, and mix. Coneomitantly determine the UV absor bances at 475 nm , of the solution obtained and the Standard solution, using Dissolution Medium as the blank. Calculate the quantity, in mg, of rifampin $\left(\mathrm{C}_{43} \mathrm{H}_{58} \mathrm{~N}_{4} \Theta_{42}\right)$ dissolved by the for meta:-

$$
45006\left(A_{\downarrow}+A_{s}\right)
$$

in which- $C$ is the concentration, in ms per mL, of USP Rifampin RS- in the Standard solution; and $A_{b}$-and $A_{s}$ are the absorbances of the solution under test and the Standard solution, respectively.

Foteranes Not less than $80 \%$ ( $Q$ ) of the labeled amount of ir fampin $\left(\mathrm{C}_{43} \mathrm{H}_{58} \mathrm{~N}_{4} \mathrm{O}_{42}\right)$ is dissolved in 30 minutes. Petermine the amount of $\mathrm{C}_{6} \mathrm{H}_{7} \mathrm{~N}_{3} \mathrm{O}$ and $\mathrm{C}_{5} \mathrm{H}_{5} \mathrm{~N}_{3} \mathrm{O}$-dissolved by employing the following method.

Mobile phase. Prepare a filtered and degassed mixture of water, 4-M monobasic petassium phosphate, and acetonitrile ( $860: 100: 40$ ). Make adjustments if necessayy (see System Suitabil ity under Chromatography ( 621 )).
fystem suitability solution Prepare a solution of isonicotinie acid in Dissoluth Medium contrining about 0.125 me per mL. Transfer 10 mL of this solution and 4 mL of the Stated stock solution to a 100 mL velumetric flack containing 15 mL of 1 M dibasic potassium phosphate and 30 mL of Mobile phase. Dilute with Mobile phase to velume, and mix.

Standard solution- Transfer 15.0 mL of the Intermediate stan thed soltion to 100 mL volumetric flask eontaining 15 mL of 4 M dibasie petassimm phesphate and 30 mL of Mobile phase. Dilute with Mobile phase to volume, and mix. This solution may be used for 20 heurs.

Fest solution Withdraw 60 mL of the solution under test, and filter, disearding the first 20 mL of the filtrate. Centrifuge the fil trate for 5 minutes. Transfer 15.0 mL of this solution to a 100 mL velumetric flask entaining 15 mL of 1 M dibasic potassimm phosphate and 30 mL of Mobile phase. Dilute with Mobile phase to volume, and mix. This solution may be used for 20 hours.

Chromatographic system (see Chromatography (624)) The liquid chromatograph is equipped with a 254 mm detector and a $4.6 \mathrm{~mm} \times 30 \mathrm{~cm}$ column that contains packing L44. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedtre: the relative retention times are about 0.7 for isonicotinic acid, 1.0 for pyrazinamide, and 1.8 for isoniazid; and the resolution, $R$, be tween isonicotinie acid and pyrazinamide is not less than 2.5 and beween pyrazinamide and isoniazid not less than- 4.0 . Chromatograph the Standard solution, and record the peak respenses as directed for Procedure: the relative standard deviations determined from the pyrazinamide and isoniazid respenses for repliente injec tiens are net mere than $1.5 \%$.

Preedure- Separately inject equal volumes (about $50-\mu \mathrm{L}$ ) of the Standurd solution and the Test solution into the ehromatograph, record the chromatograms, and measure the areas-for the major peaks. Caleulate the quantity, in me, of isoniazid $\left(\mathrm{C}_{6} \mathrm{H}_{7} \mathrm{~N}_{3} \mathrm{O}\right)$ dis solved by the formula:

$$
6000 C\left(r_{t}+r_{5}\right)
$$

in which- $C$ is the eoneentration, in mes per mL, of USP Iseniazid PS in the Stamdtard solution; and + tand ra are the isoniazid peak areas obtained from the Test solution and the Standard solution, respectively. Caleulate the quantity, in me, of pyrazinamide $\left(\mathrm{C}_{5} \mathrm{H}_{5} \mathrm{~N}_{3} \mathrm{O}\right)$ dissolved by the-same formala, exeept to read "USP Pyrazinamide-RS" where "USP Isoniazid PS" is speeiffed, and "pyrazinamide" where "isoniazid"" is speeified.
$\triangle$
AUSP28
Tolerances-Not less than $80 \%(Q)$ of the labeled ameant
$\Delta_{\text {amounts of rifampin }}\left(\mathrm{C}_{43} \mathrm{H}_{58} \mathrm{~N}_{4} \mathrm{O}_{12}\right)$ and ${ }_{\mathbf{A} \text { USP28 }}$
of isoniazid $\left(\mathrm{C}_{6} \mathrm{H}_{7} \mathrm{~N}_{3} \mathrm{O}\right)$ and not less than $75 \%$ of the labeled amount of pyrazinamide $\left(\mathrm{C}_{5} \mathrm{H}_{5} \mathrm{~N}_{3} \mathrm{O}\right)$ are dissolved in 30 minutes.

## Change to read:

Assay for rifampin, isoniazid, and pyrazinamide-
Buffer solution-Dissolve 1.4 g of dibasic sodium phosphate in 1 L of water, and adjust with phosphoric acid to a pH of 6.8 .

Solution A-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (96:4).

Solution B-Prepare a filtered and degassed mixture of acetonitrile and Buffer solution (55:45).

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve accurately weighed quantities of USP Rifampin RS, USP Isoniazid RS, and USP Pyrazinamide RS in a mixture of Buffer solution and methanol (96:4) to obtain a solution having known concentrations of about 0.16 mg per mL , 0.08 mg per mL , and 0.43 mg per mL , respectively.
$\Delta^{\text {[NOTE——Use this solution within } 10 \text { minutes.] }}{ }_{\text {AUSP28 }}$
Assay preparation - Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 8 mg of isoniazid, to a $100-\mathrm{mL}$ volumetric flask, and add about 90 mL of Buffer solution. Sonicate for about 10 minutes, allow to equilibrate to room temperature, dilute with Buffer solution to volume, and mix. [NOTE-Use this solution within 2 hours.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $238-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ base-deactivated packing L1. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-5$ | 100 | 0 | isocratic |
| $5-6$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| $6-15$ | 0 | 100 | isocratic |

Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about $1.8,0.7$, and 1.0 for rifampin, isoniazid, and pyrazinamide, respectively; the resolution, $R$, between isoniazid and pyrazinamide is not less than 4 ; the column efficiency is not less than 50,000 , not less than 6,000 , and not less than 10,000 theoretical plates for rifampin, isoniazid, and pyrazinamide, respectively; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantities, in mg , of rifampin $\left(\mathrm{C}_{43} \mathrm{H}_{58} \mathrm{~N}_{4} \mathrm{O}_{12}\right)$, isoniazid $\left(\mathrm{C}_{6} \mathrm{H}_{7} \mathrm{~N}_{3} \mathrm{O}\right)$, and pyrazinamide $\left(\mathrm{C}_{5} \mathrm{H}_{5} \mathrm{~N}_{3} \mathrm{O}\right)$ in the portion of Tablets taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Rifampin RS, calculated on the dried basis, or of USP Isoniazid RS or of USP Pyrazinamide RS, as appropriate, in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the corresponding analytes obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets, USP 27 page 1654 -See briefing under Rifampin and Isoniazid Capsules.
(PA7a: W. Wright) RTS-40695-3

## Change to read:

Assay for rifampin, isoniazid, and pyrazinamide-
Buffer solution-Dissolve 1.4 g of anhydrous dibasic sodium phosphate in 1 L of water, and adjust with phosphoric acid to a pH of 6.8.

Solution A-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (96:4).

Solution B-Prepare a filtered and degassed mixture of acetonitrile and Buffer solution (55:45).

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard preparation-Dissolve accurately weighed quantities of USP Rifampin RS, USP Isoniazid RS, and USP Pyrazinamide RS in a mixture of Buffer solution and methanol (96:4) to obtain a solution having known concentrations of about 0.16 mg per mL , 0.08 mg per mL , and 0.43 mg per mL , respectively.
${ }^{\mathbf{\Delta}}$ [NOTE-Use this solution within 10 minutes.] $\mathbf{A S S P 2 8}$
Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 8 mg of isoniazid, to a $100-\mathrm{mL}$ volumetric flask, and add about 90 mL of Buffer solution. Sonicate for about 10 minutes, allow to equilibrate to room temperature, dilute with Buffer solution to volume, and mix. [NOTE-Use this solution within 2 hours.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $238-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains a $5-\mu \mathrm{m}$ base-deactivated packing L1. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-5$ | 100 | 0 | isocratic |
| $5-6$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| $6-15$ | 0 | 100 | isocratic |

Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times for rifampin, isoniazid, and pyrazinamide are about $1.8,0.7$, and 1.0 , respectively; the resolution, $R$, between isoniazid and pyrazinamide is not less than 4 ; the column efficiencies, determined from the rifampin, isoniazid, and pyrazinamide peaks are not less than $\mathbf{\Delta}^{5} 50,000 \mathbf{A U S P 2 7}$ theoretical plates, ${ }^{\mathbf{\Delta}} 6000 \mathbf{\Delta U S P 2 7}$ theoretical plates, and $\mathbf{\Delta N}^{\mathbf{1}} 10,00 \mathbf{\Delta U S P 2 7}$ theoretical plates, respectively; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantities, in mg , of rifampin $\left(\mathrm{C}_{43} \mathrm{H}_{58} \mathrm{~N}_{4} \mathrm{O}_{12}\right)$, isoniazid $\left(\mathrm{C}_{6} \mathrm{H}_{7} \mathrm{~N}_{3} \mathrm{O}\right)$, and pyrazinamide $\left(\mathrm{C}_{5} \mathrm{H}_{5} \mathrm{~N}_{3} \mathrm{O}\right)$ in the portion of Tablets taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of the appropriate USP Reference Standard in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses of the corresponding analyte obtained from the Standard preparation and the Assay preparation, respectively.

## Briefing

Saccharin Sodium Tablets, USP 27 page 1666. It is proposed to remove the cross-reference to the Identification tests $A$ and $B$ under Saccharin Calcium by adding the text to the monograph. See the briefing for Identification test in the harmonization draft proposal for Saccharin Calcium on page 1705 of PF 29(5) [Sept.-Oct. 2003].
(EMC: C. Sheehan) RTS-40757-1

## Change to read:

Identification-
${ }^{\Delta} \mathbf{A}_{\mathbf{\Delta U S P 2 8}}$
Dissolve a quantity of Tablets, equivalent to about 1 g of saccharin, in 10 mL of water, filter if necessary, and to the solution add 5 mL of 3 N hydrochloric acid: a white precipitate of saccharin is formed. Collect the precipitate on a filter, wash with small portions of cold water until the last washing is practically free from chloride, and dry it at $105^{\circ}$ for 2 hours: the saccharin so obtained melts between $226^{\circ}$ and $230^{\circ}$, the procedure for Class I being used (see Melting Range or Temperature $\langle 741\rangle$ )., and responds to Identifican $A$ and $B$ under Saccharin Caleitm.
${ }^{\Delta}$ [Note-Use also in Identification tests $B$ and $C$.]
B: Dissolve about 100 mg in 5 mL of sodium hydroxide solution (1 in 20), evaporate to dryness, and gently fuse the residue over a small flame until it no longer evolves ammonia. Allow the residue to cool, dissolve in 20 mL of water, neutralize with 3 N hydrochloric acid, and filter: the addition of a drop of ferric chloride TS to the filtrate produces a violet color.

C: Mix 20 mg with 40 mg of resorcinol, add 10 drops of sulfuric acid, and heat the mixture in a suitable liquid bath of $200^{\circ}$ for 3 minutes. Allow it to cool, and add 10 mL of water and an excess of 1 N sodium hydroxide: a fluorescent green liquid results. USSP28 $^{\text {. }}$

## BRIEFING

Selenium Sulfide Lotion, USP 27 page 1685. It is proposed to change the title of this monograph to Selenium Sulfide Topical Suspension. See briefing under Amphotericin B Lotion.

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(NL: C. Barnstein) RTS-40807-1
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## Selenium Sulfide Lotion

(Current title-not to change until July 1, 2007) Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Selenium Sulfide Topical Suspension

## BRIEFING

Selenium Sulfide Topical Suspension-See briefing under $A m$ photericin B Lotion.
(NL: C. Barnstein) RTS-40807-1

## Add the following:

## ©Selenium Sulfide Topical Suspension

(Monograph under this new title-to become official July 1, 2007)
('Current monograph title is Selenium Sulfide Lotion)
» Selenium Sulfide Topical Suspension is an aqueous, stabilized suspension of Selenium Sulfide. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\mathrm{SeS}_{2}$. It contains suitable buffering and dispersing agents.
note-Where labeled for use as a shampoo, it contains a detergent. Where labeled for other uses, it may contain a detergent.

Packaging and storage-Preserve in tight containers.
Identification-Digest about 2 g with 5 mL of nitric acid over gentle heat for 1 hour, dilute with water to about 50 mL , and filter: the solution responds to Identification test $A$ under Selenium Sulfide, when tested as directed, beginning with "to 10 mL of the filtrate add 5 mL of water."
$\mathbf{p H}\langle 791\rangle$ : between 2.0 and 6.0.

Assay-Place a portion of well-mixed Topical Suspension, equivalent to about 100 mg of selenium sulfide and accurately weighed, in a suitable flask. Cautiously digest with 25 mL of fuming nitric acid over gentle heat for 2 hours, and proceed as directed in the Assay under Selenium Sulfide, beginning with "Cool, transfer the solution to a $250-\mathrm{mL}$ volumetric flask." Each mL of 0.05 N sodium thiosulfate is equivalent to 1.789 mg of $\mathrm{SeS}_{2}$. Where the Topical Suspension is labeled in terms of percentage ( $\mathrm{w} / \mathrm{v}$ ) or of the amount of $\mathrm{SeS}_{2}$ in a given volume of Topical Suspension, determine the density of the Topical Suspension as follows: Using a tared, $100-\mathrm{mL}$ volumetric flask, weigh 100 mL of Topical Suspension that previously has been shaken to ensure homogeneity, allowed to stand until the entrapped air rises, and finally inverted carefully just prior to transfer to the volumetric flask. From the observed weight of 100 mL of the Topical Suspension, calculate the quantity of $\mathrm{SeS}_{2}$ in each 100 mL . |  |
| :---: |
| USP28 |

(Official July 1, 2007)

Briefing
Triamcinolone Acetonide Lotion, USP 27 page 1877. It is proposed to change the title of this monograph to Triamcinolone Acetonide Topical Emulsion. See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40808-1

## Triamcinolone Acetonide Lotion

(Current title_not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Triamcinolone Acetonide Topical Emulsion

BRIEFING
Triamcinolone Acetonide Topical Emulsion-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40808-1

## Add the following:

## ©Triamcinolone Acetonide Topical Emulsion

(Monograph under this new title-to become official July 1, 2007)
(Current monograph title is Triamcinolone Acetonide Lotion)
» Triamcinolone Acetonide Topical Emulsion contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\mathrm{C}_{24} \mathrm{H}_{31} \mathrm{FO}_{6}$.

Packaging and storage-Preserve in tight containers.
USP Reference standards 〈11〉-USP Triamcinolone Acetonide RS.

Identification-It responds to the Identification test under Triamcinolone Acetonide Cream.

Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.

Minimum fill $\langle 755\rangle$ : meets the requirements.
Assay-Proceed with Topical Emulsion as directed in the Assay under Triamcinolone Acetonide Cream, except to read "Topical Emulsion" in place of "Cream" throughout. $\triangle$ USP28
(Official July 1, 2007)

BRIEFING
White Lotion, USP 27 page 1952-It is proposed to change the title of this monograph to Zinc Sulfide Topical Suspension. Insoluble white zinc sulfide is the product of reaction of zinc sulfate with sulfurated potash (potassium sulfide). See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40809-1

## White Lotion

(Current title-not to change until July 1, 2007)
Monograph title change-to become official July 1, 2007 (see Official Title Changes on the first page of InProcess Revision):
See Zinc Sulfide Topical Suspension
entiation of cultured rat pheochromocytoma cells into neurite-like cells. To assist the analyst, reference photomicrographs, representing examples of differentiated and nondifferentiated cells, are specified in the test for Bioactivity. Comments on this proposed monograph are welcomed and should be directed to the attention of the USP Expert Committee on Gene Therapy, Cell Therapy, and Tissue Engineering.
(GCT: I. DeVeau) RTS—39563-1; 40288-1; 40443-1; 40621-1; 40758-1

## Add the following:

## ${ }^{\Delta}$ Small Intestinal Submucosa Wound Matrix

» Small Intestinal Submucosa Wound Matrix is a biologically derived, collagen-based wound care product, translucent and off-white in color. It is obtained from the small intestinal submucosa layer of the domestic pig (Sus scrofa L.). This layer has been mechanically separated from the adjoining layers of the intestine to remove the serosal, mucosal, and muscular elements. The isolated submucosa is chemically cleaned, decellularized, freeze-dried, and terminally sterilized. Small Intestinal Submucosa Wound Matrix also undergoes a viral inactivation; the inactivation method is validated using parvovirus, reovirus, pseudorabies virus, and leukemia retrovirus as the test viruses. By dried weight, Small Intestinal Submucosa Wound Matrix consists of about 70 percent protein, about 20 percent carbohydrate, and about 7 percent lipid. The protein component is primarily collagen type I (approximately 90 percent), with minor amounts of elastin and collagen type III, collagen type IV, and collagen type VI. In addition to these compo-
nents, additional extracellular matrix components, such as glycosaminoglycans and basic fibroblast growth factor, are also retained.

Packaging and storage-Package in single-use, peel-open pouches that are gas permeable for sterilization purposes. Store under clean, dry conditions at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-The package is labeled to indicate the dimensions of the enclosed Small Intestinal Submucosa Wound Matrix, the expiry date, required storage conditions, and the lot number. The label indicates that the Wound Matrix is sterile if the package is intact, and that the Wound Matrix is designed for single patient, one-time use.

USP Reference standards-USP Endotoxin RS.
USP Authentic Visual References-USP Cultured Rat Pheochromocytoma Reference Photomicrographs. These photomicrographs represent examples of normal and differentiated rat pheochromocytoma cells and are used to assist in ascertaining bioactivity.

Bacterial endotoxins $\langle 85\rangle$-Immerse $70 \mathrm{~cm}^{2}$ of Small Intestinal Submucosa Wound Matrix in 40 mL of LAL Reagent Water. Extract for 60 minutes at $37^{\circ}$ with shaking. Remove a $100-\mu \mathrm{L}$ aliquot to measure the amount of bacterial endotoxins. It contains not more than 20.0 USP Endotoxin Units per $70 \mathrm{~cm}^{2}$.

Sterility $\langle 71\rangle$ : meets the requirements.
Fibroblast growth factor-2 content-
8 M Urea-Dissolve 480.4 g of urea in about 700 mL of water. Dilute with water to 1 L . [Caution-Urea is highly toxic. Avoid skin contact.]

Extraction buffer-Mix 250 mL of 8 M Urea and 750 mL of water. To this solution add 6.0 g of tromethamine and 2.5 g of heparin, and mix to dissolve.
$N$-Ethylmaleimide solution-Dissolve 25 g of N -ethylmaleimide in 90 mL of alcohol. Dilute with alcohol to 100 mL .

Phenylmethylsulfonyl fluoride solution-Dissolve 3.5 g of phenylmethylsulfonyl fluoride in 100 mL of alcohol with gentle heating. [Caution-Phenylmethylsulfonyl fluoride is highly toxic. Avoid skin contact and inhaling dust and vapors.]

Benzamidine hydrochloride solution-Dissolve 15.7 g of benzamidine hydrochloride hydrate in 90 mL of water. Dilute with water to 100 mL .

IgG: agarose suspension—Prepare a suspension containing 5 to 10 mg of human immunoglobulin G : agarose in 0.5 M sodium chloride with $0.01 \%$ thimerisal. ${ }^{1}$

Calibrator diluent-Prepare an aqueous buffered protein solution, with preservative, suitable for the performance of ELISA (see Biotechnology Derived Products $\langle 1045\rangle$ ). ${ }^{2}$
$I g G$ : agarose-diluent-Remove an aliquot of the $I g G: a$ garose suspension, allow the agarose beads to settle, and discard the supernatant. Measure the volume of the remaining agarose gel, add an equal volume of Calibrator diluent, and mix the slurry for 1 hour at $4^{\circ}$. Prepare immediately before use.

Test solution-Pulverize the Small Intestinal Submucosa Wound Matrix in liquid nitrogen using a mortar and pestle that has been prechilled to $-80^{\circ}$. Transfer 10 g of powdered tissue to 100 mL of Extraction buffer. Mix 0.5 mL each of $N$-Ethylmaleimide solution, Phenylmethylsulfonyl fluoride solution, and Benzamidine hydrochloride solution, and adjust to a pH of 7.4 using sterile solutions of either 0.5 M sodium hydroxide or 0.5 M hydrochloric acid. Extract the powdered Small Intestinal Submucosa Wound Matrix with

[^59]constant stirring at $4^{\circ}$ for 24 hours. Centrifuge the extract at $12,000 \times g$ for 30 minutes at $4^{\circ}$. Place the supernatant into dialysis tubing with a molecular weight cut-off of 3500 daltons; dialyze at $4^{\circ}$ with stirring against about 20 L of water. Change the dialysis water 3 times a day for 2 days. Collect the solution from the dialysis tubing, and centrifuge at $12,000 \times g$ for 30 minutes at $4^{\circ}$. Lyophilize the supernatant and reconstitute the lyophilisate in water, with vortexing, to a concentration of 10 mg per mL . Centrifuge at $5000 \times g$ for 3 minutes, and discard the pellet. Add $50 \mu \mathrm{~L}$ of $\operatorname{IgG}$ : $a$ -garose-diluent to the lyophilisate solution, and mix for 1 hour at $4^{\circ}$. Centrifuge at $12,000 \times g$ for 5 minutes at $4^{\circ}$, recover the supernatant, and store at $4^{\circ}$. Use within 24 hours of preparation.
Procedure-Examine duplicate aliquots of the Test solution by a suitably sensitive ELISA method: ${ }^{3}$ the analysis is considered valid if the ELISA kit generates a linear standard curve with the square of the correlation coefficient $\left(r^{2}\right)$ not less than 0.95 , and if the duplicate aliquots of the Test solution yield results that are within $20 \%$ of each other. The average content of fibroblast growth factor-2 is not less than $10,000 \mathrm{pg}$ per g of Small Intestinal Submucosa Wound Matrix.

## Glycosaminoglycan content-

1,9-Dimethylmethylene blue solution-Mix 95 mL of 0.1 M hydrochloric acid in 500 mL of water. Add 16 mg of 1,9dimethylmethylene blue, 3.04 g of aminoacetic acid, and 2.37 g of sodium chloride. Dilute with water to 1 L and adjust to a pH of 3.0 using sterile solutions of either 1.0 M sodium hydroxide or 1.0 M hydrochloric acid. Store in low-actinic glassware.

[^60]Sterile PBS solution-Prepare a sterile solution that contains 8065.0 mg and 200.0 mg of sodium chloride and potassium chloride, respectively, per L of 0.01 M sodium phosphate buffer, pH 7.4 .

Proteinase K solution-Prepare a solution of Tritirachium album proteinase K in water having an activity of 600 units per mL.

Stock heparin standard solution-Prepare a solution containing 1 mg of heparin per mL of water.

Heparin standard curve solutions-Using the Stock heparin standard solution, prepare three solutions containing $20 \mu \mathrm{~g}$ per $\mathrm{mL}, 50 \mu \mathrm{~g}$ per mL , and $100 \mu \mathrm{~g}$ per mL of heparin, respectively.

## Blank solution-Use water.

Test solution-Prepare test samples in duplicate. Accurately weigh about 25 mg of Small Intestinal Submucosa Wound Matrix and cut into small pieces (roughly $2 \mathrm{~mm} \times 2$ mm ). Transfer to a $1.5-\mathrm{mL}$ microcentrifuge tube, and add $180 \mu \mathrm{~L}$ of Sterile PBS solution and $20 \mu \mathrm{~L}$ of Proteinase $K$ solution. Mix, and incubate the sample at $56^{\circ}$ for 15 minutes; during the incubation mix intermittently on a vortex mixer. Cool the sample to room temperature. Dilute with water to obtain a concentration of 12.5 mg of digested Small Intestinal Submucosa Wound Matrix per mL.

Collagen control solution-Accurately weigh about 25 mg of a bovine collagen, type I , that contains less than 1 $\mu \mathrm{g}$ of glycosaminoglycan per mg . Transfer to a $1.5-\mathrm{mL}$ microcentrifuge tube, and add $180 \mu \mathrm{~L}$ of Sterile PBS solution and $20 \mu \mathrm{~L}$ of Proteinase $K$ solution. Mix, and incubate the sample at $56^{\circ}$ for 15 minutes; during the incubation mix intermittently on a vortex mixer. Cool the sample to room temperature. Dilute with water to obtain a concentration of 12.5 mg of digested bovine collagen per mL .

Procedure (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ )-To triplicate $100-\mu \mathrm{L}$ aliquots each of Heparin standard curve solutions, Blank solution, Test solution, and Col-
lagen control solution, add 2.5 mL of 1,9-Dimethylmethylene blue solution. Mix on a vortex mixer for 1 second and immediately read the absorbance at 525 nm . Generate a standard curve of absorbance versus concentration using the averages of each Heparin standard curve solution, correcting for the blank, and calculate the regression line and regression coefficient. The concentration of glycosaminoglycan in the Test solution and Collagen control solution is determined directly from the regression line. If the absorbance of the Test solution is greater than the highest Heparin standard curve solution, then dilute the Test solution appropriately, and repeat the Procedure beginning with "To triplicate $100-\mu \mathrm{L}$ aliquots." The test is considered valid if the regression curve has a square of the correlation coefficient ( $r^{2}$ ) not less than 0.95 ; the triplicate aliquots of the Test solution and Collagen control solution yield results that are within $20 \%$ of each other, respectively; and the average glycosaminoglycan content of the Test solution is statistically greater than the Collagen control solution using one-tailed, unequal variances, $t$-test at $\alpha=0.05$. The average glycosaminoglycan content of the Test solution is not less than $2 \mu \mathrm{~g}$ per mg.

## Metabolic activity assessment-

Dulbecco's modified Eagle's tissue culture medium-Prepare a solution that contains the components included in the following table:

|  | Content <br> (mg per L) |
| :--- | :---: |
| Calcium nitrate, tetrahydrate | 100.0 |
| Ferric nitrate, nonahydrate | 0.10 |
| Potassium chloride | 400.0 |
| Magnesium sulfate, anhydrous | 48.840 |
| Sodium chloride | $6,000.0$ |
| Sodium bicarbonate | $1,500.0$ |
| Sodium phosphate, dibasic (anhydrous) | 800.0 |


| Component | $\begin{gathered} \text { Content } \\ \text { (mg per L) } \end{gathered}$ |
| :---: | :---: |
| Glucose | 4,500.0 |
| Glutathione (reduced) | 1.0 |
| Phenol red | 5.0 |
| Sodium pyruvate | 110.0 |
| L-Arginine (free base) | 200.0 |
| L-Asparagine, monohydrate | 56.620 |
| L-Aspartic Acid | 20.0 |
| L-Cystine dihydrochloride | 65.20 |
| Aminoacetic acid | 10.0 |
| L-Histidine (free base) | 15.0 |
| Hydroxy-L-proline | 20.0 |
| L-Isoleucine | 50.0 |
| L-Leucine | 50.0 |
| L-Lysine hydrochloride | 40.0 |
| L-Methionine | 15.0 |
| L-Phenylalanine | 15.0 |
| L-Proline | 20.0 |
| L-Serine | 30.0 |
| L-Threonine | 20.0 |
| L-Tryptophan | 5.0 |
| L-Tyrosine, disodium, dihydrate | 28.830 |
| L-Valine | 20.0 |
| d-Biotin | 0.20 |
| D-Calcium pantothenate | 2.50 |
| Choline chloride | 3.0 |
| Folic acid | 1.0 |
| Inositol | 35.0 |
| Nicotinamide | 1.0 |
| p-Aminobenzoic acid | 1.0 |
| Pyridoxine hydrochloride | 1.0 |
| Riboflavin | 0.20 |


|  | Content |
| :--- | :---: |
| Component | (mg per L) |
| Thiamine hydrochloride | 1.0 |
| Cyanocobalamine | 0.0050 |

MTT reagent-Use a suitable solution of 3-(4,5-di-methylthiazol-2yl)-2,5-diphenyl tetrazolium bromide. ${ }^{4}$

Detergent reagent-Use a suitable sodium dodecyl sulfate detergent solution. ${ }^{5}$

Procedure-Remove three $12-\mathrm{mm}$ diameter circular sections of Small Intestinal Submucosa Wound Matrix, using the appropriate size biopsy punch. Immerse each section into individual wells of a 12 -well cell culture plate (dimension of each well is about 22 to 23 mm in diameter and about 17 to 18 mm in depth), each containing 1 mL of Dulbecco 's modified Eagle's tissue culture medium. Prepare a positive control by harvesting a full-thickness section of porcine jejunum immediately following slaughter. Rinse the section of jejunum in $37^{\circ}$ isotonic sodium chloride solution for 5 minutes to remove intestinal debris. Using scissors, split open the section of jejunum to form a sheet. Remove three 12mm diameter circular sections of jejunum, using the appropriate size biopsy punch. Immerse each section into individual wells of a 12 -well cell culture plate, each well containing 1 mL of Dulbecco's modified Eagle's tissue culture medium. Treat these positive control wells in the same manner as the test wells. Prepare a blank solution using 1 mL of Dulbecco's modified Eagle's tissue culture medium. Allow sections to hydrate for 5 minutes, add $50 \mu \mathrm{~L}$ of $M T T$ reagent to each of the sections and the blank, and

[^61]mix. Incubate for 3 hours at $37^{\circ}$ in an atmosphere containing $5 \%$ carbon dioxide. Add $100 \mu \mathrm{~L}$ of Detergent reagent to each well, and mix. Leave the samples at ambient temperature in the dark for 2 hours. Measure the absorbance of the resulting solution at 570 nm , adjusting for the blank. For the test to be valid, the average absorbance in the positive control wells is greater than 0.100 . The average absorbance reading for the Small Intestinal Submucosa Wound Matrix wells is less than 0.100 .

## Bioactivity-

NOTE-Aseptic cell culture techniques should be employed throughout the performance of this test.
Modified RPMI-1640 culture medium-Prepare a sterile solution that contains the components included in the following table:

| Component | Content <br> $(\mathrm{mg} \mathrm{per} \mathrm{L)}$ |
| :--- | :---: |
| Calcium chloride | 264.9 |
| Ferric nitrate, nonahydrate | 0.10 |
| Potassium chloride | 400.0 |
| Magnesium sulfate, heptahydrate | 200.0 |
| Sodium chloride | $6,400.0$ |
| Sodium bicarbonate | $3,700.0$ |
| Sodium phosphate, monobasic, | 125.0 |
| $\quad$ monohydrate | $4,500.0$ |
| Glucose | 15.0 |
| Phenol red | 110.0 |
| Sodium pyruvate | 84.0 |
| L-Arginine hydrochloride | 48.0 |
| L-Cystine | 30.0 |
| Aminoacetic acid | 42.0 |
| L-Histidine hydrochloride, monohy- |  |
| drate | 104.8 |
| L-Isoleucine | 104.8 |
| L-Leucine |  |


|  | Content <br> (mg per L) |
| :--- | :---: |
| L-Lysine hydrochloride | 146.2 |
| L-Methionine | 30.0 |
| L-Phenylalanine | 66.0 |
| L-Serine | 42.0 |
| L-Threonine | 95.2 |
| L-Tryptophan | 16.0 |
| L-Tyrosine | 72.0 |
| L-Valine | 93.6 |
| L-Calcium pantothenate | 4.0 |
| Choline chloride | 4.0 |
| Folic acid | 4.0 |
| Inositol | 7.0 |
| Nicotinamide | 4.0 |
| Pyridoxine hydrochloride | 4.0 |
| Riboflavin | 0.40 |
| Thiamine hydrochloride | 4.0 |
| Sodium 1-heptanesulfonic acid | 2383.0 |

Penicillin-streptomycin solution-Prepare a suitable buffered solution containing 10,000 USP Penicillin Units of penicillin per mL and 10 mg of streptomycin per $\mathrm{mL} .{ }^{6}$
PC12 cell line culture medium-Mix 420 mL of Modified RPMI-1640 culture medium, 50 mL of horse serum, ${ }^{7} 25 \mathrm{~mL}$ of fetal bovine serum, ${ }^{8}$ and 5 mL of Penicillin-streptomycin solution. Sterilize by passing through a $0.22-\mu \mathrm{m}$ filter.

[^62]Sterile PBS solution-Prepare as described under Glycosaminoglycan content.
Rat tail collagen solution-Prepare a suspension containing 0.2 mg of rat tail collagen, type I , in sterile water.

Cell culture apparatus-Prepare by adding a sufficient volume of Rat tail collagen solution to completely cover the bottom of each well of a 12 -well cell culture plate (dimension of each well is about 22 to 23 mm in diameter and about 17 to 18 mm in depth). Incubate under sterile conditions for 2 hours at $37^{\circ}$ or overnight at room temperature. Remove the Rat tail collagen solution by aspiration. Rinse with sterile PBS solution that has been preheated to $37^{\circ}$.

PC12 cells-Use cultured rat pheochromocytoma cells (ATCC CRL-1721).

Cultivation of PC12 cells-Starting from a frozen culture, prewarm PC12 cell line culture medium to $37^{\circ}$. Add 15 mL of prewarmed PC12 cell line culture medium to a T-75 culture flask. Place a single vial containing the frozen PC12 cells in a $37^{\circ}$ water bath with gentle agitation until they start to thaw (about 1 minute). Complete the thawing procedure by slowly rotating the vial between the hands. Rinse the outside of the vial with $70 \%$ ethanol. Transfer the contents of the vial to the T-75 flask, and mix. Incubate the cells overnight at $37^{\circ}$ in a $5 \%$ carbon dioxide atmosphere. Transfer the contents of the T-75 culture flask to a sterile centrifuge tube, centrifuge at $200 \times g$ for 5 minutes at $37^{\circ}$, and discard the supernatant. Resuspend the cells in 15 mL of PC12 cell line culture medium, and transfer the contents back into the T-75 culture flask. Incubate the cells at $37^{\circ}$ in a $5 \%$ carbon dioxide atmosphere for 3 days.

Cell feeding-At the end of 3 days, the cells will need to be fed for optimal growth. To feed the cells, remove a flask of cells from the incubator, tightening the cap in the process. Examine the T-75 flask under the microscope and check for microbial contamination and confluency. If there is microbi-
al contamination, then discard the flask. If the cells appear confluent, follow the instructions below for perpetuating the PC12 cell line (see Culture perpetuation). Otherwise, harvest the cells from the flask by pipeting the contents of the flask across the bottom of the flask several times. Transfer the cell suspension to a sterile $50-\mathrm{mL}$ centrifuge tube. Centrifuge the cells at $200 \times g$ for 5 minutes at $37^{\circ}$, and discard the supernatant. Resuspend the cells in 13 mL of PC12 cell line culture medium, prewarmed to $37^{\circ}$. Transfer the cell suspension back to the T-75 flask, and mix. Loosen the cap of the flask, and return to the incubator; incubate the cells at $37^{\circ}$ in a $5 \%$ carbon dioxide atmosphere for another 3 to 7 days.

Culture perpetuation-To perpetuate a line of PC12 cells for culture, examine under the microscope a T-75 flask containing cells and check for microbial contamination and confluency. If there is microbial contamination, discard the flask and use another. If the cells do not appear confluent, then follow the instructions above for feeding the PC12 cell line (see Cell feeding), beginning with "Otherwise, harvest the cells from the flask by pipeting the contents of the flask across the bottom of the flask several times." If the cells are confluent and there is no contamination, harvest the cells from the flask by pipeting the contents of the flask across the bottom of the flask several times to loosen up the cells from their attachment to the bottom of the flask and to break up cell clusters. Check under the microscope prior to proceeding to insure that most of the cells have detached from the plastic. Transfer the cell suspension to a sterile $50-\mathrm{mL}$ centrifuge tube, and centrifuge the cells at $200 \times$ $g$ for 5 minutes at $37^{\circ}$. Discard the supernatant and resuspend the cells with 10 mL of PC12 cell line culture medium, prewarmed to $37^{\circ}$. Dispense an equal amount of the cell suspension into each of 3 to 5 T-75 flasks, each flask containing 10 mL of PC12 cell line culture medium, prewarmed to $37^{\circ}$,
and mix. Return the passed cells to the incubator, being sure to loosen the cap of the flasks. Incubate the cells at $37^{\circ}$ in a $5 \%$ carbon dioxide atmosphere. Feed the cells after three days as directed above, beginning with "To feed the cells, remove a flask of cells from the incubator, tightening the cap in the process." [NOTE-To perform the test for Bioactivity, cells that have undergone more than 15 passages after obtaining them from ATCC should not be used.]

Positive control solution-Prepare a solution containing about 10 ng of fibroblast growth factor-2 per mL of PC12 cell line culture medium.

Negative control solution-Use PC12 cell line culture medium.

Test solution-Immerse $70 \mathrm{~cm}^{2}$ of Small Intestinal Submucosa Wound Matrix in sterile water for 5 minutes. Remove the Small Intestinal Submucosa Wound Matrix, and blot excess water using sterile gauze. Weigh the rehydrated Small Intestinal Submucosa Wound Matrix to the nearest 0.1 g and add Modified RPMI-1640 culture medium at a ratio of 7.5 mL of Modified RPMI-1640 culture medium for each 1.0 g of Small Intestinal Submucosa Wound Matrix. Incubate for 24 hours at $37^{\circ}$ with constant shaking. Remove the Small Intestinal Submucosa Wound Matrix, and pass the solution through a $0.22-\mu \mathrm{m}$ filter. Add sufficient quantities of sterile horse serum and sterile fetal bovine serum to concentrations of $10 \%$ and $5 \%$, respectively, and add a sufficient quantity of Penicillin-streptomycin solution such that there are 100 USP Penicillin Units and 0.1 mg of streptomycin per mL. Adjust the pH of the Test Solution to 7.4, using a sterile solution of either 1.0 M sodium hydroxide or 1.0 M hydrochloric acid.

Procedure-Harvest a flask of confluent PC12 cells by centrifuging at $200 \times g$ for 5 minutes. Remove the supernatant by aspiration, and resuspend the pellet to obtain a concentration of about $1 \times 10^{6}$ cells per mL of PC12 cell
line culture medium. Add to each of three wells of the Cell culture apparatus 1.0 mL of Negative control solution. To a second set of three wells add to each 1.0 mL of Positive control solution, and to a third set of three wells add to each 1.0 mL of Test solution. Add to each well about 20,000 cells, mix by gentle rocking, and incubate for 48 hours at $37^{\circ}$. For each well, count 3 random microscopic fields of cells using a microscope with a $10 \times$ ocular lens and a $20 \times$ objective lens. Each field should have at least 20 cells; avoid large clumps of cells where individual cell bodies cannot be ascertained. Determine the total number of cells in the field and, using USP Cultured Rat Pheochromocytoma Reference Photomicrographs of normal and differentiated rat pheochromocytoma cells for comparison, determine the total number of cells that have formed at least one neurite-like extension at least twice the diameter of a normal, undifferentiated cell body. For each experimental group, record the total number of cells counted and the total number of cells differentiated across all three wells, and calculate the total percentage of cells that have differentiated. For a test to be valid, the following criteria must be met: (1) none of the wells are microbially contaminated; (2) the weighted percentage of differentiated cells across the Negative control solution wells is less than $5 \%$; (3) the weighted percentage of differentiated cells across the Positive control solution wells is greater than $6 \%$; and (4) the weighted percentage of differentiated cells across the Negative control solution wells is statistically less than the weighted percentage of differentiated cells across the Positive control solution wells, using a one-sided, two-sample test for proportions at $\alpha=0.05$. The weighted percentage of differentiated cells incubated in the Test solution wells is statistically greater than those incubated in the Negative control solution wells, using a one-sided, two-sample test for proportions at $\alpha=0.05 \cdot \mathbf{\Delta U S P 2 8}$

Zinc Sulfide Topical Suspension-See briefing under Amphotericin B Lotion.
(NL: C. Barnstein) RTS-40809-1

## Add the following:

## ©Zinc Sulfide Topical Suspension <br> (Monograph under this new title-to become official July 1, 2007) <br> (Current monograph title is White Lotion)

» Prepare Zinc Sulfide Topical Suspension as follows:

$$
\begin{array}{ll}
\text { Zinc Sulfate. . . . . . . . . . . . . . . . . . . . . . . . } & 40 \mathrm{~g} \\
\text { Sulfurated Potash. . . . . . . . } \\
\hline 0 \mathrm{~g}
\end{array}
$$

Purified Water, a sufficient quantity, to make

1000 mL

Dissolve the Zinc Sulfate and the Sulfurated Potash separately, each in 450 mL of Purified Water, and filter each solution. Add the sulfurated potash solution slowly to the zinc sulfate solution with constant stirring. Then add the required amount of Purified Water, and mix.

NOTE-Prepare the Topical Suspension fresh, and shake it thoroughly before dispensing.

Packaging and storage-Dispense in tight containers. $\triangle$ USP28
(Official July 1, 2007) MONOGRAPHS


#### Abstract

BRIEFING Chaste Tree, page 1264 of $P F$ 29(4) [July-Aug. 2003]. On the basis of comments received, it is proposed to revise the previously proposed thin-layer chromatographic procedure in the test for Identification. It is also proposed to revise the test for Loss on drying to include drying conditions omitted in the original monograph. (DSB: G. Giancaspro) RTS-40335-1


## Add the following:

© Chaste Tree
» Chaste Tree consists of the dried ripe fruits of Vitex agnus-castus L. (Fam. Verbenaceae). It contains not less than 0.05 percent of agnuside and not less than 0.08 percent of casticin, calculated on the dried basis.

Packaging and storage-Store Preserve in a well-closed light resistant container, protectere frem meisture and store at controlled room temperature.

Labeling-The label states the Latin binomial and, following the official name, the part of the plant contained in the article.

USP Reference standards $\langle 11\rangle —$ USP Agnuside RS. USP Casticin RS. USP Powdered Chaste Tree Extract RS.

## Botanic characteristics-

Macroscopic-Mature chaste tree fruits are spherical to ovoid, 2 to 4 mm in diameter, very hard, usually with a short pedicil. The fruit is reddish brown to black, slightly rough,
and covered with glandular hairs. There are four grooves perpendicular to one another, and a slight depression on the apex, more evident on large fruits. The internal appearance of the fruit is yellowish. The internal structure of the fruit includes four compartments, each containing an oblong seed with a high fat content. A group of up to six spongy, light tan, immature fruits also accompanies mature fruits. The fruit is often covered by a tubular, greenish gray, fine tomentous calyx, which is persistent and has five teeth.

Microscopic-The exocarp is brown and narrow, consisting of parenchymatous cells with thin walls and partially lignified cells with many pitted thickenings on the inside. In surface view, the exocarp shows an epidermis of polygonal cells with irregular thickenings and glandular hairs, each with a short single-celled stalk and a four-celled head containing essential oil. The outer mesocarp consists of several layers of brown, isodiametric parenchyma cells. The inner mesocarp consists of finely pitted sclerenchymatous cells, some with moderately thickened walls, others consisting of isodiametric stone cells with small lumen. The endocarp consists of a layer of small brown sclereid cells. The seeds are small, having large cotyledons surrounded by thinwalled large parenchymatous cells that have ribbed thickenings. The nutritive tissue and the cells of the germ contain aleuron grains and oil globules. Starch is absent. The outer epidermis of calyx is composed of polygonal cells, covered by abundant unicellular or multicellular curved trichomes. The inner epidermis of calyx is glabrous and composed of rectangular, elongated cells with slightly wavy walls.

## Change to read:

## Identification-

${ }^{\boldsymbol{4}}$ A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -

Test solution-Transfer about 1 g of the powdered plant material to a screw-capped centrifuge tube. Add 10 mL of methanol, and heat in a water bath at $60^{\circ}$ for 10 to 15 minutes, cool, and filter. Apply $60 \mu \mathrm{~L}$ to the plate in bands that are 2 cm in length.

Standard solution-Transfer about 100 mg of USP Powdered Chaste Tree Extract RS to a screw-capped centrifuge tube. Add 1 mL of methanol, and heat in a water bath at $60^{\circ}$ for 10 minutes. Centrifuge, and use the clear supernatant. Apply 20 to -30 $90 \mu \mathrm{~L}$ to the plate.

Developing solvent system-Use the upper phase of a mixture of ethyl acetate, methanol, and water (77:15:8).

Spray reagent-Prepare a solution of $p$-dimethylaminobenzaldehyde in 1 N hydrochloric acid containing 10 mg per mL.
Procedure-Develop the chromatogram to a length of not less than 1812 cm , and dry the plate in a current of air. Spray the plate with Spray reagent, and heat for 10 minutes at $120^{\circ}$. The chromatogram obtained from the Test solution shows the following: a blue zone (at an $R_{F}$ value of about 0.21 ) thans pink in due to the presence of aucubin and that corresponds in color and $R_{F}$ value to a similar zone in the chromatogram of the Standard solution; a blue zone (at an $R_{F}$ value of about 0.44 ) turns pink in time as a result of the presence of agnuside and that corresponds in color and $R_{F}$ value to a similar zone in the chromatogram of the Standard solution; ene yellow zone at an $R_{F}$ value that is between that of agnuside and auteubin and correspends in eolor and $R_{\text {I }}$ value to a similar zone in the chromatogram of the Stactar solution; and one yellowish-green zone (above ablue zone) that is near the broad zone, violet in the middle,
that is near to the solvent front and that corresponds in color and $R_{F}$ value to a similar zone in the chromatogram of the Standard solution. Other colored zones of varying intensities may be observed in the chromatogram of the Test solution.

B: ${ }_{\Delta U S P 28}$ The chromatogram of the Test solution in the test for Content of casticin shows a peak at the retention time corresponding to the casticin peak in the chromatogram of the Standard solution.

Microbial limits $\langle 2021\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total aerobic microbial count does not exceed $10^{6}$ per g , the total combined molds and yeast count does not exceed $10^{4}$ per $g$, and the enterobacterial count does not exceed $10^{3}$.

## Change to read:

Loss on drying $\langle 731\rangle-{ }^{\Delta}$ Dry 1 g at $105^{\circ}$ for 2 hours. It $\operatorname{loses}_{\mathbf{\Delta U S P 2 8}}$ not more than $10.0 \%$.

Foreign organic matter $\langle 561\rangle$ : not more than $3.0 \%$.
Total ash $\langle 561\rangle$ : not more than $8.0 \%$.
Acid-insoluble ash $\langle 561\rangle$ : not more than $2.0 \%$.
Pesticide residues $\langle 561\rangle$ : meets the requirements.
Heavy metals, Method III $\langle 231\rangle$ : not more than $20 \mu \mathrm{~g}$ per g.

## Content of casticin-

Solution $A$-Use filtered and degassed methanol.
Solution B—Use a filtered and degassed solution of 5.88 g of phosphoric acid in 1000 mL of water.

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Casticin RS in methanol, with sonication. Dilute quantitatively, and stepwise if necessary, with metha-
nol to obtain a solution having a known concentration of about 0.05 mg per mL . Filter through a cellulose membrane having a $0.45-\mu \mathrm{m}$ or finer porosity.

Test solution-Accurately weigh approximately 1000 mg of ground plant material, and place in a suitable container with stopper. Extract twice with 40 mL of methanol, using a hand homogenizer at $19,000 \mathrm{rpm}$ for 2 minutes. Filter each supernatant, and transfer to a $250-\mathrm{mL}$ round-bottom flask. Rinse the residue with methanol, and filter the resulting solution into the flask. Evaporate the combined extract to dryness. Dissolve the residue in methanol, quantitatively transfer to a $20-\mathrm{mL}$ volumetric flask, and dilute with methanol to volume. Filter through a cellulose membrane having a $0.45-\mu \mathrm{m}$ or finer porosity.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $348-\mathrm{nm}$ detector and a $3.1-\mathrm{mm} \times 12.5-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The column temperature is maintained at $25^{\circ}$. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 50 | 50 | equilibration |
| $0-13$ | $50 \rightarrow 65$ | $50 \rightarrow 35$ | linear gradient |
| $13-18$ | $65 \rightarrow 100$ | $35 \rightarrow 0$ | linear gradient |
| $18-23$ | $100 \rightarrow 50$ | $0 \rightarrow 50$ | linear gradient |

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor for casticin is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas of the analyte peaks. Identify the retention time of the peak corresponding to casticin in the Test solution by com-
parison with the chromatogram of the Standard solution. Calculate the percentage of casticin in the portion of Chaste Tree taken by the formula:

$$
2000(C / W)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Casticin RS in the Standard solution; $W$ is the weight, in mg, of the Chaste Tree taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses of casticin obtained from the Test solution and the Standard solution, respectively.

## Content of agnuside-

Solvent: a mixture of water and methanol (95:5).
Solution $A$-Use filtered and degassed acetonitrile.
Solution B-Use a filtered and degassed solution of 5.88 g of phosphoric acid in 1000 mL of water.
Standard solution-Dissolve an accurately weighed quantity of USP Agnuside RS in Solvent, with sonication. Dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.125 mg per mL . Filter through a cellulose membrane having a $0.45-\mu \mathrm{m}$ or finer porosity.

Test solution-Accurately weigh approximately 1000 mg of ground plant material, and place in a suitable container with a stopper. Extract twice with 40 mL of methanol, using a hand homogenizer at $19,000 \mathrm{rpm}$ for 2 minutes. Centrifuge, and transfer each supernatant to a $250-\mathrm{mL}$ round-bottom flask. Rinse the residue with methanol, and filter the resulting solution into the flask. Evaporate the combined extract to dryness, and dissolve the residue in 2 mL of Solvent. Quantitatively transfer the solution to a solid-phase extraction cartridge packed with neutral aluminum oxide previously conditioned with 5 mL of Solvent. Connect the cartridge to a vacuum pressure not exceeding 300 mbar , and collect the eluate. Rinse the round-bottom flask with 2 mL of Solvent, and pass this solution through the cartridge, apply the vacuum, and collect the eluate. Rinse the cartridge
with 4 mL of Solvent, and collect the eluate. Combine the eluates from the cartridge, transfer to a $10-\mathrm{mL}$ volumetric flask, and dilute with Solvent to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a $258-\mathrm{nm}$ detector and a $3.1-\mathrm{mm} \times 12.5-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The column temperature is maintained at $25^{\circ}$. The flow rate is about 1.3 mL per minute. The chromatograph is programmed as follows.

| Time | Solution A <br> (minutes) | Solution B <br> $(\%)$ |  |
| :---: | :---: | :---: | :--- |
| 0 | 7 | 93 | Elution |
| $0-0.6$ | $7 \rightarrow 10$ | $93 \rightarrow 90$ | equilibration |
| $0.6-5$ | 10 | 90 | linear gradient |
| $5-7$ | $10 \rightarrow 14$ | $90 \rightarrow 86$ | linear gradient |
| $7-13$ | $14 \rightarrow 15$ | $86 \rightarrow 85$ | linear gradient |
| $13-13.1$ | $15 \rightarrow 100$ | $85 \rightarrow 0$ | linear gradient |
| $13.1-18$ | 100 | 0 | isocratic |
| $18-18.1$ | $100 \rightarrow 7$ | $0 \rightarrow 93$ | linear gradient |
| $18.1-23$ | 7 | 93 | re-equilibration |

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor for agnuside is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas of the analyte peaks. Identify the retention time of the peak corresponding to agnuside in the the Test solution by comparison with the chromatogram obtained from the Standard solution. Calculate the percentage of agnuside in the portion of Chaste Tree taken by the formula:

$$
1000(C / W)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Agnuside RS in the Standard solution; $W$ is the weight, in mg , of the Chaste Tree taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses of agnuside obtained from the Test solution and the Standard solution, respectively..1S (USP27)

## Briefing

Horse Chestnut, USP 27 page 2016; Powdered Horse Chestnut Extract, USP 27 page 2017. It is proposed to revise the test for Loss on drying to add previously omitted drying conditions.
(DSB: G. Giancaspro) RTS-40884-1

## Change to read:

Loss on drying $\langle 731\rangle$ :
${ }^{\boldsymbol{4}}$ Dry it at $105^{\circ}$ for 2 hours. It loses ${ }_{\triangle U S P 28}$ not more than $10.0 \%$.

## Briefing

Powdered Horse Chestnut Extract, USP 27 page 2017—See briefing under Horse Chestnut.
(DSB: G. Giancaspro) RTS-40884-2

Change to read:
Loss on drying $\langle 731\rangle$ :
${ }^{\boldsymbol{\Delta}}$ Dry 1 g at $105^{\circ}$ for 2 hours. It loses ${ }_{\Delta U S P 28}$ not more than $5.0 \%$.

## BRIEFING

Red Clover, USP 27 page 1983; Powdered Red Clover Extract, USP 27 page 1984. On the basis of comments received, the following revisions are proposed: the text of the Developing solvent system under Identification test $A$ is revised; drying conditions previously omitted in the Loss on drying test are added; in the test for Content of isoflavones the Standard preparation is revised, and in the Procedure the volume of injection is reduced due to overload of some UV detectors.
(DSB: G. Giancaspro) RTS—39793-1

## Change to read:

## Identification-

A: Thin-layer chromatographic identification test $\langle 201\rangle$ -
Test solution-Transfer about 1 g of the powdered plant material to a screw-capped centrifuge tube. Add 10 mL of a mixture of methanol and water ( $6: 4$ ), heat in a steam bath for 10 to 15 minutes, cool, and filter. Apply 20 to $30 \mu \mathrm{~L}$ to the plate in bands that are 2 cm in length.

Standard solution-Transfer about 100 mg of USP Powdered Red Clover Extract RS to a screw-capped centrifuge tube. Add 1 mL of a mixture of alcohol and water (7:3), and heat in a steam bath for 10 minutes. Centrifuge, and use the clear supernatant. Apply 20 to $30 \mu \mathrm{~L}$ to the plate.

Developing solvent system-Use the toper phase of

- $\Delta U S P 28$
a mixture of ethyl acetate, water, formic acid, and glacial acetic acid (100:27:11:11).

Spray reagent A-Prepare a solution of 2-aminoethyl diphenylborinate in methanol containing 10 mg per mL .

Spray reagent $B$-Prepare a solution of polyethylene glycol 4000 in alcohol containing 50 mg per mL .

Procedure-Develop the chromatogram to a length of not less than 18 cm , and dry the plate in a current of air. Spray the plate with Spray reagent $A$ followed by Spray reagent B, and examine the plate under UV light at 365 nm : the chromatogram obtained from the Test solution shows a blue zone at an $R_{F}$ value of about 0.7 that corresponds in color and $R_{F}$ value to that in the chromatogram obtained from the Standard solution; one yellowish green zone at an $R_{F}$ value of about 0.55 corresponding in color and $R_{F}$ value to that in the chromatogram obtained from the Standard solution; and one yellowish orange zone at an $R_{F}$ value of about 0.50 corresponding in color and $R_{F}$ value to that in the chromatogram of the Standard solution. Other colored zones of varying intensities may be observed in the chromatogram obtained from the Test solution.

B: The chromatogram of the Test solution exhibits peaks for daidzein, genistein, formononetin, and biochanin A at retention times that correspond to those in the chromatogram of the Standard solution, as obtained in the test for Content of isoflavones. Calculate the ratio of 5,7-dihydroxyisoflavones to 7-hydroxyisoflavones by the formula:

$$
(B+G) /(D+F),
$$

in which $B, G, D$, and $F$ are the percentages of biochanin A, genistein, daidzein, and formononetin, respectively, as obtained in the test for Content of isoflavones: the ratio is between 0.1 and 10 .

## Change to read:

Loss on drying $\langle 731\rangle$ :
${ }^{\Delta}$ Dry 1 g at $105^{\circ}$ for 2 hours. It loses $\mathbf{\Delta U S P 2 8 ~}$ not more than $12.0 \%$.

## Change to read:

## Content of isoflavones-

Solvent: a mixture of alcohol and water (1:1).
Solution A-Prepare a filtered and degassed mixture of water and acetonitrile ( $75: 25$ ) containing $0.05 \%$ trifluoroacetic acid.

Solution B-Use filtered and degassed acetonitrile containing $0.05 \%$ trifluoroacetic acid.

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution 1 - Pissolve an aceurately weighed quantity of USP Powdered Red Clover Extract PS in 2 N hydrechloric acid ( 0.5 mL per each mg of Extract) with shaking for 1 minute and heating in a water bath for 30 minutes. Dilute with Solvent to ob tain a solution having a known concentration of about 0.5 mg per mL . Filter through a membrane having a $0.45 \mu \mathrm{~m}$ or finer porosity.
${ }^{\Delta}$ Transfer an accurately weighed quantity of USP Powdered
Red Clover Extract RS, equivalent to about 30 mg of the labeled content of isoflavones, to a $250-\mathrm{mL}$ volumetric flask. Add 15 mL of dehydrated alcohol, sonicate until dissolved, dilute with Solvent to volume, and mix. Transfer 50.0 mL of this solution to a round-bottom flask, and evaporate to dryness under vacuum. Add 15 mL of 2 N hydrochloric acid, and heat in a water bath for 30 minutes. Quantitatively transfer the resulting solution with the aid of about 15 mL of alcohol, to a $50-\mathrm{mL}$ volumetric flask, and dilute with Solvent to volume. Centrifuge, or filter through a membrane having a $0.45-\mu \mathrm{m}$ or finer porosi-

## ty. $\mathbf{\text { Standa }}$

Standard solution 2-Dissolve an accurately weighed quantity of USP Formononetin RS in a mixture of $n$-propanol and water (1:1) with sonication. Dilute quantitatively, and stepwise if necessary, with the mixture of $n$-propanol and water (1:1) to obtain a solution having a known concentration of about 0.1 mg per mL . Filter through a membrane having a $0.45-\mu \mathrm{m}$ or finer porosity.

Test solution-Accurately weigh approximately 2500 mg of ground plant material, and place in a $120-\mathrm{mL}$ flask with a stopper. Add exactly 100 mL of Solvent, close the flask, and shake on an orbital or wrist-action shaker for not less than 12 hours. Transfer 50.0 mL of this solution to a round-bottom flask, and evaporate to dryness under vacuum
© at about $40^{\circ} \cdot \mathbf{\Delta U S P 2 8}$
Add 15 mL of 2 N hydrochloric acid, and heat in a water bath for 30 minutes. Quantitatively transfer this solution with the aid of about 15 mL of alcohol, to a $50-\mathrm{mL}$ volumetric flask, and dilute with Solvent to volume. Filter through a membrane having a $0.45-\mu \mathrm{m}$ or finer porosity, discarding the first 4 mL of the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains end-packed $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at $45^{\circ}$. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-2$ | 100 | 0 | isocratic |
| $2-2.5$ | $100 \rightarrow 87$ | $0 \rightarrow 13$ | linear gradient |
| $2.5-7.5$ | $87 \rightarrow 80$ | $13 \rightarrow 20$ | linear gradient |
| $7.5-7.8$ | $80 \rightarrow 73$ | $20 \rightarrow 27$ | linear gradient |
| $7.8-8.0$ | $73 \rightarrow 55$ | $27 \rightarrow 45$ | linear gradient |
| $8.0-11.0$ | $55 \rightarrow 50$ | $45 \rightarrow 50$ | linear gradient |
| $11.0-13.0$ | $50 \rightarrow 40$ | $50 \rightarrow 60$ | linear gradient |
| $13.0-15.0$ | $40 \rightarrow 26$ | $60 \rightarrow 74$ | linear gradient |
| $15.0-16.0$ | $26 \rightarrow 0$ | $74 \rightarrow 100$ | linear gradient |
| $16.0-18.1$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $18.1-23.0$ | 100 | 0 | isocratic |

Chromatograph Standard solution 1, and record the peak responses as directed for Procedure: the chromatograms obtained are similar to the Reference Chromatogram provided with the USP Powdered Red Clover Extract RS; the tailing factor for formononetin is not more than 2.0; and the relative standard deviation for replicate injections of Standard solution 1 is not more than $2.0 \%$.

Procedure-Separately inject equal volumes $20 \mu \mathrm{~L}$ )
${ }^{\Delta}$ (about $\left.10 \mu \mathrm{~L}\right)_{\mathbf{\Delta S P P 2 8}}$
of Standard solution 1, Standard solution 2, and the Test solution into the chromatograph, record the chromatograms, and measure the areas of the analyte peaks. Identify the retention times of the peaks corresponding to daidzein, genistein, formononetin, and biochanin A by comparison of the chromatogram of Standard solution $l$ with that obtained from the Reference Chromatogram. Separately calculate the percentages of daidzein, genistein, formononetin, and biochanin A in the portion of Red Clover taken by the formula:

$$
50 F(C / W)\left(r_{U} / r_{S}\right)
$$

in which $F$ is the conversion factor for each analyte ( 0.97 for daidzein, 1.13 for genistein, 1.00 for formononetin, and 1.05 for bioachanin A); $C$ is the concentration, in mg per mL , of USP Formononetin RS in Standard solution 2; $W$ is the weight, in g, of Red Clover taken to prepare the Test solution; ${ }^{\mathbf{\Delta}} r_{U}$ is the peak response for each relevant isoflavone obtained from the Test solution; and $r_{S}$ is the peak response for formononetin obtained from Standard solution 2. $\mathbf{\Delta U S P 2 7}$

## BRIEFING

Powdered Red Clover Extract-See briefing under Red Clover.
(DSB: G. Giancaspro) RTS-39793-2

## Change to read:

Loss on drying $\langle 731\rangle$ :
${ }^{\mathbf{\Delta}}$ Dry 1 g at $105^{\circ}$ for 2 hours. It loses $\mathbf{\Delta U S P 2 8}$ not more than $5.0 \%$.

## BRIEFING

Echinacea angustifolia, USP 27 page 1987 and page 1578 of $P F$ 26(6) [Nov.-Dec. 2000]. Changes in the Definiton are proposed according to data received indicating that the appropriate level of markers are reached after 1 year of growth. Since there is some confusion in the literature about the correct isomer of cynarin known to be present in E. angustifolia roots, it is proposed to change the name cynarin(e) to dicaffeoylquinic acids in order to describe more accurately the markers intended to be used as positive identifiers of E. angustifolia. The peak of one of the isomers of dicaffeoylquinic acids known as cynarin(e) elutes just before the retention time corresponding to echinacoside. Yet, another regioisomer might be found in E. angustifolia having a similar retention time to chicoric acid in the Chromatographic system used in the test for Content of total phenols. It is proposed to modify the visualization of the spots in the TLC identification test for alkamides according to comments received. Drying conditions previously omitted are now added. A typographical error in the requirement for $k^{\prime}$ is corrected in the test for Content of total phenols.
(DSB: G. Giancaspro) RTS—32588-1; 32989-1; 40843-1

## Change to read:

» Echinacea angustifolia consists of the dried rhizome and roots of Echinacea angustifolia DC. (Fam. Asteraceae). It is harvested in the fall after 3
${ }^{\Delta} 1_{\Delta U S P 28}$
or more years of growth. It contains not less than 0.5 percent of total phenols, calculated on the dried basis as the sum of caftaric acid $\left(\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{O}_{9}\right)$, chicoric acid $\left(\mathrm{C}_{22} \mathrm{H}_{18} \mathrm{O}_{12}\right)$, chlorogenic acid $\left(\mathrm{C}_{16} \mathrm{H}_{18} \mathrm{O}_{9}\right)$, dicaffeoylquinic acids $\left(\mathrm{C}_{25} \mathrm{H}_{24} \mathrm{O}_{12}\right)$, and echinacoside $\left(\mathrm{C}_{35} \mathrm{H}_{46} \mathrm{O}_{20}\right)$. It contains not less than 0.075 percent of dodecatetraenoic acid isobutylamides $\left(\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{NO}\right)$
${ }^{\Delta}$ on the dried basis. ${ }_{\text {©USP28 }}$

## Change to read:

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle-$
PRESENCE OF ECHINACOSIDE AND EYNAPINE

## ${ }^{\text {T}}$ DICAFFEOYLQUINIC ACIDS (CYNARIN(E) $)_{\Delta U S P 28}$

Test solution-Weigh and finely pulverize about 10 g of Echinacea angustifolia, and transfer 1 g of the powder to a suitable extraction thimble. Transfer the thimble to a continuous extraction apparatus, and extract with 50 mL of chloroform for 1 hour. Retain the chloroform extract for Identification test $B$. Continue the extraction with 50 mL of methanol, and concentrate to a small volume at $40^{\circ}$ in vacuum. With the aid of methanol, transfer the extract to a $10-\mathrm{mL}$ volumetric flask, and dilute with methanol to volume.
Standard solution 1-Dissolve an accurately weighed quantity of USP Powdered Echinacea angustifolia Extract RS in methanol to obtain a solution having a concentration of about 10

## ${ }^{\Delta} 20$ © $U S P 28$ <br> mg per mL .

Standard solution 2-Dissolve an accurately weighed quantity of eynatine
$\Delta_{1,3-d i c a f f e o y l q u i n i c ~ a c i d ~}^{\triangle U S P 28}$
in methanol to obtain a solution having a concentration of about 1 mg per mL .

Developing solvent system-Prepare a mixture of ethyl acetate, formic acid, and water (17:2:1).

Spray reagent 1 -Dissolve a suitable quantity of diphenylborinic acid, ethanolamine ester in methanol to obtain a solution having a concentration of about 10 mg per mL .

Spray reagent 2-Dissolve a suitable quantity of polyethylene glycol 4000 in alcohol to obtain a solution having a concentration of about 50 mg per mL .

Procedure-Proceed as directed in the chapter. Develop the chromatograms in Developing solvent system until the solvent front has moved not less than 18

- $12_{\mathbf{4} U S P 28}$
cm , and dry the plate in a current of air. Spray the plate with Spray reagent 1 followed by Spray reagent 2, and examine the plate under UV light at 365 nm : the chromatogram obtained from the Test solution shows a yellowish zone at an $R_{F}$ value of 0.14 characteristic of echinacoside (absent or only traces present in Echinacea purpurea) that corresponds in color and $R_{F}$ value to that in the chromatogram of Standard solution 1, and another zone characteristic of eynarine
© 1,3-dicaffeoylquinic acid
(absent in Echinacea pallida and and Echinacea purpurea) corresponding in color and $R_{F}$ value
© $\Delta U S P 28$
to that in the chromatogram of Standard solution 2. Other colored zones of varying intensities may be observed in the chromatogram of the Test solution.
B: Thin-Layer Chromatographic Identification Test $\langle 201\rangle-$
PRESENCE OF ISOBUTYLALKENYLAMIDES-
Test solution-Evaporate the chloroform extract retained from preparation of the Test solution in Identification test $A$ to dryness at $40^{\circ}$ in vacuum. To the residue, add 1 mL of alcohol, and pass through a nylon membrane filter having a porosity of $0.45 \mu \mathrm{~m}$.

Standard solution 1-Transfer an accurately weighed quantity of USP Powdered Echinacea angustifolia Extract RS to a centrifuge tube, and add chloroform to obtain a solution having a known concentration of about 40

- 100 aUSP28
mg per mL . Shake by hand to disperse, sonicate for 5 minutes, and centrifuge. Use the supernatant.

Standard solution 2-Dissolve an accurately weighed quantity of $\beta$-sitosterol in methanol to obtain a solution having a concentration of about 1 mg per mL .

Developing solvent system-Prepare a mixture of hes
${ }^{\Delta}$ hexane ${ }_{\mathbf{A U S P 2 8}}$
and ethyl acetate (2:1).
Spray reagent-Prepare a mixture of glacial acetic acid, sulfuric acid, and $p$-anisaldehyde (10:5:0.5)
${ }^{\boldsymbol{\Delta}}$ in an ice bath. $\mathbf{\Delta U S P 2 8}$
Procedure-Proceed as directed in the chapter. Develop the chromatograms in Developing solvent system until the solvent front has moved not less than 18

- 12 aUSP28
cm , and dry the plate in a current of air. Spray the plate with Sprety feagent, and examine
${ }^{\Delta}$ Examine ${ }_{\text {ASP } 28}$
the plate under UV light at 254 nm : the chromatogram obtained from the Test solution shows one main zone at an $R_{F}$ value of $\theta .5$
$\Delta_{\text {about }} 0.25 \boldsymbol{\Delta U S P} 28$
due to $2 E, 4 E, 8 Z, 10 E$-dodecatetraenoic acid isobutylamide and do-deca- $2 E, 4 E, 8 Z, 10 Z$-tetraenoic acid isobutylamide (absent in $E$. pallida) that corresponds in $R_{F}$ value to that in the chromatogram of Standard solution 1., and another zone dete $\beta$ sitosterel that eerrespends in $R_{F}$ value to the primeipal spet in the chremategram of Standard solution 2.
© UUSP28
Spray the plate with Spray reagent, and then heat the plate at $100^{\circ}$ for 5 minutes: the chromatogram obtained from the Test solution shows
$\Delta_{\text {a }}$ zone due to $\beta$-sitosterol that corresponds in $R_{F}$ value to
the principal spot in the chromatogram of Standard solution
2, below this spot, there is $\mathbf{\Delta U S P 2 8}$
a blue black
4 USP28
zone at an $R_{F}$ value of 0.5
$\Delta$
due to dodeca-2E, $4 E, 8 Z, 10 E$-tetraenoic acid isobutylamide and to dodeca- $2 E, 4 E, 8 Z, 10 Z$-tetraenoic acid isobutylamide that corresponds in $R_{F}$ value to that in the chromatogram of Standard solution 1, and below this spot, there are several yellowish zones due to $\alpha, \beta$-unsaturated isobutylamides (absent in Echinacea pallida and mostly violet in Echinacea purpurea due to the presence of $\alpha, \beta, \gamma, \delta$-unsaturated isobutylamides) that are not visible or are very weak when viewed under UV light at 254 nm .

C: The retention time of the major peak in the chromatogram of the Test solution corresponds to that of the echinacoside peak in the chromatogram of Standard solution 1, as obtained in the test for Content of total phenols.
${ }^{\Delta}$ The chromatogram of the Test solution shows a peak for
1,3-dicaffeoylquinic acid corresponding in retention time to that obtained with Standard solution 1.』USP28

## Add the following:

-Microbial limits $\langle 2021\rangle$-The total bacterial count does not exceed $10^{7}$ per $g$, the total combined molds and yeast count does not exceed $10^{5}$ per g , the coliform count is not
more than $10^{4}$ per g , the enterobacterial count is not more than $10^{4}$ per g , and it meets the requirements of the tests for absence of Salmonella species, Escherichia coli, and

Staphylococcus aureus. $\mathbf{\square 2 S}$ (USP27)

## Change to read:

Loss on drying $\langle 731\rangle$ :
${ }^{\boldsymbol{\Delta}}$ Dry it at $105^{\circ}$ for 2 hours: it $\operatorname{loses}_{\mathbf{\Delta U S P 2 8}}$ not more than $10.0 \%$.

## Change to read:

## Content of total phenols-

Solvent-Prepare a mixture of alcohol and water (7:3).
Solution A-Prepare a filtered and degassed solution of phosphoric acid ( 0.1 in 100).
Solution B-Use filtered and degassed acetonitrile.
Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard solution 1 -Dissolve an accurately weighed quantity of USP Powdered Echinacea angustifolia Extract RS in Solvent, shaking for 1 minute, and dilute
${ }^{\Delta}$ and heating in a water bath. Dilute $\boldsymbol{\Delta U S P 2 8}$
with Solvent to obtain a solution having a known concentration of about 1 mg of per mL . Pass through a membrane filter having a $0.45-\mu \mathrm{m}$ or finer porosity.

Standard solution 2-Dissolve an accurately weighed quantity of USP Chlorogenic Acid RS in Solvent, shaking for 1 minute. Dilute quantitatively, and stepwise if necessary, with Solvent to obtain a solution having a known concentration of about $40 \mu \mathrm{~g}$ per mL . Pass through a membrane filter having a $0.45-\mu \mathrm{m}$ or finer porosity.

Test solution-Transfer about 125 mg of finely powdered Echinacea angustifolia (capable of passing through a 40-mesh sieve), accurately weighed, to a entrifuge tube
© round bottom flask equipped with a condenser. $\triangle$ USP28
Add 25.0 mL of Solvent, and heat under reflux, while shaking by mechanical means, for 15 minutes. Centrifuge, or pass through a membrane filter having a $0.45-\mu \mathrm{m}$ or finer porosity.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $330-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The column temperature is maintained at $35^{\circ}$. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0-13$ | $90 \rightarrow 78$ | $10 \rightarrow 22$ | linear gradient |
| $13-14$ | $78 \rightarrow 60$ | $22 \rightarrow 40$ | linear gradient |
| $14-17$ | 60 | 40 | isocratic |
| $17-17.5$ | $60 \rightarrow 90$ | $40 \rightarrow 10$ | linear gradient |
| $17.5-22$ | 90 | 10 | equilibration |

Chromatograph Standard solution 1, and record the peak responses as directed for Procedure: the chromatogram obtained is similar to the Reference Chromatogram for total phenols provided with the USP Powdered Echinacea angustifolia Extract RS
A and the resolution, $R$, between the 1,3 -dicaffeoylquinic
acid isomer and echinacoside is not less than 1.0. $\triangle U S P 28$ Chromatograph Standard solution 2, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 3.5
${ }^{4} 3.0 ;{ }_{\mathbf{A S P} 28}$
the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.5 \%$.

Procedure-Separately inject equal volumes (about $5 \mu \mathrm{~L}$ ) of Standard solution 1, Standard solution 2, and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the relevant peaks. Identify the relevant analytes in the chromatogram obtained from the Test solution by comparison with the chromatogram obtained from Standard solution 1. Separately calculate the percentage of caftaric acid $\left(\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{O}_{9}\right)$, chicoric acid $\left(\mathrm{C}_{22} \mathrm{H}_{18} \mathrm{O}_{12}\right)$, chlorogenic acid $\left(\mathrm{C}_{16} \mathrm{H}_{18} \mathrm{O}_{9}\right)$, dicaffeoylquinic acids $\left(\mathrm{C}_{25} \mathrm{H}_{24} \mathrm{O}_{12}\right)$, and echinacoside $\left(\mathrm{C}_{35} \mathrm{H}_{46} \mathrm{O}_{20}\right)$ in the portion of Echinacea angustifolia taken by the formula:

$$
2500 F(C / W)\left(r_{i} / r_{S}\right)
$$

in which $F$ is the response factor and is equal to 0.695 for chicoric acid, 0.729 for dieaffeylquinic acid
${ }^{\Delta}$ dicaffeoylquinic acids, ${ }_{\mathbf{D}}$ USP28
0.881 for caftaric acid, 1.000 for chlorogenic acid, and 2.220 for echinacoside; $C$ is the concentration, in mg per mL , of USP Chlorogenic Acid RS in Standard solution 2; $W$ is the weight, in mg , of Echinacea angustifolia taken; and $r_{i}$ and $r_{S}$ are the peak responses for the relevant analyte obtained from the Test solution and Standard solution 2, respectively. Calculate the percentage of total phenols in the portion of Echinacea angustifolia taken by adding the individual percentages calculated.

## BRIEFING

Powdered Echinacea angustifolia Extract, USP 27 page 1989. On the basis of comments received, it is proposed to modify the visualization of the spots in the TLC identification test for alkamides. Drying conditions previously omitted are now added. In the test for Content of total phenols it is proposed to reflux the Test preparation in order to improve the recovery. It is also proposed to reduce the minimum requirement in the test for Content of dodecatetraenoic acid isobutylamides. The Labeling section is revised to add a warning statement to be applied to the label and to allow specific claims for extracts standardized to higher contents of alkamides. See also the briefing under Echinacea angustifolia.
(DSB: G. Giancaspro; DSI: J. Salguero) RTS—40843-3; 40889-1

## Change to read:

» Powdered Echinacea angustifolia Extract is prepared from Echinacea angustifolia roots by extraction with hydroalcoholic mixtures or other suitable solvents. The ratio of the starting crude plant material to Powdered Extract is between $2: 1$ and $8: 1$. It contains not less than 4.0 percent and not more than 5.0 percent of total phenols, calculated on the dried basis as the sum of caftaric acid $\left(\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{O}_{9}\right)$, chicoric acid $\left(\mathrm{C}_{22} \mathrm{H}_{18} \mathrm{O}_{12}\right)$, chlorogenic acid $\left(\mathrm{C}_{16} \mathrm{H}_{18} \mathrm{O}_{9}\right)$, dicaffeoylquinic acids $\left(\mathrm{C}_{25} \mathrm{H}_{24} \mathrm{O}_{12}\right)$, and echinacoside $\left(\mathrm{C}_{35} \mathrm{H}_{46} \mathrm{O}_{20}\right)$. It contains not less than $\theta .6$
${ }^{\Delta} 0.1_{\mathbf{\Delta U S P 2 8}}$
percent of dodecatetraenoic acid isobutylamides $\left(\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{NO}\right)$
${ }^{\Delta}$ on the dried basis. ${ }^{\text {USSP28 }}$

## Change to read:

Labeling-The label states the Latin binomial and, following the official name, the part of the plant from which the article was prepared.
${ }^{\boldsymbol{\Delta}}$ If standardized by the content of alkamides, label it to indicate the targeted content of dodecatraenoic acid isobutylamides. The label bears a statement indicating that Echinacea angustifolia may cause rare allergic reactions, rashes, or ag-
gravate asthma._UUP28
It meets the requirements for Labeling under Botanical Extracts $\langle 565\rangle$.

## Change to read:

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -
Standard solution 1, Standard solution 2, Developing solvent system, Spray reagent, and Procedure-Proceed as directed for Identification test $B$ under Echinacea angustifolia.

Test solution-Dissolve $0 .+$
${ }^{\Delta} 1.0$
g of Powdered Extract in 10 mL of methanol. Allow to stand for 15 minutes before use.

B: The retention time for the major peak in the chromatogram of the Test solution corresponds to that for the echinacoside peak in the chromatogram of Standard solution 1, as obtained in the test for Content of total phenols.

## Change to read:

Loss on drying $\langle 731\rangle$ :
${ }^{\boldsymbol{\Delta}}$ Dry 1 g at $105^{\circ}$ for 2 hours: It $\operatorname{loses}_{\mathbf{\Delta U S P 2 8}}$
not more than $5.0 \%$.

## Change to read:

## Content of total phenols-

Solvent, Solution A, Solution B, Mobile phase, Standard solution 1, Standard solution 2, and Chromatographic system-Proceed as directed for Content of total phenols under Echinacea angustifolia.
Test solution-Transfer about 60 mg of Powdered Extract, accurately weighed, to a 50 mL centriftge tube.
$\boldsymbol{\Delta}_{\text {an }}$ appropriate round bottom flask equipped with a conden-


Add 25.0 mL of Solvent, ${ }^{U S P 28}$ shake
$\Delta_{\text {and heat under reflux while shaking }}^{\mathbf{A U S P P}{ }^{\text {U }} \text {. }}$
by mechanical means for 15 minutes. Centrifuge, or pass through a membrane filter having a $0.45-\mu \mathrm{m}$ or finer porosity.
Procedure-Proceed as directed for Content of total phenols under Echinacea angustifolia. Calculate the percentage of each relevant component of total phenols in the portion of Powdered Extract taken by the formula:

$$
2500 F(C / W)\left(r_{i} / r_{S}\right),
$$

in which $F$ is the response factor and is equal to 0.695 for chicoric acid, 0.729 for dicaffeoylquinic acids, 0.881 for caftaric acid, 1.000 for chlorogenic acid, and 2.220 for echinacoside; $C$ is the concentration, in mg per mL, of USP Chlorogenic Acid RS in Standard solution 2; $W$ is the weight, in mg , of the portion of Powdered Extract taken; and $r_{i}$ and $r_{S}$ are the peak responses for the relevant analyte obtained from the Test solution and Standard solution 2, respectively. Calculate the percentage of total phenols in the portion of Powdered Extract taken by adding the individual percentages.

## Change to read:

Content of dodecatetraenoic acid isobutylamides-
Mobile phase and Standard solution 2-Proceed as directed for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia.

Standard solution 1-Dissolve an accurately weighed quantity of USP Powdered Echinacea angustifolia Extract RS in methanol, shaking for 1 minute, and dilute with methanol to volume to obtain a solution having a known concentration of about 1 mg per mL . Pass through a membrane filter having a $0.45-\mu \mathrm{m}$ or finer porosity.

Test solution-Transfer about 500 mg of Powdered Extract, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Add 80 mL of methanol, and sonicate for 30 minutes. Dilute with methanol to volume, and pass through a membrane filter having a $0.45-\mu \mathrm{m}$ or finer porosity.

Chromatographic system-Prepare as directed for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia. Chromatograph Standard solution 1, and record the peak responses as directed for Procedure: the chromatogram obtained is similar to the Reference Chromatogram for alkamides provided with the USP Powdered Echinacea angustifolia Extract RS,
$\triangle$ and the resolution, $R$, between the two isomers of dodeca-
tetraenoic acid isobutylamides is not less than $1.0 \boldsymbol{\wedge}_{\mathbf{\Delta S P}}$ _
Chromatograph Standard solution 2, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 3.5 ; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.5 \%$.

Procedure-Proceed as directed for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia. Calculate the percentage of dodecatetraenoic acid isobutylamides in the portion of Powdered Extract taken by the formula:

$$
10,000(1.353)(C / W)\left(r_{i} / r_{S}\right)
$$

in which 1.353 is the response factor for $2 E, 4 E$-hexadienoic acid isobutylamide; $C$ is the concentration, in mg per mL , of USP $2 E, 4 E$-Hexadienoic Acid Isobutylamide RS in Standard solution 2; $W$ is the weight, in mg , of the portion of Powdered Extract taken; $r_{i}$ is the sum of the peak responses of the relevant analytes obtained from the Test solution; and $r_{S}$ is the peak response obtained from Standard solution 2.

BRIEFING
Echinacea pallida, USP 27 page 1989. It is proposed to revise the Latin binomial in the Definition according to the nomenclature in Herbs of Commerce, $2^{\text {nd }}$ Edition. See also the briefing under Echinacea angustifolia for other changes.
(DSB: G. Giancaspro) RTS-40483-5

## Change to read:

» Echinacea pallida consists of the dried rhizome and roots of Echinacea pallida Nuttall
${ }^{\wedge}$ (Nutt.) Nutt. ${ }^{U S P 28}$
(Fam. Asteraceae). It is harvested in the fall after 3 or more years of growth. It contains not less than 0.5 percent of total phenols, calculated on the dried basis as the sum of caftaric acid $\left(\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{O}_{9}\right)$, chicoric acid $\left(\mathrm{C}_{22} \mathrm{H}_{18} \mathrm{O}_{12}\right)$, chlorogenic $\operatorname{acid}\left(\mathrm{C}_{16} \mathrm{H}_{18} \mathrm{O}_{9}\right)$, and echinacoside $\left(\mathrm{C}_{35} \mathrm{H}_{46} \mathrm{O}_{20}\right)$.

## Change to read:

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -
PRESENCE OF ECHINACOSIDE AND ABSENCE OF GYNARINE
${ }^{\triangle}$ DICAFFEOYLQUINIC ACIDS (CYNARIN(E)- $\Delta$ USP28
Test solution-Proceed as directed for Identification test $A$ under Echinacea angustifolia, except to use Echinacea pallida instead of Echinacea angustifolia.

Standard solution 1-Dissolve an accurately weighed quantity of USP Powdered Echinacea pallida Extract RS in methanol to obtain a solution having a known concentration of about 10 mg per mL.

Standard solution 2, Developing solvent system, Spray reagent 1, and Spray reagent 2-Proceed as directed for Identification test $A$ under Echinacea angustifolia.

Procedure-Proceed as directed in the chapter. Develop the chromatograms in Developing solvent system until the solvent front has moved not less than 48
${ }^{\Delta} 12$ _USP28
cm , and dry the plate in a current of air. Spray the plate with Spray reagent 1 followed by Spray reagent 2 , and examine the plate under UV light at 365 nm : the chromatogram obtained from the Test solution shows a yellowish zone at an $R_{F}$ value of 0.14 , characteristic of echinacoside (absent or traces in Echinacea purpurea), corresponding in color and $R_{F}$ value to that in the chromatogram of Standard solution 1, and does not show a zone characteristic of eynarine
$\Delta_{1,3-d i c a f f e o y l q u i n i c ~ a c i d ~}^{\Delta U S P 28}$
(present in Echinacea angustifolia) corresponding in color and $R_{F}$ value to that in the chromatogram of Standard solution 2. Other colored zones of varying intensities may be observed in the chromatogram of the Test solution.

B: Thin-Layer Chromatographic Identification Test $\langle 201\rangle-$ PRESENCE OF KETOALKENYNES-
Test solution-Evaporate to dryness the chloroform extract retained from preparation of the Test solution in Identification test $A$ at $40^{\circ}$ in vacuum. To the residue add 1 mL of alcohol, and pass through a nylon membrane filter having a porosity of $0.45 \mu \mathrm{~m}$.

Standard solution 1-Transfer an accurately weighed quantity of USP Powdered Echinacea pallida Extract RS to a centrifuge tube, and add chloroform to obtain a solution having a concentration of about 10 mg per mL . Shake for 1 minute, and centrifuge. Use the supernatant.

Standard solution 2-Dissolve an accurately weighed quantity of $\beta$-sitosterol in methanol to obtain a solution having a concentration of about 1 mg per mL .

Developing solvent system-Prepare a mixture of toluene and ethyl acetate $(7: 3)$.

Spray reagent 1-Prepare a $1 \%$ solution of vanillin in alcohol.
Spray reagent 2-Prepare a $10 \%$ solution of sulfuric acid in alcohol.

Procedure-Proceed as directed for Identification test A. Spray the plate with Spray reagent 1 followed by Spray reagent 2, and heat the plate at $120^{\circ}$ for 3 minutes. The chromatogram obtained from the Test solution shows green, brown, and violet zones above the spot for $\beta$-sitosterol ( $R_{F}$ range 0.6 to 0.8 ). These zones (unlike those in Echinacea angustifolia and Echinacea purpurea) are characteristic of ketoalkenynes, and correspond in $R_{F}$ value to the zones in the chromatogram obtained from Standard solution 1.

C: The retention time of the major peak in the chromatogram of the Test solution corresponds to that of the echinacoside peak in the chromatogram of Standard solution 1, as obtained in the test for Content of total phenols.
${ }^{\boldsymbol{\Delta}}$ The peak area of any peak detected at the locus of 1,3-di-
caffeoylquinic acid is not more than $1 \%$ of the peak area for
echinacoside peak. $\mathbf{\Delta}$ USP28

## Change to read:

Content of total phenols-
Solvent, Solution A, Solution B, Mobile phase, and Standard solution 2-Prepare as directed for Content of total phenols under Echinacea angustifolia.

Standard solution 1-Proceed as directed for Content of total phenols under Echinacea angustifolia, except to use USP Powdered Echinacea pallida Extract RS instead of USP Powdered Echinacea angustifolia Extract RS.

Test solution-Proceed as directed for Content of total phenols under Echinacea angustifolia, except to use finely powdered Echinacea pallida instead of Echinacea angustifolia.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—Prepare as directed for Content of total phenols under Echinacea angustifolia. Chromatograph Standard solution 1, and record the peak responses as directed for Procedure: the chromatogram obtained is similar to the Reference Chromatogram for total phenols provided with USP Powdered Echinacea pallida Extract RS. Chromatograph Standard solution 2, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 3.5 $\Delta_{3.0} ;_{\mathbf{U S P} 28}$
the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.5 \%$.

Procedure-Proceed as directed for Content of total phenols under Echinacea angustifolia. Separately calculate the percentages of caftaric acid $\left(\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{O}_{9}\right)$, chicoric acid $\left(\mathrm{C}_{22} \mathrm{H}_{18} \mathrm{O}_{12}\right)$, chlorogenic acid $\left(\mathrm{C}_{16} \mathrm{H}_{18} \mathrm{O}_{9}\right)$, and echinacoside $\left(\mathrm{C}_{35} \mathrm{H}_{46} \mathrm{O}_{20}\right)$ in the portion of Echinacea pallida taken by the formula:

$$
2500 F(C / W)\left(r_{i} / r_{S}\right)
$$

in which $F$ is the response factor and is equal to 0.695 for chicoric acid, 0.881 for caftaric acid, 1.000 for chlorogenic acid, and 2.220 for echinacoside; $C$ is the concentration, in mg per mL , of USP Chlorogenic Acid RS in Standard solution 2; $W$ is the weight, in mg , of Echinacea pallida taken; and $r_{i}$ and $r_{S}$ are the peak responses for the relevant analyte obtained from the Test solution
and Standard solution 2, respectively. Calculate the percentage of total phenols in the portion of Echinacea pallida taken by adding the individual percentages calculated.

## BRIEFING

Powdered Echinacea pallida Extract, USP 27 page 1991. It is proposed to delete the reference to dicaffeoylquinic acids from the Definition since they should be absent in E. pallida. It is also proposed to revise the Labeling section to include a warning statement to be applied to the label. See also the briefings under Echinacea angustifolia and Echinacea pallida for other changes.
(DSB: G. Giancaspro; DSI: J. Salguero) RTS—40483-6; 40889-2

## Change to read:

» Powdered Echinacea pallida Extract is prepared from Echinacea pallida roots by extraction with hydroalcoholic mixtures or other suitable solvents. The ratio of the starting crude plant material to Powdered Extract is between $2: 1$ and $8: 1$. It contains not less than 4.0 percent and not more than 5.0 percent of total phenols, calculated on the dried basis as the sum of caftaric acid $\left(\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{O}_{9}\right)$, chicoric acid $\left(\mathrm{C}_{22} \mathrm{H}_{18} \mathrm{O}_{12}\right)$, chlorogenic acid $\left(\mathrm{C}_{16} \mathrm{H}_{18} \mathrm{O}_{9}\right)$, lieaffeylquinic acids $\left(\mathrm{G}_{25} \mathrm{H}_{24} \Theta_{12}\right.$;

- $\triangle U S P 28$
and echinacoside $\left(\mathrm{C}_{35} \mathrm{H}_{46} \mathrm{O}_{20}\right)$
${ }^{\Delta}$ on the dried basis. ${ }^{\text {USP }}{ }^{28}$


## Change to read:

Labeling-The label states the Latin binomial and, following the official name, the parts of the plant from which the article was prepared.
${ }^{\boldsymbol{\Delta}}$ The label bears a statement indicating that Echinacea pal-
lida may cause rare allergic reactions, rashes, or aggravate
asthma.』USP28
It meets the requirements for Labeling under Botanical Extracts $\langle 565\rangle$.

## Change to read:

Identification-
A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle-$
Standard solution 2, Developing solvent system, Spray reagent
1, Spray reagent 2, and Procedure-Proceed as directed for Identification test $A$ under Echinacea angustifolia.

Test solution-Dissolve 0.1
${ }^{\Delta} 1.0$ AUSP28
g of Powdered Extract in 10 mL of methanol. Allow to settle before use.

Standard solution 1-Dissolve an accurately weighed quantity of USP Powdered Echinacea pallida Extract RS in methanol to obtain a solution having a known concentration of about 18
${ }^{\Delta} 100$ $\Delta$ USP28
mg per mL.
B: The retention time of the major peak in the chromatogram of the Test solution corresponds to that of the echinacoside peak in the chromatogram of Standard solution 1, as obtained in the test for Content of total phenols.

## Change to read:

## Content of total phenols-

Solvent, Solution A, Solution B, Mobile phase, and Standard solution 2-Proceed as directed for Content of total phenols under Echinacea angustifolia.

Standard solution 1-Proceed as directed for Content of total phenols under Echinacea angustifolia, except to use USP Powdered Echinacea pallida Extract RS instead of USP Powdered Echinacea angustifolia Extract RS.

Test solution-Transfer about 60 mg of Powdered Extract, accurately weighed, to a 50 mL eentrifuge tube
$\Delta_{\text {an }}$ appropriate round bottom flask equipped with a conden-
Ser. $\begin{aligned} & \text { USP28 } \\ & \text { Add } \\ & 25.0 \mathrm{~mL}\end{aligned}$ of Solvent, shake
$\Delta^{\text {and }}$ heat under reflux while shaking ${ }_{\Delta U S P 28}$
by mechanical means for 15 minutes. Centrifuge, or pass through a membrane filter having a $0.45-\mu \mathrm{m}$ or finer porosity.

Chromatographic system-Prepare as directed for Content of total phenols under Echinacea angustifolia. Chromatograph Standard solution 1, and record the peak responses as directed for Procedure: the chromatogram obtained is similar to the Reference Chromatogram for total phenols provided with USP Powdered Echinacea pallida Extract RS. Chromatograph Standard solution 2, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 3.5
-3.0; ${ }_{\text {USP28 }}$
the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.5 \%$.

Procedure-Proceed as directed for Content of total phenols under Echinacea angustifolia. Separately calculate the percentage of each relevant component of total phenols in the portion of Powdered Extract taken by the formula:

$$
2500 F(C / W)\left(r_{i} / r_{S}\right)
$$

in which $F$ is the response factor and is equal to 0.695 for chicoric acid, 0.881 for caftaric acid, 1.000 for chlorogenic acid, and 2.220 for echinacoside; $C$ is the concentration, in mg per mL , of USP Chlorogenic Acid RS in Standard solution 2; $W$ is the weight, in mg , of the portion of Powdered Extract taken; and $r_{i}$ and $r_{S}$ are the peak responses for the relevant analyte obtained from the Test solution and Standard solution 2, respectively. Calculate the percentage of total phenols in the portion of Powdered Extract taken by adding the individual percentages calculated.

Briefing
Echinacea purpurea Aerial Parts. Because there is no existing USP monograph for this article, a new monograph is being proposed.
(DSB: G. Giancaspro) RTS-40334-1

## Add the following:

## ©Echinacea purpurea Aerial Parts

## » Echinacea purpurea Aerial Parts consists of the

 aerial parts of Echinacea purpurea (L.) Moench (Fam. Asteraceae). It is harvested during the flowering stage. It contains not less than 1.0 percent of chicoric acid, and not less than 0.01 percent of dodecatetraenoic acid isobutylamides $\left(\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{NO}\right)$ on the dried basis.Packaging and storage-Store in tight, light-resistant containers at controlled room temperature.

Labeling-The label states the Latin binomial and, following the official name, the parts of the plant contained in the article.

USP Reference standards $\langle 11\rangle$ —USP Chlorogenic Acid RS. USP Powdered Echinacea purpurea Extract RS. USP
2E,4E-Hexadienoic Acid Isobutylamide RS.

## Botanical characteristics-

MACROSCOPIC-The herb is an erect, coarse, rough-hairy perennial, usually up to 90 cm tall, rarely up to 180 cm . The leaves are alternate and simple; the lowermost leaves are slender, long, and petioled, ovate to broadly lanceolate, mostly penta-nerved, acute or acuminated at the apex, abruptly narrowed or rarely cordate at the base, usually sharply dentate, and 7 to 20 cm long and 2.5 to 7.5 cm wide; the
petioles are mostly winged at the summit. The upper leaves are narrower, often almost entirely sessile, lanceolate or ovate lanceolate, and usually with 3 veins.

The flower heads are radiate, to 15 cm across, solitary or few, and long-peduncled, with 12 to 20 rays, purple, crimson, or rarely pale; the bristle disks are often orange, 3.5 to 7.5 cm long; the involucre is depressed-hemispheric; the bracts are lanceolate, spreading or appressed, imbricated in 2 to 4 series, and hairy on the outer surface with ciliate margins; the receptacle is conical, the scales of the receptacle stiff, spinescent, and conspicuously longer than the disc flowers; the chaff is carinate and cuspidate; the achenes are 3 to 4 mm in length, tetrasided, obypyramidal, and thick; the pappus has a short, dentate crown.

## MICROSCOPIC-

Leaf-The leaf has a thickness of 200 to $350 \mu \mathrm{~m}$, with an epidermis 9 to $13 \mu \mathrm{~m}$ thick, largely without chloroplasts; the stomata are 28 to $35 \mu \mathrm{~m}$, abundant on the dorsal surface and fewer on the ventral surface; the mesophyll is clearly divided into palisade parenchyma and sponge parenchyma. The palisade parenchyma is one layer thick, with elongated cells 50 to $65 \mu \mathrm{~m}$ in length, oriented at right angles to the leaf surface, containing numerous chloroplasts. The sponge parenchyma is 150 to $250 \mu \mathrm{~m}$ thick, with cells of irregular shape, and has multiple cell layers, few chloroplasts, and large intercellular spaces. The phloem bundles of the lateral veins within the sponge parenchyma are bound by a onelayer sheath of small parenchymous cells, with vascular elements of the midrib surrounded by large-celled parenchyma. The uniseriate trichomes are few in the ventral surface, numerous on the dorsal surface, typically tricelled, occasionally tetra- or pentacelled, 250 to $500 \mu \mathrm{~m}$ in length, each arising from an epidermal cell; the epidermal cell walls appear with moderate thickening; the vessels are various, scalariform, with variable reticulated width.

Petiole-The parenchyma appear without chloroplasts, in several layers adjacent to a layer of collenchyma; 5 to 7 phloem bundles of small- to medium-sized vessels are weakly lignified and embedded in the parenchyma in the form of an arc; the wing ribs of the upper surface of the slightly hollowed petiole are marginal.

Inflorescence-The epidermal cells of the ray florets are square, $50 \mu \mathrm{~m}$, with a transparent, beaded cell wall; various elements of the asteraceous exhibit inflorescence; numerous multicellular jointed trichomes of the involucral bracts are 500 to $800 \mu \mathrm{~m}$ in length; tangential sections of the paleae with numerous fiber bundles are 10 to $15 \mu \mathrm{~m}$ in diameter and 100 to $150 \mu \mathrm{~m}$ in length; cell walls are thin. The epidermis of ray florets is reddish to violet; the epidermal cells from the end of the corolla form rounded papillae; a stigma of papillary cells is present; asteraceous pollen grains are 20 to $30 \mu \mathrm{~m}$ and spherical with a warty exine.
Calcium oxalate is negative; crystals of inulin and starch granules are rare.

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ —

PRESENCE OF CHICORIC ACID AND ABSENCE OF ECHINACO-SIDE-

Test solution—Add 5 mL of diluted alcohol (7:3) to 0.5 g of the powdered plant material, and shake for 1 minute. Centrifuge, and use the supernatant solution.
Standard solution-Dissolve an accurately weighed quantity of USP Powdered Echinacea purpurea Extract RS in methanol to obtain a solution having a concentration of about 10 mg per mL .

Developing solvent system, Spray reagent 1, and Spray reagent 2-Prepare as directed for Identification test $A$ under Echinacea angustifolia.

Procedure-Proceed as directed in the chapter. Develop the chromatograms in Developing solvent system until the solvent front has moved not less than 18 cm , and dry the plate in a stream of air. Spray the plate with Spray reagent 1 followed by Spray reagent 2, and examine the plate under UV light at 365 nm : the chromatogram obtained from the Test solution shows a yellowish-green zone at an $R_{F}$ value of 0.75 due to chicoric acid and another yellowish-green zone at an $R_{F}$ value of 0.45 due to caftaric acid, both zones corresponding in color and $R_{F}$ value to zones in the chromatogram obtained from the Standard solution. The chromatogram obtained from the Test solution does not show or shows only traces of a zone at an $R_{F}$ value of 0.1 due to echinacoside (present in Echinacea angustifolia and in Echinacea pallida). Other colored zones of varying intensities may be observed in the chromatogram obtained from the Test solution.

B: The retention times for the relevant peaks in the chromatogram of the Test solution, mainly due to caftaric acid and chicoric acid, correspond to those in the chromatogram of Standard solution 1, as obtained in the test for Content of chicoric acid and caftaric acid. A peak for echinacoside is not detected or is very weak.

C: The retention times for the relevant peaks in the chromatogram of the Test solution, mainly due to dodecatetraenoic isobutyl amides, correspond to those in the chromatogram of Standard solution 1, as obtained in the test for Content of dodecatetraenoic isobutylamides.

Microbial limits $\langle 2021\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total aerobic microbial count does not exceed $10^{5}$ per g , the total combined molds and yeasts count does not exceed $10^{3}$ per g , and the enterobacterial count does not exceed $10^{3}$.

Loss on drying $\langle 731\rangle$ —Dry 1 g of the powdered plant material: it loses not more than $12 \%$ of its weight.

Foreign organic matter $\langle 561\rangle$ : not more than $3.0 \%$.
Total ash $\langle 561\rangle$ : not more than $10.0 \%$, determined on 3 g .
Acid-insoluble ash $\langle 561\rangle$ : not more than $2.5 \%$.
Pesticides residues $\langle 561\rangle$ : meet the requirements.
Heavy metals, Method III $\langle 231\rangle$ : not more than $10 \mu \mathrm{~g}$ per g.

## Content of chicoric acid and caftaric acid-

Solvent, Solution A, Solution B, Mobile phase, and Standard solution 2-Proceed as directed in the test for Content of total phenols under Echinacea angustifolia.

Standard solution 1-Dissolve an accurately weighed quantity of USP Powdered Echinacea purpurea Extract RS in Solvent, shaking for 1 minute, and dilute with Solvent to obtain a solution having a known concentration of about 5 mg per mL . Pass through a membrane filter having a $0.45-$ $\mu \mathrm{m}$ or finer porosity.

Test solution-Proceed as directed for Content of phenols under Echinacea angustifolia, except to use finely powdered Echinacea purpurea Aerial Parts instead of Echinacea angustifolia.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $330-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The column temperature is maintained at $35^{\circ}$. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0-13$ | $90 \rightarrow 78$ | $10 \rightarrow 22$ | linear gradient |
| $13-14$ | $78 \rightarrow 60$ | $22 \rightarrow 40$ | linear gradient |
| $14-17.5$ | 60 | 40 | isocratic |
| $17.5-18$ | $60 \rightarrow 90$ | $40 \rightarrow 10$ | linear gradient |
| $18-30$ | 90 | 10 | equilibration |

Chromatograph Standard solution 1, and record the peak responses as directed for Procedure: the chromatogram obtained is similar to the Reference Chromatogram for total phenols provided with USP Powdered Echinacea purpurea Extract RS. Chromatograph Standard solution 2, and record the responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2 \%$.

Procedure-Proceed as directed in the test for Content of total phenols under Echinacea angustifolia. Separately calculate the percentages of caftaric acid $\left(\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{O}_{9}\right)$ and chicoric acid $\left(\mathrm{C}_{22} \mathrm{H}_{18} \mathrm{O}_{12}\right)$ in the portion of Echinacea purpurea Aerial Parts taken by the formula:

$$
2500 F(C / W)\left(r_{U} / r_{S}\right)
$$

in which $F$ is the response factor and is equal to 0.695 for chicoric acid, 0.881 for caftaric acid, and 1.000 for chlorogenic acid; $C$ is the concentration, in mg per mL , of USP Chlorogenic Acid RS in Standard solution 2; $W$ is the weight, in mg, of Echinacea purpurea Aerial Parts taken; and $r_{U}$ and $r_{S}$ are the peak responses for the relevant analyte obtained from the Test solution and Standard solution 2, respectively. Calculate the percentage of total phenols in the portion of Echinacea purpurea Aerial Parts taken by adding the individual percentages calculated.

## Content of dodecatetraenoic acid isobutylamides-

Mobile phase and Standard solution 2-Proceed as directed in the test for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia.

Standard solution 1-Proceed as directed for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia, except to use USP Powdered Echinacea purpurea Extract RS instead of USP Powdered Echinacea angustifolia Extract RS.

Test solution-Proceed as directed for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia, except to use Echinacea purpurea Aerial Parts instead of Echinacea angustifolia.

Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia, except to use the Reference Chromatogram for alkamides provided with USP Powdered Echinacea purpurea Extract RS instead of the Reference Chromatogram provided with USP Powdered Echinacea angustifolia Extract RS.
Procedure-Proceed as directed in the test for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia. Identify the peaks of the two isomers of dodecatetraenoic acid isobutylamides in the chromatogram obtained from the Test solution by comparison with the chromatogram obtained from Standard solution 1. Calculate the percentage of dodecatetraenoic acid isobutylamides in the portion of Echinacea purpurea Aerial Parts taken by the formula:

$$
10(1.353)(C / W)\left(r_{U} / r_{S}\right),
$$

in which 1.353 is the response factor for $2 E, 4 E$-hexadienoic acid isobutylamide; $C$ is the concentration, in mg per mL , of USP $2 E, 4 E$-Hexadienoic Acid Isobutylamide RS in Standard solution 2; $W$ is the weight, in g , of Echinacea purpurea Aerial Parts taken; $r_{U}$ is the sum of the peak responses of the relevant analytes obtained from the Test solution; and $r_{S}$ is the peak response obtained from Standard solution 2. $\triangle$ USP28

## BRIEFING

Echinacea purpurea Root, USP 27 page 1991—See the briefing under Echinacea angustifolia.
(DSB: G. Giancaspro) RTS-40483-2

## Change to read:

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ PRESENCE OF CHICORIC ACID AND ABSENCE OF ECHINACOSIDE-
Test solution-Prepare as directed for Identification test $A$ under Echinacea angustifolia, except to use Echinacea purpurea Root instead of Echinacea angustifolia.

Standard solution 1-Proceed as directed for Identification test A under Echinacea angustifolia, except to use USP Powdered Echinacea purpurea Extract RS instead of USP Powdered Echinacea angustifolia Extract RS.

Standard solution 2, Developing solvent system, Spray reagent 1, and Spray reagent 2-Prepare as directed for Identification test $A$ under Echinacea angustifolia.

Procedure-Proceed as directed in the chapter. Develop the chromatograms in Developing solvent system until the solvent front has moved not less than 18 cm , and dry the plate in a current of air. Spray the plate with Spray reagent 1 followed by Spray reagent 2, and examine the plate under UV light at 365 nm : the chromatogram obtained from the Test solution shows a yellowish-green zone at an $R_{F}$ value of 0.75 due to chicoric acid and another yellow-ish-green zone at an $R_{F}$ value of 0.45 due to caftaric acid, both zones corresponding in color and $R_{F}$ value to zones in the chromatogram obtained from Standard solution 1. The chromatogram obtained from the Test solution does not show or shows only traces of a zone at an $R_{F}$ value of 0.1 due to echinacoside (present in Echinacea angustifolia and in Echinacea pallida) that corresponds to a yellowish spot in the chromatogram obtained from Standard solution 1, and does not show a zone that corresponds in color and $R_{F}$ value to the spot for eynarine
${ }^{\boldsymbol{\Delta}}$ 1,3-dicaffeoylquinic acid (cynarin) $\boldsymbol{\Delta U S P 2 8}$
(present in Echinacea angustifolia) in the chromatogram obtained from Standard solution 2. Other colored zones of varying intensities may be observed in the chromatogram obtained from the Test solution.

B: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ PRESENCE OF ISOBUTYLALKENYLAMIDES-
Test solution-Proceed as directed for Identification test $B$ under Echinacea angustifolia, except to use the chloroform extract retained from Identification test $A$ under Echinacea purpurea Root instead of the chloroform extract retained from Identification test A under Echinacea angustifolia.

Standard solution 1-Dissolve an accurately weighed quantity of USP Echinacea purpurea Extract RS in methanol to obtain a solution having a known concentration of about 10
$\wedge_{100}{ }_{\text {ASP2 }}$
mg per mL.
Standard solution 2, Developing solvent system, and Spray re-agent-Proceed as directed for Identification test $B$ under Echinacea angustifolia.

Procedure-Proceed as directed in the chapter. Develop the chromatograms in Developing solvent system until the solvent front has moved not less than 18

[^63]cm , and dry the plate in a current of air. Examine the plate under UV light at 254 nm : the chromatogram obtained from the Test solution shows ene zone corresponding in $R_{t}$ value to the zone due to $\beta$ sitesterol in the chromatogram of Standet solution 2, and

- $\Delta U S P 28$
one main zone corresponding in $R_{F}$ value to the zone due to dode-ca- $2 E, 4 E, 8 Z, 10 E$-tetraenoic acid isobutylamide and dodeca$2 E, 4 E, 8 Z, 10 Z$-tetraenoic acid isobutylamide in the chromatogram of Standard solution 1
- and below this zone there are several other zones due to
$\alpha, \beta, \gamma, \delta$-unsaturated isobutylamides. ${ }_{\text {UUSP2s }}$
Spray the plate with Spray reagent, and then heat the plate at $100^{\circ}$ for 5 minutes. Examine the plate under long-wavelength UV light: the zone due to dodeca- $2 E, 4 E, 8 Z, 10 E$-tetraenoic acid isobutylamide and dodeca- $2 E, 4 E, 8 Z, 10 Z$-tetraenoic acid isobutylamide turns blue-black, and below this zone there are several other zones due to $\alpha, \beta, \gamma, \delta$-unsaturated isobutylamides (not detectable in Echinacea pallida) that turn violet (unlike the corresponding zones in the chromatogram of Echinacea angustifolia that are mostly yellowish due to $\alpha, \beta$-unsaturated isobutylamides).
${ }^{\Delta}$ A zone due to $\beta$-sitosterol that corresponds in $R_{F}$ value to the principal spot in the chromatogram of Standard solution

2 is also observed. $\triangle U S P 28$
$\mathbf{C}$ : The retention times for the relevant peaks in the chromatogram of the Test solution, mainly due to caftaric acid and chicoric acid, correspond to those in the chromatogram of Standard solution 1, as obtained in the test for Content of total phenols. An echinacoside peak is not detectable or is very weak.

## Briefing

Powdered Echinacea purpurea Extract, USP 27 page 1993. It is proposed to revise the Definition to allow the preparation of extracts both from the aerial parts and from the roots, in accordance with the proposed new monograph for Echinacea purpurea Aerial Parts, appearing elsewhere in this issue of $P F$. It is also proposed to revise the Labeling section to add a warning statement to be applied to the label and a requirement indicating the proportion of starting roots/aerial parts if the article were prepared from a mixture of them. Since the Content of dodecatetraenoic isobutylamides is lower in the leaves and stems, extracts prepared from variable proportions of aerial parts may contain variable content of these compounds. Therefore, it is proposed to label the standardized target Content of dodecatetraenoic isobutylamides in the article. See also the briefing under Echinacea angustifolia for other changes.
(DSB: G. Giancaspro; DSI: J. Salguero) RTS—40843-4; 40889-3

## Change to read:

» Powdered Echinacea purpurea Extract is prepared from dried Echinacea purpurea Root,
© Echinacea purpurea aerial parts, or a mixture of
them ${ }_{\Delta S P 28}$
by extraction with hydroalcoholic mixtures or other suitable solvents. The ratio of the starting crude plant material to Powdered Extract is between $2: 1$ and $8: 1$. It contains not less than 4.0 percent of total phenols, calculated on the dried basis as the sum of caftaric acid $\left(\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{O}_{9}\right)$, chicoric acid $\left(\mathrm{C}_{22} \mathrm{H}_{18} \mathrm{O}_{12}\right)$, chlorogenic acid $\left(\mathrm{C}_{16} \mathrm{H}_{18} \mathrm{O}_{9}\right)$, and echinacoside $\left(\mathrm{C}_{35} \mathrm{H}_{46} \mathrm{O}_{20}\right)$
${ }^{\Delta}$ on the dried basis. ${ }^{\text {UUSP28 }}$
It contains not less than 0.025 percent of alkamides

- dodecatetraenoic acid isobutylamides
$\left(\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{NO}\right)_{,}$, $_{\text {USP2 }}$
calculated on the dried basis. as dodecatetraeneic acid isebulamides $\left(\mathrm{C}_{16} \mathrm{H}_{25} \mathrm{NO}\right)$.
- $\mathbf{\Delta U S P 2 8}$


## Change to read:

Labeling-The label states the Latin binomial and, following the official name, the parts of the plant from which the article was prepared.
${ }^{\boldsymbol{\Delta}}$ If derived from root and aerial parts, indicate the corresponding percentages. Label it to indicate the content of total phenols and dodecatetraenoic isobutylamides. The label bears a statement indicating that Echinacea purpurea may cause rare allergic reactions, rashes, or aggravate asth-
ma. $\quad$ USP28
It meets the requirements for Labeling under Botanical Extracts $\langle 565\rangle$.

## Change to read:

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -
Test solution-Weigh and finely pulverize about 10 g of Powdered Extract, and transfer 1 g of the powder to a suitable extraction thimble. Transfer the thimble to a continuous extraction apparatus, and extract with 50 mL of chloroform for 1 hour. Evaporate the chloroform extract to dryness at $40^{\circ}$ in vacuum. To the residue, add 1 mL of alcohol, and pass through a nylon membrane filter having a porosity of $0.45 \mu \mathrm{~m}$.

Standard solution 1-Dissolve an accurately weighed quantity of USP Powdered Echinacea purpurea Extract RS in methanol to obtain a solution having a known concentration of about 10
$\Delta_{100}$ aUSP28
mg per mL .

Standard solution 2, Developing solvent system, Spray reagent, and Procedure-Proceed as directed for Identification test $B$ under Echinacea angustifolia.

B: The retention times of the peaks for chicoric and caftaric acids in the chromatogram of the Test solution correspond to those in the chromatogram of Standard solution 1, as obtained in the test for Content of total phenols.

## Change to read:

## Content of total phenols-

Solvent, Solution A, Solution B, Mobile phase, Standard solution 2, and Chromatographic system-Proceed as directed for Content of total phenols under Echinacea angustifolia.

Standard solution 1-Dissolve an accurately weighed quantity of USP Powdered Echinacea purpurea Extract RS in Solvent, shaking for 1 minute, and dilute with Solvent to obtain a solution having a known concentration of about 5 mg per mL . Pass through a membrane filter having a $0.45-\mu \mathrm{m}$ or finer porosity.

Test solution-Transfer about 60 mg of Powdered Extract, accurately weighed, to a 50 mL entrifuge tube.
© suitable round bottom flask equipped with a con-
denser. $\quad$ USP28
Add 25 mL of Solvent, and shake
${ }^{\Delta}$ heat under reflux while shaking ${ }_{\Delta U S P 28}$
by mechanical means for 15 minutes. Centrifuge, or pass through a membrane filter having a $0.45-\mu \mathrm{m}$ or finer porosity.

Procedure-Proceed as directed in the test for Content of total phenols under Echinacea purpurea Root. Calculate the percentage of each relevant component of total phenols in the portion of Powdered Extract taken by the formula:

$$
2500 F(C / W)\left(r_{i} / r_{S}\right)
$$

in which $F$ is the response factor and is equal to 0.695 for chicoric acid, 0.881 for caftaric acid, 1.000 for chlorogenic acid, and 2.220 for echinacoside; $C$ is the concentration, in mg per mL , of USP Chlorogenic Acid RS in Standard solution 2; $W$ is the weight, in mg , of the portion of Powdered Extract taken; $r_{i}$ and $r_{S}$ are the peak responses for the relevant analyte obtained from the Test solution and Standard solution 2, respectively. Calculate the percentage of total phenols in the portion of Powdered Extract taken by adding the individual percentages.

## Change to read:

## Content of alkamides

© dodecatetraenoic acid isobutylamides- $\quad$ USP28
Mobile phase and Standard solution 2-Proceed as directed for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia.

Standard solution 1-Proceed as directed for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia, except to use USP Powdered Echinacea purpurea Extract RS instead of USP Powdered Echinacea angustifolia Extract RS.

Test solution-Proceed as directed for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia, except to use Powdered Echinacea purpurea Extract instead of Powdered Echinacea angustifolia Extract.

Chromatographic system-Proceed as directed for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia, except to use the Reference Chromatogram for alkamides provided with USP Powdered Echinacea purpurea Extract RS instead of the Reference Chromatogram provided with USP Powdered Echinacea angustifolia Extract RS.

Procedure-Proceed as directed in the test for Content of dodecatetraenoic acid isobutylamides under Echinacea angustifolia. Calculate the percentage of alkmides
${ }^{\mathbf{\Delta}}$ dodecatetraenoic acid isobutylamides $\mathbf{\Delta U S P 2 8}$
in the portion of Powdered Extract taken by the formula:

$$
10(1.353)(C / W)\left(r_{i} / r_{S}\right)
$$

in which 1.353 is the response factor for $2 E, 4 E$-hexadienoic acid isobutylamide; $C$ is the concentration, in mg per mL , of USP $2 E, 4 E$-Hexadienoic Acid Isobutylamide RS in Standard solution 2; $W$ is the weight, in g , of the portion of Powdered Extract taken; $r_{i}$ is the sum of the peak responses of the relevant analytes obtained from the Test solution; and $r_{S}$ is the peak response obtained from Standard solution 2.

## Briefing

American Ginseng, USP 27 page 2005 and page 2243 of $P F$ 27(2) [Mar.-Apr. 2001]-See briefing under Asian Ginseng.
(DSB: G. Giancaspro) RTS-40775-3

## Change to read:

» American Ginseng consists of the dried roots of Pa nax quinquefolius Einné
${ }^{\Delta}$ L. $\mathbf{\Delta U S P 2 8}$
(Fam. Araliaceae). It contains not less than 4.0 percent of total ginsenosides, calculated on the dried basis.

## Add the following:

${ }^{\Delta}$ Microbial limits $\langle 2021\rangle$ : The total aerobic mierobiat eount dees not exceed $1 \theta^{7}$-efu-per g; the total combined molds and yeasts count dees not exceed $10^{5}$ efu per g; the eoliferm ceunt dees net exceed $10^{4}$-efuper g. the enterobue terial count dees not exceed $1 \theta^{4}$-efu per g.; and it meets the requirements of the tests for absense-of Satmonella species, Escherichia eoli, and Staphyltsens atrents. meets the requirements under Asian Ginseng. $\mathbf{\Delta U S P 2 8}$

## Change to read:

Content of ginsenosides-
Solution A: water.
Solution B: acetenitrile-
Mobile phase Use variable mixtures of Solution 4 and Solution $B$ as directed for Chromatographic syistem. Make adjustments-if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
${ }^{\triangle}$ Solution A, Solution B, Mobile phase, and Chromatographic system-Proceed as directed in the Content of
ginsenosides under Powdered Asian Ginseng Extract. $\mathbf{A}$ USP28
Standard solution 1-Transfer an accurately weighed quantity of USP Powdered American Ginseng Extract RS, equivalent to about 2 mg of ginsenoside $\mathrm{Rb}_{1}$, to a suitable container. Add 20 mL of water, and mix. Transfer the mixture to a chromatographic tube
 tayer, and wit for 15 minttes. Elute 75 mL of butyl aleohol sattr rated with water, colleet the elmate, and evaporate it to diyness ina retary evaperator in vaetumat $55^{\circ}+60^{\circ}$. Dissolve the residue of methandin 10.0 mL .
${ }^{\Delta}$ Dissolve in 10.0 mL of a mixture of water and alcohol
(6:4). $\mathbf{\Delta U S P 2 8}$
Standard solution 2-Transfer an accurately weighed quantity of USP Powdered Asian Ginseng Extract RS, equivalent to about 2 mg of ginsenoside $\mathrm{Rg}_{1}$, to a suitable container. Pros for Sted 1 , begining with "Add 20 mL of water".
${ }^{\boldsymbol{\Delta}}$ Dissolve in 10.0 mL of a mixture of water and alcohol
(6:4). $\mathbf{A}$ USP28
Test solution-Reduce about 100 g of American Ginseng to a powder, and transfer about 1.0 g of the powder, accurately weighed, to a $100-\mathrm{mL}$ round-bottom flask fitted with a reflux condenser. Add 50 mL of a mixture of water and alcohol (6:4) and a few grains of pumice, boil on a water bath under reflux for 1 hour, cool, and filter. Wash the flask and the residue with 20 mL of a mixture of water and alcohol (6:4), and pass through the same filter. Combine the filtrates, and evaporate in a rotary evaporator at $50^{\circ}$ to dryness. To the residue stained add 20 mL of water, mix, and proeed as directed for Stald solution -, beginning with "Transfer the mixture to a chromatographic tube".
${ }^{\boldsymbol{\Delta}}$ Dissolve the residue in 10.0 mL of a mixture of water and alcohol (6:4) $\mathbf{\Delta U S P 2 8}^{\text {U }}$

Chw (624) - The Higuid ehromatograph is equipped with -203 nm deteetor and a $3.9 \mathrm{~mm} \times 30 \mathrm{~cm}$ columm thateontains paeking L1. The flow rate is abut 1 mL per minute. The ehremategraph is programmed as follows.

| Fime (minutes) | $\text { Solution } 4$ <br> (\%) | $\begin{gathered} \text { Solution } B \\ (\%) \end{gathered}$ | Elution |
| :---: | :---: | :---: | :---: |
| $\theta$ | 82 | 18 | equilibration |
| -0-10 | 82 | 18 | isperatic |
| 10-50 | $82 \rightarrow 60$ | $\xrightarrow{8 \rightarrow 40}$ | tinear gradient |
| 50-80 | 60 | 40 | isperatie |

[NOTE-This system-separates ginsenesides $\mathrm{Rb}_{4}, \mathrm{Re}, \mathrm{Rf}, \mathrm{Rg}_{2}, \mathrm{Rg}_{4} ;$ $\mathrm{Re}, \mathrm{Pb}_{2}$, and Red.] Chrematograph each Standtud solution, and reeord the peak respenses as directed for Proceture: the chromatogram is similar to the Reference Chromatogramprovided with USP Powdered Ameriem Ginseng Extract PS being used. The relative retention times for ginsenoside $\mathrm{Rg}_{5}+$ and ginsenoside Re are 1.0 and 1.03, respectively; the resolution, $R$, between ginseneside $\mathrm{R} \mathrm{r}_{+}$and ginseneside Re is not less than 0 ., the resolution, $R$, between gin seneside $\mathrm{Rb}_{+}$and a neighbering miner penk, at relative retention times of 1.86 and 1.89 , respectively, is net less than 1.0 ; the column efficiencies determined frem ginsenoside $\mathrm{P}_{\mathrm{g}_{+}}$and ginseneside Pb
are not less than 17,000 and 11,000 theoretical plater, respectively; the tailing factors for the ginsenoside $R g_{+}$and ginsenoside $R b_{+}$ peaks are not more than 1.0 and 1.2 , respectively; and the relative standard deviation for replicate injections is not more than $4.0 \%$ determined frem ginseneside $\mathrm{Rg}_{+}$and ginseneside $\mathrm{Rb}_{4}$ :
$\Delta$
© Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of each Standard solution and the Test solution into the chromatograph, and record the chromatograms. Identify ginsenosides $\mathrm{Rg}_{1}$, $\mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, and Rd in the Standard solutions and the Test solution by comparing the chromatograms with the Reference Chromatogram provided with USP Powdered American Ginseng Extract RS, and measure the peak responses. Calculate the percentages of individual ginsenosides in the portion of American Ginseng taken by the formula:

$$
\begin{aligned}
& { }^{\mathbf{\Delta}} 1000(C / W)\left(r_{U} / r_{S}\right)_{\mathbf{\Delta U S P 2 8}}
\end{aligned}
$$

in which $C$ is the concentration, in mg per mL , of ginsenoside $\mathrm{Rg}_{1}$, $\mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, or Rd in the appropriate Standard solution; $W$ is the weight, in mg , of American Ginseng taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses of ginsenoside $\mathrm{Rg}_{1}$, $\mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, or Rd obtained from the Test solution and the appropriate Standard solution, respectively. Calculate the percentage of total ginsenosides in the portion of American Ginseng taken by adding the individual percentages.

## BRIEFING

Powdered American Ginseng, USP 27 page 2006—See briefing under Powdered Asian Ginseng.
(DSB: G. Giancaspro) RTS-40775-8

## Change to read:

» Powdered American Ginseng is American Ginseng reduced to a fine or a very fine powder.
${ }^{\Delta}$ It contains not less than 4.0 percent of total ginsenosides calculated on the dried basis. $\triangle U S P 28$

## Briefing

Powdered American Ginseng Extract, USP 27 page 2007See briefing under Asian Ginseng.
(DSB: G. Giancaspro) RTS-40775-4

## Change to read:

Microbial limits $\langle 2021\rangle$-The total aerobic microbial count does not exceed $10^{4}$ per $g$; the total combined molds and yeasts count does not exceed $10^{3}$ per g ; and it meets the requirements of the tests for absence of Salmonella species, and Escherichia coli. Stor eocus atrents.
$\Delta$
4USP28

## Change to read:

Content of ginsenosides-
Solution A, Solution B, Mobile phase, Standard solution 1, Standard solution 2, and Chromatographic system-Proceed as directed for Content of ginsenosides under American Ginseng.

Test solution-Transfer 600 mg
$\Delta_{\text {a quantity }}^{\text {AUSP28 }}$
of Powdered Extract,
© equivalent to 5 mg of ginsenosides, $\triangle U S P 28$ accurately weighed, to a suitable container. Add 20 mL of water, mix, and proeed as directed for Standard solution 1 , beginning with "Transfer the mixture to a chrematographic tube".
${ }^{\Delta}$ Dissolve in 10.0 mL of a mixture of water and alcohol

## (6:4) sonicating for 10 minutes and filter. $\triangle U S P 28$

Procedure-Proceed as directed for Content of ginsenosides under American Ginseng. Calculate the percentages of individual ginsenosides in the portion of Powdered Extract taken by the formula:

$$
10(C / H)\left(r_{\&}+r_{\text {s }}\right),
$$

in which $C$ is the concentration, in mg per mL , of ginsenoside $\mathrm{Rg}_{1}$, $\mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, or Rd in the appropriate Standard solution; $W$ is the weight, in mg , of Powdered Extract taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses of ginsenoside $\mathrm{Rg}_{1}$, $\mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, or Rd obtained from the Test solution and the appropriate Standard solution, respectively. Calculate the percentage of total ginsenosides in the portion of Powdered Extract taken by adding the individual percentages.

Briefing

> American Ginseng Capsules. Because there is no existing $U S P$ monograph for this article, the following new monograph is proposed.
(DSB: G. Giancaspro) RTS-40775-1

## Add the following:

## AAmerican Ginseng Capsules

» American Ginseng Capsules contain Powdered American Ginseng Extract. Capsules contain not less than 90.0 percent and not more than 110.0 percent of Extract, calculated as the sum of ginsenosides $\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, and Rd .

Packaging and storage-Preserve in tight containers, protected from light. Store at controlled room temperature.
Labeling-The label states the Latin binomial and, following the official name, the article from which the Capsules were prepared. The label also indicates the amount of Extract, in mg per Capsule. Label the Capsules to indicate the percentage of ginsenosides in the Extract contained in the Capsules. For soft-gelatin Capsules, state the method for Content of ginsenosides with which the product complies only if Method 1 is not used.

USP Reference standards—USP Powdered American Ginseng Extract RS.

## Identification-

A: Proceed as directed for Identification $A$ under American Ginseng using the following Test solutions.

Test solution for soft-shell gelatin capsules-Transfer a portion of the content of the Capsules, equivalent to about 100 mg of Extract, to a separatory funnel containing 30 mL of a solution consisting of a mixture of hexanes, methanol,
and water (20:15:10), dissolve in this mixture, and collect the lower layer. Wash the upper layer with three $15-\mathrm{mL}$ portions of a mixture of methanol and water (15:10), and combine the washings with the lower layer. Evaporate to dryness under vacuum at $45^{\circ}$ to $50^{\circ}$. Dissolve the residue in 5 mL of methanol.

Test solution for hard-shell gelatin capsules-Transfer a portion of the content of the Capsules, equivalent to about 100 mg of Extract, to a conical flask. Extract at $55^{\circ}$ with three $20-\mathrm{mL}$ portions of a mixture of water and methanol (8:2). Evaporate the combined extracts to dryness under vacuum at $45^{\circ}$ to $50^{\circ}$. Dissolve the residue in 5 mL of methanol.
B: The retention times of the peaks for ginsenosides $\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rb}_{2}, \mathrm{Rc}_{2}$, and Rd in the chromatogram of the Test solution correspond to those in the chromatogram of Standard solution 1, as obtained in the test for Content of ginsenosides under American Ginseng. The ratio of the peak response for $\mathrm{Rb}_{2}$ to the peak response for $\mathrm{Rb}_{1}$ is less than 0.4 ; and the ratio of the peak response for $\mathrm{Rg}_{1}$ to the peak response for $\mathrm{Rb}_{1}$ is less than 0.3 . The chromatogram shows no significant peak at the retention time corresponding to that of the $R_{F}$ for ginsenoside in the chromatogram of Standard solution 2, as obtained in the test for Content of ginsenosides under American Ginseng.

Microbial limits $\langle 2021\rangle$ —The total aerobic microbial count does not exceed $10^{4}$ per g . The total combined molds and yeasts count does not exceed $10^{3}$ per g . It meets the requirements of the tests for absence of Salmonella species and Escherichia coli.

Dissolution $\langle 2040\rangle$ : [To come.]
Disintegration $\langle 2040\rangle$ : meet the requirements.
Weight variation $\langle 2091\rangle$ : meet the requirements.

## Content of ginsenosides-

METHOD 1-
Mobile phase and Chromatographic system-Proceed as directed in the test for Content of ginsenosides under American Ginseng.

Standard solution-Transfer an accurately weighed quantity of USP Powdered American Ginseng Extract RS, and dilute quantitatively, and stepwise if necessary, with a mixture of water and alcohol (6:4) to obtain a solution having a known concentration of about 0.2 mg per mL of ginsenoside $\mathrm{Rb}_{1}$.

Test solution (for soft-gelatin capsules)-Using a suitable cutting instrument, open not fewer than 20 Capsules, and transfer the contents to a suitable container. Mix to homogenize, and transfer an accurately weighed portion, expected to contain an amount of Extract equivalent to 12 mg of ginsenosides, to a suitable flask with a stopper. Add 5.0 mL of tetrahydrofuran, and sonicate for 5 minutes. Add 25.0 mL of a mixture of methanol and water (40:60), and shake for 50 minutes in an automatic shaker. Transfer about 15.0 mL of the obtained emulsion to a centrifuge tube with a stopper, add about 800 mg of sodium chloride, shake for 30 seconds, and centrifuge to obtain a clear upper phase. Dilute 1.0 mL of the upper phase with 4 mL of water in a suitable tube, and transfer the solution to a column containing 360 mg of packing L2 that has been previously treated with 3.0 mL of methanol followed by 8.0 mL of water. [NOTE-Elute slowly, not faster than 1 drop per second, in all elution steps. Do not use vacuum.] Rinse the tube with 5 mL of water, transfer to the column taking the precaution of slow elution, and discard the eluate. Repeat the elution with 5 mL of a mixture of methanol and water (40:60), and discard the eluate. Elute the ginsenosides with 5.0 mL of methanol. Eva-
porate the solution under a stream of nitrogen at $40^{\circ}$ (about 50 minutes), and dissolve the residue with 1.0 mL of a solution of acetonitrile and water (2:8).

Procedure-Proceed as directed for Procedure in the test for Content of ginsenosides under American Ginseng. Separately calculate the quantity, in mg , of each relevant ginsenoside ( $\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, and Rd ) in the portion of American Ginseng Capsules taken to prepare the Test solution by the formula:

$$
0.3 P C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Powdered American Ginseng Extract RS in the Standard solution; $P$ is the labeled percentage of the corresponding ginsenoside in the USP Powdered American Ginseng Extract RS; $r_{U}$ is the peak response for each relevant ginsenoside in the chromatogram of the Test solution; and $r_{S}$ is the peak response of the corresponding ginsenoside in the chromatogram of the Standard solution. Calculate the content of ginsenosides, in mg , as the sum of the individual quantities of each relevant ginsenoside $\left(\operatorname{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb} b_{2}\right.$, and Rd ).

METHOD 2-
Mobile phase and Chromatographic system-Proceed as directed in the test for Content of ginsenosides under American Ginseng.
Solvent $A$ : upper phase of a mixture consisting of hexane, methanol, and water (4:3:2).

Solvent B: lower phase consisting of a mixture of hexane, methanol, and water (4:3:2).
Standard solution-Prepare a solution of USP Powdered American Ginseng Extract RS in a mixture of water and alcohol (6:4) having a known concentration of about 1 mg of $\mathrm{Rb}_{1}$ per mL .

Test solution 1 (for soft-gelatin capsules)-Using a suitable cutting instrument, open not fewer than 20 Capsules, and transfer the contents to a suitable container. Mix to homogenize, and transfer an accurately weighed portion, expected to contain an amount of Extract equivalent to 15 mg of total ginsenosides, to a $50-\mathrm{mL}$ flask. Add 10.0 mL of Solvent $A$, and sonicate for 3 to 5 minutes at $25^{\circ}$ to $30^{\circ}$. Transfer the solution to a $125-\mathrm{mL}$ separator funnel. To the residue, add 10 mL of Solvent B, and sonicate for 3 to 5 minutes at $25^{\circ}$ to $30^{\circ}$. Transfer the solution to the same separator funnel. Repeat the above procedure twice (the total volume will be about 60 mL ). Shake, and then allow the phases to separate. Collect the combined lower phase in a round-bottom flask, and wash the combined upper phase twice with 10 mL of Solvent B. Evaporate the combined lower phase to dryness under vacuum at $45^{\circ}$ to $50^{\circ}$. Quantitatively transfer the residue to a $10.0-\mathrm{mL}$ volumetric flask using small volumes of methanol, and dilute with methanol to volume.

Test solution 2 (for hard-gelatin capsules)-Accurately weigh the contents of not fewer than 20 Capsules, and composite the contents. Transfer an accurately weighed portion of the composite, expected to contain an amount of Extract equivalent to approximately 15 mg of total ginsenosides, to a conical flask. Add 15 mL of methanol, and shake to mix. Sonicate the mixture at $25^{\circ}$ to $30^{\circ}$ for 30 minutes. Cool, pass through filter paper, and return the residue to the conical flask. Add another 15 mL of methanol, sonicate the mixture at $25^{\circ}$ to $30^{\circ}$ for 30 minutes, and filter. Wash the residue with three $15-\mathrm{mL}$ portions of methanol. Evaporate the combined extracts and washing to dryness under vacuum at $45^{\circ}$ to $50^{\circ}$. Quantitatively transfer the residue to a $10.0-\mathrm{mL}$ volumetric flask using small volumes of methanol, and dilute with methanol to volume.

Procedure-Proceed as directed for Procedure in the test for Content of ginsenosides under American Ginseng. Separately calculate the quantity, in mg , of each relevant ginsenoside ( $\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, and Rd ) in the portion of Capsules taken to prepare the Test solution 1 or Test solution 2 by the formula:

$$
0.1 P C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Powdered American Ginseng Extract RS in the Standard solution; and the other terms are as defined for Method 1. Calculate the content of ginsenosides, in mg , as the sum of the individual quantities of each relevant ginsenoside $\left(\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2} \text {, and } \mathrm{Rd}\right)_{\cdot \mathbf{\Delta U S P 2 8}}$

## Briefing

American Ginseng Tablets. Because there is no existing USP monograph for this article, the following monograph is proposed. (DSB: G. Giancaspro) RTS-40775-2

## Add the following:

## ©American Ginseng Tablets

» American Ginseng Tablets contain Powdered American Ginseng Extract. Tablets contain not less than 90.0 percent and not more than 110.0 percent of Extract, calculated as the sum of ginsenosides $\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, and Rd .

Packaging and storage-Preserve in tight containers, protected from light. Store at controlled room temperature.

Labeling-The label states the Latin binomial and, following the official name, the article from which the Tablets were prepared. The label also indicates the amount of Extract, in mg per Tablet. Label the Tablets to indicate the percentage of total ginsenosides in the Extract contained in the Tablets.

USP Reference standards—USP Powdered American Ginseng Extract RS.

## Identification-

A: Proceed as directed for Identification $A$ under American Ginseng using the following Test solution.

Test solution-Reduce the Tablets to a very fine powder. Transfer a quantity of the powder, equivalent to about 100 mg of Extract, to a conical flask. Extract at $55^{\circ}$ with three $20-\mathrm{mL}$ portions of a mixture of water and methanol (8:2). Evaporate the combined extracts to dryness under vacuum at $45^{\circ}$ to $50^{\circ}$. Dissolve the residue in 5 mL of methanol.

B: The retention times of the peaks for ginsenosides $\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rb}_{2}, \mathrm{Rc}_{2}$, and Rd in the chromatogram of the Test solution correspond to those in the chromatogram of Standard solution 1, as obtained in the test for Content of ginsenosides under American Ginseng. The ratio of the peak reaponse for $R b_{2}$ to the peak response for $R b_{1}$ is less than 0.4 ; and the ratio of the peak response for $\mathrm{Rg}_{1}$ to the peak response for $R b_{1}$ is less than 0.3 . The chromatogram shows no significant peak at the retention time corresponding to that of the $R_{F}$ for ginsenoside in the chromatogram of Standard solution 2, as obtained in the test for Content of ginsenosides under American Ginseng.
Microbial limits $\langle 2021\rangle$-The total aerobic microbial count does not exceed $10^{4}$ per g . The total combined molds and yeasts count does not exceed $10^{3}$ per g . It meets the requirements of the tests for absence of Salmonella species and Escherichia coli.

Dissolution $\langle 2040\rangle$ - [To come.]
Disintegration $\langle 2040\rangle$ : meet the requirements.

Weight variation $\langle 2091\rangle$ : meet the requirements.

## Content of ginsenosides-

Mobile phase and Chromatographic system-Proceed as directed for the Content of ginsenosides under American Ginseng.

Standard solution-Prepare a solution of USP Powdered American Ginseng Extract RS in a mixture of water and alcohol (6:4) having a known concentration of about 1 mg of $\mathrm{Rb}_{1}$ per mL .
Test solution-Accurately weigh not fewer than 20 Tablets, and reduce to a very fine powder. To a conical flask, transfer an accurately weighed portion of the powder expected to contain an amount of Extract equivalent to about 15 mg of total ginsenosides. Add 15 mL of methanol, and shake to mix. Sonicate the mixture at $25^{\circ}$ to $30^{\circ}$ for 30 minutes. Cool, pass through filter paper, and return the residue to the conical flask. Add another 15 mL of methanol, sonicate the mixture at $25^{\circ}$ to $30^{\circ}$ for 30 minutes, and filter. Wash the residue with three $15-\mathrm{mL}$ portions of methanol. Evaporate the combined extracts and washings to dryness under vacuum at $45^{\circ}$ to $50^{\circ}$. Quantitatively transfer the residue to a $10.0-\mathrm{mL}$ volumetric flask using small volumes of methanol, and dilute with methanol to volume.

Procedure-Proceed as directed for Procedure in the test for Content of ginsenosides under American Ginseng. Separately calculate the quantity, in mg , of each relevant ginsenoside ( $\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, and Rd ) in the portion of Tablets taken to prepare the Test solution by the formula:

$$
0.1 P C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Powdered American Ginseng Extract RS in the Standard solution; $P$ is the labeled content of the corresponding ginsenoside in the USP Powdered American Ginseng Extract RS; and $r_{U}$ and $r_{S}$ are the peak responses of the relevant ginsenosides obtained from the Test solution and the Stan-
dard solution, respectively. Calculate the content of ginsenosides as the sum of the individual quantities of $\mathrm{Rg}_{1}, \mathrm{Re}$, $\mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, and $\mathrm{Rd}_{\mathbf{\Delta U S P 2 8}}$
$\boldsymbol{\Delta}$ and dissolve in 10.0 mL of a mixture of water and alcohol
$(6: 4)_{\Delta U S P 28}$
[NOTE-The concentrations of ginsenoside $\mathrm{Rg}_{1}$ and ginsenoside $R b_{1}$ in this solution are not expected to be equal, and are determined on the basis of the labeled quantities present in USP Powdered Asian Ginseng Extract RS.]Transfer the mixture-to a ehromatographic tube fllled with diatomaceous earth eapable of holding an aqueuts layer of 20 mL . Wait for 15 minutes, elute 75 mL of butyl aleohel saturated with water, collect the eluate, and evaporate the eluate in a rotary evaperater in vacumen at $55^{\circ}$ to $60^{\circ}$ to dryness. Dissolve the residue in 10.0 mL of methanel.
$\Delta$
${ }^{\wedge} \mathrm{U}$ USP28
Test solution-Reduce about 100 g of Asian Ginseng to a powder, and transfer about 1.0 g of the powder, accurately weighed, to a $100-\mathrm{mL}$ round-bottom flask fitted with a reflux condenser. Add 50 mL of a mixture of water and alcohol (6:4) and a few grains of pumice, and boil on a water bath under reflux for 1 hour. Cool, and filter. Wash the flask and the residue with 20 mL of a mixture of water and alcohol (6:4), and pass through the same filter. Combine the filtrates, and evaporate in a rotary evaporator at $50^{\circ}$ to dryness. To the residue so obtained add 20 mL of water, mix, and proeed as directed for Standerd solution, beginning with "Transfer the mix tare to a chrematographic tube".

Chromatographic system (see-Chromatography $\langle 624\rangle$ ). The liquid chromatograph is equipped with a 203 nm detector and a $3.9 \mathrm{~mm} \times 30 \mathrm{~cm}$ columm that contains packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Fime(minutes) | $\begin{gathered} \text { Solution } A \\ (\%) \end{gathered}$ | $\begin{gathered} \text { Solution } B \\ (\%) \end{gathered}$ | Elution |
| :---: | :---: | :---: | :---: |
| $\theta$ | 82 | 18 | equilibration |
| -0-10 | 82 | 18 | isocratic |
| 10-50 | $82 \rightarrow 60$ | $18 \rightarrow 40$ | linear gradient |
| 50-80 | 60 | 40 | isocratic |

 Re, $R b_{2}$, and Rd .] Chromatograph about $10-\mu \mathrm{of}$ the standerd solution, and record the peak responses as directed for Procture: the chromatogram is similar to the Reference Chromatogram provided with the lot of USP Powdered Asian Ginseng Extract RS being used; the relative retention times for ginsenoside $\mathrm{R}_{\mathrm{g}_{+}}$and ginseneside Re are 1.0 and 1.03 , respectively; the resolution, $R$, between ginsenoside $\mathrm{Reg}_{+}$and ginseneside Re is not less than 0 .9; the resolution, $R$, between ginsenoside $R b_{+}$and a neighboring minor peak, at relative retention times of 1.86 and 1.89 , respectively, is not less than 1.0 ; the column efficieney determined from the gin senoside $\mathrm{Rg}_{4}$ and ginsenoside Rb peaks is not less than 17,000 and 41,000 theoretieal plates, respectively; the tailing factors for ginse neside $\mathrm{Rg}_{4}$ - and ginseneside $\mathrm{Rb}_{4}$ are not mere than 1.0 and 1.2 , re spectively; and the relative standard deviation for replicate injections is not more than $4.0 \%$ for ginseneside P है + and gimsene side $\mathrm{Pb}_{4}$ :
${ }^{\boldsymbol{\Delta}}$ Dissolve the residue in 10.0 mL of a mixture of water and alcohol (6:4). $\mathbf{A} U S P 28$
Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentages of ginsenosides $\mathrm{Rb}_{1}$ and $\mathrm{Rg}_{1}$ in the portion of Asian Ginseng taken by the formula:

$$
1000(C / W)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of ginsenoside $\mathrm{Rg}_{1}$ or ginsenoside $\mathrm{Rb}_{1}$ in the Standard solution; $W$ is the weight, in mg , of Asian Ginseng taken to prepare the Test solution; and $r_{U}$
and $r_{S}$ are the peak responses of ginsenoside $\mathrm{Rg}_{1}$ or ginsenoside $\mathrm{Rb}_{1}$ obtained from the Test solution and the Standard solution, respectively.

## Briefing

Powdered Asian Ginseng, USP 27 page 2008. It is proposed to add the content of marker compounds in the Definition for consistency with other USP botanicals monographs.
(DSB: G. Giancaspro) RTS-40775-5

## Change to read:

» Powdered Asian Ginseng is Asian Ginseng reduced to a fine or very fine powder.
${ }^{\Delta}$ It contains not less than 0.2 percent of ginsenoside $\mathrm{Rg}_{1}$ and not less than 0.1 percent of ginsenoside $\mathrm{Rb}_{1}$, both calculated on the dried basis. ${ }_{\triangle U S P 28}$

Briefing

Powdered Asian Ginseng Extract, USP 27 page 2008. On the basis of comments received, it is proposed to modify the temperature and the gradient in the chromatographic procedure for Content
of ginsenosides. It is reported that performing the chromatographic run at $25^{\circ}$ improves the resolution, and a washing step added after the elution of analytes avoids carry over of late eluting peaks in subsequent chromatograms.
(DSB: G. Giancaspro) RTS-40775-6

## Change to read:

Content of ginsenosides-
Diluent-Prepare a mixture of water and alcohol (6:4).
Solution A-Use filtered and degassed water.
Solution B-Prepare a filtered and degassed mixture of acetonitrile and water (8:2).

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard solution-Transfer an accurately weighed amount of USP Powdered Asian Ginseng Extract RS to a suitable volumetric flask, fill the flask with Diluent to about $60 \%$ of its nominal volume, dissolve by sonicating for 10 minutes, dilute with Diluent to volume to obtain a solution having a known concentration of about 24 mg per mL , mix, and filter.
Test solution- Proceed as directed for Standard solution, except to use Powdered Extract.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $203-\mathrm{nm}$ detector, a 4.6$\mathrm{mm} \times 2.0-\mathrm{cm}$ guard column that contains packing L1, and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ analytical column that contains
${ }^{\mathbf{\Delta}} 3-\mathrm{\mu m}_{\mathbf{\Delta} U S P 28}$
packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $40^{\circ}$
$\triangle 25^{\circ}$
$25^{\circ} \cdot \mathbf{\Delta U S P 2 8}$
The chromatograph is programmed as follows. Chromatograph the Standard solution, and record the peak areas as directed for Procedure: the chromatogram is similar to the Reference Chromatogram provided with the lot of USP Powdered Asian Ginseng Extract RS being used; and the relative standard deviation, determined for the sum of the peak areas for the six major ginsenosides, for replicate injections is not more than $2.0 \%$.

| $\begin{gathered} \text { Time } \\ \text { (minutes) } \end{gathered}$ | Solution A (\%) | Solution B (\%) | Elution |
| :---: | :---: | :---: | :---: |
| 0 | 76 | 24 | equilibration |
| 0-12 | 76 | 24 | isocratic |
| 12-28 | $76 \rightarrow 65$ | $24 \rightarrow 35$ | linear gradient |
| 28-51.5 | $65 \rightarrow 56.5$ | $35 \rightarrow 43.5$ | linear gradient |
| 51.5-52.5 | $\begin{gathered} 56.5 \rightarrow \\ 76 \\ \mathbf{\Delta}^{0} \Delta_{\text {USP } 28} \end{gathered}$ | $\begin{gathered} 43.5 \rightarrow 24 \\ \mathbf{\Delta}_{100_{\Delta U S P 28}} \end{gathered}$ | linear gradient |
| ${ }^{\text {5 5 }}$ 52.5-64.5 ${ }_{\text {©USP28 }}$ | ${ }^{\text {® }} 0 \rightarrow 7 \mathbf{*}_{\text {^USP28 }}$ | ${ }^{\wedge} 100 \rightarrow 24{ }_{\text {^USP28 }}$ | ${ }^{\text {4 }}$ linear gradient ${ }_{\text {AUSP28 }}$ |
| 52.5-64.5 | 76 | 24 | isocratic |
| ${ }^{\text {4 } 64.5-77 ~}{ }_{\text {^USP28 }}$ |  |  |  |

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, identify the peaks for the ginsenosides by comparison with the Reference Chromatogram provided with the lot of USP Powdered Asian Ginseng Extract RS being used, and measure the peak areas for the six major ginsenosides. Calculate the percentage of each relevant ginsenoside $\left(\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}\right.$, $R b_{2}$, and $R d$ ) in the portion of Powdered Extract taken by the formula:

$$
\left(W_{S} / W_{T}\right)\left(r_{U} / r_{S}\right) P
$$

in which $W_{S}$ is the weight, in mg, of USP Powdered Asian Ginseng Extract RS taken to prepare the Standard solution; $W_{T}$ is the weight, in mg, of Powdered Extract taken to prepare the Test solution; $r_{U}$ and $r_{S}$ are the peak areas for each relevant ginsenoside obtained from the Test solution and the Standard solution, respectively; and $P$ is the labeled amount, in percentage, of each relevant ginsenoside in USP Powdered Asian Ginseng Extract RS. Calculate the Content of ginsenosides, in percentage, by adding the percentages of each relevant ginsenoside.

## Briefing

Asian Ginseng Capsules-This proposed new monograph was previously published in Pharmacopeial Previews (see page 775 of PF 26(3) [May-June 2000]), but was later canceled because of concerns that the monograph had two different tests for Content of ginsenoside. The Expert Committee has since decided to accept the use of multiple procedures within the same monograph; therefore, the current version is being forwarded to In-Process Revision.
(DSB: G. Giancaspro) RTS-40774-1

## Add the following:

## ©Asian Ginseng Capsules

## » Asian Ginseng Capsules contain Powdered

 Asian Ginseng Extract. Capsules contain not less than 90.0 percent and not more than 110.0 percent of Extract calculated as the sum of ginsenosides $\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, and Rd .Packaging and storage-Preserve in tight containers, protected from light. Store at controlled room temperature.

Labeling-The label states the Latin binomial and, following the official name, the article from which the Capsules were prepared. The label also indicates the amount of Extract, in mg per Capsule. Label the Capsules to indicate the content of ginsenosides as a percentage of the Extract contained in the Capsules. State the method for Content of ginsenosides with which the product complies only if Method 1 is not used.

USP Reference standards $\langle 11\rangle$ —USP Powdered Asian Ginseng Extract RS.

## Identification-

A: For soft-shell gelatin capsules-Transfer a portion of the contents of the Capsules, equivalent to about 100 mg of Extract to a separatory funnel containing 30 mL of a mixture of hexanes, methanol, and water (20:15:10), dissolve, and collect the lower layer. Wash the upper layer with three portions of 15 mL each of a mixture of methanol and water (15:10), and combine the washings with the lower layer. Evaporate to dryness under vacuum at $45^{\circ}$ to $50^{\circ}$. Dissolve the residue in 10 mL of a mixture of methanol and water ( $15: 10$ ), and proceed as directed for Identification under Asian Ginseng, beginning with "Apply separately in bands."

For hard-shell gelatin capsules-Transfer a portion of the contents of the Capsules equivalent to about 100 mg of Extract to a conical flask. Extract at $55^{\circ}$ with three portions of 20 mL each of a mixture of water and methanol (8:2). Evaporate the combined extracts to dryness under vacuum at $45^{\circ}$ to $50^{\circ}$. Dissolve the residue in 10 mL of a mixture of methanol and water (15:10), and proceed as directed for Identification under Asian Ginseng, beginning with "Apply separately in bands."

B: The retention times of the relevant analytes obtained in the chromatogram of the Test solution in the Procedure under Content of ginsenosides correspond to those obtained
in the chromatogram of the Standard solution. The chromatogram of the Test solution shows a peak at the retention time corresponding to that of the $R_{F}$ for ginsenoside in the chromatogram of the Standard solution.

Microbial Limits $\langle 2021\rangle$ - The total aerobic microbial count does not exceed $10^{4}$ per g . The total combined molds and yeasts count does not exceed $10^{3}$ per g. It meets the requirements of the tests for absence of Salmonella species and Escherichia coli.

Disintegration $\langle 2040\rangle$ : meet the requirements.
Dissolution $\langle 711\rangle$ : [To come.]
Weight variation $\langle 2091\rangle$ : meet the requirements.

## Content of ginsenosides-

METHOD 1-
Mobile phase and Chromatographic system-Proceed as directed for Content of ginsenosides under Powdered Asian Ginseng Extract.

Standard solution-Transfer an accurately weighed amount of USP Powdered Asian Ginseng Extract RS to a suitable container, and dilute quantitatively and stepwise, if necessary, with a mixture of water and alcohol (6:4) to obtain a solution having a known concentration of about 0.1 mg per mL of ginsenoside $\mathrm{Rb}_{1}$.

Test solution (for soft-gelatin capsules)-Using a suitable cutting instrument open not fewer than 20 capsules, and transfer the contents to a suitable container. Mix to homogenize, and transfer an accurately weighed portion expected to contain an amount of Extract equivalent to 12 mg of ginsenosides to a suitable flask with a stopper. Add 5.0 mL of tetrahydrofuran, and sonicate for 5 minutes. Add 25.0 mL of a mixture of methanol and water ( $40: 60$ ), and shake for 50 minutes in an automatic shaker. Transfer about 15.0 mL of the obtained emulsion to a centrifuge tube with a stopper, add about 800 mg of sodium chloride, shake for 30 seconds, and centrifuge to obtain a clear upper phase. Dilute 1.0 mL
of the upper phase with 4 mL of water in a suitable tube, and transfer the solution to a column containing 360 mg of packing L2 that has been previously treated with 3.0 mL of methanol followed by 8.0 mL of water. [NOTE-Elute slowly, not faster than 1 drop per second in all elution steps. Do not use vacuum.] Rinse the tube with 5 mL of water, transfer to the column taking the precaution of slow elution, and discard the eluate. Repeat the elution with 5 mL of a mixture of methanol and water (40:60), and discard the eluate. Elute the ginsenosides with 5.0 mL of methanol. Evaporate the solution under a stream of nitrogen at $40^{\circ}$ (about 50 minutes), and dissolve the residue with 1.0 mL of a solution of acetonitrile and water (2:8).

Procedure-Proceed as directed for Procedure in Content of ginsenosides under Powdered Asian Ginseng Extract. Separately calculate the quantity, in mg, of each relevant ginsenoside ( $\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, and Rd ) in the portion of Asian Ginseng Capsules taken to prepare the Test solution by the formula:

$$
0.3 P C\left(r_{U} / r_{S}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Powdered Asian Ginseng Extract RS in the Standard solution; $P$ is the labeled percentage of the corresponding ginsenoside in the USP Powdered Asian Ginseng Extract RS; $r_{U}$ is the peak response for each relevant ginsenoside in the chromatogram of the Test solution; and $r_{S}$ is the peak response of the corresponding ginsenoside in the Standard solution. Calculate the content of ginsenosides, in mg , as the sum of the individual quantities of each relevant ginsenoside ( $\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, and Rd ).

METHOD 2-
Solvent $A$ : upper 2 phase of a mixture of hexane-metha-nol-water (4:3:2)

Solvent B: lower phase of a mixture of hexane methanol water (4:3:2)

Mobile phase and Chromatographic system—Proceed as directed for Content of ginsenosidesunder Powdered Asian Ginseng Extract.

Standard solution - Prepare a solution of USP Asian Ginseng Extract RS in a mixture of water and alcohol (6:4) having a known concentration of about 0.5 mg of $\mathrm{Rb}_{1}$ per mL .
Test solution I (for soft-gelatin capsules)-Using a suitable cutting instrument open not fewer than 20 capsules, and transfer the contents to a suitable container. Mix to homogenize, and transfer an accurately weighed portion expected to contain an amount of Extract equivalent to 15 mg of total ginsenosides to a 50 mL flask. Add 10.0 mL of Solvent $A$ and sonicate for $3-5$ minutes at $25-30^{\circ} \mathrm{C}$.

Transfer the solution to a 125 mL separator funnel. To the residue, add 10 mL of Solvent $B$ and sonicate for 3-5 minutes at $25-30^{\circ} \mathrm{C}$. Transfer the solution to the same separator funnel. Repeat the above procedure twice (Total volume about 60 mL ). Shake and then allow the phases to separate. Collect the lower phase in a round bottom flask and wash the upper phase twice with 10 mL of Solvent B. Evaporate the combined lower phases to dryness under vacuum at $45^{\circ}$ to $50^{\circ}$. Quantitatively transfer the residue to a $10.0-\mathrm{mL}$ volumetric flask using small volumes of methanol, and complete with methanol to volume.

Test solution II (for hard-gelatin capsules)—Accurately weight the contents of not fewer than 20 Capsules, and composite the contents. Transfer an accurately weighed portion of the composite expected to contain an amount of Extract equivalent to approximately 15 mg of total ginsenosides to a conical flask. Add 15 mL of methanol, and shake to mix. Sonicate the mixture at $25^{\circ}$ to $30^{\circ}$ for 30 minutes. Cool, pass through filter paper, and return the residue to the conical flask. Add another 15 mL of methanol, sonicate the mixture at $25^{\circ}$ to $30^{\circ}$ for 30 minutes, and filter. Wash the residue with three portions of 15 mL of methanol each. Evaporate
the combined extracts and washing to dryness under vacuum at $45^{\circ}$ to $50^{\circ}$. Quantitatively transfer the residue to a $10.0-\mathrm{mL}$ volumetric flask using small volumes of methanol, and complete with methanol to volume.

Procedure-Proceed as directed for Procedure in Content of ginsenosides under Powdered Asian Ginseng Extract. Separately calculate the quantity, in mg, of each relevant ginsenoside ( $\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}$, and Rd ) in the portion of Asian Ginseng Capsules taken to prepare Test solution I or Test solution II by the formula:

$$
0.1 P C\left(r_{U} / r_{S}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Powdered Asian Ginseng Extract RS in the Standard solution; and the other terms are as defined under Method 1. Calculate the content of ginsenosides, in mg , as the sum of the individual quantities of each relevant ginsenoside $\left(\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}\right.$, $\mathrm{Rc}, \mathrm{Rb}_{2}$, and Rd ). $\mathbf{\Delta U S P 2 8}$

BRIEFING

Asian Ginseng Tablets, USP 27 page 2009—See briefing under Asian Ginseng.
(DSB: G. Giancaspro) RTS—30727-10

## Change to read:

## Content of ginsenosides-

Solution A, Solution B, Mobile phase, and Chromatographic system-Proceed as directed for Content of ginsenosides under Powdered Asian Ginseng Extract.

Standard solution-Transfer about 200 mg of USP Powdered Asian Ginseng Extract RS, accurately weighed, to a suitable container, dissolve in 5 mL of water, and transfer quantitatively, with the rid of an additional 5 mL of water, to a chromagraphic tube filled with diatomaceeus eath capableof holding a 20 mL aqueeus tayer. Wait for 15 minates, and elate the coltma with 75 mL of $n-$ bulylaleohol saturated with water. Evaporate to dryness in waemm between $55^{\circ}$ and $60^{\circ}$, and dissolve the residue in 5.0 mL of metha noly
${ }^{\Delta} 5.0 \mathrm{~mL}$ of a mixture of water and alcohol (6:4), and filter. $\mathbf{A S P P 2 8}$

Test solution-Weigh and powder not fewer than 20 Tablets. Transfer an accurately weighed amount of the powder, equivalent to about 200 mg of Powdered Extract, to a conical flask, and extract three times, each with a $20-\mathrm{mL}$ portion of a mixture of methanol and water (8:2), in a $55^{\circ}$ bath for 30 minutes, stirring with a magnetic stirrer. Evaporate the combined extracts to dryness in vacuum between $45^{\circ}$ and $50^{\circ}$. Dissolve the residue in 5 mL of water, and trancfer quantitatively, with the rid of an additional 5 mL of water, to chremagraphic fube filled with diatemaerus eath eapable of holding 20 mL aquern layer. Wait for 15 minutes, and elute the column with 75 mL of $n$ butyl aleohal saturated with water. Evaperate to drymess in vacumm between $55^{\circ}$ and $60^{\circ}$, and dissolve the residue in 5.0 mL of methanel
© 5.0 mL of a mixture of water and alcohol (6:4), and filter. ${ }^{\text {USP2 }} 8$
$\stackrel{\text { Procedure-Proceed as directed for Content of ginsenosides un- }}{ }$ der Powdered Asian Ginseng Extract, except to calculate the quantity, in mg , of each relevant ginsenoside $\left(\mathrm{Rg}_{1}, \mathrm{Re}, \mathrm{Rb}_{1}, \mathrm{Rc}, \mathrm{Rb}_{2}\right.$, and Rd ) in the portion of Tablets taken by the formula:

$$
0.05 P C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Powdered Asian Ginseng Extract RS in the Standard solution; and the other terms are as defined therein. Calculate the quantity, in mg , of ginsenosides by adding the individual amounts calculated as above.

## Briefing

Powdered Licorice Extract, USP 27 page 2019 and page 1365 of $P F 26(5)$ [Sept.-Oct. 2000]. It is proposed to revise the Labeling section to add a warning statement to be applied to the label.
(DSI: J. Salguero) RTS-40887-1

## Change to read:

Labeling-The label states the Latin binomial and, following the official name, the part of the plant from which the article was derived. The label also indicates the content of glycyrrhizic acid, the extracting solvent or solvent mixture used for preparation, and the ratio of the starting material to final product.
${ }^{\Delta}$ The label bears a statement indicating that "Excessive amounts or long-term use of Licorice may cause high blood pressure or low potassium, which have been associated with irregular heartbeat and/or muscle weakness. Licorice may worsen the effects of congestive heart failure, cirrhosis, or
kidney failure. Diuretic use may increase the risk. If you are pregnant or nursing a baby, seek the advice of a health professional before using this product." ${ }_{\triangle U S P 28}$
It meets the requirements for Labeling under Botanical Extracts $\langle 565\rangle$.

## Add the following:

-Microbial limits $\langle 2021\rangle$-The total bacterial count does not exceed $10^{4}$ per g , the total combined molds and yeasts count does not exceed $10^{3}$ per g , and the enterobacterial count does not exceed $10^{3}$ per g. It meets the requirements of the tests for absence of Salmonella species, Escherichia coli, and Staphylococcus aureus.■2S (USP27)

## BRIEFING

Lycopene, page 851 of $P F$ 29(3) [May-June 2003]. This new monograph, which previously appeared in Pharmacopeial Previews, is now being forwarded to In-Process Revision with modifications based on comments received. The existence of lycopene from different sources in the market created confusion among the consumers and manufacturers of dietary supplements. To clarify the situation, the USP Expert Committee on Nomenclature and Labeling proposes the addition of a Labeling section requiring the indication of whether the article is obtained from natural sources or prepared synthetically.
(NL: W. Paul; DSB: G. Giancaspro) RTS—40413-1; 40331-1

## Add the following:

## ©Lycopene

$\mathrm{C}_{40} \mathrm{H}_{56} \quad 536.88 \quad[502-65-8]$.

## » Lycopene is a mixture of geometrical isomers of

 lycopene. It contains not less than 96.0 percent and not more than 101.0 percent of lycopene $\left(\mathrm{C}_{40} \mathrm{H}_{56}\right)$, calculated on the dried basis.Packaging and storage-Preserve in tight, light-resistant containers, under inert gas, and store in a cool place.

USP Reference standards $\langle 11\rangle$-USP Lycopene RS.
Labeling-Label it to indicate whether the article is obtained from natural sources or is prepared synthetically. If obtained from natural sources, label it to indicate the natural source including its Latin binomial.

## Identification-

A: Ultraviolet-Visible Absorption $\langle 197 \mathrm{U}\rangle-$ Spectral range: 300 to 700 nm .

Solution: Prepare as directed below for the Test solution in the test for Content of lycopene.

Ratio: $A_{476} / A_{508}$, between 1.10 and 1.14.
B: The retention time of the major peak in the chromatogram of the Test solution corresponds to that in the chromatogram of the Standard solution, as obtained in the test for Content of all-E-lycopene, 5Z-lycopene, and related compounds.

Loss on drying $\langle 731\rangle$ —Dry it in vacuum over phosphorous pentoxide at $40^{\circ}$ for 4 hours: it loses not more than $0.2 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.2 \%$.
Heavy metals, Method II $\langle 231\rangle$ : not more than $10 \mu \mathrm{~g}$ per g. Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

## Content of all-E-lycopene, 5Z-lycopene, and related

 compounds-Mobile phase-Prepare a filtered and degassed mixture of tert-butyl methyl ether, methanol, and tetrahydrofuran (784:665:74, w:w:w). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve a suitable quantity of USP Lycopene RS in Mobile phase to obtain a solution containing about 2 mg per 100 mL .

Test solution-Transfer about 15 mg of Lycopene to a 25mL volumetric flask, and dissolve in tetrahydrofuran containing 50 mg of butylated hydroxytoluene per L. Dilute with the same solvent to volume. Pipet 2 mL into a $50-$ mL volumetric flask, and add 8 mL tetrahydrofuran. Dilute with tert-butyl methyl ether to volume. Use this solution for injection.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $472-\mathrm{nm}$ detector, one $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ L61 packing; and a second column connected in series containing $3-\mu \mathrm{m}$ packing L61. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.07 for $5 Z-$ lycopene, and 1.0 for all- $E$-lycopene; the resolution, $R$, between all- $E$-lycopene and 5Z-lycopene is not less than 1.0; the tailing factor is not less than 0.8 and not more than 2.0 ; and the relative standard deviation for replicate injections for the all- $E$-lycopene is not more than $2.0 \%$. [NOTE-New columns may require up to 30 injections before the system suitability requirements are met.]

Procedure—Inject about $10 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure the peak area responses. Calculate the percentage of related compounds in the portion of Lycopene taken by the formula:

$$
T\left(r_{s} / r_{T}\right)
$$

in which $T$ is the percentage of total lycopene isomers obtained in the test for Content of lycopene; $r_{s}$ is the sum of the responses of all peaks excluding the peak for all- $E$-lycopene and the peak for $5 Z$-lycopene; and $r_{T}$ is the total detected area. Not more than $7.0 \%$ of other related compounds cal-
culated as lycopene are found. Calculate the percentage of the $5 Z$-lycopene isomer in the portion of Lycopene taken by the formula:

$$
T\left(r_{5 Z} / r_{T}\right),
$$

in which $r_{5 Z}$ is the peak response for the 5Z-lycopene isomer, and the other terms are as described above. Not more than $23.0 \%$ of the $5 Z$-lycopene isomer is found. Calculate the percentage of all-E-lycopene taken by the formula:

$$
T\left(r_{E} / r_{T}\right)
$$

in which $r_{E}$ is the peak response of the all- $E$-lycopene isomer, and the other terms are as described above. Not less than $70.0 \%$ of all- $E$-lycopene is found.

## Content of lycopene-

Test stock solution-Transfer about 25 mg of Lycopene to a $100-\mathrm{mL}$ volumetric flask, add about 25 mg of butylated hydroxytoluene and about 60 mL of methylene chloride, and sonicate to dissolve. Dilute with methylene chloride to volume.

Test solution-Transfer 2.0 mL of the Test stock solution to a $200-\mathrm{mL}$ volumetric flask, and dilute with cyclohexane to volume.

Procedure-Determine the absorbance of the Test solution at the wavelength of maximum absorbance at about 476 nm , using cyclohexane as the blank. Calculate the percentage of $\mathrm{C}_{40} \mathrm{H}_{56}$ in the portion of Lycopene taken by the formula:

$$
1000 \mathrm{~A} / 331 \mathrm{~W},
$$

in which $A$ is the absorbance of the Test solution; $W$ is the weight, in g , of Lycopene taken to prepare the Test stock solution; and 331 is the absorptivity of the pure lycopene in cyclohexane. $\mathbf{\Delta}$ USP28

## Briefing

Lycopene Preparation, page 852 of $P F$ 29(3) [May-June 2003]. This new monograph, which previously appeared in Pharmacopeial Previews, is now being forwarded to In-Process Revision with modifications on the basis of comments received. It is proposed to revise the limits for all- $E$ - and $5 Z$-isomers. See also the briefing under Lycopene for proposed changes in Labeling requirements.
(NL: W. Paul; DSB: G. Giancaspro) RTS-40413-2

## Add the following:

## ©Lycopene Preparation

» Lycopene Preparation is a combination of Lycopene with one or more inert substances and suitable antioxidants. It may be in a solid or oily liquid form. It contains not less than 95.0 percent and not more than 120 percent of the labeled amount of lycopene $\left(\mathrm{C}_{40} \mathrm{H}_{56}\right)$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight, light-resistant containers, under inert gas. Store the oil preparations in a cool place and the solid preparations at controlled room temperature.

Labeling-Label it to state the name and content of added antioxidants and inert substances. Label it to indicate whether the article is prepared with Lycopene from natural sources or from synthetic Lycopene. If prepared with Lycopene from natural sources, label it to indicate the natural source including its Latin binomial.

USP Reference standards-USP Lycopene RS.

Identification, Ultraviolet-Visible Absorption $\langle 197 \mathrm{U}\rangle$ FOR OILY PREPARATIONS-

Spectral range: 300 to 700 nm .
Solution: Prepare as directed below for the Test solution in the test for Content of lycopene (for oily preparations).

Ratio: $A_{476} / A_{508}$ between 1.10 and 1.14 in cyclohexane. FOR SOLID PREPARATIONS-

Spectral range: 300 to 700 nm .
Solution: Prepare as directed below for the Test solution in the test for Content of lycopene (for solid preparations).

Ratio: $A_{472} / A_{504}$ between 1.09 and 1.13 in isopropyl alcohol.

Water, Method $I\langle 921\rangle$ : not more than $1.0 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $1.0 \%$.
Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

Solvent: dimethylformamide.
Content of all-E-lycopene, 5Z-lycopene, and related compounds-
Mobile phase, Standard solution, and Chromatographic system-Proceed as directed for Content of all-E-lycopene, 5Z-lycopene and related compounds under Lycopene.

Test solution for oil preparations-Transfer a quantity of oil preparation, equivalent to about 15 mg of lycopene, to a $25-\mathrm{mL}$ volumetric flask, and dissolve in tetrahydrofuran containing 50 mg of butylated hydroxytoluene per L. Dilute with the same solvent to volume. Pipet 2 mL into a $50-\mathrm{mL}$ volumetric flask, and add 8 mL of tetrahydrofuran. Dilute with tert-butyl methyl ether to volume. Use this solution for injection.
Test solution for solid preparations-Transfer a quantity of solid preparation, equivalent to 5 mg of lycopene, into a $250-\mathrm{mL}$ volumetric flask, and add about 60 units of bacterial alkaline protease preparation or another suitable enzyme and about 25 mg of butylated hydroxytoluene. Add 2.5
mL of water, place in an ultrasonic bath at $50^{\circ}$ for 10 min utes, and shake occasionally until the material is finely divided with no lumps. Add 5 mL of tetrahydrofuran, 40 mL of dehydrated alcohol, and place again for about 1 minute in the ultrasonic bath. Cool to room temperature, and dilute with tert-butyl methyl ether to volume. Shake vigorously. Allow the precipitate to settle, and filter the supernantant.

Procedure-Proceed as directed for Content of all-E-lycopene, 5Z-lycopene, and related compounds under Lycopene. Calculate the percentage of related compounds in the portion of Lycopene Preparation taken by the formula:

$$
r_{s} / r_{T}
$$

in which $r_{s}$ is the sum of the responses of all peaks excluding the peak for all- $E$-lycopene and the peak for 5Z-lycopene; and $r_{T}$ is the total detected area in the chromatogram: not more than $7.0 \%$ of other related compounds, calculated as lycopene, are found. Calculate the percentage of 5Z-lycopene isomer in the portion of Lycopene Preparation taken by the formula:

$$
r_{5 Z} / r_{T}
$$

in which $r_{s Z}$ is the peak response for the 5Z-lycopene isomer, and the other terms are as described above: not more than $23.0 \% 30.0 \%$ of the $5 Z$-lycopene isomer is found. Calculate the percentage of all- $E$-lycopene in the portion of Lycopene Preparation taken by the formula:

$$
r_{E} / r_{T}
$$

in which $r_{E}$ is the peak response of the all- $E$-lycopene isomer, and the other terms are as described above: not less than $70.0 \% 65.0 \%$ of all- $E$-lycopene is found.

## Content of lycopene

## TEST FOR OILY PREPARATIONS-

Test stock solution-Transfer an accurately weighed quantity of Lycopene Preparation containing about 25 mg of lycopene to a $100-\mathrm{mL}$ volumetric flask, and add about 25 mg of butylated hydroxytoluene and about 60 mL of methylene chloride. Sonicate to dissolve, and dilute with methylene chloride to volume.
Test solution-Transfer 2.0 mL of the Test stock solution to a $200-\mathrm{mL}$ volumetric flask, and dilute with cyclohexane to volume.

Procedure-Determine the absorbance of the Test solution at the wavelength of maximum absorbance at about 476 nm , using cyclohexane as the blank. Calculate the percentage of lycopene in the portion of Lycopene Preparation taken by the formula:

$$
1000 \mathrm{~A} / 331 \mathrm{~W},
$$

in which $A$ is the absorbance of the Test solution; $W$ is the weight, in g , of the portion of Lycopene Preparation taken to prepare the Test stock solution; and 331 is the absorptivity of the pure lycopene in cyclohexane.

## TEST FOR SOLID PREPARATIONS-

Test stock solution-Transfer an accurately weighed quantity of Lycopene Preparation containing about 5 mg of lycopene into a $200-\mathrm{mL}$ volumetric flask. Add about 60 units of bacterial alkaline protease preparation or another suitable enzyme and about 25 mg of butylated hydroxytoluene. Add 2.5 mL of diluted ammonium hydroxide (2 in 100). Incubate in a water bath (about $40^{\circ}$ ) until the matrix has dissolved (about 1 to 2 minutes), while rotating the flask to avoid having material stick to the glass surface. Add 5 mL of tetrahydrofuran, and shake until no colored precipitate remains. Add another portion of 2 mL of tetrahydrofuran. Add 40 mL of dehydrated alcohol, and shake until the mixture is
homogeneous. Add 100 mL of diethyl ether, and shake vigorously. Dilute with diethyl ether to volume, shake vigorously, and allow to stand until the solid has settled.

Test solution-Transfer 2.0 mL of the supernatant from the Test stock solution to a $25-\mathrm{mL}$ volumetric flask, and dilute with isopropyl alcohol to volume.

Procedure-Determine the absorbance of the Test solution at the wavelength of maximum absorbance at about 472 nm , using isopropyl alcohol as the blank. Calculate the percentage of lycopene in the portion of Lycopene Preparation taken by the formula:

$$
250 \mathrm{~A} / 320 \mathrm{~W},
$$

in which $A$ is the absorbance of the Test solution; $W$ is the weight, in g , of the portion of Lycopene Preparation taken to prepare the Test stock solution; and 320 is the absorptivity of the pure lycopene in isopropyl alcohol. $\Delta$ USP28

## BRIEFING

Lycopene Tomato Extract, page 855 of $P F 29$ (3) [May-June 2003]. This new monograph, which previously appeared in Pharmacopeial Previews, is now being forwarded to In-Process Revision with modifications on the basis of comments received. It is proposed to revise the Definition to allow the addition of tocopherols as antioxidants, to correct the Latin binomial, and to better reflect the products available in the international market. Since this article is prepared by extraction from ethyl acetate, a limit for this solvent is proposed. A test for Limit of aflatoxins is also included. It is also proposed to revise the limit for Water content and to revise the Labeling section for consistency with other USP monographs for articles of botanical origin.
(DSB: G. Giancaspro) RTS-40208-1

## Add the following:

## ©Lycopene Tomato Extract Containing Lycopene

## » Eyeopene Tomato Extract Containing Lycopene

 is an ethyl acetate extract of the natural tomato lipids., witheut any addition of ether ingredients It is produced from the pulp of ripe fruits of Lyeopersicullum L. Lycopersicon esculentum Mill. (Fam. Solanaceae), after removing the tomato serum. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of lycopene $\left(\mathrm{C}_{40} \mathrm{H}_{56}\right)$. It contains not less than 5.7 4.7 percent and not more than 12 percent of lycopene $\left(\mathrm{C}_{40} \mathrm{H}_{56}\right)$, not less than 0.8 percent of the combined amount of phytofluene $\left(\mathrm{C}_{40} \mathrm{H}_{68}\right)$ and phytoene $\left(\mathrm{C}_{40} \mathrm{H}_{64}\right)$, not less than 0.2 percent of beta carotene $\left(\mathrm{C}_{40} \mathrm{H}_{56}\right)$, and not less than 1.0 percent of tocopherols $\left(\mathrm{C}_{28} \mathrm{H}_{48} \mathrm{O}_{2}\right)$ on the anhydrous basis. Tocopherols may be added as antioxidants.Packaging and storage-Preserve in tight, light-resistant containers, and store in a cool place.

Labeling-Label it to state the content of lycopene in percentage and that the material should be heated to $50^{\circ}$ and mixed before use. Label it to indicate the Latin binomial and the part of the plant from which the article is derived.

USP Reference standards $\langle 11\rangle$ —USP Lycopene RS. USP Eyeopent Tomato Extract Containing Lycopene RS.

Clarity of solution-Warm the sample to $50^{\circ}$ in a water bath. Mix well with a glass rod or a spatula. Accurately weigh about 1 g of the Extract directly into a $100-\mathrm{mL}$ volumetric flask. Add 50 mL of methylene chloride, and sonicate
the solution for 1 minute to completely dissolve the sample. Bring to room temperature, dilute with methylene chloride to volume, and mix well. The solution is clear: no deposit or turbidity is formed.

## Identification-

A: Presence of lycopene, phytofluene, and phytoeneButylated hydroxytoluene stock solution, Diluting solution, Standard solution A, Standard solution B, and Test solution-Proceed as directed in the test for Content of lycopene.

Chromatographic system-Proceed as directed in the test for Content of other carotenoids and tocopherols. The chromatogram of the Test solution exhibits peaks at the retention times for lycopene, phytofluene, and phytoene corresponding to those obtained in the chromatogram of the System suitability solution, as directed in the test for Content of other carotenoids and tocopherols.

B: Ratio of all-E-lycopene and 5Z-lycopene-
Butylated hydroxytoluene stock solution-Proceed as directed in the test for Content of lycopene.

Mobile phase-Prepare a filtered and degassed solution of $0.05 \%$ diisopropylethylamine in $n$-hexane. Mix well, and sonicate for 3 to 4 minutes.

Test solution-Proceed as directed in the test for Content of lycopene, except to make the final dilution by transferring 5 mL to a $100-\mathrm{mL}$ volumetric flask and diluting with $n$-hexane to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with two $4.0-\mathrm{mm} \times$ $25-\mathrm{cm}$ columns that contain $5-\mu \mathrm{m}$ packing L3 (300 $\AA$ pore size), connected in a series and kept at $22^{\circ}$, and a $472-\mathrm{nm}$ detector. The flow rate is 0.5 mL per minute. The peak for all- $E$-lycopene elutes between 30 to 45 minutes; the relative retention time for all- $E$-lycopene is 1.00 ; and the relative re-
tention time for 5Z-lycopene is in the range from 1.04 to 1.10. Both peaks have a maximum absorbance at about 472 nm .

Procedure-Inject about $10 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, measure the peak responses of the two major peaks, and calculate their area ratio by the formula:

$$
r_{U 1} / r_{U 2}
$$

in which $r_{U 2}$ is the peak response of all- $E$-lycopene; and $r_{U 1}$ is the peak response of $5 Z$-lycopene. The area ratio is not more than 0.10 .

Viscosity $\langle 911\rangle$ : Equilibrate the Extract at $37^{\circ}$ in a $30-\mathrm{mL}$ glass vial. Determine the viscosity using a rotational viscosimeter equipped with a spindle (No. 6 spindle) having a cylinder 1.47 cm in diameter and 0.16 cm high attached to a shaft 0.32 cm in diameter, with a distance of 3.02 cm from the top of the cylinder to the lower tip of the shaft. The spindle is rotating at the appropriate speed and immersion depth to obtain a scale reading between $10 \%$ and $90 \%$ of full scale. Calculate the viscosity, in centipoises, by multiplying the scale reading by the constant for the spindle and speed used: the viscosity is not more than 5000 centipoises.

Microbial limits $\langle 2021\rangle$ : It meets the requirements of the tests for absence of Salmonella species, Escherichia coli, and Pseudomonas aeruginosa. The total aerobic microbial count does not exceed 1000 per g, and the total combined molds and yeasts count does not exceed 200 per g.

Limit of aflatoxins $\langle 561\rangle$ : not more than $4 \mu \mathrm{~g}$ per kg of total aflatoxins B1, B2, G1, and G2; not more than $2 \mu \mathrm{~g}$ per kg of aflatoxin B1.

Water, Method Ia $\langle 921\rangle$ : not more than $0.5 \% 0.8 \%$.
Particle size distribution-Transfer 1 drop to a microscope slide, and spread evenly. Isopropanol may be used as a diluent, if necessary. Examine the slide under a microscope
equipped with a calibrated ocular micrometer, using about $450 \times$ magnification (see Optical Microscopy $\langle 776\rangle$ ). Scan the slide, and note the size of the individual particles: not fewer than $98 \%$ of the particles are less than $20 \mu \mathrm{~m}$ in length when measured along the longest axis, not fewer than $60 \%$ of the particles are less than $5 \mu \mathrm{~m}$, and not fewer than $40 \%$ of the particles are less than $2 \mu \mathrm{~m}$.

Pesticide residues $\langle 561\rangle$ : meets the requirements.
Heavy metals, Method II $\langle 231\rangle: 10 \mu \mathrm{~g}$ per g.
Organic volatile impurities, Method IV $\langle 467\rangle$ —Use diethyl phthalate as the solvent in preparation of the Standard Solution and the Test Solution. Heat the sealed vial at $70^{\circ}$ for 120 minutes: meets the requirements. The limit for ethyl acetate is 50 ppm .

## Content of lycopene-

Butylated hydroxytoluene stock solution-Dissolve 2.5 g of butylated hydroxytoluene in methylene chloride to make 500 mL . [NOTE-This solution can be stored protected from light for up to 3 months.]

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile, methanol, methylene chloride, and $n$-hexane (850:100:25:25). Add $0.05 \%$ of diisopropylethylamine, mix well, and sonicate for 3 to 4 minutes.

Diluting solution—Prepare a mixture of acetonitrile, methylene chloride, methanol, $n$-hexane, and butylated hydroxytoluene (600:150:150:100:0.5). Add $0.05 \%$ of diisopropylethylamine, mix well, and sonicate for 3 to 4 minutes.

Standard solution A-Transfer an accurately weighed quantity of USP Lycopene RS, equivalent to 6 to 8 mg of lycopene, to a $100-\mathrm{mL}$ volumetric flask, and dissolve in 10 mL of methylene chloride, using a sonicator. Dilute with Diluting solution to volume to obtain a solution having a known concentration of about 0.07 mg of lycopene per mL .

Determine the exact concentration of Standard solution $A$ by employing the following method.

Standard solution B-Transfer 2.0 mL of Standard solution $A$ to a $100-\mathrm{mL}$ volumetric flask, add 10 mL of alcohol and 10 mL of Butylated hydroxytoluene stock solution, dilute with $n$-hexane to volume, and mix.

Procedure-Determine the absorbance of this solution at the maximum absorbance at about 472 nm . Calculate the concentration of Standard solution $A$, in ppm of lycopene, by the formula:

$$
50,000 A_{x} / 345,
$$

in which $A_{x}$ is the absorbance of Standard solution B, and 345 is the absorptivity for pure lycopene in $n$-hexane at 472 nm .

Standard solution C-Transfer an accurately weighed quantity of USP Tomato Extract Containing Lycopene RS, equivalent to 6 to 8 mg of lycopene, to a $100-\mathrm{mL}$ volumetric flask, and dissolve in 10 mL of methylene chloride, using a sonicator. Dilute with Diluting solution to volume to obtain a solution having a known concentration of about 0.07 mg of lycopene per mL .

Test solution-Warm the sample of the Extract to $50^{\circ}$ in a water bath. Mix well with a glass rod or a spatula. Accurately weigh a quantity of 1 to 1.2 g of the sample into a $100-\mathrm{mL}$ volumetric flask. Add 10 mL of Butylated hydroxytoluene stock solution and 30 mL of methylene chloride, and sonicate the solution for 1 minute in order to dissolve the sample completely. Cool to room temperature, dilute with methylene chloride to volume, and mix well. Transfer 5.0 mL to a $50-\mathrm{mL}$ volumetric flask, and dilute with Diluting solution to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a 472 -nm detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7 maintained at a temperature of $39 \pm 1^{\circ}$. The
flow rate is about 0.7 mL per minute. Chromatograph Standard solution $A$, record the chromatograms, and measure the peak responses as directed for Procedure: the retention time for lycopene is about 6 minutes; and the relative standard deviation of the lycopene peak area for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes ( $10 \mu \mathrm{~L}$ ) of Standard solution A or Standard solution C, and the Test solution into the chromatograph, record the chromatograms, and measure the responses of the major lycopene peaks. Calculate the percentage of lycopene in the portion of Extract taken by the formula:

$$
100(C / W)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in ppm, of Standard solution $A$ or Standard solution $C$; $W$ is the weight, in mg , of Extract taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the areas of the lycopene peak responses obtained from the Test solution and Standard solution A or Standard solution $C$, respectively.

## Content of other carotenoids and tocopherols (phyto-

 fluene, phytoene, beta carotene, and tocopherols)-Butylated hydroxytoluene stock solution, Diluting solution, Standard solution A, Standard solution B, Standard solution C, and Test solution-Proceed as directed in the test for Content of lycopene.

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile, methanol, methylene chloride, and $n$-hexane (475:475:25:25). Add $0.05 \%$ of diisopropylethylamine, mix well, and sonicate for 3 to 4 minutes.
System suitability solution-Prepare a solution of USP Lyeopene Tomat Extract RS- in Diluting solution, having a-encentration of about 1 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $4.6-\mathrm{mm} \times 25-$ cm column that contains $5-\mu \mathrm{m}$ packing L1 maintained at a
temperature of $39 \pm 1^{\circ}$ and a detector set at 472 nm for lycopene, at 450 nm for beta carotene, at 350 nm for phytofluene, and at 288 nm for phytoene and tocopherol. The flow rate is about 0.6 mL per minute.

Chromatograph fysurn Standard solution $C$, record the chromatograms, and measure the peak responses and the peak retention times as directed for Procedure: the chromatogram of fyst solut Standard solution $C$ is similar to the Reference Chromatogram provided with the USP Lyemato Extract Containing Lycopene RS; the relative retention times in the chromatogram of Sysem sutability solandard solution $C$ are about 0.6 for the peaks of the tocopherol isomers, 1.0 for the peaks of the lycopene isomers, 1.5 to 1.7 for the peaks of the beta carotene isomers, 1.6 to 1.8 for the peaks of the phytofluene isomers, and 1.8 to 2.2 for the phytoene peak; and the relative standard deviation for replicate injections for the peak of the lycopene isomers is not more than $2 \%$.

Procedure-Separately inject equal volumes ( $10 \mu \mathrm{~L}$ ) of Standard solution $A$ and the Test solution into the chromatograph, and record the chromatograms. Identify the locus of the peaks for the lycopene isomers, beta carotene isomers, phytofluene isomers, and phytoene by comparison with the Reference Chromatogram provided with the corresponding lot of USP Lyene Tomato Extract Containing Lycopene RS. Measure the sum of the peak responses of the lycopene isomers at 472 nm in the Standard solution A. In the Test solution, measure the sum of the peak responses of the beta carotene isomers at 450 nm , the sum of the peak responses of the phytofluene isomers at 350 nm , the response of the phytoene at 288 nm , and the sum of the peak responses of all tocopherols at 288 nm .

Determine the concentration of Standard solution $A$ as directed in the test for Content of lycopene.

Calculate the percentage of beta carotene in the portion of Extract taken by the formula:

$$
100(C / W)\left(r_{U 1} / r_{S}\right)(345 / 259.2)
$$

in which $C$ is the concentration, in ppm, of Standard solution Aor Standard solution $C$; $W$ is the weight, in mg, of Extract taken to prepare the Test solution; $r_{U I}$ is the sum of the peak responses for the beta carotene isomers at 450 nm obtained from the Test solution; $r_{S}$ is the sum of the peak responses for the lycopene isomers at 472 nm obtained from Standard solution A; and 345 and 259.2 are the absorptivities for pure lycopene and for pure beta carotene, respectively.

Calculate the percentage of phytofluene in the portion of Extract taken by the formula:

$$
100(C / W)\left(r_{U 2} / r_{S}\right)(345 / 135)
$$

in which $C$ is the concentration, in ppm, of Standard solution $A$ or Standard solution $C$; $W$ is the weight, in mg , of Extract taken to prepare the Test solution; $r_{U 2}$ is the sum of the peak responses for phytofluene isomers at 350 nm obtained from the Test solution; $r_{S}$ is the sum of the peak responses for the lycopene isomers at 472 nm obtained from the Standard solution A or Standard solution C; and 345 and 135 are the absorptivities for pure lycopene and for pure phytofluene, respectively.
Calculate the percentage of phytoene in the portion of Extract taken by the formula:

$$
100(C / W)\left(r_{U 3} / r_{S}\right)(345 / 125)
$$

in which $C$ is the concentration, in ppm, of Standard solution A or Standard solution C; $W$ is the weight, in mg , of Extract taken to prepare the Test solution; $r_{U 3}$ is the area of the phytoene peak response at 288 nm obtained from the Test solution; $r_{S}$ is the sum of the peak responses for
the lycopene isomers at 472 nm obtained from Standard solution $A$; and 345 and 125 are the absorptivities for pure lycopene and for pure phytoene, respectively.

Calculate the percentage of tocopherols in the portion of
Extract taken to prepare the Test solution by the formula:

$$
100(C / W)\left(r_{U 4} / r_{S}\right)(345 / 8.5)
$$

in which $C$ is the concentration, in ppm, of Standard solution $A$ or Standard solution $C$; $W$ is the weight, in mg , of Extract taken to prepare the Test solution; $r_{U 4}$ is the sum of the peak responses for all the tocopherol peaks at 288 nm obtained from the Test solution; $r_{S}$ is sum of the peak responses for the lycopene isomers at 472 nm obtained from the Standard solution A; 345 is the absorptivity for pure lycopene; and 8.5 is the average absorptivity for toco-


## Briefing

Pyridoxine Hydrochloride Injection, USP 27 page 1609. It is proposed to correct the formula in the Procedure in the Assay.
(DSN: L. Evans) RTS-40728-1

## Change to read:

Assay-
Ammonium chloride-ammonium hydroxide buffer-Dissolve 16 g of ammonium chloride in 70 mL of water, add 16 mL of ammonium hydroxide, dilute with water to 100 mL , mix, and filter.

Chlorimide solution-Dissolve 40 mg of 2,6-dichloroquinonechlorimide in 100 mL of isopropyl alcohol. Store the solution in a refrigerator, and use within one month. Do not use the solution if it has become pink.

Standard stock solution-Dissolve a suitable quantity of USP Pyridoxine Hydrochloride RS, accurately weighed, in 0.1 N hydrochloric acid, quantitatively dilute with the same solvent to obtain a solution having a known concentration of about 0.1 mg per mL , and mix. Keep the solution in an amber bottle, in a cool place.
Standard preparation-In a $100-\mathrm{mL}$ volumetric flask dilute 10.0 mL of Standard stock solution with water to volume, and mix. Prepare this solution daily as needed.

Assay preparation-Dilute an accurately measured volume of Injection, equivalent to about 100 mg of pyridoxine hydrochloride, quantitatively and stepwise with water to a concentration of about $10 \mu \mathrm{~g}$ of pyridoxine hydrochloride per mL .
Procedure-
(a) Pipet 5 mL of the clear Assay preparation into a flask, add 25.0 mL of isopropyl alcohol, and mix. Pipet 5 mL of the isopropyl alcohol dilution into a glass-stoppered, $25-\mathrm{mL}$ graduated cylinder or test tube, and add in succession, mixing after each addition, 1.0 mL of Ammonium chloride-ammonium hydroxide buffer, 1.0 mL of sodium acetate solution ( 1 in 5 ), and 1.0 mL of water. Cool to about $25^{\circ}$, then add 1.0 mL of Chlorimide solution, shake vigorously for 10 seconds, accurately timed. Sixty seconds, accurately timed, after the addition of the Chlorimide solution, determine the absorbance at the wavelength of maximum absorbance at about 650 nm , with a suitable spectrophotometer, using water as the blank. [NOTE-Make the reading promptly to avoid errors due to fading of the color.] Designate the absorbance as $A_{U}$.
(b) Repeat procedure (a), but substitute 1.0 mL of boric acid solution (1 in 20) for the 1.0 mL of water. Designate the absorbance as $A_{U}{ }^{\prime}$.
(c) Repeat procedure (a), but substitute 5.0 mL of the Standard preparation for the 5.0 mL of the Assay preparation. Designate the absorbance as $A_{S}$.
(d) Repeat procedure (c), but substitute 1.0 mL of boric acid solution (1 in 20) for the 1.0 mL of water. Designate the absorbance as $A_{S}{ }^{\prime}$.

Calculate the quantity, in mg, of Pyridoxine Hydrochloride $\left(\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{NO}_{3} . \mathrm{HCl}\right)$ in each mL of the Injection taken by the formula:

$$
10(C H)\left(A_{t}-A_{t}{ }^{\prime}\right)\left(A_{s}-A_{s}^{\prime}\right)
$$

$$
\mathbf{\Delta}_{10}(C / V)\left(A_{U}-A_{U}^{\prime}\right) /\left(A_{S}-A_{S}^{\prime}\right),_{\mathbf{\Delta U S P 2 8}}
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Pyridoxine Hydrochloride RS in the Standard preparation; $V$ is the volume, in mL , of Injection taken; and $A_{b}$ and $A_{s}$ are as defined therein.
$\boldsymbol{\Delta}_{\text {the }}$ other terms are as defined above. $\quad$ USP28

## Briefing

Powdered St. John's Wort Extract, USP 27 page 2033 and page 702 of $P F$ 29(3) [May-June 2003]. It is proposed to revise the Labeling section to include a warning statement to be applied to the label.
(DSI: J. Salguero) RTS-40894-1

## Change to read:

» Powdered St. John's Wort Extract is prepared from comminuted St. John's Wort extracted with 80 percent methanol or other suitable solvents. The ratio of the starting crude plant material to Powdered Extract is between $3: 1$ and $7: 1$.
$\square_{1 S}$ (USP27)
It contains not less than $\theta .2$
-90.0.1 $\mathbf{n i s}_{\text {(USP27) }}$
percent
-and not more than 110.0 percent $_{1 \text { IS }_{(U S P 27)}}$ of the

- labeled ${ }_{\text {1S (USP27) }}$
combined total of hypericin $\left(\mathrm{C}_{30} \mathrm{H}_{16} \mathrm{O}_{8}\right)$ and pseudohypericin $\left(\mathrm{C}_{30} \mathrm{H}_{16} \mathrm{O}_{9}\right)$ and not less than 3.0
-90.0 $\mathbf{n I S ~}_{\text {(USP27) }}$
percent
-and not more than 110.0 percent $_{1 \text { IS (USP }^{27)}}$ of hyperforin $\left(\mathrm{C}_{35} \mathrm{H}_{52} \mathrm{O}_{4}\right)$.


## Change to read:

Labeling-The label states the Latin binomial and, following the official name, the part of the plant from which the article was prepared. The label also indicates the content of hypericin, pseudohypericin, and hyperforin; the extracting solvent or solvent mixture used for preparation; and the ratio of the starting crude plant material to Powdered Extract.
${ }^{\Delta}$ The label bears a statement indicating that "Rare cases of allergic reactions and photosensitivity have been reported with the use of St. John's Wort. St. John's Wort interacts with numerous medications. Check with your health care provider before using." $\Delta U S P 28$

## Change to read:

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ (presence of hypericin, pseudohypericin, hyperoside, and rutin)-

Test solution-Transfer about 1 g of Powdered Extract, accurately weighed, to a $50-\mathrm{mL}$ flask, add 20.0 mL of methanol, shake well, and use the clear supernatant.

Standard solution-Transfer about 0.25 g of USP Powdered St. John's Wort Extract RS, accurately weighed, to a $25-\mathrm{mL}$ flask, add 5.0 mL of methanol, shake well, and use the clear supernatant.

Developing solvent system-Prepare a mixture of ethyl acetate, water,

- glacial acetic acid, $\mathbf{m}_{1 S}$ (USP27) and formic acid $(50: 40: 10)$
-(10:2.6:1.1:1.1), $\boldsymbol{m}_{1 S}$ (USP27)
and use the upper phase of the mixture. [NOTE-Saturate the chromatographic chamber with the Developing solvent system vapors prior to the development of the chromatogram.]

Spray reagent $A$-Prepare a solution of diphenylborinic acid, ethanolamine ester in methanol containing 10 mg per mL .

Spray reagent B-Prepare a solution of polyethylene glycol 400 in alcohol containing 50 mg per mL .

Procedure-Develop the chromatogram until the solvent front has moved not less than 18 cm , and dry the plate with the aid of a current of air. Spray the plate with Spray reagent $A$, then with Spray reagent B, and examine the plate under UV light at 365 nm : the two red zones due to hypericin and pseudohypericin at $R_{F}$ values of about $\theta .89$
${ }^{-0.85}{ }_{\text {日 } 1 \mathrm{SS}}$ (USP27) and 0.88
-0.80, $\mathbf{1 S}_{1 S}$ (USP27)
respectively, in the chromatogram of the Test solution, correspond in color and $R_{F}$ value to those in the chromatogram of the Standard solution; the two yellow zones due to hyperoside and rutin at $R_{F}$ values of about 0.20

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\(\square_{0.50} \operatorname{mS}_{1 S}\) (USP27)
and 0.52
```

-0.35, $\quad$ 1S (USP27)
respectively, in the chromatogram of the Test solution, correspond in color and $R_{F}$ value to those in the chromatogram of the Standard solution. Other colored zones of varying intensities may be observed in the chromatogram of the Test solution.

B: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ (presence of hyperforin)-

Test solution and Standard solution-Proceed as directed for Identification test $A$.

Developing solvent system-Prepare a mixture of solvent hexane and ethyl acetate (8:2). [NOTE-Saturate the chromatographic chamber with the Developing solvent system vapors prior to the development of the chromatogram.]

Spray reagent Transfer
-Prepare a solution containing $_{\mathbf{m}_{1 S}(\text { USP27) }}$
0.38 g of ceric ammonium sulfate and 3.8 g of ammonium molybdate tor
$\boldsymbol{- i n}_{\mathbf{n}_{1 S}}$ (USP27)
$100-\mathrm{mL}$ tolumetrie flack, add 2.4 mL
${ }^{-1}{ }^{1 S}$ (USP27)
of
$\mathrm{m}_{\mathrm{n} 1 \mathrm{~S}}$ (USP27)
sulfuric acid. dilute carefully with water to volume, and mix.
$\boldsymbol{m}_{\text {■ }}$ (USP27)

Procedure-Develop the chromatogram until the solvent front has moved not less than 18 cm , and dry the plate with the aid of a current of air. Spray the plate with Spray reagent, heat the plate at $140^{\circ}$ for 15 minutes, and examine under UV light: the blue zone due to hyperforin at an $R_{F}$ value of about 0.54 in the chromatogram of the Test solution corresponds in color and $R_{F}$ value to that in the chromatogram of the Standard solution.

## Add the following:

-Microbial limits $\langle 2021\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total bacterial count does not exceed $10^{4}$ per g, and the total combined molds and yeasts does not exceed
$10^{3}$ per g.mis (USP27)

## Change to read:

Heavy metals, Method II $\langle 231\rangle$ : 0.005\%.

- $50 \mu \mathrm{~g}$ per g .■1S (USP27)


## Change to read:

Other requirements-It meets the requirements for Residue on Evaporation--
■and $_{\text {■1S (USP27) }}$
Residual Solvents Hern Meter
■ $\quad 1 \mathrm{~S}$ (USP27)
■1S (USP27)
under Botanical Extracts $\langle 565\rangle$.

## BriEfing

Oil- and Water-Soluble Vitamins Tablets, USP 27 page 2051-See briefing under Oil- and Water-Soluble Vitamins with Minerals Tablets.
(DSN: L. Evans) RTS-40079-7

## Add the following:

${ }^{4}$ Assay for biotin, Method 3-Proceed as directed in the Assay for biotin, Method 3 under Oil- and Water-Soluble Vitamins with Minerals Tablets. $\mathbf{\Delta U S P 2 8}$

Briefing
Oil- and Water-Soluble Vitamins with Minerals Oral Solution, USP 27 page 2057-See briefing under Oil- and Water-Soluble Vitamins with Minerals Tablets.
(DSN: L. Evans) RTS-40079-6

## Change to read:

Assay for biotin,
$\Delta_{\text {Method }} 1_{\Delta U S P 28}$
-Proceed as directed in the Assay for biotin, Method 2 under Oiland Water-Soluble Vitamins with Minerals Tablets, except to read Oral Solution in place of Tablets and to use the following Assay preparation.

Assay preparation-Transfer an accurately measured volume of Oral Solution to a volumetric flask, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a concentration of 0.1 ng of biotin per mL .

## Add the following:

4Assay for biotin, Method 2-Proceed as directed in the Assay for biotin, Method 3 under Oil- and Water-Soluble Vitamins with Minerals Tablets, except to read Oral Solution in place of Tablets and to use the following Assay preparation.

Assay preparation-Transfer an accurately measured volume of Oral Solution to a volumetric flask, and dilute quantitatively, and stepwise if necessary with water, to obtain a solution having a concentration of $0.6 \mu \mathrm{~g}$ of biotin per mL . Adjust the solution with either dilute acetic acid or 0.1 N sodium hydroxide to a pH of between 6.0 and 7.0. $\mathbf{\text { USP28 }}$

## Briefing

Oil- and Water-Soluble Vitamins with Minerals Tablets, USP 27 page 2063; Oil- and Water-Soluble Vitamins Tablets, USP 27 page 2051; Oil- and Water-Soluble Vitamins with Minerals Oral Solution, USP 27 page 2057; Water-Soluble Vitamins Tablets, USP 27 page 2084; Water-Soluble Vitamins with Minerals Tablets, USP 27 page 2089. It is proposed to add a third alternative Assay for biotin to the Oil- and Water-Soluble Vitamins with Minerals Tablets monograph, which also affects the monographs listed above. It has been reported that the current two methods are inadequate for the analysis of some marketed products. The proposed method incorporates the use of solid-phase extraction
into the sample preparation. Analyses are performed with a Waters Oasis MAX Vac RC cartridge to prepare the sample preparation and a Phenomenex Luna brand of L1 column for the liquid chromatographic procedure. The typical retention time for the biotin peak is 22 minutes.
(DSN: L. Evans) RTS-40079-1; 40079-2; 40079-3; 400794; 40079-5

## Add the following:

^Assay for biotin, Method 3-[NOTE-Use low-actinic glassware throughout this procedure.]

Buffer-Transfer 800 mL of water and 100 mL of triethylamine to a $1000-\mathrm{mL}$ volumetric flask. Add 80 mL of $85 \%$ phosphoric acid, dilute with water to volume, and mix.

Mobile phase-Transfer 80 mL of acetonitrile and 10 mL of Buffer to a $1000-\mathrm{mL}$ volumetric flask. Dilute with water to volume, mix, filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography〈621〉).
Standard preparation-Transfer about 25 mg of USP Biotin RS, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Transfer 1.5 mL of this solution to a $250-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain a solution having a known concentration of about $0.6 \mu \mathrm{~g}$ per mL of USP Biotin RS. [NOTE-A portion of the Standard preparation will be used to determine the percent recovery of biotin from the Solid-phase extraction procedure.]

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about $60 \mu \mathrm{~g}$ of biotin, to a $100-\mathrm{mL}$ volumetric flask. Add about 80 mL of water, and sonicate for 30 to 40 minutes with occasional mixing. Cool to room temperature, dilute with water to volume, mix, and filter. Adjust the pH of the solution with either dilute acetic acid or 0.1 N sodium hydroxide to between 6.0 and 7.0.

Solid-phase extraction-[NOTE-Condition the extraction column specified in this procedure in the following manner. Wash the column with a $2-\mathrm{mL}$ portion of methanol. Equilibrate with a $2-\mathrm{mL}$ portion of water.] Separately pipet 5.0 mL of the Assay preparation and Standard preparation into freshly conditioned solid-phase extraction columns consisting of a mixed-mode packing with a sorbent-mass of 60 mg . [NOTE-The mixed-mode packing consists of anion-exchange and reversed-phase sorbents. The reverse-phase component is a polymer of copolymer $N$-vinylpyrrolidone and divinylbenzene. The anion exchange moiety is a trialkyamino group. * ] Wash the column with 10 mL of $30 \%(\mathrm{v} / \mathrm{v})$ methanol in water. Apply an appropriate volume (about 4.9 $\mathrm{mL})$ of $30 \%(\mathrm{v} / \mathrm{v})$ methanol in 0.1 N hydrochloric acid to the column. Collect the eluate in a $5-\mathrm{mL}$ volumetric flask, containing $100 \mu \mathrm{~L}$ of $40 \%(\mathrm{w} / \mathrm{v})$ sodium acetate in water, and dilute with $30 \%(\mathrm{v} / \mathrm{v})$ methanol in 0.1 N hydrochloric acid to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $200-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column containing packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than $2 \%$. Chromatograph the portion of Standard preparation that has undergone solid-phase extraction, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2 \%$; and the recovery is between $95 \%$ and $100 \%$.

Procedure-Separately inject equal volumes (about 100 $\mu \mathrm{L})$ of the Standard preparation and the Assay preparation that have undergone solid-phase extraction, into the chro-

[^64]matograph, record the chromatograms, and measure the responses for the biotin peak. Calculate the quantity, in $\mu \mathrm{g}$, of biotin $\left(\mathrm{C}_{10} \mathrm{H}_{16} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{~S}\right)$ in the portion of Tablets taken by the formula:
$$
100 C\left(r_{U} / r_{S}\right),
$$
in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Biotin RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the biotin peak responses obtained from the Assay preparation and the Standard preparation, respectively._USSP28

## BRIEFING

Water-Soluble Vitamins Tablets, USP 27 page 2084—See briefing under Oil- and Water-Soluble Vitamins with Minerals Tablets.
(DSN: L. Evans) RTS-40079-8

## Add the following:

${ }^{4}$ Assay for biotin, Method 3—Proceed as directed in the Assay for biotin, Method 3 under Oil- and Water-Soluble Vitamins with Minerals Tablets. $\mathbf{\Delta U S P 2 8}$

## Add the following:

${ }^{4}$ Assay for biotin, Method 3-Proceed as directed in the Assay for biotin, Method 3 under Oil- and Water-Soluble Vitamins with Minerals Tablets. $\mathbf{U S P 2 8}$

## Briefing

Excipients, USP and NF Excipients, Listed by Category, $N F$ 22 page 2809 and page 2008 of PF 29(6) [Nov.-Dec. 2003]. The proposed revisions complement the following proposed new monographs that appear elsewhere in this number of $P F$ : Cellulose Acetate Butyrate; Corn Starch; Wheat Starch; Potato Starch; Sodium Sulfite; Sodium Tartrate; Succinic Acid; Acesulfame Potassium; Adipic Acid; Galactose; Citric Acid Monohydrate; and Anhydrous Citric Acid.
(EMC) RTS-40209-1; 40209-2; 40209-3; 40209-4; 402095; 40773-2; 40773-4; 40773-5; 40773-6; 40814-3; 40814-4; 40862-2; 40864-1

## Change to read:

Acidifying Agent
Acetic Acid
Acetic Acid, Glacial
Eitric Acid
${ }^{\mathbf{4}}$ Citric Acid, Anhydrous ${ }_{\Delta N F 23}$
${ }^{\mathbf{\Delta}}$ Citric Acid Monohydrate ${ }_{\mathbf{\Delta} N F 23}$
Fumaric Acid
Hydrochloric Acid
Hydrochloric Acid, Diluted
Malic Acid
Nitric Acid
Phosphoric Acid
Phosphoric Acid, Diluted
Propionic Acid
Sulfuric Acid
Tartaric Acid

## Change to read:

Antimicrobial Preservative
Benzalkonium Chloride
Benzalkonium Chloride Solution
Benzethonium Chloride
Benzoic Acid
Benzyl Alcohol
Butylparaben
${ }^{\Delta}$ Cetrimonium Bromide ${ }_{\text {AFF22 }}$
Cetylpyridinium Chloride
Chlorobutanol
Chlorocresol
Cresol
Ethylparaben
Methylparaben
Methylparaben Sodium
Phenol
-2-Phenoxyethanol ${ }_{\text {2S (NF22) }}$ Phenylethyl Alcohol

Water-Soluble Vitamins with Minerals Tablets, USP 27 page 2089-See briefing under Oil- and Water-Soluble Vitamins with Minerals Tablets.
(DSN: L. Evans) RTS-40079-9

Phenylmercuric Acetate
Phenylmercuric Nitrate
Potassium Benzoate
Potassium Sorbate
Propylparaben
Propylparaben Sodium
Sodium Benzoate
Sodium Dehydroacetate
Sodium Propionate
Sorbic Acid
Thimerosal
Thymol

## Change to read:

Antioxidant
Ascorbic Acid
Ascorbyl Palmitate
Butylated Hydroxyanisole
Butylated Hydroxytoluene
Hypophosphorous Acid
Monothioglycerol
Potassium Metabisulfite
Propyl Gallate
Sodium Formaldehyde Sulfoxylate
Sodium Metabisulfite
${ }^{\mathbf{4}}$ Sodium Sulfite ${ }_{\mathbf{\Delta N F 2 3}}$
Sodium Thiosulfate
Sulfur Dioxide
Tocopherol
Tocopherols Excipient

## Change to read:

Buffering Agent
Acetic Acid
${ }^{\Delta}$ Adipic Acid ${ }_{\Delta N F 23}$
Ammonium Carbonate
Ammonium Phosphate
Boric Acid
Gitrie Acid
${ }^{\mathbf{4}}$ Citric Acid, Anhydrous ${ }_{\mathbf{\Delta N F 2 3}}$
${ }^{\boldsymbol{4}}$ Citric Acid Monohydrate ${ }_{\mathbf{\Delta} N F 23}$
Lactic Acid
Phosphoric Acid
Potassium Citrate
Potassium Metaphosphate
Potassium Phosphate, Monobasic
Sodium Acetate
Sodium Citrate
Sodium Lactate Solution
Sodium Phosphate, Dibasic
Sodium Phosphate, Monobasic
${ }^{\mathbf{4}}$ Succinic Acid ${ }_{\mathbf{\Delta} N F 23}$

Change to read:
Coating Agent
-Ammonio Methacrylate Copolymer Dispersion $\mathbf{m a S}_{\text {(NF22) }}$ Carboxymethylcellulose Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
Cellulose Acetate Butyrate
${ }^{\Delta}$ Cellaburate ${ }_{\Delta{ }^{N F 23}}$
Cellulose Acetate Phthalate (see Cellacefate)
${ }^{\text {- }}$ Copovidone ${ }_{\text {■2S (NF22) }}$

- Corn Syrup Solids $_{\mathbf{m}}$ 2S (NF22)

Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose ${ }^{\boldsymbol{\Delta}}$ (see Hypromellose) $\boldsymbol{\Delta N F L 2}$
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
${ }^{\boldsymbol{\Delta}}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) $\mathbf{\Delta N F 2 2}^{\text {N }}$
${ }^{\text {■ Hypromellose Acetate Succinate }}{ }_{\text {(2s }}$ (NF22)
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate
Shellac
-Starch, Pregelatinized Modified $_{\text {■2S (NF22) }}$
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

## Change to read:

Emollient
Alkyl (C12-15) Benzoate
-Hydrogenated Soybean Oil $\mathbf{I I S}_{\text {(NF22) }}$

## Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Cholesterol
Diethanolamine (Adjunct)
-Diethylene Glycol Menestearates Stearates $\mathbf{m}_{1 S}$ (NF22)

${ }^{\Delta}$ Glyceryl Distearate ${ }_{\text {A }}{ }^{*}$ F22
${ }_{\Delta}$ Glyceryl Monolinoleate $\mathbf{A N F 2 2}^{\text {G }}$
${ }^{\Delta}$ Glyceryl Monooleate $\mathbf{\Delta N F 2 2}^{\text {and }}$
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
-Polyoxyl Lauryl Ether $_{\mathbf{m}_{1 S} \text { (NF22) }}$
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 40 Stearate
-Polyoxyl Stearyl Ether ${ }_{1 S}$ (NF22)
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
■Sodium $^{\text {Cetostearyl Sulfate }}{ }_{\text {■1S (NF22) }}$
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Stearic Acid
Trolamine
Wax, Emulsifying

## Change to read: <br> Humectant

${ }^{\text {■ Corn Syrup Solids }}{ }_{\text {■2S (NF22) }}$
Glycerin
Hexylene Glycol
Propylene Glycol
Sorbitol
-Sorbitol, Anhydrized Liquid $_{\mathbf{■}^{2 S}(\text { NF22 }}$

## Change to read: <br> Ointment Base

## Eapryleaproyl Macrogolglyeerides

${ }^{\text {■ Caprylocaproyl Polyoxylglycerides_(N2S (NF22) }}$
Diethylene Glycol Monoethyl Ether
■Lauroyl Macrogolglycerides $_{\text {■2S (NF22) }}$
Lineoyl Maerogelglycerides
■Lineoyl Polyoxylglycerides $_{\mathbf{m}_{2 S} \text { (NF22) }}$
Lanolin
Ointment, Hydrophilic
Ointment, White
Oleoyl Macrogolglycerides
-Oleoyl Polyoxylglycerides $_{\mathbf{U}_{2 S}(\text { NF22 }}$
Ointment, Yellow
Polyethylene Glycol Ointment
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White
Rose Water Ointment
Squalane

## Stearoyl Macrogolglyeerides

-Stearoyl Polyoxylglycerides ${ }_{\text {■2S (NF22) }}$
Vegetable Oil, Hydrogenated, Type II

## Change to read:

## Plasticizer

Acetyltributyl Citrate
Acetyltriethyl Citrate
Castor Oil

Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin
Polyethylene Glycol
Propylene Glycol
■Sorbitol, Anhydrized Liquid $_{\mathbf{m}_{2 S}(\text { NF22 })}$
Triacetin
Tributyl Citrate
Triethyl Citrate

Change to read:
Polymer Membrane
Cellulose Acetate
Cellulose Acetate Butyrate
${ }^{\boldsymbol{\Delta}}$ Cellaburate $\boldsymbol{\Delta N F 2 3}$

## Change to read:

Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)
${ }^{\mathbf{4}}$ Sodium Tartrate $\mathbf{\Delta N F 2 3 ~}^{\text {N }}$

## Change to read:

Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol

## Caprylocaproyl Macrogelgyeerides

${ }^{-}$Caprylocaproyl Polyoxylglycerides ${ }_{\text {. }}^{2 S}$ (NF22)
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
■Lauroyl Macrogolglycerides $_{\text {■2S (NF22) }}$
Eineoyl Macrogolglyeerides
-Lineoyl Polyoxylglycerides $_{\mathbf{m}_{2 S}(\text { NF22 }}$
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Oleoyl Macrogelgyeerides
-Oleoyl Polyoxylglycerides ${ }_{\text {n2S (NF22) }}$
Peanut Oil
Polyethylene Glycol
Propylene Glycol
Sesame Oil
Stearoyl Macrogelgycerides
■Stearoyl Polyoxylglycerides ${ }_{\mathbf{■ S}}$ (NF22) $^{\text {( }}$

Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

## Change to read:

Suspending and/or Viscosity-Increasing Agent
Acacia
Agar
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
${ }^{-}$Carbomer Homopolymer ${ }_{\text {us (NF22) }}$
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium
${ }^{\text {■ }}$ Corn Syrup Solids $\mathbf{m}_{\text {2S }}$ (NF22)
Dextrin
Gelatin
-Gellan $^{\text {Gum }}{ }_{\text {1S (NF22) }}$
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose ${ }^{\mathbf{\Delta}}$ (see Hypromellose) ${ }_{\mathbf{A} N F 22}$
${ }^{\Delta}$ Hypromellose (formerly Hydroxypropyl Methylcellu-
lose) $\mathbf{A N F}^{22}$
Magnesium Aluminum Silicate
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
${ }^{\mathbf{\Delta}}$ Starch, Corn $\mathbf{\Delta N F 2 3}$

${ }^{\Delta}$ Starch, Wheat ${ }_{\Delta N F 23}$
Tragacanth
Xanthan Gum

## Change to read:

Sweetening Agent
${ }^{\boldsymbol{\Delta}}$ Acesulfame Potassium $\mathbf{\Delta N F 2 3}$
Aspartame
${ }^{\mathbf{\Delta}}$ Aspartame Acesulfame $_{\mathbf{\Delta N F 2 2}}$
${ }^{\text {■ Corn Syrup Solids }}{ }_{\text {■ } 2 \text { S (NF22) }}$
Dextrates
Dextrose
Dextrose Excipient
Fructose
${ }^{\mathbf{4}}$ Galactose $\mathbf{\Delta N F 2 3}$
-Maltose $_{\text {■2S (NF22) }}$
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

## Change to read:

Tablet Binder
Acacia
Alginic Acid
${ }^{-}$Carbomer Homopolymer ${ }_{\text {2S (NF22) }}$
Carboxymethylcellulose, Sodium
Cellulose, Microcrystalline

${ }^{\text {■ }}$ Corn Syrup Solids $\mathbf{m}_{\text {2S }}$ (NF22)
Dextrin
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
$\mathbf{H y d r o x y p r o p y l}^{\text {Methylcellulose }}{ }^{\boldsymbol{\Delta}}$ (see Hypromellose) $\boldsymbol{\Delta N F 2 2}$
${ }^{\Delta}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) ${ }_{\mathbf{A F} 22}$
${ }^{\bullet}$ Hypromellose Acetate Succinate ${ }_{\text {2S (NF22) }}$

- Maltose $_{\text {■2S (NF22) }}$

Methylcellulose
Polyethylene Oxide
Povidone
${ }^{\mathbf{\Delta}}$ Starch, Corn $\mathbf{\Delta N F 2 3}$
${ }^{\triangle}$ Starch, Potato ${ }_{\mathbf{4} N F 23}$
Starch, Pregelatinized
-Starch, Pregelatinized Modified $_{\text {© } 2 \text { (NF22) }}$
${ }^{\boldsymbol{\Delta}}$ Starch, Tapioca $\Delta N F 22$
${ }_{\text {Starch, Wheat }}^{\Delta N F 23}$
Syrup

## Change to read:

Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered


## Dextrates

Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose

- Maltose $_{\text {■2S (NF22) }}$

Mannitol
Sorbitol
Stareh
${ }^{\mathbf{\Delta}}$ Starch, Corn ${ }_{\mathbf{\Delta} N F 23}$
${ }^{\Delta}$ Starch, Potato ${ }_{\mathbf{A} N F 23}$
Starch, Pregelatinized
-Starch, Pregelatinized Modified $\mathbf{m}_{\text {2S (NF22) }}$
${ }^{\boldsymbol{4}}$ Starch, Tapioca ${ }_{\mathbf{\Lambda} N F 22}$
${ }^{\mathbf{\Delta}}$ Starch, Wheat ${ }_{\Delta N F 23}$
Sucrose
Sugar, Compressible
Sugar, Confectioners

## Change to read:

Tablet Disintegrant
Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone

- Maltose $_{\mathbf{m}_{2 S}(N F 22)}$

Polacrilin Potassium
Sodium Starch Glycolate
Stareh
${ }^{\mathbf{\Delta}}$ Starch, Corn $\mathbf{\Delta N F 2 3}$
${ }^{\mathbf{4}}$ Starch, Potato ${ }_{\mathbf{4} N F 23}$
Starch, Pregelatinized

- Starch, Pregelatinized Modified $\mathbf{M S S}_{\text {(NF22) }}$
${ }^{\boldsymbol{\Delta}}$ Starch, Tapioca $\boldsymbol{\Delta N F 2 2}$
${ }^{\mathbf{4}}$ Starch, Wheat ${ }_{\mathbf{\Delta} N F 23}$


## Change to read:

Tonicity Agent
${ }^{\text {■ }}$ Corn Syrup Solids $\mathbf{m}_{\text {2S }}$ (NF22)
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

## Change to read:

Vehicle
FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound
${ }^{-}$Corn Syrup Solids ${ }_{\text {■S }}{ }^{\text {(NF22) }}$
Peppermint Water
Sorbitol Solution
Syrup

OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
Safflower Oil
Sesame Oil
Soybean Oil
Squalane
SOLID CARRIER
Sugar Spheres
STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

## MONOGRAPHS (NF)

## Briefing

Acesulfame Potassium. Because there is no existing NF monograph for this excipient, a new monograph is being proposed. This new monograph is based on the Acesulfame Potassium monographs derived from the $46^{\text {th }}$ Session of the Joint FAO/WHO Expert Committee on Food Additives. Responses to manufacturer comments have also been incorporated.
(EMC: K. Russo) RTS-40209-5

## Add the following:

## ©Acesulfame Potassium



## $\mathrm{C}_{4} \mathrm{H}_{4} \mathrm{NO}_{4} \mathrm{SK} \quad 201.24$

6-Methyl-1,2,3-oxathiazine-4(3H)-one-2,2-dioxide potassium salt.

3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide potassium salt [55589-62-3].
»Acesulfame Potassium contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{4} \mathrm{H}_{4} \mathrm{NO}_{4} \mathrm{SK}$, calculated on the dried basis.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle$ —USP Acesulfame Potassium RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: A solution (1 in 10 ) responds to the tests for Potassium $\langle 191\rangle$.

Acidity or alkalinity—Dissolve 4.0 g in 20 mL of carbon dioxide-free water, add 0.1 mL of bromothymol blue TS. If the solution is yellow, not more than 0.2 mL of 0.01 N sodium hydroxide is required to produce a blue color. If the solution is blue, not more than 0.2 mL of 0.01 N hydrochloric acid is required to produce a yellow color.

Loss on drying $\langle 731\rangle$ —Dry at $105^{\circ}$ for 3 hours: it loses not more than $1.0 \%$ of its weight.

Limit of fluoride- [NOTE-Use plasticware throughout this test.]

Buffer solution-Dissolve 210 g of citric acid monohydrate in 400 mL of water. Adjust with concentrated ammonia to a pH of 7.0 , dilute with water to 1000 mL , and mix (Solution A). Dissolve 132 g of monobasic ammonium phosphate in water, dilute with water to 1000 mL , and mix (Solution B). To a suspension of 292 g of edetate disodium in about 500 mL of water, add about 200 mL of ammonium hydroxide, and mix to dissolve (Solution C). Adjust with ammonium hydroxide to a pH between 6 and

7, dilute with water to make 1000 mL , and mix. Mix equal volumes of Solution A, Solution B, and Solution C, and adjust with ammonium hydroxide to a pH of 7.5 .
Standard stock solution-Weigh accurately 0.442 g of sodium fluoride, previously dried at $300^{\circ}$ for 12 hours, into a 1-L volumetric flask, dilute with water to volume, and mix. Store the solution in a closed plastic container. Immediately before use, pipet 5 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Each mL of this solution contains $10 \mu \mathrm{~g}$ of fluoride ion.

Standard solutions-To separate $50-\mathrm{mL}$ volumetric flasks pipet $0.5,1.5,5$, and 15 mL of the Standard stock solution, add to each volumetric flask 15.0 mL of Buffer solution, dilute with water to volume, and mix.
Test solution-Place 1 g of Acesulfame Potassium, accurately weighed, in a $50-\mathrm{mL}$ volumetric flask, dissolve in water, add 15.0 mL of Buffer solution, dilute with water to volume, and mix.

Procedure-Concomitantly measure the potential (see Titrimetry $\langle 541\rangle$ ), in mV , of the Standard solutions and the Test solution, with a suitable pH meter equipped with a flu-oride-specific ion electrode and a silver-silver chloride reference electrode. When taking the measurements, transfer the solution to a $25-\mathrm{mL}$ beaker, and immerse the electrodes. Insert a polytef-coated stirring bar into the beaker, place the beaker on a magnetic stirrer having an insulated top, and allow to stir until equilibrium is attained (about 1 to 2 minutes). Rinse, and dry the electrodes between measurements, taking care not to scratch the crystal in the flouride-specific ion electrode. Measure the potential of each Standard solution, and plot the fluoride concentration, in $\mu \mathrm{g}$ per mL , versus the potential, in mV , on semilogarithmic paper. Measure the potential of the Test solution, and
determine from the standard curve the fluoride concentration, in $\mu \mathrm{g}$ per mL . Calculate the percentage of fluoride in the portion of Acesulfame Potassium taken by the formula:

$$
5(C / W)
$$

in which $C$ is the fluoride concentration, in $\mu \mathrm{g}$ per mL , from the standard curve; and $W$ is the weight, in mg, of Acesulfame Potassium taken to prepare the Test solution: not more than $0.0003 \%$ of fluoride is found.

Heavy metals, Method $I\langle 231\rangle: 10 \mu \mathrm{~g}$ per g.

## Chromatographic purity-

Tetrabutylammonium hydrogen sulfate solution-Dissolve 3.3 g of tetrabutylammonium hydrogen sulfate in 1 L of water, and mix.

Mobile phase-Prepare a mixture of Tetrabutylammonium hydrogen sulfate solution and acetonitrile (3:2), filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve suitable quantities of USP Acesulfame Potassium RS and ethyparaben in water to obtain a solution containing about $2 \mu \mathrm{~g}$ per mL of each.

Standard solution-Dissolve an accurately weighed quantity of USP Acesulfame Potassium RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.2 $\mu \mathrm{g}$ per mL .

Test solution-Transfer about 100 mg of Acesulfame Potassium, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in water, dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $227-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.0 mL per minute. Chro-
matograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between acesulfame potassium and ethyparaben peaks is not less than 2 .

Procedure-[NOTE-Use peak areas where peak responses are indicated.] Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms for a run time not less than 3 times the retention time of the acesulfame potassium peak, and measure the responses of the peaks: the response of any peak at a retention time other than that of acesulfame potassium in the chromatogram obtained from the Test solution does not exceed the response of the acesulfame potassium peak in the chromatogram obtained from the Standard solution ( $0.002 \%$ ).

Assay-Dissolve about 150 mg of Acesulfame Potassium, accurately weighed, in 50 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically (see Titrimetry $\langle 541\rangle$ ). Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 20.12 mg of $\mathrm{C}_{4} \mathrm{H}_{4} \mathrm{NO}_{4} \mathrm{SK} \cdot{ }_{\Delta N F 23}$

## Briefing

[^65]
## Add the following:

## ©Adipic Acid

$\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{4} \quad 146.1$
Hexanedioic acid.
1,4-Butanedicarboxylic acid [124-04-9].
» Adipic Acid contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{4}$, calculated on the dried basis.

Packaging and storage-Store in tight containers.
Identification-Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
Melting range $\langle 741\rangle$ : between $151^{\circ}$ and $154^{\circ}$.
Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ to constant weight: it loses not more than $0.2 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.

## Limit of nitrates-

Standard stock solution-Dissolve about 815 mg of potassium nitrate in 500 mL of water, and mix.

Standard solution-Dilute 1 mL of the Standard stock solution with water to 10 mL , and mix. Dilute 1 mL of this solution with water to 50 mL to obtain a solution containing 2 ppm of nitrate. Use 1.5 mL of this solution, and proceed as directed under Procedure, beginning with "add 2 mL of concentrated ammonia".

Test solution-Transfer 5 g of Adipic Acid to a $50-\mathrm{mL}$ volumetric flask. Dissolve in water, with heating, and dilute with water to volume. Allow to cool and crystallize, then pass through a sintered-glass filter. Wash the filter with
water, and collect the filtrate and washings until a volume of 50 mL is obtained. [NOTE-This solution is to be used in the tests for Chloride, Sulfate, Iron, and Heavy metals.]

Procedure-To 1.0 mL of the Test solution add 2 mL of concentrated ammonia, 0.5 mL of manganese sulfate solution (1 in 100), 1 mL of sulfanilamide solution (1 in 100), and dilute with water to 20 mL . Add 100 mg of zinc powder, and cool in an ice bath for 30 minutes, shaking periodically. Filter 10 mL of the solution, and cool in an ice bath, then add 2.5 mL of hydrochloric acid and 1 mL of a naphthylethylenediamine dihydrochloride solution (1 in 100). Allow to stand at room temperature for 15 minutes: the color of the Test solution is not darker than a concomitantly prepared Standard solution; the limit is $0.003 \%$. The test is invalid if a concomitantly prepared blank solution (prepared using 1 mL of water instead of 1 mL of the Test solution) is darker than a solution containing 2 mg of potassium permanganate per L .

Chloride $\langle 221\rangle$-A 5-mL portion of the Test solution from the Limit of nitrates test shows no more chloride than a corresponding $0.14-\mathrm{mL}$ portion of 0.020 N hydrochloric acid: the limit is $0.02 \%$.

Sulfate $\langle 221\rangle$ —A $5-\mathrm{mL}$ portion of the Test solution from the Limit of nitrates test shows no more sulfate than a corresponding $0.26-\mathrm{mL}$ portion of 0.020 N sulfuric acid: the limit is $0.05 \%$.

Iron $\langle 241\rangle$-Use a $10-\mathrm{mL}$ portion of the Test solution from the Limit of nitrates test: the limit is $0.001 \%$.

Heavy metals, Method $I\langle 231\rangle$ : 0.001\%.
Assay-Dissolve 60 mg of Adipic Acid in 50 mL of water. Add 0.2 mL of phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS to a permanent pale pink endpoint. Each mL of 0.1 N sodium hydroxide is equivalent to 7.31 mg of $\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{4 \cdot \Delta N F 23}$

## Briefing

Betadex, NF 22 page 2831 and page 206 of $P F 30(1)$ [Jan.-Feb. 2004]. It is proposed to revise the upper limit of the acceptance criteria from 101.0 percent to 102.0 percent in response to comments received that the precision of the Assay does not support the current specification.
(EMC: D. Bempong) RTS-40181-1

## Change to read:

» Betadex is a nonreducing cyclic compound composed of seven alpha-(1-4) linked D-glucopyranosyl units. It contains not less than 98.0 percent and not more than 101.0
$\boldsymbol{\Delta r}^{102.0} \mathbf{\Delta}^{\text {NF23 }}$
percent of $\left(\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{5}\right)_{7}$, calculated on the anhydrous basis.

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and water (65:35). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard solution-Dissolve 2.0 g of glycerol in water contained in a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Pass through a $0.45-\mu \mathrm{m}$ membrane filter. Use fresh, or store in a freezer, thaw in hot water, and mix.

Standard preparation-Dissolve an accurately weighed quantity of USP Beta Cyclodextrin RS in water, and dilute quantitatively with water to obtain a solution having a known concentration of about 10 mg per mL . Use fresh, or store in a freezer, thaw in hot water, and mix. Mix 1.0 mL of this solution with 1.0 mL of Internal standard solution.

System suitability preparation-Prepare a solution in water containing about 5 mg per mL each of USP Alpha Cyclodextrin RS and USP Beta Cyclodextrin RS. Pass through a $0.45-\mu \mathrm{m}$ membrane filter.

Assay preparation-Transfer about 1 g of Betadex, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Pass this solution through a $0.45-\mu \mathrm{m}$ membrane filter. Mix 1.0 mL with 1.0 mL of Internal standard solution.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The tiquid ehrematograph is equipped with a refractive inder detector that is maintained at a constant temperature of $25^{\circ}$, a $4.6 \mathrm{~mm} *$ 25 cm colum that contains 10 um packing L 8 , and a guard col umm that contains packing $L 8$. The columms are maintained at a eonstant temperature of $25 \pm 2^{\circ}$, and the flow rate is about 2.0 mL per minute.
${ }^{\Delta}$ The chromatograph is equipped with a refractive index detector, a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $10-\mu \mathrm{m}$ packing L8, and a guard column that contains packing L8. The columns and, if necessary, the detector are maintained at a constant temperature of about $25 \pm 2^{\circ}$, and the flow rate is about 2.0 mL per minute. If the detector or the columns
are operated at a temperature other than $25 \pm 2^{\circ}$, the system also must be shown to meet all system suitability require-
ments. ANF23 $^{\text {N }}$
Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the alpha cyclodextrin and beta cyclodextrin peaks exhibit baseline separation, the relative retention times being about 0.8 and 1.0 , respectively; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Assay preparation and the Standard preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\left(\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{5}\right)_{7}$ in the portion of Betadex taken by the formula:

$$
100 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of anhydrous beta cyclodextrin in the Standard preparation, as determined from the concentration of USP Beta Cyclodextrin RS, corrected for moisture content by a titrimetric water determination; and $R_{U}$ and $R_{S}$ are the peak response ratios of the beta cyclodextrin peak to the internal standard peak obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Calcium Silicate, NF 22 page 2834. On the basis of comments received, it is proposed to revise the Definition to include crystalline or amorphous Calcium Silicate. It is proposed to revise the limits in the tests for pH and Ratio of silicon dioxide to calcium oxide and to replace the test for Limit of fluoride with a revised version. Revisions are also proposed in the Assay for silicon dioxide and in the Assay for calcium oxide.
(EMC: D. Bempong) RTS-39546-1

## Change to read:

» Calcium Silicate,

is a compound of calcium oxide and silicon dioxide. It contains not less than 4.0 percent of calcium oxide and not less than 45.0
${ }^{4} 35.0_{\Delta N F 23}$
percent of silicon dioxide.

## Change to read:

$\mathbf{p H}\langle 791\rangle$ : between 8.4 and 10.2,
$\Delta_{11.2}$, NF 23.
determined in a well-mixed aqueous suspension (1 in 20).

## Change to read:

## Limit of fluoride-

NOTE Stere all selutions in plastic centainers.
Buffer seldtion Adt 800 mL of het water to 74.4 g of edetate disodium and 24.2 g of tris(hydroxymethyl)aminemethane, and stir until dissolved. Adjust with 5 N sodium hydroxide to a pH of 7.5-7.7. Allow the-selation to eoel, and adjust with 5 N ditum hydroxide to a pHof 8.0 . Dilute with water to 1000 mL , and mix.

Electrode syistem Use a fluride specific, ion-indicating elec trode and a calomelreference-electrodeconnected to a pH meter eapable of measuring petentials with a reproducibility of $\pm 0.2$ $\mathrm{mV}($ seep $H\langle 794\rangle$ ).

Standard steck solution- Dissolve an aceurately weighed quan tity of USP Sodium Plurride RS quantitatively in water to obtain a solution containing $221 \mu \mathrm{~g}$ per mL . Each mL of this stock solution entains 100 per of fluride ion.

Standard selutions [NOTE Prepare on the day of use.] Transfer 10.0 mL of Standturd stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. This solution eontains 10 his of fluorideion per mL (Standard solution A). Transfer 1.0 mL of Standard stock solution to a secend 100 mL voltmetrie flask, dilute with water to volume, and mix. This selution contains $1.0 \mu \mathrm{~g}$ of fluoride ion per mL (Standard solution $B$ ).

Fest solution Transfer 5.0 o of of Calcium Silicate to a 150 mL pelytefbeaker. Add 40 mL of water and 20 mL of 1 N hydrechlorie acid. Heat to near beiling for 1 minnte, stirring continuously. Coet in an iee bath, transfer the suspension to a 100 mL volumetrie flack, dilute with water to volume, and mix.

Proecdure Tramsfer 20.0 mL Of Standard solution A, Standard solution $B$, and the Test solution to separate polytef beakers, add 10.0 mL of Buffer solution to each beaker, and stir with a plastic coated stirring bar. Concomitantly measure the petentials, in mV, of the-selations. [NOTE When taking measurements, immerse the electrodes in the solution, stir on a magnetic stirrer having an insulated top until equilibritm is attained (1 to 2 minutes), and re eerd the petential. Rimse and dry the electrodes between measurements, taking eare to avoid damaging the erystal of the ion speeifie electrode.] Plet the logarithms of the fleorideion concentrations, in Hg per mL , of the Standard solutions versus petential, in mV. Frem the measured potential of the Test solution and the standard respense line, determine the eoneentration, $C$, in he per $m b$, of fltt oride-ion in the Test solution. Caleulate the quantity, in ug of fleride perg of Caleitm Silieate by multiplying $C$ by 20 . The limit is 10 सf per है
${ }^{\mathbf{4}}$ [NOTE-Store all solutions in plastic containers.]
Buffer solution-Transfer 147 g of sodium citrate to a

Standard stock solution-Dissolve an accurately weighed quantity of USP Sodium Fluoride RS in water to obtain a solution containing $221 \mu \mathrm{~g}$ per mL . Each mL of this stock solution contains $100 \mu \mathrm{~g}$ of fluoride ion.

Test solution-Transfer about 2.0 g of Calcium Silicate, accurately weighed, to a $100-\mathrm{mL}$ plastic beaker containing a magnetic stir bar. Add 20 mL of water and 2.0 mL of hydrochloric acid. Cover with a watch glass, and heat with stirring to a vigorous boil. Remove from heat, and cool. Transfer the cooled suspension to a $100-\mathrm{mL}$ plastic beaker. Add 25 mL of Buffer solution, and adjust with ammonium hydroxide or hydrochloric acid to a pH between 5 and 6 . Add 50 mL of Ionic strength adjustment buffer and water to make 100 mL of solution.

Standard response line-Obtain a standard response line with four standard solutions containing $0,0.10,0.20$, and $0.40 \mu \mathrm{~g}$ per mL of fluoride as follows. Add 23 mL of water, 2 mL of hydrochloric acid, and 25 mL of Buffer solution to a $100-\mathrm{mL}$ plastic beaker. Adjust with ammonium hydroxide to a pH between 5 and 6, and add Ionic strength adjustment buffer to obtain 100 mL of solution. Insert the electrode into the solution, stir for at least 15 minutes, and record the potential for the standard solution containing $0 \mu \mathrm{~g}$ of fluoride per mL . When the electrode has stabilized, add $100 \mu \mathrm{~L}$ of the Standard stock solution to the beaker, and stir. Allow the electrode to stabilize for 5 minutes, and measure the potential for the standard solution containing $0.10 \mu \mathrm{~g}$ of fluoride per mL . Similarly add another $100 \mu \mathrm{~L}$ and $200 \mu \mathrm{~L}$ of the Standard stock solution and record the potential for the standard solutions, containing $0.20 \mu \mathrm{~g}$ per mL of fluoride and $0.40 \mu \mathrm{~g}$ per mL of fluoride, respectively. After each addition, continue to stir for 5 minutes before recording the reading.
electrode and a calomel reference electrode connected to a pH meter capable of measuring potentials with a reproduci-
bility of $\pm 0.2 \mathrm{mV}$ (see $p H\langle 791\rangle$ ).

Procedure-Insert the calibrated electrode into the Test solution, stir for 5 minutes, and record the measurement. From the measured potential of the Test solution and the standard response line, determine the concentration, $C$, in $\mu \mathrm{g}$ per mL , of fluoride ion in the Test solution. Calculate the quantity, in $\mu \mathrm{g}$ per g of fluoride in Calcium Silicate by the formula:

$$
100 C / W
$$

in which $W$ is the weight, in g , of Calcium Silicate taken. The limit is $10 \mu \mathrm{~g}$ per $\mathrm{g}_{\boldsymbol{\Delta}}{ }^{\mathrm{N} F 23}$

Change to read:
Assay for silicon dioxide-Transfer about 400 mg of Caleimmsi tieate,
$\Delta_{\text {the }}$ appropriate amount of Calcium Silicate (see Table 1.) $\mathbf{\Delta N F 2 3}$
accurately weighed, to a beaker, add 5 mL of water and 10 mL of perchloric acid, and heat until dense white fumes of perchloric acid are evolved. Cover the beaker with a watch glass, and continue to heat for 15 minntes lenger.
$\Delta_{2}$ hours. $_{\mathbf{A N F}^{N F}{ }^{23}}$
Allow to cool, add 30 mL of water, filter, and wash the precipitate with 200 mL of hot water. [NOTE-Retain the combined filtrate and washings for use in the Assay for calcium oxide.] Transfer the filter paper and its contents to a platinum crucible, heat slowly to dryness, then heat sufficiently to char the filter paper.After and ander at about $1300^{\circ}$
${ }^{\Delta} 900^{\circ}$ to $1000^{\circ}{ }_{\Delta N F 23}$
to constant weight. Moisten the residue with 5 drops of sulfurie
$\Delta$ perchloric
acid, add 15 mL of hydrofluoric acid, heat cautiously on a hot plate until all of the acid is driven off, and ignite at a temperature not lower than $1000^{\circ}$ to constant weight. Cool in a desiccator, and weigh: the loss in weight represents the weight of $\mathrm{SiO}_{2}$. The percentage of silicon dioxide in the Calcium Silicate is between $90.0 \%$ and $110.0 \%$ of the content stated in the labeling, or within the range of percentages stated in the labeling.
${ }^{\wedge}$ Table 1.

| Sample weight | Calcium oxide content |
| :--- | :---: |
| about 400 mg | greater than $25 \%$ |
| about 600 mg | $11-25 \%$ |
| about 1000 mg | $4-10 \%$ |

## Change to read:

Assay for calcium oxide-Neutralize the combined filtrate and washings retained from the Assay for silicon dioxide to litmus with 1 N sodium hydroxide. Add, while stirring, about 30 mL
$\triangle 10 \mathrm{~mL}$
of 0.05 M edetate disodium VS from a $50-\mathrm{mL}$ buret. Add 15 mL of 1 N sodium hydroxide and 300 mg of hydroxy naphthol blue, and continue the titration to a blue endpoint. Each mL of 0.05 M edetate disodium is equivalent to 2.804 mg of CaO . The percentage of CaO in the Calcium Silicate is between $90.0 \%$ and $110.0 \%$ of the content stated in the labeling, or within the range of percentages stated in the labeling.

## Change to read:

Ratio of silicon dioxide to calcium oxide-Divide the percentage of silicon dioxide obtained in the Assay for silicon dioxide by the percentage of calcium oxide obtained in the Assay for calcium oxide: the quotient obtained is between 4.3
${ }^{\Delta} 0.5{ }_{\text {A }}{ }^{2}$ F23
and 20 .

## BRIEFING

Cellulose Acetate Butyrate, page 7861 of $P F 25(2)$ [Mar.-Apr. 1999]. It is proposed to change the title to Cellaburate. It is also proposed to revise the Definition to specify that the acetyl and butyryl limits are calculated on the previously dried basis to be consistent with the determination of the limits in the test for Acetyl and butyryl content.
(EMC: D. Bempong) RTS-40864-1

## Add the following:

## $\Delta$ Cellulose Acetate Butyrate

## Cellaburate

(Graphic formula to come)

Cellulose, acetate butanoate.
Cellulose, acetate butyrate.
Acetylbutyrylcellulose.
Cellulose butyrate acetate.
Cellulose acetate butyrate [9004-36-8].
» Cellulese Acetate Butyrate Cellaburate is a reaction product of cellulose, acetic anhydride or acetic acid, and butyric acid or butyric anhydride. It contains not less than 1.0 percent and not more than 41.0 percent acetyl $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}\right)$ groups, by weight, and not less than 5.0 percent and not more than 57.356 .0 percent butyryl $\left(\mathrm{C}_{4} \mathrm{H}_{7} \mathrm{O}\right)$ groups, by weight, calculated on the anhydrous, previously dried, acid-free basis.

Packaging and-storage-Preserve in tight containers.
Labeling-The labeling indicates the nominal percentage ranges of acetyl and butyryl groups.

USP Reference standards $\langle 11\rangle$ USP Cellulose Acetate Bumate RS. USP Cellaburate RS.

Identification, Infrared Absorption $\langle 197 \mathrm{~F}\rangle$-Dissolve 150 mg in 1 mL of acetone. Evenly cast 1 drop of the solution on a sodium chloride plate. Heat the plate at $105^{\circ}$ for 10 minutes.

Water, Method $I\langle 921\rangle$ : not more than $5.0 \%$, a mixture of methylene chloride and methanol (2:1) being used in place of the methanol solvent.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : 0.002\%.

## Limit of free acid-

Indicator solution-Transfer about 0.5400 .675 g of bromocresol purple, accurately weighed, to a 1-L volumetric flask. Dissolve in 20025 mL of 0.0100 .10 N sodium hydroxide, dilute with water to volume, and mix.

Calibration solutions-Pipet 1, 2, 3, and 4 mL of 0.001 N acetic acid VS into four $100-\mathrm{mL}$ volumetric flasks, respectively. Pipet 4 mL of the Indicator solution into each flask
and into an empty $100-\mathrm{mL}$ volumetric flask, and dilute each flask with water to volume to obtain solutions containing $0.0,0.60,1.20,1.80$, and $2.40 \mu \mathrm{~g}$ of acetic acid per mL.

Control solution-Place 96 mL of water in a suitable bottle, add a stirring bar, cap the bottle, and stir for 75 minutes at room temperature. Pipet 4 mL of Indicator solution into the bottle, and mix.

Test solution-Transfer about 1 to 2 g of Cellulose Ace Bute, Cellaburate, accurately weighed, to a bottle, and add 96 mL of water. Add a stirring bar, cap the bottle, and stir for 75 minutes at room temperature. Pipet 4 mL of Indicator solution into the bottle, stir to mix, and allow the solid to settle for 2 minutes.

Calibration-Determine the absorbances of the Calibration solutions in a $1-\mathrm{cm}$ cell at the wavelength of maximum absorption of the basic form of bromocresol purple at about 589 nm , with a suitable spectrophotometer, using water as the blank. The absorbance difference, $A_{S}$, between the 0.0 $\mu \mathrm{g}$ per mL solution and the other solutions is expressed by the formula:

$$
a \epsilon_{s}+\left(60 \times 10^{6}\right)
$$

in which a is the absorptivity of the basic form of bromocresol purple, in mL per em mole; $b$ is the cell path length, in $\mathrm{em} ; \mathrm{G}_{\mathrm{s}}$ is the concentration of the acetic acid, in $\mu \mathrm{g}$ per mL ; and $60 \times 10^{6}$ is the molecular weight of acetic acid in $\mu \mathrm{g}$ per mole. Plot $A_{\varsigma}$ Grgus $G_{\varsigma}$ adheres to Beer's law over the range stated under Calibration solutions. Plot $A_{S}$ versus $C_{S}$ (the concentration of the acetic acid in $\mu \mathrm{g}$ per mL ) on linear graph paper, and draw the straight line best fitting the points including the origin.

Procedure-Pass 10 mL of the Test solution through a polytef syringe filter that has been presoaked in isopropyl alcohol. Determine the absorbance of the filtered Test solution in a $1-\mathrm{cm}$ cell at about 589 nm on the same spectrophotometer, using water as the blank. In the same manner,
determine the absorbance of the Control solution. Calculate the percentage of free acid, as acetic acid, in the portion of Gellule Aee Butyrate Cellaburate taken by the formula:

$$
\left(100 C_{U} / W_{U}\right) / 10,000
$$

in which 100 is the total volume, in mL, of the Test solution; $C_{U}$ is the concentration of free acid, calculated as acetic acid, in $\mu \mathrm{g}$ per mL , based on the absorbance difference between the Control solution and the Test solution read directly from the calibration plot; and $W_{U}$ is the weight, in g , of Cellulose Ace Cellaburate taken to prepare the Test solution. [NOTE-If the $C_{U}$ value is greater than $2.42 .8 \mu \mathrm{~g}$ per mL , reduce the test sample size by half in the Test solution, and repeat the determination.] Not more than $0.1 \%$ is found.

## Acetyl and butyryl content-

Internal standard solution-Prepare a solution of isovaleric acid in pyridine containing about 4.6 mg per mL , and store it in a tightly closed container.

Saponification solution-Place 250 mL of $n$-propyl alcohol in a $500-\mathrm{mL}$ volumetric flask, add 65.5 g of potassium hydroxide, and mix to dissolve. Dilute with $n$-propyl alcohol to volume, and mix.

Acid solution-Place 250 mL of $n$-propyl alcohol in a $500-\mathrm{mL}$ volumetric flask, add 166 mL of hydrochloric acid, and mix. Dilute with $n$-propyl alcohol to volume, and mix.

Standard preparation-Transfer about 0.20 g of glacial acetic acid and 0.31 g of butyric acid, each accurately weighed, to a $50-\mathrm{mL}$ volumetric flask. Dilute with Internal standard solution to volume, and mix.
Test preparation-Transfer about 0.15 g of Cellulese Ace, Cellaburate, previously dried at $105^{\circ}$ for 1 hour and accurately weighed, into a $25-\mathrm{mm} \times 160-$ mm test tube. Pipet 10 mL of Internal standard solution into the test tube, and dissolve by stirring and heating at $110^{\circ}$ for 30 minutes. While stirring, add 5 mL of Saponification solu-
tion slowly into the tube. Heat at $110^{\circ}$ for 10 minutes. Cool, and add 5 mL of the Acid solution. Mix on a vortex mixer, and allow the precipitate to settle.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector, a $0.53-\mathrm{mm} \times 30-\mathrm{m}$ fused silica column bonded with a $1-\mu \mathrm{m}$ layer of phase G35, and a split injection system with a split ratio of about $35: 1$. Helium is used as the carrier gas flowing at a rate of about 8 mL per minute. The injection port, column, and detector block temperatures are maintained at $250^{\circ}, 125^{\circ}$, and $250^{\circ}$, respectively. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.45 for acetic acid, 0.85 for butyric acid, and 1.00 for isovaleric acid; the tailing factor for the butyric acid peak is not more than 1.5; and the relative standard deviation for replicate injections is not more than $3.0 \%$.
Calibration-Inject about $1 \mu \mathrm{~L}$ of the Standard preparation into the chromatograph, and record the chromatogram as directed for Procedure. Repeat two more times. Calculate the average unit weight response, $F_{S A}$, of acetic acid per 10 mL of the Internal standard solution by the formula:

$$
(10 / 50) q_{R A} / R_{S A},
$$

in which 10/50 is the volume ratio of the Internal standard solution in the Test preparation and in the Standard preparation; $q_{R A}$ is the weight, in g , of acetic acid in the Standard preparation; and $R_{S A}$ is the average peak response ratio of acetic acid and isovaleric acid. Similarly, calculate the average unit weight response, $F_{S B}$, of butyric acid per 10 mL of the Internal standard solution by the formula:

$$
(10 / 50) q_{R B} / R_{S B},
$$

in which $10 / 50$ is the volume ratio of the Internal standard solution in the Test preparation and in the Standard preparation; $q_{R B}$ is the weight, in g , of butyric acid in the Standard preparation; and $R_{S B}$ is the average peak response ratio of butyric acid and isovaleric acid.

Procedure-Inject about $1 \mu \mathrm{~L}$ of the upper clear solution from the Test preparation into the chromatograph, record the chromatogram, and measure the peak area responses. Calculate the percentage of acetyl in the portion of Cellulose Ace Cellaburate taken by the formula:

$$
(43 / 60)(100) R_{U A} F_{S A} / W_{U}
$$

in which $43 / 60$ is the ratio of the formula weights of acetyl and acetic acid; $R_{U A}$ is the peak area response ratio of acetic acid and isovaleric acid in the Test preparation; $F_{S A}$ is as defined under Calibration; and $W_{U}$ is the weight, in g , of Cet Ale Aellaburate taken to prepare the Test preparation. Similarly, calculate the percentage of butyryl in the portion of Cellule Cellaburate taken by the formula:

$$
(71 / 88)(100) R_{U B} F_{S B} / W_{U},
$$

in which $71 / 88$ is the ratio of the formula weights of butyryl and butyric acid; $R_{U B}$ is the peak area response ratio of butyric acid and isovaleric acid in the Test preparation; $F_{S B}$ is as defined under Calibration; and $W_{U}$ is the weight, in g , of Gellulose Ace Butyrate Cellaburate taken to prepare the Test preparation. $\mathbf{\Lambda N F 2 3 ~}^{\text {N }}$

## Briefing

Galactose. Because there is no existing $N F$ monograph for this excipient, a new monograph is proposed based on the Galactose monograph in the European Pharmacopeia Fourth Edition and manufacturer comments.
(EMC: K. Russo) RTS-40209-2

## Add the following:

©Galactose

$\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \quad 180.16$
$\alpha$-D-Galactopyranose. [3646-73-9].
» Galactose is one of the products of the metabolism of lactose, a naturally occuring sugar in dairy products, by the digestive enzyme lactase.

Packaging and storage-Store in tight containers.
USP Reference standards $\langle 11\rangle$ —USP Dextrose RS. USP
Galactose RS. USP Lactose Monohydrate RS.
Appearance of solution-Dissolve, with heating at $50^{\circ}$, 10.0 g of galactose in 50 mL of carbon dioxide-free water. The solution is not more intensely colored than a solution prepared immediately before use by mixing 3.0 mL of ferric chloride CS, 3.0 mL of cobaltous chloride CS, and 2.4 mL of cupric sulfate CS with dilute hydrochloric acid ( 10 g per L ) to make 10 mL , and diluting 1.5 mL of this solution with the dilute hydrochloric acid to 100 mL . Make the comparison by viewing the substance and the solution downward in matched color-comparison tubes against a white surface (see Color and Achromicity $\langle 631\rangle$ ).

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -

Test solution-Dissolve 10 mg in 20 mL of a mixture of methanol and water (3:2).

Standard solution 1: $500 \mu \mathrm{~g}$ per mL in a mixture of methanol and water (3:2).
Standard solution 2-Prepare a solution using USP Galactose RS, USP Dextrose RS and USP Lactose Monohydrate RS each at a concentration of $500 \mu \mathrm{~g}$ per mL in a mixture of methanol and water (3:2).

Application volume: $2 \mu \mathrm{~L}$.
Developing solvent system: propanol and water (85:15).
Procedure-Develop the plate in an unsaturated tank.
After the solvent front has developed over 15 cm , remove the plate from the tank. Dry the plate with warm air, then spray the plate with a thymol solution [ 0.5 g in a mixture of alcohol and sulfuric acid (95:5)]. Heat for 10 minutes in an oven at $130^{\circ}$. The $R_{F}$ of the principal spot obtained from the Test solution corresponds to that obtained from the Standard solution. [NOTE-There must be three clearly resolved spots in the chromatogram for Standard solution 2 in order for the results to be valid.]

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $+78.0^{\circ}$ and $+81.5^{\circ}$ at $20^{\circ}$.

Test solution: Transfer 10.0 g to a $100-\mathrm{mL}$ volumetric flask, and dissolve in 80 mL of water. Add 0.2 mL of ammonia TS, allow to stand for 30 minutes, then dilute with water to volume.

Microbial limits $\langle 61\rangle$ : It meets the requirements of the test for absence of Salmonella species, Escherichia coli, Staphylcoccus aureus, and Pseudomonas auruginosa. The total
aerobic microbial count does not exceed $10^{3}$ cfu per g , and the total combined molds and yeasts count does not exceed $10^{2}$ cfu per g .

Acidity-Dissolve 10.0 g , with heating at $50^{\circ}$, in 40 mL of carbon dioxide-free water. Dilute with carbon dioxide-free water to 50 mL [NOTE-Use this solution for the Barium test.] To 30 mL of this solution, add 0.3 mL of phenolphthalein TS, and titrate with 0.01 N sodium hydroxide to a pink color: not more than 1.5 mL of 0.01 N sodium hydroxide is required to produce a pink color.

Water, Method $I\langle 921\rangle$ : not more than $1.0 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.

## Barium-

Standard solution-To 5 mL of the solution prepared for the Acidity test, add 6 mL of water.
Test solution-To 5 mL of the solution prepared for the Acidity test, add 5 mL of water and 1 mL of dilute sulfuric acid. Allow to stand for 1 hour: any opalescence in the Test solution is not more intense than that of the Standard solution.

## Limit of lead-

Diluent-Dilute 12 mL of acetic acid with water to 100 mL . Mix equal parts of this solution and water to prepare the Diluent.
Lead standard stock solution-Transfer an accurately weighed amount of lead nitrate, about 400 mg , to a $250-$ mL volumetric flask. Dilute with water, to volume and mix.
Lead standard solution-Dilute 1.0 mL of Lead standard stock solution with water to 10 mL . Dilute 1.0 mL of this solution with water to 10 mL .
Standard solutions-Into three identical flasks, add 0.5 $\mathrm{mL}, 1.0 \mathrm{~mL}$, and 1.5 mL of Lead standard solution, respectively, and then add to each flask a $20.0-\mathrm{g}$ amount of galactose. Dilute with Diluent to 100 mL . To each flask add 2.0 mL of ammonium pyrrolidinedithiocarbamate solution (10
g per L ) and 10.0 mL of methyl isobutyl ketone, then shake for 30 seconds. [NOTE-Protect from light.] Allow the layers to separate, and use the methyl isobutyl ketone (upper) layer for analysis.

Test solution-Dissolve 20.0 g of Galactose in Diluent, and dilute with Diluent to 100 mL . Add 2.0 mL of ammonium pyrrolidinedithiocarbamate solution ( 10 g per L ) and 10.0 mL of methyl isobutyl ketone, then shake for 30 seconds. [NOTE-Protect from light.] Allow the layers to separate, and use the methyl isobutyl ketone (upper) layer for analysis.

Procedure-Concomitantly determine, at least in triplicate, the absorbances of the Standard solutions and the Test solution at 283.3 nm , with a suitable atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ), equipped with a lead hollow-cathode lamp as the radiation source and an air-acetylene flame. Record the average steady readings for each of the Standard solutions and the Test solution. Plot the absorbances of the Standard solutions and the Test solution versus the amount of lead added. Extrapolate the line joining the points on the graph until it meets the concentration axis. The distance between this point and the intersection of the axes represents the concentration of lead in the Test solution: not more than $0.5 \mu \mathrm{~g}$ per $g$ is found. $\boldsymbol{\Delta}^{\text {NF23 }}$

## Briefing

Maleic Acid, page 2005 of PF 28(6) [Nov.-Dec. 2002]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded to In-Process Revision.
(EMC: E. Gonikberg) RTS-40862-1

## Add the following:

## ©Maleic Acid

$\mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$
116.07
(Z)-Butenedioic acid
Cis-Butenedioic acid $\quad[110-16-7]$.
» Maleic Acid contains not less than 99.0 percent and not more that 101.0 percent of $\mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$, calculated on the anhydrous basis.

## Packaging and storage-Preserve in glasserner

 tight glass containers, protected from light. Store at room temperature.USP Reference standards $\langle 11\rangle —$ USP Fumaric Acid RS. USP Maleic Acid RS.

## Identification-

A: Dissolve about 500 mg of Maleic Acid in 10 mL of water: the pH of the solution is not less than 2 .

B: The principal spot in the chromatogram obtained from Test solution 2 corresponds in color, size, and $R_{F}$ value to that in the chromatogram obtained from the Maleic acid standard solution, as obtained in the test for Limit of fumaric acid.

C: Dissolve about 35 mg of resorcinol in 10 mL of sulfuric acid (Resorcinol solution). Dissolve about 100 mg of Maleic Acid in 10 mL of water (Test solution). To 0.3 mL of the Test solution add 3 mL of the Resorcinol solution, and heat in a water bath for 15 minutes: no color develops. To 3 mL of the Test solution add 1 mL of bromine TS, heat in a water bath for 15 minutes to remove the bromine, then heat
to boiling, and cool. To 0.2 mL of this solution, add 3 mL of the Resorcinol solution, and heat in a water bath for 15 minutes: a violet-pink color develops.

## Color and clarity of solution-

Dilute hydrochloric acid solution-Mix 27.5 mL of hydrochloric acid with sufficient water to make 1000 mL .

Reference solution-Mix 2.4 mL of ferric chloride CS and 0.6 mL of cobaltous chloride CS with Dilute hydrochloric acid solution to make 10 mL . Dilute 5 mL of this solution with Dilute hydrochloric acid solution to make 100 mL .

Test solution-Dissolve about 5 g of Maleic Acid in 50 mL of water.

Procedure-Place the Reference solution and the Test solution in matched color-comparison tubes, and compare the solutions by viewing them downward against a white surface (see Color and Achromicity $\langle 631\rangle$ ): the Test solution is clear and not more intensely colored than the Reference solution.

Water, Method $I\langle 921\rangle$ : not more than $2.0 \%$ is found.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on a $1.0-\mathrm{g}$ portion.

Heavy metals, Method II $\langle 231\rangle$ -
Test solution-Transfer 1.0 g of Maleic Acid to a quartz crucible, add 0.5 g of magnesium oxide, and mix. Ignite the crucible to dull redness until a homogeneous white or gray-ish-white mass is obtained. Ignite at $800^{\circ}$ for 1 hour, cool, and dissolve the residue by adding two $5-\mathrm{mL}$ portions of diluted hydrochloric acid. Add 0.1 mL of phenolphthalein TS, and then add ammonium hydroxide until a pink color is obtained. Cool, add glacial acetic acid until the solution is decolorized, then add 0.5 mL of glacial acetic acid in excess, and dilute with water to 20.0 mL .

Standard solution-To 0.5 g of magnesium oxide, add 1.0 mL of Standard Lead Solution, and evaporate to dryness at $105^{\circ}$ for 1 hour. Following the procedure described above
for preparation of the Test solution, ignite, dissolve in diluted hydrochloric acid, add ammonia and then acetic acid, and dilute with water to 20.0 mL .

Procedure-To 12 mL of the Test solution, add 2.0 mL of pH 3.5 Acetate Buffer, mix, add to 1.2 mL of thioacetamideglycerin base TS, and mix immediately. To 10 mL of the Standard solution, add 2.0 mL of the Test solution and 2.0 mL of pH 3.5 Acetate Buffer, mix, add 1.2 mL of thioaceta-mide-glycerin base TS, and mix immediately. Prepare a blank, using a mixture of 10 mL of water and 2.0 mL of the Test solution. Compared to the blank, the solution obtained from the Standard solution shows a light brown color. Dilute each of the solutions obtained from the Test solution and the Standard solution with water to 50 mL , allow to stand for 2 minutes, and view downward over a white surface. The color of the solution obtained from the Test solution is not darker than that of the solution obtained from the Standard solution: not more than $10 \mu \mathrm{~g}$ per g .

## Limit of fumaric acid-

Adsorbent: $0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture.

Test solution 1-Dissolve an accurately weighed quantity of Maleic Acid in acetone to obtain a solution having a concentration of about 100 mg per mL .
Test solution 2-Transfer about 1.0 mL of Test solution 1 to a $50-\mathrm{mL}$ volumetric flask, dilute with acetone to volume, and mix.

Maleic acid standard solution-Dissolve an accurately weighed quantity of USP Maleic Acid RS in acetone to obtain a solution having a known concentration of about 2 mg per mL.

Fumaric acid standard solution-Dissolve an accurately weighed quantity of USP Fumaric Acid RS in acetone to obtain a solution having a known concentration of about 1.5 mg per mL .

Resolution solution-Prepare a mixture of Maleic acid standard solution and the Fumaric acid standard solution (1:1).

Developing solvent system-Prepare a mixture of heptane, butanol, chloroform, and anhydrous formic acid (44:36:16:16).

Procedure-Proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$, using an unsaturated chamber. Separately apply $10 \mu \mathrm{~L}$ of the Resolution solution and $5 \mu \mathrm{~L}$ each of Test solution 1, Test solution 2, the Maleic acid standard solution, and the Fumaric acid standard solution. Dry the plate at $100^{\circ}$ for 15 minutes, and examine the plate under short-wavelength UV light at 254 nm . The chromatogram obtained from the Resolution solution exhibits two clearly separated spots, and any spot corresponding to fumaric acid in the chromatogram of Test solution 1 does not exceed, in size or intensity, the principal spot obtained in the chromatogram of the Fumaric acid standard solution: not more than $1.5 \%$ of fumaric acid is found.

## Limit of iron -

Diluted standard iron solution-Immediately before use, dilute 1 volume of the Standard Iron Solution, prepared as directed under Iron $\langle 241\rangle$, with 9 volumes of water. [NOTE-This solution contains the equivalent of $1 \mu \mathrm{~g}$ of iron per mL.]

Potassium thiocyanate solution-Dissolve 9.7 g of potassium thiocyanate in 100 mL of water.

Test solution-Dissolve about 1 g of Maleic Acid, accurately weighed, in 10 mL of water. Add 2 mL of diluted hydrochloric acid and 0.05 mL of bromine TS. After 5 min utes, remove the excess of bromine with the aid of a current of air, add 3 mL of Potassium thiocyanate solution, and shake well.

Standard solution-To 5 mL of Diluted standard iron solution add 6 mL of water. Add 1 mL of diluted hydrochloric acid and 0.05 mL of bromine TS. After 5 minutes, remove the excess of bromine with the aid of a current of air, add 3 mL of Potassium thiocyanate solution, and shake well.

Procedure-Allow the Standard solution and the Test solution to stand for 5 minutes. Any red color in the Test solution is not more intense than that in the Standard solution: not more than $5 \mu \mathrm{~g}$ per g.

Assay—Dissolve about 500 mg of Maleic Acid, accurately weighed, in 50 mL of water, and titrate with 1 N sodium hydroxide VS, using phenolphthalein TS as the indicator. Each mL of 1 N sodium hydroxide is equivalent to 58.04 mg of $\mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4 \cdot \boldsymbol{\Delta} \times 23}$

## BRIEFING

Nitrogen, NF 22 page 2899; Nitrogen 97 Percent, NF 22 page 2899. These monographs are being revised to add new USP Reference Standards.
(AER: K. Zaidi) RTS-40629-1

## Add the following:

${ }^{4}$ USP Reference standards $\langle 11\rangle — U S P$ Nitrogen RS. USP Oxygen-Helium RS. anF23

## Change to read:

Identification -The flame-of a burning woed splinter is extinguished when inserted inte a test tube-fllled with Nitrogen. [NOTE-Exercise caution.]
${ }^{4}$ Prepare a gas chromatograph as directed in the Assay, and inject USP Nitrogen RS and the nitrogen sample into a gas chromatrograph. The retention time of the major peak in the chromatogram of the nitrogen sample corresponds to that in the chromatogram of the USP Nitrogen RS. $\mathbf{\Delta N F 2 3}^{N}$

## Change to read:

Assay-Introduce a specimen of Nitrogen into a gas chromatograph by means of a gas sampling valve. Select the operating conditions of the gas chromatograph such that the standard peak signal resulting from the following procedure corresponds to not less than $70 \%$ of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 3 m in length and 4 mm in inside diameter and is packed with a molecular sieve prepared from a synthetic alkali-metal aluminosilicate capable of absorbing molecules having diameters of up to 0.5 nm , which permit complete separation of oxygen from nitrogen. Use industrial grade helium $(99.99 \%)$ as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by aoxygen helium certified stan dard (see under Reagents in the seetion Reagents, Indicators, and Solutions),
${ }^{\text {the }}$ the USP Oxygen-Helium RS, , $_{\text {NF23 }}$
and is equivalent to not more than $1.0 \%$ of oxygen when compared to the peak response of the
${ }^{\boldsymbol{\Delta}}$ USP Oxygen-Helium RS, ${ }_{\mathbf{\Delta N F 2 3}}$
indicating not less than $99.0 \%$, by volume, of $\mathrm{N}_{2}$.

## BRIEFING

Nitrogen 97 Percent, NF 22 page 2899-See briefing under Ni trogen. In addition, minor editorial style changes have been made.
(AER: K. Zaidi) RTS-40629-2

## Add the following:

${ }^{\Delta}$ USP Reference standards $\langle 11\rangle$ —USP Nitrogen 97 Per-


## Change to read:

Identification-The flame of a burning splinter is extinguished when inserted into a test fllled with Nitrogen 97 Per eent. [NOTE-Exereise eatution.]
${ }^{\Delta}$ Prepare a gas chromatograph as directed in the Assay, and inject USP Nitrogen 97 Percent RS and a sample of Nitrogen 97 Percent into the gas chromatograph. The retention time of the major peak in the chromatogram of the test sample corresponds to that in the chromatogram of the USP Nitrogen 97 Percent RS. $\mathbf{\Delta N F 2 3 ~}$

## Change to read:

Assay-Proceed as directed in the Assay under Nitrogen. The peak response produced by the assay specimen exhibits a retention time corresponding to that produced by moxysen heliumeertified stan dard (see mader Reagents in the section Reagents, Indientors, and solutions)
$\Delta_{\text {the USP Oxygen-Helium }} \mathrm{RS}_{\mathbf{A}^{N F 23}}$
and is equivalent to not more than $3.0 \%$ of oxygen when compared to the peak response of the-oxysen helimm certified standard,
${ }^{\boldsymbol{\Delta}}$ USP Oxygen-Helium RS, ${ }_{\mathbf{\Delta}}$ NF23
indicating not less than $97.0 \%$, by volume, of $\mathrm{N}_{2}$.

## Briefing

Polyoxyl Stearyl Ether, page 1118 of PF 29(4) [July-Aug 2003]. It is proposed to revise the name of the USP Reference Standard to reflect the chemical composition of the material.
(EMC: E. Gonikberg) RTS-40862-3

## Add the following:

## ■Polyoxyl Stearyl Ether

Polyethylene glycol monostearyl ether [9005-00-9].

## » Polyoxyl Stearyl Ether is a mixture of the mono-

 stearyl ethers of mixed polyethylene glycols, the average polymer length being equivalent to not less than 2 and not more than 20 oxyethylene units (nominal value). It may contain various amounts of free stearyl alcohol and some free polyethylene glycol.Packaging and storage-Preserve in tight containers, and store in a cool, dry place.

Labeling-Label it to indicate the average nominal number of oxyethylene units.

## Change to read:

USP Reference standards $\langle 11\rangle$ USP Polyoxyl Steatyl Ether RS. ${ }^{\text {A }}$ USP Polyoxyl 10 Stearyl Ether RS._nF23

Appearance of solution-Dissolve 5.0 g of Polyoxyl Stearyl Ether in 50.0 mL of alcohol. The solution is not more intensely colored than a solution prepared immediately before use by mixing 12.0 mL of ferric chloride CS, 5.0 mL of cobaltous chloride CS , and 2.0 mL of cupric sulfate CS with dilute hydrochloric acid ( 10 g per L ) to make 50.0 mL , and diluting 12.5 mL of this solution with dilute hydrochloric acid ( 10 g per L ) to make 100.0 mL . Make the comparison by viewing the substance and the solution downward in matched color-comparison tubes against a white surface (see Color and Achromicity $\langle 631\rangle$ ).

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~F}\rangle$-Use a thin film of melted test specimen.

B: Dissolve or disperse 0.1 g in alcohol, add 10 mL of diluted hydrochloric acid, 5 mL of barium chloride TS, and 10 mL of phosphomolybdic acid solution (1 in 10): a precipitate is formed.

Acid value $\langle 401\rangle$ : not more than 1.0, determined on 5.0 g . Hydroxyl value $\langle 401\rangle$ : within the ranges specified in the table below.

Alkalinity—Dissolve 2.0 g of Polyoxyl Stearyl Ether in a hot mixture of 10 mL of alcohol and 10 mL of water. Add 0.05 mL of bromothymol blue TS, and titrate with 0.1 N hydrochloric acid to a yellow endpoint: not more than 0.5 mL of 0.1 N hydrochloric acid is required.

Water, Method $I\langle 921\rangle$ : not more than $3.0 \%$.
Limit of free ethylene oxide and dioxane-[CautionEthylene oxide is toxic and flammable. Prepare these solutions in a well-ventilated fume hood, using great care. Protect both hands and face by wearing polyethylene protective gloves and an appropriate face mask. Store all solutions in hermetic containers, and refrigerate at a temperature between $4^{\circ}$ and $8^{\circ}$.] [NOTE-Before using the Polyethylene Glycol 200 in this test, remove any volatile components from it by placing 500 mL of Polyethylene Glycol 200 in a $1000-\mathrm{mL}$ round-bottom flask, attaching the flask to a rotary evaporator, and evaporating at a temperature of $60^{\circ}$ and under a vacuum of 10 to 20 mm Hg for 6 hours.]
Acetaldehyde solution-Prepare a solution of acetaldehyde in water, containing a known concentration of about $10 \mu \mathrm{~g}$ per mL . [NOTE-Prepare the Acetaldehyde solution fresh just prior to use.]
Ethylene oxide stock solution-Fill a chilled pressure bottle with liquid ethylene oxide, and store in a freezer when not in use. Use a small piece of polyethylene film to protect the liquid from contact with the rubber gasket. Tare a glassstoppered conical flask, add about 50 mL of Polyethylene Glycol 200, and reweigh the flask. Transfer about 5 mL of the liquid ethylene oxide to a $100-\mathrm{mL}$ beaker chilled in a mixture of sodium chloride and wet ice (1:3). Using a gas-tight syringe that has been previously cooled to $-10^{\circ}$, transfer about $300 \mu \mathrm{~L}$ (corresponding to about 250 mg ) of liquid ethylene oxide to the Polyethylene Glycol 200, and swirl gently to mix. Replace the stopper, reweigh the flask, and determine the amount of ethylene oxide absorbed by
weight difference. Adjust the weight of the mixture with Polyethylene Glycol 200 to 100.0 g , replace the stopper, and swirl gently to mix. This stock solution contains about 2.5 mg of ethylene oxide per g. [NOTE-Prepare this stock solution fresh just prior to use, and store in a refrigerator.]

Ethylene oxide solution-Tare a glass-stoppered conical flask, and chill it in a refrigerator. Add about 35 mL of Polyethylene Glycol 200, and reweigh the flask. Using a gastight gas chromatographic syringe that has been chilled in a refrigerator, transfer about 1 g of the chilled Ethylene oxide stock solution, accurately weighed, to the tared, conical flask. Adjust the weight of the solution with Polyethylene Glycol 200 to 50.0 g , replace the stopper, and swirl gently to mix. Transfer about 10 g of this solution, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask. Add 30 mL of water, and mix. Dilute with water to volume, and mix to obtain a solution containing about $10 \mu \mathrm{~g}$ of ethylene oxide per mL . [NOTE-Prepare this solution fresh just prior to use, and store in a refrigerator.]

Dioxane solution-Dissolve about 1.0 g of dioxane, accurately weighed, in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.5 mg of dioxane per mL .

Standard solution A-Transfer 0.1 mL of Ethylene oxide solution to a $10-\mathrm{mL}$ pressure headspace vial, add 0.1 mL of Acetaldehyde solution and 0.1 mL of Dioxane solution, seal the vial, and mix.

Standard solution B-Transfer about 1.0 g of the substance under test, accurately weighed, to another $10-\mathrm{mL}$ pressure headspace vial, add 0.1 mL of Ethylene oxide solution, 0.1 mL of Dioxane solution, and 1.0 mL of $N, N$-dimethylacetamide. Seal the vial, and mix.

Test solution-Transfer about 1.0 g of the substance under test, accurately weighed, to a $10-\mathrm{mL}$ pressure headspace vial, add 1.0 mL of $N, N$-dimethylacetamide and 0.2 mL of water, seal the vial, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— [NOTE--The use of a headspace apparatus that automatically transfers a measured amount of headspace is allowed.] The gas chromatograph is equipped with a flame-ionization detector, maintained at about $250^{\circ}$, and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ glass or quartz capillary column bonded with a $1.0-\mu$ m layer of phase G1. The injection port is equipped with a split injection port with a split ratio of 20:1 and is maintained at about $150^{\circ}$. The column temperature is maintained at $50^{\circ}$ for 5 minutes after injection, then programmed to increase at the rate of $5^{\circ}$ per minute to $180^{\circ}$, then at the rate of $30^{\circ}$ per minute to $230^{\circ}$ and then maintained at $230^{\circ}$ for 5 minutes. Each vial is heated at a temperature of $90^{\circ}$ for 45 minutes before a suitable portion of its headspace is injected. The carrier gas is helium flowing with a linear velocity of about 20 cm per second. [NOTE-If the headspace apparatus is used, then an injection time of 12 seconds and a transfer line temperature of $150^{\circ}$ are recommended.] Chromatograph the gaseous phase of Standard solution $A$, and record the peak responses as directed for Procedure: the relative retention times are about 0.94 for acetaldehyde and 1.0 for ethylene oxide; the resolution, $R$, between acetaldehyde and ethylene oxide is not less than 2.0 ; the dioxane peak is detected with a signal-to-noise ratio of not less than 5 ; and the relative standard deviation for replicate injections is not more than $15 \%$.

Procedure-Using a heated, gas-tight gas chromatographic syringe, separately inject equal volumes (about 1 mL ) of the gaseous headspace of Standard solution $B$ and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks: the mean areas of the ethylene oxide and dioxane peaks in the
chromatogram obtained from the Test solution are not greater than half the mean areas of the corresponding peaks in the chromatogram obtained from Standard solution B. Calculate the concentration of ethylene oxide, in $\mu \mathrm{g}$ per g , in the portion of the substance under test taken by the formula:

$$
A r_{U} /\left[\left(r_{S} W_{U}\right)-\left(r_{U} W_{S}\right)\right]
$$

in which $A$ is the quantity, in $\mu \mathrm{g}$, of ethylene oxide added to Standard solution B; $r_{U}$ and $r_{S}$ are the ethylene oxide peak responses obtained from the Test solution and Standard solution $B$, respectively; and $W_{U}$ and $W_{S}$ are the weights, in g , of the substance under test taken to prepare the Test solution and Standard solution B, respectively: not more than $1 \mu \mathrm{~g}$ per g is found.

Calculate the concentration of dioxane, in $\mu \mathrm{g}$ per g , in the portion of the substance under test taken by the formula:

$$
A_{D} r_{U} / 5\left[\left(r_{S} W_{U}\right)-\left(r_{U} W_{S}\right)\right]
$$

in which $A_{D}$ is the amount, in $\mu \mathrm{g}$, of dioxane added to Standard solution $B ; r_{U}$ and $r_{S}$ are the dioxane peak responses obtained from the Test solution and Standard solution B, respectively; and $W_{U}$ and $W_{S}$ are as defined above: not more than $10 \mu \mathrm{~g}$ per g is found. $\mathrm{IS}_{\text {(NF22) }}$

## Briefing

Sesame Oil, NF 22 page 2926. Due to difficulties experienced in procuring the System suitability solution reagents, 1,2-dilinoleoyl-3-oleoyl- rac-glycerol (OLL) and 1,2-dilinoleoyl-3-palmitoyl-racglycerol (PLL), for the test for Triglyceride composition, it is proposed to make these materials available as new Reference Stan-
dards. USP Sesame Oil Related Compound A RS and USP Sesame Oil Related Compound B RS will now replace the current reagents OLL and PLL, respectively.
(EMC: C. Sheehan) RTS-40837-1

## Add the following:

${ }^{4}$ USP Reference standards $\langle 11\rangle —$ USP Sesame Oil Related Compound A RS. USP Sesame Oil Related Compound B RS. ^ $^{N F 23}$

## Change to read:

## Triglyceride composition-

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and methylene chloride ( $60: 40$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

NOTE-The fatty acid radicals are designated as linoleic (L), oleic $(\mathrm{O})$, palmitic $(\mathrm{P})$, and stearic ( S ), and the common abbreviations for triglycerides used are as follows: trilinolein (LLL), 1,2-dilino-leoyl-3-oleoyl-rac-glycerol (OLL), 1,2-dilinoleoyl-3-palmitoyl-rac-glycerol (PLL), 1,2-dioleoyl-3-linoleoyl-rac-glycerol (OOL), 1-palmitoyl-2-oleoyl-3-linoleoyl-rac-glycerol (POL), triolein (OOO), 1-linoleoyl-2-oleoyl-3-stearoyl-rac-glycerol (SOL), and 1,2-dioleoyl-3-palmitoyl-rac-glycerol (POO).

System suitability solution-Transfer 30 mgen of OLL and PLL, aceurately weighed, to a 10 mL volumetric flask, dis solve in and dilute with Mobile phase to volume, and mix.
${ }^{\Delta}$ Dissolve an accurately weighed quantity of USP Sesame Oil Related Compound A RS and USP Sesame Oil Related Compound B RS in Mobile phase to obtain a solution having a known concentration of about 3 mg of each per mL . [NOTE-USP Sesame Oil Related Compound A RS is OLL and USP Sesame Oil Related Compound B RS is PLL]. aFF23

Test solution-Transfer about 200 mg of Oil, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The chromatograph is equipped with a refractive index detector and two $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ columns in series that contain packings L 1 and are maintained at a constant temperature about $30^{\circ}$. The flow rate is about 1.0 mL per minute. Chromatograph the System suitability solution, and record the peak areas as directed for Procedure: the relative retention times are about 0.93 for OLL and 1.0 for PLL; the resolution, $R$, between OLL and PLL is not less than 1.8 ; the relative standard deviation for replicate injections, determined from peak areas, is not more than $1.5 \%$; and the relative standard deviation for replicate injections, determined from peak area ratios of OOL to POL, is not more than $2.2 \%$.

Procedure-Inject about $20 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure the areas for the eight major triglyceride peaks, eluting from 0 to about 40 min utes, with relative retention times stated in the table below and in the order specified. Calculate the percentage of each of these triglycerides in the portion of Oil taken by the formula:

$$
100(A / B)
$$

in which $A$ is the peak area for each individual triglyceride; and $B$ is the sum of the areas of all the peaks, excluding the solvent peak.

| Triglyceride | Relative Retention Time | Composition (\%) |
| :---: | :---: | :---: |
| LLL | 0.55 | 7.0 to 19.0 |
| OLL | 0.65 | 13.0 to 30.0 |
| PLL | 0.69 | 5.0 to 9.0 |
| OOL | 0.77 | 14.0 to 25.0 |
| POL | 0.82 | 8.0 to 16.0 |
| OOO | 0.93 | 5.0 to 14.0 |
| SOL | 0.97 | 2.0 to 8.0 |
| POO | 1.0 | 2.0 to 8.0 |

## BRIEFING

Sodium Stearyl Fumarate, $N F 22$ page 2934. It is proposed to increase the volume of chloroform added in the Assay from 1 mL to 10 mL . This is due to reports received that the sodium stearyl sulfate sample did not dissolve completely in 1 mL of chloroform and 20 mL of glacial acetic acid as specified in the monograph.
(EMC: D. Bempong) RTS-40750-1

## Change to read:

Assay-Transfer about 250 mg of Sodium Stearyl Fumarate, accurately weighed, to a $50-\mathrm{mL}$ conical flask, mix with $1-\mathrm{mt}$

## © $10 \mathrm{~mL}^{\text {NF23 }}$

of chloroform, and add 20 mL of glacial acetic acid to dissolve. Add quinaldine red TS, and titrate with 0.1 N perchloric acid VS. Each mL of 0.1 N perchloric acid is equivalent to 39.05 mg of $\mathrm{C}_{22} \mathrm{H}_{39} \mathrm{NaO}_{4}$.

Briefing
Sodium Sulfite, page 2007 of $P F 28(6)$ [Nov.-Dec. 2002]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded to In-Process Revision.
(EMC: E. Gonikberg) RTS-40862-2

## Add the following:

©Sodium Sulfite
$\mathrm{Na}_{2} \mathrm{SO}_{3} \quad 126.0 \quad[7757-83-7]$.
" Sodium Sulfite contains not less than 95.0 percent and not more than 100.5 percent of $\mathrm{Na}_{2} \mathrm{SO}_{3}$.

Packaging and storage-Preserve in tight containers. Store at room temperature.

## Identification-

A: Dissolve 5 g of Sodium Sulfite in 100 mL of water: the pH of the solution is between 8.0 and 10.0. [NOTE-Reserve portions of the solution so obtained for use in Identification test $B$ and in the test for Color and clarity of solution.]

B: To 5 mL of the solution from Identification test $A$, add 0.5 mL of iodine TS: the solution is colorless and it meets the requirements of the barium chloride test for Sulfate $\langle 191\rangle$.
$\mathbf{C}$ : It meets the requirements of the pyroantimonate precipitate test for Sodium $\langle 191\rangle$.

Color and clarity of solution-Examine the solution prepared for Identification test $A$ : the solution is clear and colorless.

Heavy metals, Method $I\langle 231\rangle$ : $10 \mu \mathrm{~g}$ per g , the Test Preparation being prepared as follows. To 8.0 g of Sodium Sulfite add 25 mL of water. Shake until mostly dissolved, and
slowly and carefully add 15 mL of hydrochloric acid. Heat to boiling. Cool, and dilute with water to 100.0 mL . Use a $25-\mathrm{mL}$ portion.

## Limit of iron-

Standard solution-Immediately before use, dilute 1 volume of Standard Iron Solution, prepared as directed under Iron $\langle 241\rangle$, to 10 mL with water. [NOTE-This solution contains the equivalent of $1 \mu \mathrm{~g}$ of iron per mL .]

Test solution-To 10.0 g of Sodium Sulfite add 25 mL of water. Shake until mostly dissolved, and carefully and slowly add 15 mL of hydrochloric acid. Heat to boiling. Cool, and dilute with water to 100.0 mL . Use a $10-\mathrm{mL}$ portion.

Procedure-To the Standard solution and the Test solution separately add 2 mL of a citric acid solution having a concentration of 200 g per liter, and then add 0.1 mL of thioglycolic acid. Mix, make alkaline with stronger ammonia water, and dilute with water to 20 mL . Allow to stand for 5 minutes. Any pink color in the Test solution is not more intense than that in the Standard solution: not more than 10 $\mu \mathrm{g}$ per g is found.

## Limit of selenium-

Selenium standard solution-[Caution-Selenium is toxic; handle it with care.] Dissolve about 0.1 g of metallic selenium, accurately weighed, in 2 mL of nitric acid. Evaporate to dryness, add 2 mL of water, and evaporate to dryness. Repeat the addition of water and the evaporation to dryness three more times. Dissolve the residue so obtained in 50 mL of diluted hydrochloric acid, transfer to a $1000-\mathrm{mL}$
volumetric flask, dilute with diluted hydrochloric acid to volume, and mix to obtain a solution having a known concentration of about $100 \mu \mathrm{~g}$ of selenium per mL .
Procedure-Prepare a test solution as follows. To 3.0 g of Sodium Sulfite add 10 mL of formaldehyde TS, and slowly and carefully add 2 mL of hydrochloric acid. Heat in a water bath for 20 minutes. In parallel prepare a Standard solution as follows. To 1.0 g of Sodium Sulfite add 0.2 mL of Selenium standard solution and 10 mL of formaldehyde TS, and slowly and carefully add 2 mL of hydrochloric acid. Heat in a water bath for 20 minutes. Any pink color in the test solution is not more intense than that in the Standard solution: not more than $10 \mu \mathrm{~g}$ per g is found.

Limit of thiosulfates-To 2.0 g of Sodium Sulfite add 100 mL of water. Shake to dissolve, and add 10 mL of formaldehyde TS and 10 mL of acetic acid. Allow to stand for 5 minutes. Add 0.5 mL of starch TS and titrate with 0.1 N iodine VS. Perform a blank determination (see Residual Titrations under Titrimetry $\langle 541\rangle$ ), and note the difference in volumes required: the difference is not more than 0.15 mL (0.1\%).

## Limit of zinc-

Zinc standard stock solution-Prepare a solution containing 1 mL of acetic acid and the amount of zinc sulfate equivalent of 0.440 g of $\mathrm{ZnSO}_{4} \cdot 7 \mathrm{H}_{2} \mathrm{O}$ in 100.0 mL of water. [NOTE-This solution contains the equivalent of $1000 \mu \mathrm{~g}$ of Zn per mL .]

Zinc standard solutions-Dilute a volume of the Zinc standard stock solution quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about $25 \mu \mathrm{~g}$ of zinc per mL . Transfer 1.0$\mathrm{mL}, 2.0-\mathrm{mL}$, and $4.0-\mathrm{mL}$ portions of this solution to separate $100-\mathrm{mL}$ volumetric flasks. Dilute the contents of each flask with water to volume, and mix to obtain solutions having known concentrations of about $0.25 \mu \mathrm{~g}$ of zinc per mL , $0.5 \mu \mathrm{~g}$ of zinc per mL , and $1.0 \mu \mathrm{~g}$ of zinc per mL , respectively.

Test solution-To 10.0 g of Sodium Sulfite add 25 mL of water. Shake until mostly dissolved, and carefully and slowly add 15 mL of hydrochloric acid. Heat to boiling. Cool, and dilute with water to 100.0 mL . Transfer 2.0 mL of this solution to a $10-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Procedure-Concomitantly determine the absorbances of the Zinc standard solutions and the Test solution at the zinc emission line at 213.9 nm with an atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ), equipped with a zinc hollow-cathode lamp and an air-acetylene flame. Plot the absorbances of the Zinc standard solutions versus concentration of zinc, in $\mu \mathrm{g}$ per mL , and draw the straight line best fitting the plotted points. From the graph so obtained, determine the concentration of zinc, in $\mu \mathrm{g}$ per mL , in the Test solution: not more than $25 \mu \mathrm{~g}$ per g is found.

Assay-Transfer about 250 mg of Sodium Sulfite, accurately weighed, to a $500-\mathrm{mL}$ beaker, add 50.0 mL of 0.1 N iodine VS, and shake to dissolve. Add 1 mL of starch TS, and titrate with 0.1 N sodium thiosulfate VS to a clear endpoint. Perform a blank determination (see Residual Titrations under Titrimetry $\langle 541\rangle$ ), and make any necessary correction. Each mL of 0.1 N sodium thiosulfate is equivalent to 6.30 mg of $\mathrm{Na}_{2} \mathrm{SO}_{3 \cdot \mathbf{\Delta N F 2 3}}$

## Briefing

Sodium Tartrate. Because there is no existing $N F$ monograph for this excipient, a new monograph is being proposed. This new monograph is based on the Sodium Tartrate monograph in the Food Chemicals Codex V and related monographs from the $7^{\text {th }}$ Session of the Joint FAO/WHO Expert Committee on Food Additives.
(EMC: K. Russo) RTS-40209-4

## Add the following:

## ${ }^{\Delta}$ Sodium Tartrate


$\mathrm{C}_{4} \mathrm{H}_{4} \mathrm{Na}_{2} \mathrm{O}_{6} \cdot 2 \mathrm{H}_{2} \mathrm{O} \quad 230.08$
Disodium L-tartrate.
Disodium (+)-2,3-dihydroxybutanedioic acid [868-188].
» Sodium Tartrate contains not less than 99.0 percent and not more than 100.5 percent of $\mathrm{C}_{4} \mathrm{H}_{4} \mathrm{Na}_{2} \mathrm{O}_{6} \cdot 2 \mathrm{H}_{2} \mathrm{O}$, calculated on the dried basis.

## Packaging and storage-Store in a tight container.

## Identification-

A: Responds to the tests for Sodium $\langle 191\rangle$.
B: Responds to the tests for Tartrate $\langle 191\rangle$.
$\mathbf{p H}\langle 791\rangle$ : between 7 and 9 ( 1 in 10 solution).
Loss on drying $\langle 731\rangle$-Dry it at $150^{\circ}$ for 3 hours: it loses between $14.0 \%$ and $17.0 \%$ of its weight.

Heavy metals, Method $I\langle 231\rangle: 0.002 \%$.
Limit of oxalate-Dissolve 1.0 g of Sodium Tartrate in 10 mL of water, then add 5 drops of diluted acetic acid and 2 mL of calcium chloride TS: no turbidity develops within 1 hour. Not more than $0.1 \%$ is found.

Assay-Transfer about 250 mg of Sodium Tartrate, accurately weighed and previously dried at $150^{\circ}$ for 3 hours, to a $250-\mathrm{mL}$ beaker, and dissolve by stirring and heating to near the boiling point in 150 mL of acetic acid. Cool the solution to room temperature. Titrate with 0.1 N perchloric acid VS (in glacial acetic acid), determining the endpoint potentiometrically. Perform a blank determination, and make any necessary adjustments (see Titrimetry $\langle 541\rangle$ ). Each mL of 0.1 N perchloric acid is equivalent to 9.703 mg of $\mathrm{C}_{4} \mathrm{H}_{4} \mathrm{Na}_{2} \mathrm{O}_{6 \cdot \boldsymbol{\wedge} F 23}$

## Briefing

Succinic Acid. Because there is no existing $N F$ monograph for this excipient, a new monograph is being proposed. This new monograph is based on the Succinic Acid monograph in the Food Chemicals Codex V.
(EMC: K. Russo) RTS-40209-3

## Add the following:

## $\triangle$ Succinic Acid


$\mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{4} \quad 118.09$
Butanedioic acid [110-15-6].
» Succinic Acid contains not less than 99.0 percent and not more then 100.5 percent of $\mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{4}$.

Packaging and storage-Store in a well-closed container. Identification-Place a drop of a saturated solution of the sample in a micro test tube, and add a drop of ammonium chloride solution ( 0.5 in 100) and several mg of zinc powder. Cover the mouth of the tube with a disk of filter paper moistened with a solution in hexane containing $p$-dimethylaminobenzaldehyde (5 in 100) and trichloroacetic acid (20 in 100). Heat with a small flame for about 1 minute: a pink to red-violet stain appears on the paper.

Melting range $\langle 741\rangle$ : between 185.0 and 190.0.
Residue on ignition $\langle 281\rangle$ : not more than $0.025 \%$.
Heavy metals, Method $I\langle 231\rangle: 0.002 \%$.
Assay-Dissolve about 250 mg , accurately weighed, in 25 mL of carbon dioxide-free water. Add 2 drops of phenolphthalein TS and titrate with 0.1 N sodium hydroxide VS to the production of a permanent pink color. Each mL of 0.1 N sodium hydroxide is equivalent to 5.905 mg of $\mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{4 \cdot \boldsymbol{\Delta} \text { NF23 }}$

## GENERAL CHAPTERS

## General Tests and Assays

## General Requirements for Tests and Assays

## Briefing

$\langle 11\rangle$ Reference Standards, USP 27 page 2111, the Fifth Interim Revision Announcement on page 1395 of PF 29(5) [Sept.-Oct. 2003], the Sixth Interim Revision Announcement on page 1815 of PF 29(6) [Nov.-Dec. 2003], the First Interim Revision Announcement on page 31 of PF 30(1) [Jan.-Feb. 2004], page 5180 of $P F$ 23(6) [Nov.-Dec. 1997], page 6925 of $P F$ 24(5) [Aug.-Sept. 1998], page 8222 of $P F 25(3)$ [May-June 1999], page 8561 of $P F 25(4)$ [July-Aug. 1999], page 8893 of $P F 25(5)$ [Sept.Oct. 1999], page 218 of $P F 26$ (1) [Jan.-Feb. 2000], page 471 of $P F$ 26(2) [Mar.-Apr. 2000], page 793 of $P F$ 26(3) [May-June 2000], page 1101 of $P F 26(4)$ [July-Aug. 2000], page 1369 of $P F 26(5)$ [Sept.-Oct. 2000], page 1832 of $P F$ 27(1) [Jan.-Feb. 2001], page 2268 of PF 27(2) [Mar.-Apr. 2001], page 2806 of PF 27(4) [JulyAug. 2001], page 3071 of $P F$ 27(5) [Sept.-Oct. 2001], page 3348 of PF 27(6) [Nov.-Dec. 2001], page 433 of PF 28(2) [Mar.-Apr. 2002], page 839 of $P F 28(3)$ [May-June 2002], page 1224 of $P F$ 28(4) [July-Aug. 2002], page 1468 of $P F$ 28(5) [Sept.-Oct. 2002], page 1913 of $P F 28(6)$ [Nov.-Dec. 2002], page 163 of $P F 29(1)$ [Jan.-Feb. 2003], page 483 of $P F$ 29(2) [Mar.-Apr. 2003], page 710 of $P F$ 29(3) [May-June 2003], page 1137 of $P F$ 29(4) [July-Aug. 2003], page 1601 of $P F 29(5)$ [Sept.-Oct. 2003], page 2022 of PF 29(6) [Nov.-Dec. 2003], and page 211 of PF 30(1) [Jan.-Feb. 2004].
(HDQ) RTS-40629-4; 40629-5; 40629-7; 40629-8; 406299; 40864-1; 38283-2; 40861-1; 40773-9; 40773-10; 40837-1

## Change to read:

USP $\alpha$ - $d$-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane RS-
( (NAME Change) See USP Propoxyphene Related Compound B $R S$. $\triangle$ USP28
Add the following:
${ }^{\mathbf{4}}$ USP Air-Helium RS. ${ }_{\text {_USP28 }}$

## Add the following:

${ }^{\boldsymbol{A}}$ USP Alcohol RS——Do not dry. ${ }^{\text {USPP28 }}$

Add the following:
${ }^{\Delta}$ USP Dehydrated Alcohol RS——Do not dry. $\mathbf{\Delta U S P 2 8}$
Add the following:
${ }^{\Delta}$ USP Anecortave Acetate RS. ${ }^{\text {USSP28 }}$

## Add the following:

${ }^{\wedge}$ USP Anecortave Acetate Related Compound A RS. ${ }_{\text {IUSP2 }}$

## Add the following:

${ }^{4}$ USP Cellulose Aeetate Butyrate RS-USP Cellaburate RS—Dry a portion at $105^{\circ}$ for 1 hour before using. Keep container tightly closed. Protect from light, and store in a cold place. $\mathbf{\Delta U S P 2 8}$
Add the following:
${ }^{\mathbf{4}}$ USP L-Fluorodopa RS. ${ }_{\mathbf{\Delta} U S P 28}$

## Add the following:

${ }^{\boldsymbol{\Delta}}$ USP Lycopene RS—[To come.] $\mathbf{\Delta U S P 2 8 ~}$

## Add the following:

${ }^{\Delta}$ USP Methylphenidate Related Compound B RS [ $\left(R^{*}, S^{*}\right)$ methyl $\alpha$-phenyl-2-piperidineacetate hydrochloride] $\left(\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{NO}_{2} \cdot \mathrm{HCl} \diamond 269.77\right)$ [To come.] $]_{\triangle S P 28}$

## Add the following:

${ }^{4}$ USP Methylphenidate Related Compound C RS [ $\left(R^{*}, S^{*}\right) \alpha$-phenyl-2-piperidineacetic acid hydrochloride] $\left(\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{NO}_{2} \cdot \mathrm{HCl} \triangleleft 255.74\right)$-[To come.] $\mathbf{\Delta U S P 2 8}$

## Add the following:

-USP Methylphenidate Related Compound D RS [ $\left(R^{*}, R^{*}\right) \alpha$-phenyl-2-piperidineacetic acid hydrochloride]
$\left(\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{NO}_{2} \cdot \mathrm{HCl} \diamond 255.74\right)$-[To come.] $\mathbf{\Delta U S P 2 8}$

## Add the following:

${ }^{4}$ USP Methylphenidate Related Compound ERS [ $\left(R^{*}, S^{*}\right) \alpha$-phenyl-2-piperidineacetamide hydrochloride] $\left(\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{NO}_{2} \cdot \mathrm{HCl} \triangleleft 254.76\right)$-[To come.] $]_{\Delta S P 28}$

## Add the following:

${ }^{4}$ USP Methylphenidate Related Compound F RS [ $\left(R^{*}, R^{*}\right) \alpha$-phenyl-2-piperidineacetamide hydrochloride] $\left(\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{NO}_{2} \cdot \mathrm{HCl} \diamond 254.76\right)$-[To come.] $]_{\text {USP28 }}$

## Add the following:

${ }^{\Delta}$ USP Methylphenidate Related Compound G RS [Ethyl
$\alpha-$ phenyl-2-piperidineacetate hydrochloride]
$\left(\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{NO}_{2} \cdot \mathrm{HCl} \diamond 283.79\right)$-[To come.] $]_{\Delta S P 28}$

## Add the following:

${ }^{\Delta}$ USP Methylphenidate Related Compound H RS
[ $\alpha$-phenyl-2-pyridylacetamide] $\left(\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O} \triangleleft 212.25\right)$ [To come.] $]_{\mathbf{U S P 2 8}}$

## Add the following:

${ }^{\boldsymbol{\Delta}} \mathbf{U S P}$ Nitrogen RS-[To come.] $]_{\mathbf{\Delta S P 2 8}}$

## Add the following:

${ }^{\boldsymbol{\Delta}}$ USP Nitrous Oxide RS—[To come.] $]_{\Delta U S P 28}$

## Add the following:

${ }^{\boldsymbol{4}} \mathbf{U S P}$ Oxygen-Helium RS-[To come.] $]_{\mathbf{\Delta S P 2 8}}$

## Change to read:



## Add the following:

${ }^{\boldsymbol{\Delta}}$ USP Propoxyphene Related Compound B RS $\left(\mathrm{C}_{21} \mathrm{H}_{27}\right.$ $\mathrm{NO}_{2} \diamond 325.45$ )-Do not dry before using. Keep container tightly closed and protected from light. $\triangle U S P 28$

## Add the following:

${ }^{\Delta}$ USP Cultured Rat Pheochromocytoma Reference
Pictographs-[To come.] $]_{\triangle S P P 28}$

## Add the following:

${ }^{\mathbf{4}}$ USP Saccharin Calcium RS——Dry at $105^{\circ}$ for 2 hours before using. ${ }^{\text {UUSP28 }}$

## Add the following:

${ }^{4}$ USP Saccharin Sodium RS—Dry at $105^{\circ}$ for 2 hours before using. IUSP28 $^{\text {. }}$

## Add the following:

${ }^{\triangle}$ USP Sesame Oil Related Compound A RS[To come.] $]_{\triangle S P 28}$

## Add the following:

${ }^{\wedge}$ USP Sesame Oil Related Compound B RS-
[To come.] ${ }_{\mathbf{U S P 2 8}}$

## Add the following:

${ }^{\wedge}$ USP Tomato Extract Containing Lycopene RS[To come.] $]_{\Delta S P 28}$

# Chemical Tests and Assays 

## LIMIT TESTS

## BRIEFING

〈231〉 Heavy Metals, USP 27 page 2204 and page 217 of PF 30 (1) [Jan.-Feb. 2004]. On the basis of comments received, it is proposed that, when necessary, the adjustment of the pH can be made using a pH meter or short-range pH indicator paper.

$$
\text { (PA4: H. Pappa) } \quad \text { RTS-40683-1; 40815-1 }
$$

## Change to read:

## Method I

pH 3.5 Acetate Buffer-Dissolve 25.0 g of ammonium acetate in 25 mL of water, and add 38.0 mL of 6 N hydrochloric acid. Adjust, if necessary, with 6 N ammonium hydroxide or 6 N hydrochloric acid to a pH of 3.5 , dilute with water to 100 mL , and mix.

Standard Preparation-Into a $50-\mathrm{mL}$ color-comparison tube pipet 2 mL of Standard Lead Solution ( $20 \mu \mathrm{~g}$ of Pb ), and dilute with water to 25 mL . Adjust
${ }^{\boldsymbol{\Delta}}$ Using a pH meter or short-range pH indicator paper as external indicator, adjust ${ }_{\text {USP28 }}$
with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0 , using short range pH indientor paper as external indi--ator,
dilute with water to 40 mL , and mix.
Test Preparation-Into a $50-\mathrm{mL}$ color-comparison tube place 25 mL of the solution prepared for the test as directed in the individual monograph; or, using the designated volume of acid where specified in the individual monograph, dissolve and dilute with water to 25 mL the quantity, in g , of the substance to be tested, as calculated by the formula:

$$
2.0 /(1000 L)
$$

in which $L$ is the Heavy metals limit, in percentage. Adjust
$\Delta$ as a percentage. Using a pH meter or short-range pH indi-
cator paper as external indicator, adjust ${ }_{\Delta U S P 28}$
with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0 , using shert range pH indieator paper as external indiear,
${ }^{\Delta}$ USSP28
dilute with water to 40 mL , and mix.
Monitor Preparation-Into a third $50-\mathrm{mL}$ color-comparison tube place 25 mL of a solution prepared as directed for Test Preparation, and add 2.0 mL of Standard Lead Solution. Adjust
${ }^{\Delta}$ Using a pH meter or short-range pH indicator paper as ex-
ternal indicator, adjust $U S P 28$
with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0 , tring short range pH indieator paper as external indient

## A.USP28

diflute with water to 40 mL , and mix.
Procedure-To each of the three tubes containing the Standard Preparation, the Test Preparation, and the Monitor Preparation, add 2 mL of pH 3.5 Acetate Buffer, then add 1.2 mL of thioaceta-mide-glycerin base TS, dilute with water to 50 mL , mix, allow to stand for 2 minutes, and view downward over a white surface ${ }^{*}$ : the color of the solution from the Test Preparation is not darker than that of the solution from the Standard Preparation, and then sity of the of the
${ }^{\boldsymbol{\Delta}}$ the color of the solution from the $\mathbf{\Delta U S P 2 8 ~}$
Monitor Preparation is equal to or greater
$\Delta_{\text {darker }}{ }_{\mathbf{\Delta S P 2 8}}$
than that of the
$\boldsymbol{\Delta}_{\text {solution }}$ from the $\mathbf{A U S P 2 8}$
Standard Preparation. [NOTE-If the color of the Monitor Preparation is lighter than that of the Standard Preparation, use Method II instead of Method I for the substance being tested.]

## Change to read:

## Method II

pH 3.5 Acetate Buffer-Prepare as directed under Method I. Standard Preparation-Prepare directe under Method

${ }^{\Delta}$ Pipet 4 mL of the Standard Lead Solution into a suitable test tube, and add 10 mL of 6 N hydrocloric acid. | USP28 |
| :--- |

Test Preparation-Use a quantity, in g, of the substance to be tested as calculated by the formula:

$$
\begin{gathered}
2.0 /(1000 L), \\
4.0 /(1000 L), \mathbf{\Delta U S P 2 8}
\end{gathered}
$$

in which $L$ is the Heavy metals limit, in $\Delta_{\text {as }} \mathrm{a}_{\Delta U S P 28}$
percentage. Transfer the weighed quantity of the substance to a suitable crucible, add sufficient sulfuric acid to wet the substance, and carefully ignite at a low temperature until thoroughly charred. (The crucible may be loosely covered with a suitable lid during the charring.) Add to the carbonized mass 2 mL of nitric acid and 5 drops of sulfuric acid, and heat cautiously until white fumes no longer are evolved. Ignite, preferably in a muffle furnace, at $500^{\circ}$ to $600^{\circ}$, until the carbon is completely burned off
(no longer than 2 hours). If carbon remains, allow the residue to cool, add a few drops of sulfuric acid, evaporate, and
ignite again._USP28
Cool, add 4 mb
$\triangle 5 \mathrm{~mL}$
of 6 N hydrochloric acid, cover,
$\Delta_{\text {and }}^{\Delta U S P 28}$
digest on a steam bath for 15 minntes, uneover, and slowly evape rate on a steam bath to drymess. Moisten the residue with 1 drep of hydrochlorie acid, add 10 mL of hot water, and digent for 2 min utes. Add 6 N ammenitm hydroxide dropwise, until the solution is just alkaline to litmus paper, dilute with water to 25 mL , and adjust with 1 N acetic acid to a pHbetween 3.0 and 4.0 , using shert range pH indieator paper as external indieator. Filter if neeessary, rinse the erueible and the filter with 10 mL of water, combine the filtrate and rinsing in a 50 mL color comparisen tube, dilute with water to 40 mL , and mix.
$\triangle 10$ minutes. Cool, and quantitatively transfer the solution to a test tube. Rinse the crucible with a second $5-\mathrm{mL}$ portion of 6 N hydrochloric acid, and transfer the rinsing to the test tube.
Monitor Preparation-Pipet 4 mL of the Standard Lead Solution into a crucible identical to that used for the Test Preparation and containing a quantity of the substance under test that is equal to $10 \%$ of the amount required for the Test Preparation. Evaporate on a steam bath to dryness. Ignite at the same time, in the same muffle furnace, and under the same conditions used for the Test Preparation. Cool, add 5 mL of 6 N hydrochloric acid, cover, and digest on a steam bath for 10 minutes. Cool, and quantitatively transfer to a test tube. Rinse the crucible with a second $5-\mathrm{mL}$ portion of 6 N hydrochloric acid, and transfer the rinsing to the test tube. $\Delta U S P 28$

Procedure- T
${ }^{\Delta}$ Adjust the solution in AUSP28
each of the tubes containing the Standard Preparation,
$\Delta$
the Tesp Preparation,

[^66]$\Delta$ and the Monitor Preparation with ammonium hydroxide, added cautiously and dropwise, to a pH of 9 . Cool, and adjust with glacial acetic acid, added dropwise, to a pH of 8 , and then add 0.5 mL in excess. Using a pH meter or shortrange pH indicator paper as external indicator, check the pH , and adjust, if necessary, with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0. Filter, if necessary, washing the filter with a few mL of water, into a $50-\mathrm{mL}$ color-comparison tube, and then dilute with water to 40
mL . ${ }^{\text {USP28 }}$
Add 2 mL of pH 3.5 Acetate Buffer, then add 1.2 mL of thioaceta-mide-glycerin base TS, dilute with water to 50 mL , mix, allow to stand for 2 minutes, and view downward over a white surface ${ }^{*}$ : the color of the solution from the Test Preparation is not darker than that of the solution from the Standard Preparation,
$\Delta$ and the color of the solution from the Monitor Preparation is equal to or darker than that of the solution from the Standard Preparation. [NOTE-If the color of the solution from the Monitor Preparation is lighter than that of the solution from the Standard Preparation, proceed as directed for Method III for the substance being tested.] $]_{\text {USP28 }}$

## Change to read:

## Method III

pH 3.5 Acetate Buffer-Prepare as directed under Method I.
Standard Preparation-Transfer a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid to a clean, dry, $100-\mathrm{mL}$ Kjeldahl flask, and add a further volume of nitric acid equal to the incremental volume of nitric acid added to the Test Preparation. Heat the solution to the production of dense, white fumes, cool, cautiously add 10 mL of water and, if hydrogen peroxide was used in treating the Test Preparation, add a volume of 30 percent hydrogen peroxide equal to that used for the substance being tested, and boil gently to the production of dense, white fumes. Again cool, cautiously add 5 mL of water, mix, and boil gently to the production of dense, white fumes and to a volume of 2 to 3 mL . Cool, dilute cautiously with a few mL of water, add 2.0 mL of Standard Lead Solution (20 $\mu \mathrm{g}$ of Pb ), and mix. Transfer to a $50-\mathrm{mL}$ color-comparison tube, rinse the flask with water, adding the rinsing to the tube until the volume is 25 mL , and mix.

Test Preparation-
${ }^{\Delta}$ Unless otherwise indicated in the individual monograph, use a quantity, in g , of the substance to be tested as calculated by the formula:
in which $L$ is the Heavy metals limit, as a percentage. $\triangle$ USP28 If the substance is a solid-Transfer the
$\Delta_{\text {weighed }}^{\text {USP28 }}$
quantity of the test substance sper in swh
$\Delta_{\triangle U S P 28}$
to a clean, dry, $100-\mathrm{mL}$ Kjeldahl flask. [NOTE-A $300-\mathrm{mL}$ flask may be used if the reaction foams excessively.] Clamp the flask at an angle of $45^{\circ}$, and add a sufficient quantity of a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid to moisten the substance thoroughly. Warm gently until the reaction commences, allow the reaction to subside, and add additional portions of the same acid mixture, heating after each addition, until a total of 18 mL of the acid mixture has been added. Increase the amount of heat, and boil gently until the solution darkens. Cool, add 2 mL of nitric acid, and heat again until the solution darkens. Continue the heating, followed by addition of nitric acid until no further darkening occurs, then heat strongly to the production of dense, white fumes. Cool, cautiously add 5 mL of water, boil gently to the production of dense, white fumes, and continue heating until the volume is reduced to a few mL . Cool, cautiously add 5 mL of water, and examine the color of the solution. If the color is yellow, cautiously add 1 mL of 30 percent hydrogen peroxide, and again evaporate to the production of dense, white fumes and a volume of 2 to 3 mL . If the solution is still yellow in color, repeat the addition of 5 mL of water and the peroxide treatment. Cool, dilute cautiously with a few mL of water, and rinse into a $50-\mathrm{mL}$ color-comparison tube, taking care that the combined volume does not exceed 25 mL .
If the substance is a liquid-Transfer the
$\Delta_{\text {weighed }}{ }_{\text {USP28 }}$
quantity of the test substance specified in the individual menograh

to a clean, dry, $100-\mathrm{mL}$ Kjeldahl flask. [NOTE-A $300-\mathrm{mL}$ flask may be used if the reaction foams excessively.] Clamp the flask at an angle of $45^{\circ}$, and cautiously add a few mL of a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid. Warm gently until the reaction commences, allow the reaction to subside, and proceed as directed for If the substance is a solid, beginning with "add additional portions of the same acid mixture."
${ }^{\Delta}$ Monitor Preparation-Proceed with the digestion using the same amount of sample and the same procedure as directed in the Test Preparation until the step "Cool, dilute cautiously with a few mL of water." Add 2.0 mL of Lead Standard Solution ( $20 \mu \mathrm{~g}$ of lead), and mix. Transfer to a $50-\mathrm{mL}$ color comparison tube, rinse the flask with water, adding the rinsing to the tube until the volume is

25 mL , and mix. $\triangle$ USP28
Procedure-Treat the Test Preparation, the Standard Preparation
$\boldsymbol{a n d}_{\text {and }}$ the Monitor Preparation $\mathbf{\Delta U S P 2 8}$ as follows: Adjust
${ }^{\wedge}$ Using a pH meter or short-range pH indicator paper as ex-
ternal indicator, adjust $_{\triangle U S P 28}$
the solution to a pH between 3.0 and 4.0 , using shert range pH in dieater paper asexternal indieater,

- $\mathbf{\Delta U S P} 28$
with ammonium hydroxide (a dilute ammonia solution may be used, if desired, as the specified range is approached), dilute with water to 40 mL , and mix.

To each tube add 2 mL of pH 3.5 Acetate Buffer, then add 1.2 mL of thioacetamide-glycerin base TS, dilute with water to 50 mL , mix, allow to stand for 2 minutes, and view downward over a white surface ${ }^{*}$ : the color of the Test Preparation is not darker than that of the Standard Preparation,
$\mathbf{\Delta}^{\text {and }}$ the color of the Monitor Preparation is equal to or dar-
ker than that of the Standard Preparation. $\Delta U S P 28$

## Physical Tests and Determinations

## Briefing

<611 $\rangle$ Alcohol Determination, USP 27 page 2270 and page 1606 of $P F 29(5)$ [Sept.-Oct. 2003]. On the basis of comments received, the previously published proposal for the Test Preparation and the Standard Preparation under Method II is modified to allow for the preparation of an alternative internal standard solution instead of using the USP Alcohol Determination-Acetonitrile RS.
(PA2: H. Pappa) RTS-40736-1

## Change to read:

## METHOD II-GAS-LIQUID CHROMATOGRAPHIC METHOD

Method II is to be used where specified in the individual monograph. For a discussion of the principles upon which it is based, see Gas Chromatography under Chromatography $\langle 621\rangle$.
${ }^{\wedge}$ USP Reference Standards—USP Alcohol Determina-
tion-Acetonitrile RS. USP Alcohol Determination-Alco-

## hol $R S_{.}$_USP28

Apparatus-Under typical conditions, use a gas chromatograph equipped with a flame-ionization detector and a $1.8-\mathrm{m} \times$ 4-mm (ID) glass column packed with 100- to 120-mesh chromatographic column packing No. S3, using nitrogen or helium as the carrier. Prior to use, condition the column overnight at $235^{\circ}$ with a slow flow of carrier gas. The column is maintained at $120^{\circ}$, and
the injection port and detector are maintained at $210^{\circ}$. Adjust the carrier flow and temperature so that acetonitrile, the internal standard, elutes in 5 to 10 minutes.
Solutions-
Standard Solution- Dilute 5.0 mL of dehy drated aleohol with water to 250 mL .
Internal Standtud Solution- Dilute 5.0 mL of acetonitrile with water to 250 mL .

- $\triangle$ USP28

Test Stock Preparation-Dilute the specimen under examination stepwise with water to obtain a solution containing approximately $2 \%(\mathrm{v} / \mathrm{v})$ of alcohol.

Test Preparation-Pipet 10 mL each of the Test Solland the Internal Standed Solution into a 100 mL
$\Delta 5 \mathrm{~mL}$ each of the Test Stock Preparation and the USP Alcohol Determination-Acetonitrile RS [NOTE-Alternatively, a $2 \%$ aqueous solution of acetonitrile of suitable quality may be used as the internal standard solution.] into
a $50-\mathrm{mL}$
volumetric flask, and dilute with water to volume.
Standard Preparation-Pipet 10 mL - of the Star tion and the Internal Standerd Solution into a 100 -mb
$\triangle 5 \mathrm{~mL}$ each of the USP Alcohol Determination-Alcohol RS and the USP Alcohol Determination-Acetonitrile RS
[NOTE-Alternatively, a $2 \%$ aqueous solution of acetonitrile of suitable quality may be used as the internal standard solu-
tion.] into a $50-\mathrm{mL}_{\mathbf{\Delta U P} 28}$
volumetric flask, dilute with water to volume, and mix.
Procedure-Inject about $5 \mu \mathrm{~L}$ each of Test Preparation and Standard Preparation, in duplicate, into the gas chromatograph, record the chromatograms, and determine the peak response ratios. Calculate the percentage of alcohol ( $\mathrm{v} / \mathrm{v}$ ) in the specimen under test according to the formula:

$$
2 R_{6} P / R_{8}
$$

$$
{ }^{\mathbf{\Delta}} C D\left(R_{U} / R_{S}\right), \mathbf{\Delta U S P 2 8}
$$

in which
${ }^{\Delta} C$ is the labeled concentration of USP Alcohol Determina-
tion-Alcohol RS; ${ }_{\mathbf{\Delta S S P 2 8}}$
$D$ is the dilution factor (the ratio of the volume of the Test Stock Preparation to the volume of the specimen taken); and $R_{U}$ and $R_{S}$ are the peak response ratios obtained for the Test Preparation and the Standard Preparation, respectively.

System Suitability Test-In a suitable chromatogram, the resolution factor, $R$, is not less than 2 ; the tailing factor of the alcohol peak is not greater than 1.5; and six replicate injections of the Standard Preparation show a relative standard deviation of not more than $2.0 \%$ in the ratio of the peak of alcohol to the peak of the internal standard.

Briefing
<621 Chromatography, USP 27 page 2272 and page 228 of PF 30(1) [Jan.-Feb. 2004]. On the basis of comments received, it is proposed to revise the section on Thin-Layer Chromatography in order to update the text in accordance with current technology.
(PA4: H. Pappa) RTS-40633-1

## Change to read:

## INTRODUCTION

This chapter defines the terms and procedures used in chromatography and provides general information. Specific requirements for chromatographic
${ }^{\boldsymbol{4}}$ procedures for ${ }_{\Delta U S P 28}$
drug substances and dosage forms, including adsorbent and developing solvents, are given in the individual monographs.

Chromatography is defined as a procedure by which solutes are separated by a dynamic differential migration process in a system consisting of two or more phases, one of which moves continuously in a given direction and in which the individual substances exhibit different mobilities by reason of differences in adsorption, partition, solubility, vapor pressure, molecular size, or ionic charge density. The individual substances thus
$\Delta_{\text {separated }}{ }_{\text {4SSP28 }}$
can be identified or determined by analytical methods.
© procedures. $\Delta$ USP28
The general chromatographic technique requires that a solute undergo distribution between two phases, one of them fixed (stationary phase), the other moving (mobile phase). It is the mobile phase that transfers the solute through the medium until it eventually emerges separated from other solutes that are eluted earlier or later. Generally, the solute is transported through the separation medium by means of a flowing stream of a liquid or a gaseous solvent known as the "eluant." The stationary phase may act through adsorption, as in the case of adsorbents such as activated alumina ; siliea gel, and ion exchange resins,
$\Delta_{\text {and silica gel, }}^{\mathbf{\Delta U S P 2 8}}$
or it may act by dissolving the solute, thus partitioning the latter between the stationary and mobile phases. In the latter proeess, a tiquid conting held on an inert support serves as the stationary phase.
${ }^{\boldsymbol{\Delta}}$ In the latter process, a liquid coated onto an inert support, or chemically bonded onto silica gel, or directly onto the wall of a fused silica capillary, serves as the stationary phase. $\triangle U S P 28$
Partitioning is the predominant mechanism of separation in gas-liquid chromatography, paper chromatography, and forms of column chromatography
$\boldsymbol{\Delta}_{\text {and thin-layer chromatography }}^{\mathbf{A S S P 2 8}}{ }$
designated as liquid-liquid ehromatography.
${ }^{\Delta}$ separation. $\triangle U S P 28$
In practice, separations frequently result from a combination of adsorption and partitioning effects.
${ }^{\Delta}$ Other separation principles include ion exchange, ion pair formation, size exclusion, hydrophobic interaction, and chiral recognition. $\triangle$ USP28
The types of chromatography useful in qualitative and quantitative analysis that are employed in the $U S P$
${ }^{\Delta}$ procedures ${ }_{\triangle U S P 28}$
are column, gas, paper, thin-layer,
© (including high-performance thin-layer chromatogra-
phy), ${ }_{\text {, USP28 }}$
and pressurized liquid chromatography (commonly called highpressure or high-performance liquid chromatography). Paper and thin-layer chromatography are ordinarily more useful for purposes of identification, because of their convenience and simplicity. Column chromatography offers a wider choice of stationary phases and is useful for the separation of individual compounds, in quantity, from mixtures. Both ehromatography and pressurized liv wid chromatography require more elaberate apparatus and usually provide high resolution metheds that will identify and quatitate very small amounts of material.
${ }^{\star}$ Modern high-performance thin-layer chromatography, gas chromatography, and pressurized liquid chromatography require more elaborate apparatus but usually provide high resolution and identify and quantitate very small amounts of material. $\triangle$ USP28

## Change to read:

Use of Reference Substances in Identity Tests-In paper and thin-layer chromatography, the ratio of the distance (this distance being measured to the point of maximum intensity of the spot
$\left.\Delta^{\text {or zone }}\right)_{\Delta U S P 28}$
traveled on the medium by a given compound to the distance traveled by the front of the mobile phase, from the point of application of the test substance, is designated as the $R_{F}$ value of the compound. The ratio between the distances traveled by a given compound and a reference substance is the $R_{R}$ value. $R_{F}$ values vary with the experimental conditions, and thus identification is best accomplished where an authentic specimen of the compound in question is used as a reference substance on the same chromatogram.

For this purpose, chromatograms are prepared by applying on the thin-layer adsorbent or on the paper in a straight line, parallel to the edge of the chromatographic plate or paper, solutions of the substance to be identified, the authentic specimen, and a mixture of nearly equal amounts of the substance to be identified and the authentic specimen. Each sample application contains approximately the same quantity by weight of material to be chromatographed. If the substance to be identified and the authentic specimen are identical, all chromatograms agree in color and $R_{F}$ value and the mixed chromatogram yields a single spot; i.e., $R_{R}$ is 1.0 .

## Change to read:

Location of Components-The spots
$\Delta^{\text {or zones }}{ }_{\Delta U S P 28}$
produced by paper or thin-layer chromatography may be located by the following: ( 1 ) direet inspection if the eompounds are visible tuder white or either short wavelength ( 254 nm ) or long wave-
length ( 360 nm ) UV light, (2) inspection in white or UV light after treatment with reagents that will make the spots visible (reagents are most conveniently applied with an atomizer), (3) use of a Gei ger Müller counter or auteradiographic techniques in the ease of the presence of radionctive-substanees, or (4) evidenee resulting from stimulation or inhibition of bacterial growth by the placing ef removed pertions of the adserbent and substance on inoeulated mediat.
© (1) direct inspection if the compounds are visible under white or either short-wavelength ( 254 nm , quenching of fluorescence of indicator) or long-wavelength ( 365 nm , self-fluorescence) UV light, (2) inspection in white or UV light after treatment (derivatization) with reagents that will make the substance visible (reagents are most conveniently applied by dipping the plate into the reagent solution or spraying such solution onto the plate with an atomizer), (3) scanning the plate prior to or after derivatization at any desired wavelength (in absorption or fluorescence mode) using a scanning densitometer, (4) use of a GeigerMüller counter or autoradiographic techniques in the case of the presence of radioactive substances, or (5) evidence resulting from biological activity (such as stimulation or inhibition of growth of microorganisms, bioluminescence, or biochemical reactions) by the placing of removed portions of the adsorbent and substance on inoculated media, or performing biochemical tests directly on the plate by covering the plate with, or dipping it into, a suspension of the biological test system. $\triangle$ USP28
In open-column chromatography, in pressurized liquid chromatography performed under conditions of constant flow rate, and in gas chromatography, the retention time, $t$, defined as the time elapsed between sample injection and appearance of the peak concentration of the eluted sample zone, may be used as a parameter of identification. Solutions of the substance to be identified or derivatives thereof, of the reference compound, and of a mixture of equal amounts of these two are chromatographed successively on the same column under the same chromatographic conditions. Only one peak should be observed for the mixture. The ratio of the retention times of the test substance, the reference compound, and a mixture of these, to the retention time of an internal standard is called the relative retention time $R_{R}$ and is also used frequently as a parameter of identification.

The deviations of $R_{R}, R_{F}$, or $t$ values measured for the test substance from the values obtained for the reference compound and mixture should not exceed the reliability estimates determined statistically from replicate assays of the reference compound.

Chromatographic identification by these methods under given conditions strongly indicates identity but does not constitute definitive identification. Coincidence of identity parameters under 3 to 6 different sets of chromatographic conditions (temperatures, column packings, adsorbents, eluants, developing solvents, various
chemical derivatives, etc.) increases the probability that the test and reference substances are identical. However, many isomeric compounds cannot be separated. Specific and pertinent chemical, spectroscopic, or physicochemical identification of the eluted component combined with chromatographic identity is the most valid criterion of identification. For this purpose, the individual components separated by chromatography may be collected for further identification
© or chromatographic separation may be combined with other analytical techniques. Some of those investigations (such as UV, IR, RAMAN, and MS) can also be made directly on the thin-layer chromatography plate. $\mathbf{\perp}$ USP28

## Change to read:

## THIN-LAYER CHROMATOGRAPHY

In thin-layer chromatography, the adsorbent is a relatively thin, uniform layer of dry, finely powdered material applied to a glass, plastic, or metal sheet or plate, glass plates being most commonly employed. The coated plate can be considered an "open chromatographic column" and the separations achieved may be based upon adsorption, partition, or a combination of both effects, depending on the particular type of suppert,
${ }^{\Delta}$ stationary phase, ${ }_{\mathbf{A}}$ USP28
its preparation, and its use with different solvents. Thin-layer chromatography on ion-exchange flms
$\Delta^{\text {layers }}{ }_{\Delta U S P 28}$
can be used for the fractionation of polar compounds. Presumptive identification can be effected by observation of spots
$\Delta_{\text {or zones }}{ }_{\text {USPP28 }^{28}}$
of identical ${ }_{R}{ }_{F}$ value and about equal magnitude obtained, respectively, with an unknown and a reference sample chromatographed on the same plate. A visual comparison of the size of the spots
${ }^{4}$ or intensity of the spots or zones ${ }_{\triangle U S P 28}$
may serve for semiquantitative estimation. Quantitative measurements are possible by means of densitometry, flteresenee, and fluorescence quenching;
(absorbance or fluorescence measurements), $\boldsymbol{\Delta U S P 2 8}$ or the spots may be carefully removed from the plate, followed by elution with a suitable solvent and spectrophotometric measurement. For two-dimensional thin-layer chromatography, the chromatographed plate is turned at a right angle and again chromatographed, usually in another chamber equilibrated with a different solvent system.

Apparatus-Acceptable apparatus and materials for thin-layer chromatography consist of the following.

Flat glass plates of convenient size, typieally $20 \mathrm{~cm} \times 20 \mathrm{~cm} .^{+}$
An aligning tray a flat surface upen which to align and rest the plates during the applieation of the adsorbent.

A storage rack to hold the prepared plates during drying and tramsportation. The rack holding the plates should be kept in a desiccater or be capable of being sealed in order to protect the plates from the enviremment after removal from the drying oven.
The adsorbent consists of finely divided adsorbent materials, normally 5 to -40 um in diameter, suitable for chromatography. It ean be applied directly to the glass plate or can be bended to the

[^67]plate by means of plaster of paris (hydrated calcium sulfate) [at a ratio of $5 \%$ to $15 \%]$ or with starch paste or other binders. The for mer will not yield as hard a surface as will the stareh, but it is not affected by strengly oxidizing spray reagents. The adsorbent may eontain fluorescing material to aid in the visualization of spots that absorb ultraviolet light.

A spreater, which, when moved over the glass plate, will apply a uniform layer of adsorbent of desired thickness over the entire strface of the plate.

Adeveloping ehamber that ean aceommodateoneor more plates and can be properly elosed and sealed as deseribed under Aseent ing Chromatogetyly. The chamber is fitted with a plate suppurt wack that supports the plates, back to back, with the lidof the chamber in place.

A template (generally made of plastic) to aid in placing the test spots at definite intervals, to mark distanees as needed, and to aid in tabeling the plates.

A graduat mieropipe capable of delivering $10 \mu \mathrm{~L}$ velumes. Fotal volumes of test and standard solutions are specified in the individual menegraph.
A reagent spratyer that will-emit a fine-spray and will not itself be attacked by the reagent.

An ultraviolet light source suitable for observations with short $(254 \mathrm{~nm})$ and long ( 360 nm ) UV wavelengths.
${ }^{\triangle} \mathrm{A}$ TLC or HPTLC plate. The chromatography is generally carried out using precoated plates or sheets (on glass, aluminum, or polyester support) of suitable size. It may be necessary to clean the plates prior to separation. This can be done by migration of, or immersion in, an appropriate solvent. The plates may also be impregnated by procedures such as development, immersion, or spraying. At the time of use, the plates may be activated, if necessary, by heating in an oven at $120^{\circ}$ for 20 minutes. The stationary phase of TLC plates has an average particle size of $10-15 \mu \mathrm{~m}$, and that of HPTLC plates an average particle size of $5 \mu \mathrm{~m}$. Alternatively flat glass plates of convenient size, typically 20 $\mathrm{cm} \times 20 \mathrm{~cm}$ can be coated as described under Preparation of Chromatographic Plates.

A suitable manual, semiautomatic, or automatic application device can be used to ensure proper positioning of the plate and proper transfer of the sample, with respect to volume and position, onto the plate. Alternatively, a template can be used to guide in manually placing the test spots at definite intervals, to mark distances as needed, and to aid in labeling the plates. For the proper application of the solutions, micropipets, microsyringes, or calibrated disposable capillaries are recommended.

For ascending development, a chromatographic chamber made of inert, transparent material and having the following specifications is used: a flat bottom or twin trough, a tightly fitted lid, and a size suitable for the plates. For horizontal development, the chamber is provided with a reservoir for the mobile phase, and it also contains a device for directing the mobile phase to the stationary phase.
Devices for transfer of reagents onto the plate by spraying, immersion, or exposure to vapor and devices to facilitate any necessary heating for visualization of the separated spots or zones.

A UV light source suitable for observations under short ( 254 nm ) and long ( 365 nm ) wavelength UV light.
A suitable device for documentation of the visualized chromatographic result.

Procedure-Apply the prescribed volume of the test solution and the standard solution in sufficiently small portions to obtain circular spots of 2 to 5 mm in diameter ( 1 to 2 mm on HPTLC plates) or bands of 10 to 20 mm by 1 to 2 mm ( 5 to 10 mm by 0.5 to 1 mm on HPTLC plates) at an appropriate distance from the lower edge-during chromatography the application position must be 3 mm (HPTLC) to 5 mm (TLC) above the level of the developing solvent-and from the sides of the plate. Apply the solutions on a line parallel to the lower edge of the plate with an interval of at least 10 mm ( 5 mm on HPTLC plates) between the centers of spots or 4 mm ( 2 mm on HPTLC plates) between the edges of bands, and allow to dry.
Ascending Development-Line at least one wall of the chromatographic chamber with filter paper. Pour into the chromatographic chamber a quantity of the mobile phase sufficient for the size of the chamber to give, after impregnation of the filter paper, a level of depth appropriate to the dimension of the plate used. For saturation of the chromato-
graphic chamber, close the lid, and allow the system to equilibrate. Unless otherwise indicated, the chromatographic separation is performed in a saturated chamber.

Place the plate in the chamber, ensuring that the plate is as vertical as possible and that the spots or bands are above the surface of the mobile phase, and close the chamber. The stationary phase faces the inside of the chamber. Remove the plate when the mobile phase has moved over the prescribed distance. Dry the plate, and visualize the chromatograms as prescribed. For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

Horizontal Development-Introduce a sufficient quantity of the developing solvent into the reservoir of the chamber using a syringe or pipet. Place the plate horizontally in the chamber, connect the mobile phase direction device according to the manufacturer's instructions, and close the chamber. If prescribed, develop the plate starting simultaneously at both ends. Remove the plate when the mobile phase has moved over the distance prescribed in the monograph. Dry the plate, and visualize the chromatograms as prescribed.

For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

Detection-Observe the dry plate first under short-wavelength UV light ( 254 nm ) and then under long-wavelength UV light ( 365 nm ) or as stated in the monograph. If further directed, spray, immerse, or expose the plate to vapors of the specified reagent, heat the plate when required, observe, and compare the test chromatogram with the standard chromatogram. Document the plate after each observation. Measure and record the distance of each spot or zone from the point
of origin, and indicate for each spot or zone the wavelength under which it was observed. Determine the $R_{F}$ values for the principal spots or zones (see Glossary of Symbols).

Quantitative Measurement-Using appropriate instrumentation, substances separated by TLC and responding to ultraviolet-visible (UV-Vis) irradiation prior to or after derivatization can be determined directly on the plate. While moving the plate or the measuring device, the plate is examined by measuring the reflectance of the incident light. Similarly, fluorescence may be measured using an appropriate optical system. Substances containing radionuclides can be quantified in three ways: (1) directly by moving the plate alongside a suitable counter or vice versa; (2) by cutting the plates into strips and measuring the radioactivity on each individual strip using a suitable counter; or (3) by scraping off the stationary phase, dissolving it in a suitable scintillation cocktail, and measuring the radioactivity using a liquid scintillation counter (see Radioactivity $\langle 821\rangle$ ).

The apparatus for direct quantitative measurement on the plate is a densitometer that is composed of a mechanical device to move the plate or the measuring device along the x axis and the $y$-axis, a recorder, a suitable integrator or a computer; and, for substances responding to UV-Vis irradiation, a photometer with a source of light, an optical device capable of generating monochromatic light, and a photo cell of adequate sensitivity, all of which are used for the measurement of reflectance. In the case where fluorescence is measured, a suitable filter is also required to prevent the light used for excitation from reaching the photo cell while permitting the emitted light or specific portions thereof to pass. The linearity range of the counting device must be verified.

For quantitative tests, it is necessary to apply to the plate not less than three standard solutions of the substance to be examined, the concentrations of which span the expected
value in the test solution (e.g., $80 \%, 100 \%$, and $120 \%$ ). Derivatize with the prescribed reagent, if necessary, and record the reflectance or fluorescence in the chromatograms obtained. Use the measured results for the calculation of the amount of substance in the test solution.

## Preparation of Chromatographic Plates-

## Apparatus-

Flat glass plates of convenient size, typically $20 \mathrm{~cm} \times 20$
cm .
An aligning tray or a flat surface upon which to align and rest the plates during the application of the adsorbent.
A storage rack to hold the prepared plates during drying and transportation. The rack holding the plates should be kept in a desiccator or be capable of being sealed in order to protect the plates from the environment after removal from the drying oven.

The adsorbent consists of finely divided adsorbent materials, normally 5 to $40 \mu \mathrm{~m}$ in diameter, suitable for chromatography. It can be applied directly to the glass plate or can be bonded to the plate by means of plaster of Paris (calcium sulfate hemihydrate [at a ratio of $5 \%$ to $15 \%$ ]) or with starch paste or other binders. The plaster of Paris will not yield as hard a surface as will the starch, but it is not affected by strongly oxidizing spray reagents. The adsorbent may contain fluorescing material to aid in the visualization of spots that absorb UV light.
A spreader, which, when moved over the glass plate, will apply a uniform layer of adsorbent of desired thickness over
the entire surface of the plate. USP28
Procedure- [NOTE-In this procedure, use purified water that is obtained by distillation.] Clean the
-glass $_{\triangle U S P 28}$
plates scrupulously, as by immersion in chremic acidecernsing mixtere,
${ }^{\Delta}$ using an appropriate cleaning solution (see Cleaning Glass
Apparatus $\langle 1051\rangle$ ),
rinsing them with copious quantities of water until the water runs off the plates without leaving any visible water or oily spots, then dry. It is important that the plates be completely free from lint and dust when the adsorbent is applied.

Arrange the plate or plates on the aligning tray, place a 5- $\times 20-$ cm plate adjacent to the front edge of the first square plate and another $5-\times 20-\mathrm{cm}$ plate adjacent to the rear edge of the last square, and secure all of the plates so that they will not slip during the application of the adsorbent. Position the spreader on the end plate opposite the raised end of the aligning tray. Mix 1 part of adsorbent with 2 parts of water (or in the ratio suggested by the supplier) by shaking vigorously for 30 seconds in a glass-stoppered conical flask, and transfer the slurry to the spreader. Usually 30 g of adsorbent and 60 mL of water are sufficient for five $20-\times 20-\mathrm{cm}$ plates. Complete the application of adsorbents using plaster of Paris binder within 2 minutes of the addition of the water, because thereafter the mixture begins to harden. Draw the spreader smoothly over the plates toward the raised end of the aligning tray, and remove the spreader when it is on the end plate next to the raised end of the aligning tray. (Wash away all traces of adsorbent from the spreader immediately after use.) Allow the plates to remain undisturbed for 5 minutes, then transfer the square plates, layer side up, to the storage rack, and dry at $105^{\circ}$ for 30 minutes. Preferably place the rack at an angle in the drying oven to prevent the condensation of moisture on the back sides of plates in the rack. When the plates are dry, allow them to cool to room temperature, and inspect the uniformity of the distribution and the texture of the adsorbent layer; transmitted light will show uniformity of distribution, and reflected light will show uniformity of texture. Store the satisfactory plates over silica gel in a suitable chamber.
Place two flter paper wieks, 18 cm in height and as wide as the length of the developing chamber, into the chamber, add about 100 mL of the solvent (sufficient to have a depth of 5 to 10 mm at the bottom of the chamber), seal the cover to the top of the chamber, and allow the system to equilibrate; it is essential that the wieks become completely wet. Alternatively, the chamber may be completely lined with filter paper. In either ease, assure that the fllter paper dips int the solvent at the bettem of the chamber. Where rapor saturation of the chamber by these methods is undesirable, it is so indiented in the individual menograph.

Apply the test solution and the standard solution, as direeted in the individual menegraph, at peints abeut 1.5 em apart and about 2 em from the lower edge of the plate (the lower edge is the first part over which the spreader moved in the application of the adsorbent fayer), and allow to dry. Aveid physieal disturbance of the adsor bent during the spetting procedure (by the pipet or other applicator) or when handling the plates. The template will aid in determining the spet peints and the 10 to 15 em distance through whieh the solvent fromt should pass.

Place a mark 10 to 15 em abeve the spet peint. Arrange the plate en the supperting rack (test spets toward the bottom), and introduce the rack into the developing chamber. Allow the solvent in the chamber to reach the lower edge of the adsorbent, but do not allow the spet peints to be immersed. Put the cover in place, and maintain the system matil the solvent aseends to a point 10 to 15 cm above the initial spets, this usually requires about 15 minutes to 1 hour. Remove the plate from the developing chamber, mark the solvent front, air dry the plates, and observe first under short wavelength UV light ( 254 mm ) and then under long wavelength UV light $(360 \mathrm{~nm})$. Measure and record the distance of each spot from the peint of origin, and indiente for each spe the wavelength under which it was observed. Determine the $R_{F}$ values for the principat spets (see Glossaty of Symbels). If futher directed, spray the spets with the reagent specified, observe, and compare the test chromatogram with the standard chromatogram.

## Contintous-Development Thin-Layer Chromatography

In contrast to conventional thin layer chromatography, which is earried out in a closed tank, the eontintrous development or continyous flow technique allows the upper end of the plate to project
through a slot in the cover of the developing chamber. When the developing solvent reaches the slot, continuous evaporation-0ceurs, producing a steady flow of solvent over the plate. In conventional thin layer chromatography, spet migration ceases when the solvent reaches the top of the plate, after which the spots simply enlarge by diffusion. In the continteus flow process, spet migration contintes as long as the plate remains in the tank and the develeping solvent is net exhatusted.

Development may be continted for several hours after the solvent reaches the top of the plate, to provide adequate migration of the spots. Ustally spots of a standardsolution, a test solution, and a mixture of equal amounts of test and standard solutions, are initially applied at a standard distance from the base of the plate. Iden tity of the standard and test substanees is conflirmed by their migrating equal distances from the origin and by the observation that the two substances applied as a mixture show no tendeney to separate.

A major advantage of contintrous development thin layer ehromatography stems from the greater solvent selectivity for sol vents of low solvent strength. Solvent strength refers to the propery of a developing solvent that causes solutes to migrate, and it is strongly influeneed by the polarity of the solvent. Inereasing the solvent strength by adding a more polar solvent eauses the $R_{t}$ walue to increase. Solvent selectivity refers to the ability of a solvent system to produre differen $R_{\text {F }}$ values for closely related substances. In eonventional thin layer chromatography, a solvent system giving an $R_{F}$ value in the range of 0.3 to 0.7 , but with adequate selectivity to permit separation of the substanees being examined is usually selected. It is math easier to find solvent systems produring adequate migration than to find those affording adequate selectivity.

Solvent systems of lower strength generally exhibit higher selec tivity, but are diffieult to employ in conventional thin layer ehrematography beeatse they result in very little migration before the solvent reaches the top of the plate. Migration may be in ereased, however, by repeated drying and redevelopment of the plate or, more conveniently, by providing means for ovaperation of solvent at the top of the plate, whieh results in continurus devel epment. Two techniques are used: contintuous development and short bed continuous development thin layer chrematography.

An $R_{\text {F }}$ value cannot be measured in continuous development thin layer ehrematography. Substances may be compared either by their migration distance over a fixed period of time or by comparisen with the migration of a standard substance applied to the plate.

## GONTINUOUS DEVELOPMENT

Apparatus. Aeceptable apparatus and materials for contintuens development thin layer chromatography are the same as those deseribed under conventional Thin Layer Chromagraphy, exeeptas follows.

Adeveloping ehamber is use that eonsists of a reetangular tank, approximately $23 \mathrm{~cm} \times 23 \mathrm{~cm} \times 9 \mathrm{~cm}$, equipped with a glass solvent trough and a platform about 3.75 em high to elevate the solvent trough above the base of the tank. The chamber is fitted with a cover having a $21 \times 6 \mathrm{~cm}$ slot in the front edge.

Proeedure- Apply the standard solution, the test solution, and a mixture of equal amounts of the standard solution and the test solution to a line about 2 cm from the base of the plate. Place the plate in the ele ated empty solvent treugh with the adsorbent en the underside of the leaning plate. The adsorbent rests against a piece of heary (about 1 mm thick) ${ }^{2}$ flter paper measuring $20 \mathrm{~cm}-$ 3 cm , folded lengthwise and placed over the front edge of the tank. Place the developing solvent in the trough; set the cover in place, and seal all openings exeept where the adsorbent contacts the paper wiek. The plate extends about $1-\mathrm{em}$ beyond the top of the tank.

[^68]After the solvent reaches the top of the plate, allow development to eontinue for an appropriate time. Then remove and dry the plate, and detect the spots by suitable means.

## SHORT BED-CONTINUOUS DEVELOPMENT

A major advantage of the short bed technique derives frem the faet that solvent velocity is inversely related to bed length. Since spot migration depends upon the otal amount of solvent passing over the plate, the short bed permits useful migration to be ob tained in a reasonable time with solvent having very low solvent strength. Lower diffusion in solvents of low solvent strength produres smaller and mere dense spets, which enhanees beth detect ability and diseermment of small differenees in migration distanee.
Apparatus Aceeptable apparatus and materials for short bed eontintrus development thin layer chromatography are the same as these described under conventional Thin Latyer Chrematog raphy, except as follows.

A shallow developing chamber ${ }^{3}$ approximately $22 \mathrm{~cm}-9 \mathrm{~cm}$ $* 3 \mathrm{~cm}$, equipped with a cover plate and tight fitting polytef wings that enable the chamber to be sealed against the plate, is used. The inside bettom of the chamber contains ridges that suppert the plate and allow it to be inserted at different angles, thereby warying the length of the plate contained within the tank.

Procedure Apply the standard solution, the test solution, and a mixture of equal parts of the standard solution and the test solut tion to a line about 2 cm from the base of the plate. Place the plate in the developing chamber (adsorbent side up), and add the devel eping solvent to the chamber. No paper wiek is employed. After the solvent reaches the top of the plate, allow development to cont tince for an appropriate time. Then remove and dry the plate, and detect the spets by suritable means.
-
4USP28

## Change to read:

## SYSTEM SUITABILITY

System suitability tests are an integral part of gas and liquid chromatographic methods. They are used to verify that the resolution and reproducibility of the chromatographic system are adequate for the analysis to be done. The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such.

The resolution, $R$, [NOTE-All terms and symbols are defined in the Glossary of Symbols] is a function of column efficiency, $N$, and is specified to ensure that closely eluting compounds are resolved from each other, to establish the general resolving power of the system, and to ensure that internal standards are resolved from the drug. Column efficiency may be specified also as a system suitability requirement, especially if there is only one peak of interest in the chromatogram; however, it is a less reliable means to ensure resolution than direct measurement. Column efficiency is a measure of peak sharpness, which is important for the detection of trace components.

Replicate injections of a Standard preparation used in the assay or other standard solution are compared to ascertain whether requirements for precision are met. Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation,

[^69]$S_{R}$, if the requirement is $2.0 \%$ or less; data from six replicate injections are used if the relative standard deviation requirement is more than $2.0 \%$.
The tailing factor, $T$, a measure of peak symmetry, is unity for perfectly symmetrical peaks and its value increases as tailing becomes more pronounced (see Fig. 2). In some cases, values less than unity may be observed. As peak asymmetry increases, integration, and hence precision, becomes less reliable.


Fig. 2. Asymmetrical chromatographic peak.
These tests are performed by collecting data from replicate injections of standard or other solutions as specified in the individual monograph. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions (see Procedures under Tests and Assays in the General Notices). Adjustments of operating eonditions to meet system suit ability requirements may be neeessary.
${ }^{\Delta}$ If adjustments of operating conditions to meet system suitability requirements are necessary, each of the following is the maximum specification that can be considered, unless otherwise directed in the monograph. Adjustments are permitted only when Referene Standards suitable standards (including Reference Standards) are available for all lytes compounds used in the suitability test and are used to show that the adjustments have improved the quality of the chromatography in meeting system suitability requirements. Adjustments to chromatographic systems performed in order to comply with system suitability requirements are not to be made to compensate for column failure or to circumvent replacing a deteriorated column. Multiple adjustments that may have a cumulative effect in the performance of the system are to be avoided.
pH of Mobile Phase (HPLC)-The pH of the aqueous buffer used in the preparation of the mobile phase can be adjusted to within $\pm 0.2 \pm 0.5$ units of the value or range specified.

Concentration of Salts in Buffer (HPLC)—The concentration of the salts used in the preparation of the aqueous buffer used in the mobile phase can be adjusted to within $\pm 10 \%$, provided the permitted pH variation (see above) is met.

## Ratio of Components in Mobile Phase (HPLC) The

ameunt of the miner The following adjustment limits apply to minor components of the mobile phase (specified at $50 \%$ or less). The amount(s) of these component(s) can be adjusted by $\pm 30 \%$ relative or $\pm 2 \%$ absolute (i.e., in relation to the total mobile phase), whichever is larger. However, the change in any component cannot exceed $\pm 10 \%$ absolute, nor can the final concentration of any component be reduced to zero. Adjustment can be made to one minor component in a ternary mixture. Examples of adjustments for binary and ternary mixtures are given below.

## Binary Mixtures-

SPECIFIED RATIO OF 50:50-Thirty percent of 50 is $15 \%$ absolute, but this exceeds the maximum permitted change of $\pm 10 \%$ absolute in either component. Therefore, the mobile phase ratio may be adjusted only within the range of 40:60 to $60: 40$.

SPECIFIED RATIO OF 95:5-Thirty percent of 5 is $1.5 \%$ absolute. However, because adjustments up to $\pm 2 \%$ absolute are allowed, the ratio may be adjusted within the range of 93:7 to 97:3.

SPECIFIED RATIO OF 2:98-Thirty percent of 2 is $0.6 \%$ absolute. In this case an absolute adjustment of $\pm 2 \%$ is not allowed because it would reduce the amount of the first component to zero. Therefore the maximum allowed adjustment is within the range of 1.4:98.6 to 2.6:97.4.

## Ternary Mixtures-

SPECIFIED RATIO OF 60:35:5-For the second component, $30 \%$ of 35 is $10.5 \%$ absolute, which exceeds the maximum permitted change of $\pm 10 \%$ absolute in any component.

Therefore the second component may be adjusted only within the range of $25 \%$ to $45 \%$ absolute. For the third component, $30 \%$ of 5 is $1.5 \%$ absolute. Since $\pm 2 \%$ absolute is permitted and provides more flexibility, the third component may be adjusted within the range of $3 \%$ to $7 \%$ absolute. In all cases, a sufficient quantity of the first component is used to give a total of $100 \%$. Therefore, mixture ranges of 50:45:5 to 70:25:5 or 58:35:7 to 62:35:3 would meet the requirement.

## Detar Wavelength of UV-Visible Detector

(HPLC)—Deviations from the wavelengths specified in the method are not permitted. The procedure specified by the detector manufacturer, or another validated procedure, is to be used to verify that error in the detector wavelength is, at most, $\pm 3 \mathrm{~nm}$.

Column Length (GC, HPLC): can be adjusted by as much as $\pm 70 \%$. $-50 \%$ to $+100 \%$.

Column Inner Diameter (GC, HPLC): can be adjusted by as much as $\pm 25 \% 50 \% . \pm 25 \%$ for HPLC and $\pm 50 \%$ for GC.

Film Thickness (Capillary GC): can be adjusted by as much as $-50 \%$ to $+100 \%$.

Particle Size (HPLC): can be reduced by as much as 50\%.

Particle Size (GC): going from a larger to a smaller or a smaller to a larger (if it is the same "Range Ratio", which is the diameter of the largest particle divided by the diameter of the smallest particle) particle size GC mesh support is acceptable, provided the chromatography meets the requirements of the system suitability.

Flow Rate (GC, HPLC): can be adjusted by as much as $\pm 50 \%$.

Injection Volume (GC, HPLC): can be reduced as far as is consistent with accepted precision and detection limits. It
provided there-are no adverse-effects-on facters such as baseline, peak shapes, resolution, linearity, and retention times.

Column Temperature (HPLC): can be adjusted by as much as $\pm 20^{\circ} . \pm 10^{\circ}$. Column thermostating is recommended to improve control and reproducibility of retention time.

Column Temperature (GC): can be adjusted by as much as $\pm 2 \%$ in terms of abselute temperature. $\pm 10 \%$.

Oven Temperature Program (GC)—Adjustment of temperatures is permitted as stated above. For the times specified for the temperature to be maintained or for the temperature to be changed from one value to another, an adjustment of up to $\pm 20 \%$ is permitted.

Gradient Elution (HPLC)—The configuration of the equipment employed may significantly alter the resolution, retention time, and relative retentions described in the method. Should this occur, it may be due to excess dwell time, which is the volume between the point at which the two eluants meet and the top of the column. USPP28 $^{\text {Und }}$
Unless otherwise directed in the monograph, system suitability parameters are determined from the analyte peak.
To ascertain the effectiveness of the final operating system, it should be subjected to suitability testing. Replicate injections of the standard preparation required to demonstrate adequate system precision may be made before the injection of samples or may be interspersed among sample injections. System suitability must be demonstrated throughout the run by injection of an appropriate control preparation at appropriate intervals.
The control preparation can be a standard preparation or a solution containing a known amount of analyte and any additional materials useful in the control of the analytical system, such as excipients or impurities. Whenever there is a significant change in equipment or in a critical reagent, suitability testing should be performed before the injection of samples. No sample analysis is acceptable unless the requirements of system suitability have been met. Sample analyses obtained while the system fails
$\Delta_{\text {System suitability }}^{\text {AUSP28 }^{\text {U }}}$
requirements are unacceptable.

## Change to read:

## CHROMATOGRAPHIC REAGENTS

The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer. [NOTE-Particle sizes given in this listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category
of packings or phases listed below, there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

## Packings

L1-Octadecyl silane chemically bonded to porous silica or ceramic micro-particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L2-Octadecyl silane chemically bonded to silica gel of a controlled surface porosity that has been bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L3-Porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.
L4-Silica gel of controlled surface porosity bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L5-Alumina of controlled surface porosity bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L6-Strong cation-exchange packing-sulfonated fluorocarbon polymer coated on a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter. L7-Octylsilane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L8-An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support, $10 \mu \mathrm{~m}$ in diameter.

L9- $10-\mu \mathrm{m}$ irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating.

L10-Nitrile groups chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L11-Phenyl groups chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L12-A strong anion-exchange packing made by chemically bonding a quaternary amine to a solid silica spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L13-Trimethylsilane chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L14-Silica gel $10 \mu \mathrm{~m}$ in diameter having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating.
L15-Hexylsilane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L16-Dimethylsilane chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L17-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form, 7 to $11 \mu \mathrm{~m}$ in diameter.

L18-Amino and cyano groups chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L19-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the calcium form, about $9 \mu \mathrm{~m}$ in diameter.

L20-Dihydroxypropane groups chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.
L21-A rigid, spherical styrene-divinylbenzene copolymer, 5 to $10 \mu \mathrm{~m}$ in diameter.

L22-A cation-exchange resin made of porous polystyrene gel with sulfonic acid groups, about $10 \mu \mathrm{~m}$ in size.

L23-An anion-exchange resin made of porous polymethacrylate or polyacrylate gel with quaternary ammonium groups, about $10 \mu \mathrm{~m}$ in size.

L24-A semi-rigid hydrophilic gel consisting of vinyl polymers with numerous hydroxyl groups on the matrix surface, 32 to $63 \mu \mathrm{~m}$ in diameter. ${ }^{5}$

L25-Packing having the capacity to separate compounds with a molecular weight range from 100-5000 (as determined by polyethylene oxide), applied to neutral, anionic, and cationic water-so-

[^70]luble polymers. A polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contained some residual carboxyl functional groups) was found suitable.
L26-Butyl silane chemically bonded to totally porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L27-Porous silica particles, 30 to $50 \mu \mathrm{~m}$ in diameter.
L28-A multifunctional support, which consists of a high purity, $100 \AA$, spherical silica substrate that has been bonded with anionic exchanger, amine functionality in addition to a conventional reversed phase C8 functionality.

L29-Gamma alumina, reverse-phase, low carbon percentage by weight, alumina-based polybutadiene spherical particles, 5 $\mu \mathrm{m}$ in diameter with a pore volume of $80 \AA$.

L30-Ethyl silane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L31-A strong anion-exchange resin-quaternary amine bonded on latex particles attached to a core of $8.5-\mu \mathrm{m}$ macroporous particles having a pore size of $2000 \AA$ and consisting of ethylvinylbenzene cross-linked with $55 \%$ divinylbenzene.

L32-A chiral ligand-exchange packing-L-proline copper complex covalently bonded to irregularly shaped silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L33-Packing having the capacity to separate dextrans by molecular size over a range of 4000 to $500,000 \mathrm{Da}$. It is spherical, silica-based, and processed to provide pH stability. ${ }^{6}$

L34-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the lead form, about $9 \mu \mathrm{~m}$ in diameter.

L35-A zirconium-stabilized spherical silica packing with a hydrophilic (diol-type) molecular monolayer bonded phase having a pore size of $150 \AA$.

L36-A 3,5-dinitrobenzoyl derivative of L-phenylglycine covalently bonded to $5-\mu \mathrm{m}$ aminopropyl silica.

L37-Packing having the capacity to separate proteins by molecular size over a range of 2,000 to $40,000 \mathrm{Da}$. It is a polymethacrylate gel.
L38-A methacrylate-based size-exclusion packing for watersoluble samples.

L39-A hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin.

L40-Cellulose tris-3,5-dimethylphenylcarbamate coated porous silica particles, 5 to $20 \mu \mathrm{~m}$ in diameter.

L41-Immobilized $\alpha_{1}$-acid glycoprotein on spherical silica particles, $5 \mu \mathrm{~m}$ in diameter.

L42-Octylsilane and octadecylsilane groups chemically bonded to porous silica particles, $5 \mu \mathrm{~m}$ in diameter.

L43-Pentafluorophenyl groups chemically bonded to silica particles
$\square$ by a propyl spacer, $\quad$ 1S (USP27)
5 to $10 \mu \mathrm{~m}$ in diameter.
L44-A multifunctional support, which consists of a high purity, $60 \AA$, spherical silica substrate that has been bonded with a cationic exchanger, sulfonic acid functionality in addition to a conventional reversed phase C8 functionality.

L45-Beta cyclodextrin bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L46-Polystyrene/divinylbenzene substrate agglomerated with quaternary amine functionalized latex beads, $10 \mu \mathrm{~m}$ in diameter.

L47-High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, $8 \mu \mathrm{~m}$ in diameter. ${ }^{\text {? }}$

L48-Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion-exchange microbeads, $15 \mu \mathrm{~m}$ in diameter.

[^71]L49-A reversed-phase packing made by coating a thin layer of polybutadiene onto spherical porous zirconia particles, 3 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{8}$
L50-Multifunction resin with reversed-phase retention and strong anion-exchange functionalities. The resin consists of ethylvinylbenzene, $55 \%$ cross-linked with divinylbenzene copolymer, 3 to $15 \mu \mathrm{~m}$ in diameter, and a surface area not less than $350 \mathrm{~m}^{2}$ per g . Substrate is coated with quaternary ammonium functionalized latex particles consisting of styrene cross-linked with divinylbenzene. ${ }^{9}$
L51-Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{10}$
L52-A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{11}$
L53-Weak cation-exchange resin consisting of ethylvinylbenzene, $55 \%$ cross-linked with divinylbenzene copolymer, 3 to 15 $\mu \mathrm{m}$ diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than $500 \mu \mathrm{Eq} /$ column.

L54-A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 $\mu \mathrm{m}$ in diameter.
${ }^{\boldsymbol{\Delta}}$ L55-A strong cation-exchange resin made of porous silica coated with polybutadiene-maleic acid copolymer, about $5 \mu \mathrm{~m}$ in diameter. ${ }^{14} \Delta U S P 27$
${ }^{4}$ L56-Propyl silane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{15}{ }_{\Delta U S P 27}$
-L53 \#\# (Alendronic Acid Tablets, PRP-X100)—An an-ion-exchange resin consisting of a rigid, spherical styrenedivinylbenzene copolymer with trimethylammonium groups at a loading of about 2 mEq per $\mathrm{g}, 3$ to $20 \mu \mathrm{~m}$ in diameter. ${ }^{\mathrm{a}}{ }^{2 S}$ (USPP7)

[^72]-L54 \#\# (Maltose, Aminex HPX-87N)—Strong cationexchange resin consisting of sulfonated cross-linked styr-ene-divinylbenzene copolymer in the sodium form, about
7 to $11 \mu \mathrm{~m}$ in diameter. ${ }^{\mathrm{b}}{ }^{2 S}$ (USP27)
-L57 \#\# (Nevirapine, Supelcosil ABZ)—Spherical, porous silica gel, 3 or $5 \mu \mathrm{~m}$ in diameter, the surface of which has been covalently modified with palmitamidopropyl groups and endcapped with acetamidopropyl groups to a ligand density of about $6 \mu$ moles per $\mathrm{m}^{2}$. ${ }^{\mathrm{c}}$. ${ }^{2 S}$ (USP27)
-L58 \#\# (Albumin Human, Antithrombin III Human, TSKgel G3000 SW) -Packing having the capacity to separate proteins by molecular weight over the range of 10 to 500 kDa . It is spherical ( $10 \mu \mathrm{~m}$ ), silica-based, and processed to provide hydrophilic characteristics and pH stability. ${ }^{\text {d }}$ 2S (USP27)
-L64 \#\# (Lycopene, Lycopene Preparation, YMC 30)C30 silane bonded phase on a fully porous spherical silica, 3 to $15 \mu \mathrm{~m}$ in diameter. $\boldsymbol{m}_{2 S}$ (USP27)
-L\#\# (Clopidogrel Bisulfate, Ultron ES-OVM)—A chir-al-recognition protein, ovomucoid, chemically bonded to silica particles, about $5 \mu \mathrm{~m}$ in diameter, with a pore size of $120 \AA$. $\mathbf{L S S}_{\text {(USP27) }}$
-L\#\# (Enoxaparin Sodium Injection, IonPac AG11)-[To come.] $]_{\text {2S (USP27) }}$
-L\#\# (Enoxaparin Sodium Injection, IonPac AS11)-[To come.] $]_{\text {2S (USP27) }}$
-L\#\# (Enoxaparin Sodium, Dowex 1X8)—[To come.] ${ }^{2 S}$ (USP27)
-L\#\# (Enoxaparin Sodium, Dowex 50WX2)—[To
come.] ${ }_{\text {WS }}$ (USP27)

## Phases

G1-Dimethylpolysiloxane oil.
G2-Dimethylpolysiloxane gum.
G3-50\% Phenyl-50\% methylpolysiloxane.
G4-Diethylene glycol succinate polyester.
G5-3-Cyanopropylpolysiloxane.
G6-Trifluoropropylmethylpolysiloxane.
G7-50\% 3-Cyanopropyl-50\% phenylmethylsilicone.
G8-80\% Bis(3-cyanopropyl)-20\% 3-cyanopropylphenylpoly-
siloxane (percentages refer to molar substitution).
G9-Methylvinylpolysiloxane.
G10-Polyamide formed by reacting a $\mathrm{C}_{36}$ dicarboxylic acid with 1,3-di-4-piperidylpropane and piperidine in the respective mole ratios of 1.00:0.90:0.20.

G11—Bis(2-ethylhexyl) sebacate polyester.
G12-Phenyldiethanolamine succinate polyester.
G13-Sorbitol.
G14-Polyethylene glycol (av. mol. wt. of 950 to 1050).
G15-Polyethylene glycol (av. mol. wt. of 3000 to 3700).
G16-Polyethylene glycol compound (av. mol. wt. about 15,000 ). A high molecular weight compound of polyethylene glycol with a diepoxide linker. Available commercially as Polyethylene Glycol Compound 20M, or as Carbowax 20M, from suppliers of chromatographic reagents.

G17-75\% Phenyl-25\% methylpolysiloxane.
G18-Polyalkylene glycol.
G19-25\% Phenyl-25\% cyanopropyl-50\% methylsilicone.
G20-Polyethylene glycol (av. mol. wt. of 380 to 420).
G21-Neopentyl glycol succinate.
G22-Bis(2-ethylhexyl) phthalate.
G23-Polyethylene glycol adipate.
G24-Diisodecyl phthalate.
G25-Polyethylene glycol compound TPA. A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with terephthalic acid. Available commercially as Carbowax 20M-TPA from suppliers of chromatographic reagents.

G26-25\% 2-Cyanoethyl-75\% methylpolysiloxane.
G27-5\% Phenyl-95\% methylpolysiloxane.
G28-25\% Phenyl-75\% methylpolysiloxane.
G29-3,3'-Thiodipropionitrile.
G30-Tetraethylene glycol dimethyl ether.
G31-Nonylphenoxypoly(ethyleneoxy) ethanol (av. ethyleneoxy chain length is 30); Nonoxynol 30 .

G32-20\% Phenylmethyl-80\% dimethylpolysiloxane.
G33-20\% Carborane-80\% methylsilicone.
G34-Diethylene glycol succinate polyester stabilized with phosphoric acid.

G35-A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with nitroterephthalic acid.

G36-1\% Vinyl-5\% phenylmethylpolysiloxane.
G37-Polyimide.
G38-Phase G1 containing a small percentage of a tailing inhibitor. ${ }^{16}$

G39—Polyethylene glycol (av. mol. wt. about 1500).
G40-Ethylene glycol adipate.
G41-Phenylmethyldimethylsilicone ( $10 \%$ phenyl-substituted).
G42-35\% phenyl-65\% dimethylpolysiloxane (percentages re-
fer to molar substitution).
G43-6\% cyanopropylphenyl-94\% dimethylpolysiloxane (percentages refer to molar substitution).

G44-2\% low molecular weight petrolatum hydrocarbon grease and $1 \%$ solution of potassium hydroxide.

G45-Divinylbenzene-ethylene glycol-dimethylacrylate.
G46-14\% Cyanopropylphenyl-86\% methylpolysiloxane.
G47-Polyethylene glycol (av. mol. wt. of about 8000).
G48-Highly polar, partially cross-linked cyanopolysiloxane.

[^73]■G49 Proprietary derivatized phenyl greups on a pelysilexane
backbene- ${ }^{\text {T }}$ 2S (USP27)
-G50 \#\# (Docosahexaenoic Acid)—Polyethylene glycol, cross-linked (av. mol. wt. of more than 20,000)..$^{\mathrm{e}} \mathbf{L S S}_{\text {(USP27) }}$

## Supports

NOTE--Unless otherwise specified, mesh sizes of 80 to 100 or, alternatively, 100 to 120 are intended.

S1A-Siliceous earth for gas chromatography has been flux-calcined by mixing diatomite with $\mathrm{Na}_{2} \mathrm{CO}_{3}$ flux and calcining above $900^{\circ}$. The siliceous earth is acid-washed, then water-washed until neutral, but not base-washed. The siliceous earth may be silanized by treating with an agent such as dimethyldichlorosilane ${ }^{18}$ to mask surface silanol groups.
S1AB-The siliceous earth as described above is both acid- and base-washed. ${ }^{18}$

S1C-A support prepared from crushed firebrick and calcined or burned with a clay binder above $900^{\circ}$ with subsequent acidwash. It may be silanized.

S1NS-The siliceous earth is untreated.
S2-Styrene-divinylbenzene copolymer having a nominal surface area of less than $50 \mathrm{~m}^{2}$ per g and an average pore diameter of 0.3 to $0.4 \mu \mathrm{~m}$.

S3-Copolymer of ethylvinylbenzene and divinylbenzene having a nominal surface area of 500 to $600 \mathrm{~m}^{2}$ per g and an average pore diameter of $0.0075 \mu \mathrm{~m}$.

S4-Styrene-divinylbenzene copolymer with aromatic -O and N groups, having a nominal surface area of 400 to $600 \mathrm{~m}^{2}$ per $g$ and an average pore diameter of $0.0076 \mu \mathrm{~m}$.

S5-40- to 60-mesh, high-molecular weight tetrafluorethylene polymer.

S6-Styrene-divinylbenzene copolymer having a nominal surface area of 250 to $350 \mathrm{~m}^{2}$ per g and an average pore diameter of $0.0091 \mu \mathrm{~m}$.

S7-Graphitized carbon having a nominal surface area of $12 \mathrm{~m}^{2}$ per g.

S8-Copolymer of 4-vinyl-pyridine and styrene-divinylbenzene.

S9-A porous polymer based on 2,6-diphenyl-p-phenylene oxide.

S10-A highly polar cross-linked copolymer of acrylonitrite and divinylbenzene.

S11—Graphitized carbon having a nominal surface area of 100 $\mathrm{m}^{2}$ per g modified with $\mathrm{small}^{19}$ amounts of petrolatum and polyethylene glycol compound. ${ }^{19}$

S12-Graphitized carbon having a nominal surface area of 100 $\mathrm{m}^{2}$ per g .

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Machery Nagel, Ine., 215-River Vale Read, River Vale, NJ 07675.

[^74]
## GENERAL CHAPTERS

## General Information

## BRIEFING


#### Abstract

$\langle 1043\rangle$ Ancillary Materials for Cell, Gene, and Tissue-Engineered Products. This new general information chapter is being proposed by the USP Expert Committee on Gene Therapy, Cell Therapy, and Tissue Engineering (GCT). Interested parties are encouraged to send in comments to USP headquarters by June 30, 2004 for consideration.


(GCT: I. DeVeau) RTS-40763-1

## Add the following:

- $\langle 1043\rangle$ ANCILLARY MATERIALS FOR CELL, GENE, AND TISSUE-ENGINEERED PRODUCTS


## INTRODUCTION

A wide variety of reagents and materials, many of which are unique or complex, are required for the manufacture of cell, gene, and tissue-engineered products. These materials include plasma- or serum-derived products, biological extracts, antibiotics, cytokines, culture media, antibodies, polymeric matrices, separation devices, density gradient media, toxins, conditioned media supplied by "feeder cell layers", fine chemicals, enzymes, and processing buffers. Many of these items are used to ensure the survival and promote the growth of certain cell populations, although their mechanism of action may not be entirely understood. Examples include fetal bovine serum (FBS) and various media supplements. Other items, such as highly purified cholera toxin, are introduced into the processing stream during man-
ufacturing to exert a specific biochemical effect and are immediately washed out in subsequent processing steps to avoid unwanted toxicity at a later point. The finished biological products produced in such processes are often complex mixtures that, in some cases, cannot be completely characterized. Careful scrutiny of the materials used in manufacturing is necessary to prevent the introduction of adventitious agents or toxic impurities, as well as to ensure the ultimate safety, effectiveness, and consistency of the final product.

In cell, gene, and tissue-engineered product manufacturing, these reagents and materials are collectively called ancillary materials (AMs). AMs have also been referred to as ancillary products, ancillary reagents, processing aids, and process reagents. AMs were first discussed under the synonym ancillary products in the U.S. Food and Drug Administration Notice, "Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products" (Federal Register 58(197), October 14, 1993, pp. 53248-53251). This document established the FDA's authority to regulate human somatic cell therapy products and gene therapy products. AMs are also synonymous with "processing materials" that were defined in 21 CFR Part 1271, "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule" (Federal Register 66(5), January 8, 2001, pp. 1508-1559). AMs can be analogous to "components", and in some cases, "containers" as described in the current good manufacturing practice (cGMP) regulations for finished pharmaceuticals as outlined in 21 CFR 211.80 through 211.94 and 211.101(b) and (c).

The defining property of AMs is that they are not intended to be present in the final product. They are materials used as processing and purification aids or agents that exert their ef-
fect on the therapeutic substance. Materials or components that are intended to be in the final product dosage form (e.g., genetic materials, biopolymeric supports, physiological buffers) are not AMs. Cell banks and virus banks are also not considered AMs; there are a number of guidances that describe requirements for their certification. However "helper" viruses and "helper" plasmids may be considered AMs when they are not intended to be part of the final product.

The quality of an AM can affect the stability, safety, potency, and purity of a cell, gene, or tissue-engineered product. For example, the mechanism by which an AM exerts its effect may not be known, and the impact of normal variation of the AM on the quality and safety of the therapeutic product may not be understood. Alternatively, AMs of human or animal origin may present an infectious disease transmission risk. Other AMs, if administered to humans, may cause an immune reaction. Finally, an AM with toxic properties that is introduced into a manufacturing process and is not adequately removed in subsequent processing steps will expose the patient to a toxic substance and may impair the effectiveness of the therapeutic entity. These risks to the quality and safety of the therapeutic product are often heightened with cell, gene, and tissue-engineered products, due to the limited ability to conduct extensive in-process and release tests. For example, lack of in-process holding steps or limited shelf life may create the need to administer the cell, gene, or tissue-engineered products before in-process or final-release testing results are available. In other cases, the scarcity of suitable donor tissue or the complex logistics in the transport of biological materials may limit the amount of material available for testing. To minimize these risks, whenever possible, it is necessary to implement rigorous material qualification and prudent application of manufacturing process controls.

Frequently, these novel therapeutic products are created using complicated biological processes. The AMs employed in these procedures may be selected primarily for their unique functional contributions or biological effects. Whenever possible, it is preferable to source AMs that are approved or licensed therapeutic products because they are well characterized, have an established toxicological profile, and are manufactured according to controlled and documented procedures. Conversely, the AM may be intended "for research use" and may, therefore, lack the level of qualification necessary for use in the production of a therapeutic product. In either case, the manufacturer of the cell, gene, or tissue-engineered product should develop comprehensive and scientifically sound qualification plans to ensure the traceability, consistency, suitability, purity, and safety of the AM. In cases where AMs are products approved for use for therapeutic purposes, the level of qualification will probably be less extensive than that for a material intended for research purposes. However, their suitability in the manufacturing process will still need to be established when the AM is being used beyond the scope of its intended use or labeling. The purpose of this chapter is to provide guidance in developing appropriate qualification programs for AMs employed in cell, gene, and tissue-engineered product manufacturing.

## QUALIFICATION OF ANCILLARY MATERIALS

Qualification is the process of acquiring and evaluating data to establish the source, identity, purity, biological safety, and overall suitability of a specific AM. The responsibility for AM qualification resides with the developer or manufacturer of the cell, gene, or tissue-engineered product. This section outlines the basis by which a manufacturer can establish rational and scientifically sound programs for qualifying AMs, although the broad nature of the cell, gene, and
tissue-engineered products and of the AM used to produce these products make it difficult to recommend specific tests or protocols for a qualification program. Thorough documentation is the cornerstone of any qualification program.

A well-designed qualification program becomes more comprehensive as product development progresses. In the early stages of product development, safety is the primary focus. In the later stages, AM production and qualification activities should be comprehensively developed to support eventual licensure of the cell, gene, and tissue-engineered product. On some occasions, complex or unique substances that have been shown to be essential for process control or production may not be available from suppliers that produce them in compliance with cGMP. In these situations, the manufacturer will have to develop a scientifically sound strategy for qualification. A qualification program for AMs used in cell, gene, and tissue-engineered product manufacturing should address each of the following areas: (1) identification, (2) selection and suitability for use in manufacturing, (3) characterization, (4) vendor qualification, and (5) quality assurance and control.

## Identification

The first step in any qualification program is the listing of all of the AMs used in a given product manufacturing and where in the manufacturing process they are to be employed. The source and intended use for each material should be established, and the necessary quantity or concentration of each material should be determined. Also, alternate sources for each material should be identified.

## Selection and Suitability for Use

Developers of cell, gene, and tissue-engineered products should establish and document selection criteria for AMs and qualification criteria for each vendor early in the design phase of product development. Selection criteria should include assessments of microbiological and chemical purity, identity, and biological activity pertinent to the specific manufacturing process. It is important to address these issues early in product development because certain AMs that are initially considered necessary may be impossible or prohibitively expensive to qualify, thereby justifying the investigation of alternatives or replacements. Examples include some animal- or human-derived materials that in some cases have alternate (i.e., plant or chemically synthesized) sources.

AMs of animal or human origin should be selected cautiously due to the potential infectious or zoonotic disease risks associated with these materials. Vendors should be selected that can supply documentation regarding the country of origin for animal-derived AMs to address concerns regarding transmissible spongiform encephalopathies and other diseases of agricultural concern, like tuberculosis and brucellosis. In many cases, the chain of custody for an-imal-derived AMs (i.e., abattoir $\rightarrow$ intermediate processing center $\rightarrow$ final processing center) will need to be documented. Vendors of human-derived AMs should be able to supply documentation regarding material traceability. For instance, human plasma-derived AMs should be sourced from licensed facilities that control the donor pool and appropriately screen the individual donors for relevant human infectious diseases. In some cases, vendors of animal- and human-derived AMs supply different grades of materials, some of which will be more suitable for use in cell, gene, and tissue-engineered product manufacturing than other grades. For example, FBS can be obtained that has been pro-
cessed to reduce the risk of bovine viral contamination by subjecting it to validated irradiation and nanofiltration processes. Also, many animal and human plasma-derived components are subjected to chemical (detergent or solvent treatment) or physical (heat exposure for extended periods of time) treatments that have been shown through validation studies to significantly reduce the risk of adventitious microbial or viral contamination associated with starting AMs. Such AMs are preferred for use in cell, gene, and tissue-engineered product manufacturing processes because they significantly reduce the risks associated with the original material.

The complexity of risk assessment can be reduced by employing one of a number of quantitative or semiquantitative approaches, such as failure mode effects analysis (FMEA), quality function deployment (QFD), or hazard analysis and critical control point (HACCP). These programs typically assign a point value to each risk parameter for an AM that results in cumulative scores that make it easier to prioritize effort and resources for decreasing the risks associated with AMs. For example, an AM that has a strong safety profile and is used in minimal amounts in upstream steps of the manufacturing process and is thoroughly washed from the system would accumulate a low point score. Conversely, an AM that is known to be toxic and is employed in downstream processing would, therefore, possess a higher potential for appearing as a residual in the final product and would be assigned a higher point value. One can also assign points based on the risk classification (see Risk Classification).

## Characterization

Specific quality control characterization tests need to be developed or adopted and implemented for each AM. The set of tests for each AM should assess a variety of quality attributes, including identity, purity, functionality, and freedom from microbial or viral contamination. The appropriate level of testing for each AM is derived from its risk assessment profile and the knowledge gained during development. Test specifications should be developed for each AM to ensure consistency and performance of the manufacturing process. Acceptance criteria should be established and justified on the basis of the data obtained from lots used in preclinical and early clinical studies, lots used for demonstration of manufacturing consistency, and relevant development data, such as those arising from analytical procedure development and stability studies.

Some AMs that are biological in nature may be difficult to fully characterize. Because these materials exert their effects through complex biological activities, and biochemical testing may not be predictive of the AM's process performance, functional or performance testing may be needed. Performance variability of such materials may have a detrimental impact on the potency and consistency of the final therapeutic product. Examples of complex functionality testing for AMs include growth promotion testing of individual lots of FBS on the cell line used in manufacturing, performance testing of digestive enzyme preparations, and in vitro tissue culture cytotoxicity assays. (see aspects of Performance Testing).

## Vendor Qualification

Vendors supplying AMs should be qualified at the earliest opportunity. An early audit of the vendor's manufacturing facility, including their GMP and AM testing program, are basic elements of a vendor qualification program. A review of the vendor's processing procedures and documentation program is essential in establishing confidence in the vendor as a reliable supplier. Additionally, vendors that have been certified through an ISO inspection program or audited by other governmental agencies tend to have robust quality systems in place. Reports of past audits of U.S. suppliers obtained through the Freedom of Information (FOI) Act may augment the qualification process.

It is important to develop a good working relationship with a vendor. In some cases, the vendor may provide higher manufacturing standards, custom formulation services, or replacement of substandard components upon request, with or without additional costs. A good rapport is essential if further investigation into AM suppliers is warranted. It is also critical to ensure that the vendor takes appropriate steps to prevent cross contamination between its products during manufacture. Vendors should be familiar with the principles of validation, especially cleaning validation, as well as viral inactivation and sterilization validation. Finally, systems should be established where vendors supply written certification of processing or sourcing changes to customers, well in advance of the implementation of the changes so that customers can evaluate the potential impact of such changes.

## Quality Control and Quality Assurance

Because the components of the qualification program are multifaceted and need to be in compliance with cGMP, they should be monitored by a quality assurance/quality control unit (QAU). Typical QAU activities include the following systems or programs: (1) incoming receipt, segregation, inspection, and release of materials prior to use in manufacturing, (2) vendor auditing and certification, (3) certificate of analysis verification testing, (4) formal procedures and policies for out-of-specification materials, (5) stability testing, and (6) archival sample storage.

## RISK CLASSIFICATION

A scientifically sound and rational qualification program should be designed for each AM and should take into account the source and processes employed in its manufacture. Whenever available, AMs that are approved or licensed therapeutic products are preferable because they are wellcharacterized with an established toxicological profile and are manufactured according to controlled and documented procedures. Licensed biologics, approved drugs, and approved or cleared medical devices or implantable materials that have been incorporated into cell, gene, or tissue-engineered product manufacturing processes present a known or more favorable safety profile for the patient than nonapproved or nonlicensed versions. Qualification programs for these AMs should reflect the extensive scrutiny that these items were subjected to in their development and manufacture. Consequently, greater emphasis should be placed on the investigation of the impact of inherent variability of these AMs on final product function. For instance, a manufacturer may utilize human serum albumin, intended for human administration, as a supplement to a cell cultivation medium for a cell-based product. Because the cell-based product is marketed as a licensed biological, one need not
repeat all the testing already performed by the supplier as part of material qualification. In contrast, the impact of lot-to-lot variability on cell growth rate or maintenance of an important differentiated cellular property may be a prudent area of investigation. Alternatively, the stability of this material at the concentration employed in processing or its potential for interaction with other processing components may also be areas worthy of investigation. Such approaches to AM qualification therefore focus on the AM as a potential source of variability that may influence final product potency and safety. Qualification programs for these AMs should be comprehensive to minimize consumer risk and ensure that unacceptable lots or adulteration will be detected.

The qualification program must also take into account the quantity of the AM employed in manufacturing as well as its point of introduction in the manufacturing process. A relevant example is the use of FBS as a supplement to a tissue culture medium used to expand a stem cell population from a specific tissue for eventual administration to a patient (see Manufacturing Overview under Cell and Gene Therapy Products $\langle 1046\rangle$ ). A qualification program for such an AM would include (a) assurance that the serum was sourced from a country or region known to be free of bovine spongiform encephalopathy (BSE); (b) assurance that the source herds are monitored and test negative for specific diseases relevant in agricultural settings (e.g., tuberculosis, brucello-
sis, foot and mouth disease); (c) testing of the serum for sterility, mycoplasma, endotoxin content, and adventitious bovine viruses known to be associated with the material; ${ }^{1}$ (d) the review and archiving of the supplier's certificate of analysis; (e) lot-to-lot assessment of the ability of the serum to consistently expand a representative cell population using a standardized cell culture quality control assay; and (f) onsite audit of the supplier to ensure that the material is sourced and processed in a manner deemed acceptable by a responsible QA unit.

To aid manufacturers and developers in the design of their qualification programs for a variety of AMs, tiers of sample risk categories are presented in Tables 1-4 and are provided as a guide. Risk is also dependent on the amount and the stage at which the AM is used in the manufacturing process. Tables 1-4 do not address the impact of quantity or stage of use.
Tier 1-These AMs are low-risk, highly qualified materials that are well-suited for use in manufacturing. The AM is either a licensed biologic, an approved drug, an approved or cleared medical device, or it is intended for use as an implantable biomaterial. Generally these components or materials are obtained as a sterile packaging system or dosage form intended for their label use, but are instead utilized "off label" in the manufacturing process for the cell, gene, or tissue-engineered product.

[^75]Tier 2-These AMs are low-risk, well-characterized material that are well-suited for use in manufacturing. Their intended use is for drug, biologic, or medical device manufacture, including cell, gene, and tissue-engineered products as AMs, and they are produced under relevant cGMPs. Most animal-derived materials are excluded from this category.

Tier 3-These AMs are a moderate risk material that will require a higher level of qualification than previous tier materials. Frequently, these materials are produced for in vitro diagnostic use and are not intended for use in the production of cell, gene, or tissue-engineered products. In some cases, upgrade of AM manufacturing processes may be necessary in order to employ the AM in manufacturing of these products (e.g., modification of the production process for a diagnostic grade monoclonal antibody to include robust viral removal steps in purification).

Tier 4-This is the highest risk level for AMs. Extensive qualification is necessary prior to use in manufacturing. The material is not produced in compliance with cGMPs. AMs are not intended for use in the production of cell, gene, or tissue-engineered products. This risk level includes highly
toxic substances with known biological mechanisms of action, and also includes most complex, animal-derived fluid materials not subjected to adventitious viral removal or inactivation procedures. These materials may require (a) an upgrade of AM manufacturing processes; (b) treatment of AMs to inactivate or remove adventitious agents, diseasecausing substances, or specific contaminants (e.g., animal viruses, prions); (c) testing of each lot of material to ensure that it is free of adventitious agents, disease-causing substances, or specific contaminants; (d) validation of the manufacturing process of the cell, gene, or tissue-engineered product to assess consistency of removal of a known toxic substance or lot-release testing to demonstrate reduction levels considered to be safe; or (e) validation of the manufacturing process of the cell, gene, or tissue-engineered product to assess consistency of removal or inactivation of adventitious agents, disease-causing substances, or specific contaminants associated with the material. Developers in the early stages of development should evaluate the necessity of these materials and explore alternative substances or sources.

Table 1. AM Risk Tier 1
Low-Risk, Highly Qualified Materials with Intended Use as Therapeutic Drug or Biologic, Medical Device, or Implantable Material

| Example | Typical Use in Cell, Gene, or Tissue-Engineered Product Manufacturing | Qualification or Risk Reduction Activities |
| :---: | :---: | :---: |
| Recombinant insulin for injection | Cell culture medium additive | DMF cross reference (when possible or practical) <br> Certificate of analysis |
| Organ preservation fluid | Process biological fluid employed in tissue transport or processing |  |
| Human serum albumin for injection | Cell culture medium |  |
| Sterile fluids for injection | Process biological fluid employed in tissue transport, cell processing, purification | Assess lot-to-lot effect on process performance ${ }^{2}$ <br> Assess removal from final pro- |
| Implantable biomaterials (formed collagen, silicone, polyurethane constructs intended for surgical implantation) | Scaffolds, matrices for immobilized cellular cultivation | Stability assessment on AM as stored for use in manufacturing ${ }^{3}$ |
| Recombinant deoxyribonuclease for inhalation or injection | Process enzyme employed in viral vector manufacturing, stem cell processing |  |
| Antibiotics for injection ${ }^{4}$ | Cell culture medium and biopsy transport fluid additive to reduce risk of bacterial contamination |  |
| Injectable monoclonal antibodies | Immunologically targeting specific cell populations for selection or removal |  |
| Injectable cytokines | Cell culture medium |  |
| Vitamins for injection; defined nutrients, chemicals, or excipients intended for injection | Cell culture medium additive employed in cell expansion, controlled cellular differentiation/ activation step, or manufacture of a viral vector |  |
| IV bags, transfer sets and tubing, cryopreservation bags, syringes, needles | Storage vessels or container closure systems, closed aseptic transfer systems |  |

[^76]Table 2. AM Risk Tier 2
Low-Risk, Well Characterized Materials with Intended Use as AMs, Produced in Compliance with GMPs

| Example | Typical Use in Cell, Gene, or Tissue-Engineered Product Manufacturing | Qualification or Risk Reduction Activities |
| :---: | :---: | :---: |
| Recombinant growth factors, cytokines ${ }^{5}$ | Cell culture medium additive | DMF cross reference (when possible or practical) |
| Immunomagnetic beads | Immunomagnetic separation of cells |  |
| Human AB serum | Cell culture medium additive |  |
| Progesterone, estrogen,vitamins, purified chemicals (USP-grade) | Cell culture medium additives, induction agents, buffer components | Assess lot-to-lot effect on process performance ${ }^{6}$ |
| Sterile process buffers | Process biological fluid employed in tissue transport, cell processing, purification | Stability assessment on AM as stored for use in manufacturing ${ }^{7}$ |
| Biocompatible polymers, scaffolds, hydrogels | Scaffolds, matrices for immobilized cellular cultivation | When relevant, confirm certificate of analysis test results critical to product (could include functional assay) <br> Vendor audit |
| Proteolytic enzymes | Process enzyme |  |
| Tissue culture media | Cell culture medium additive |  |
| Monoclonal antibodies | Immunologically targeting specific cell populations for selection or removal |  |
| Density gradient media | Cell separation via centrifugation |  |

[^77]Table 3. AM Risk Tier 3
Moderate-Risk Materials Not Intended for Use as AMs (frequently produced for in vitro diagnostic use or reagent grade materials)


[^78]Table 4. AM Risk Tier 4
High-Risk Materials

|  | Typical Use in Cell, Gene, <br> or Tissue-Engineered <br> Product | Qualification or Risk <br> Reduction Activities |
| :--- | :--- | :--- |
| FBS | Cell culture medium additive | Same as in Table 3, plus |
| Animal-derived (including <br> human) extracts | Cell culture medium additive | Verify traceability to country of <br> origin <br> Assure country of origin is qua- <br> lified as safe with respect to <br> source-relevant animal diseases, |
| including TSE |  |  |\(\left|\begin{array}{l}Adventitious agent testing for <br>

animal source-relevant viruses\end{array}\right|\)

## PERFORMANCE TESTING

In cases where AMs are chosen for their ability to provide a particular biological function in producing the therapeutic product, performance testing becomes an essential component of their overall qualification. This is especially true when the AM plays a critical role in modulating a complex biochemical effect and has a large impact on product manufacturing yield, purity, or final product potency. These AMs tend to be complex substances or mixtures, are frequently biologically sourced, and can exhibit significant lot-to-lot variability. As a result, these AMs usually have no simple identity test, nor can they be easily characterized by physical or chemical tests. The development of well-defined performance assays for complex AMs will not only ensure process reproducibility and final product quality, but in many cases will satisfy the identity testing criteria in accordance with 21 CFR 211.84(d).

In some cases, the initial qualification of an AM for use in manufacturing should be the investigation of the effect of the amount of the AM on the desired response (increased yield, purity, or potency of the therapeutic product). The amount of the AM used in manufacturing should be chosen to consistently yield the desired effect while minimizing issues by removing the AM in subsequent processing steps. Such testing frequently assesses the important functional attribute expected of the AM in a scaled-down or simulated manufacturing process. Some examples follow:

- If an AM is added to the culture media because it promotes cellular proliferation or the secretion of a critical therapeutic agent, the assay could demonstrate that each lot of AMs produces the expected rate and amount of cellular proliferation or the expected level of secreted therapeutic agent.
- If a monoclonal antibody is used to purify a particular cell type, the new lot of monoclonal antibody could be shown to purify the cell population with the expected recovery and purity for the desired cell type.
- If a deoxyribonuclease is used to degrade cellular DNA, new lots could be tested for the ability of the deoxyribonuclease to degrade DNA.
- If a particular type of density gradient material is used to purify a vector or cell, new lots of the material used to make the gradient could be shown to purify the vector or cell to an acceptable level.
- If a plasmid or viral vector is used in the production of a gene therapy vector (e.g., helper function), new lots of the helper vector could be shown to produce the expected amounts of the gene therapy vector.
- If a cell therapy is produced in a hollow-fiber bioreactor, new lots of the bioreactor could be shown to produce the anticipated amount of cell product.

The actual assay used may well evolve as the manufacturing process is developed further and the critical relationships of the AM and the final product are better understood.

Because most performance testing yields relative results, it is often helpful to assay a new lot of AMs side by side with an approved lot of AMs or an official reference standard, if available. This simultaneous comparison helps to reduce the variability due to different lots of cells or vectors and will help discern variability associated with the different lots of AMs. If performance testing involves assays to demonstrate that the new lot of AMs does not affect the impurity profile of the final therapeutic product, either by generating new impurities or by increasing the level of existing impurities, it is helpful to assay both for the total level of impurities, as well as look for the presence of new impurities. An immunologically-based binding assay can typically assess only the total level of impurities. For example, a Western blot of the gene therapy product that is probed both with an-
tibodies to the product and antibodies to host cell proteins is useful for detecting new protein species and significant increases in the levels of host cell impurities. This initial qualification is enhanced by a performance assay that has a quantitative readout with a clear change in the signal when a significant change in the amount of AMs is introduced into the assay (e.g., dose response). A threshold-type response (i.e., there are two levels of response to the AM and neither large changes in an AM below a certain dose nor above a certain dose change the response) can make it more difficult to select a concentration of AM that consistently results in the desired effect and minimizes the residual levels of the AM in the final therapeutic product.

## ANCILLARY MATERIALS RESIDUAL LEVEL

## ASSESSMENT AND REMOVAL

AMs are not intended to be present in the final dosage form in cell, gene, and tissue-engineered products. Their presence in the final product could lead to undesired effects in the recipient or have a detrimental effect on product potency. Undesired effects in humans include direct toxicity of the AM or an unwanted immunogenic response. Some examples include the following:

- In the generation of a tumor vaccine using a patient's tumor biopsy as the starting material, a chemical entity is introduced to denature the cell surface proteins and tumor antigens to enhance their antigenicity. The chemical entity is known to be highly toxic.
- Antibiotics may be added to a transport solution for human cells to address microbial contamination issues associated with the procurement procedure. Residual levels of the antibiotic may affect the proliferative capacity of the final engineered cellular product. Residual antibiotics could also cause an anaphylactic response in some individuals.
- FBS, employed in the cultivation of an engineered human skin graft, may cause the development of a humoral antibody response directed against bovine proteins.
- Aggregated mouse immunoglobulin, a trace impurity in a purified preparation of mouse monoclonal antibody used to target a cell population for immunoselection, may be immunogenic.
- A cytokine, employed as an immunomodulator in the generation of a gene-modified autologous tumor vaccine product, may elicit a severe reaction in the recipient.
- Cholera toxin, employed as part of a cell culture medium for a cell therapy product intended for intravenous administration, will be highly toxic to the recipient if it is not removed during processing.

These risks can be mitigated through the design of processes to include steps to adequately remove the AM through dilution, separation, or inactivation, as well as the development of analytical detection assays to assess the AM levels during processing and in the final therapeutic product. Assessment and removal strategies for residual AMs should be considered in the early phases of process development. There are two different approaches for assessing residual AM levels in the final therapeutic product: (1) Validation studies can demonstrate that the process is capable of removing more of the AM than would be present in a worst-case scenario. (2) The residual levels of an AM can be measured for each lot at an appropriate step in the manufacturing process.
Validation of an AM removal is often best performed by spiking the impure product with "worst case" or higher levels of the AM and showing the purification process is capable of removing the AM to "undetectable levels". Clearance factors can then be generated for each purification step in a manner analogous to that done in viral clearance
studies. When designing the validation studies, the following three considerations should be included: (1) The assay should be able to accurately quantitate the AM in each sample matrix. (2) If the validation is conducted at a scale smaller than that used for routine lot production, the comparability of this smaller scale process to the full scale process needs to be demonstrated. This usually means that the smaller scale process is operated using the same critical parameters as the full scale process with the product generated at each step having a similar purity and yield. (3) As with any spiking study, one has to demonstrate that the additional, higher level of AM has not affected the purification process. If the second approach of measuring residual levels of the AM in each lot is used, the specification for the maximum amount of AM in the final therapeutic product is based on the amount of the AM in the lots used in toxicological or clinical studies or known toxicological data.

The development of sensitive and reproducible analytical assays for AMs is another important component of a risk reduction approach. Two types of assays are useful in assessing the levels of residual AM impurity: a limit test and a quantitative test. Either test should be accurate, precise, robust, and have a low limit of detection. Assays for residual AMs may be performed on the product before it is formulated (e.g., on the drug substance) to avoid any interference of the components used in the formulation with the assay for residual AMs or in the final drug product. Spike-recovery controls are often included in such assays to demonstrate that the sample matrix does not inhibit the detection of the AM. Preferably, assays should be designed to detect all forms of AMs including aggregates, fragments, or conjugates. Aggregated protein has been shown to be particularly immunogenic.

Immunoassays such as ELISA are most commonly used to assess residual levels of AMs. An ELISA for bovine serum albumin (BSA) has been used to assess residual levels of FBS. Polymerase chain reaction (PCR) technology has been employed to assess residual levels of host cell DNA. Labeling cells with ${ }^{3} \mathrm{H}$ thymidine or performing PCR for a feeder cell-specific gene sequence are two ways to assess for residual levels of feeder cells. If "wash out" of the AM is achieved by exhaustive dilution associated with further processing activities, it may be useful to calculate the dilution factor for the AM during this processing. In some cases, this is sufficient to ensure that the AM has been reduced to safe levels for early clinical development. Data should be obtained later in clinical development to confirm the wash out of the AM at the expected step(s). This approach is particularly useful when there is pre-existing knowledge of the therapeutic levels and toxicity of the AM. In other cases, information regarding the safety and tolerability of the AM should be collected (in preclinical toxicology studies or later with human clinical studies) in order to determine the safe or nontoxic levels that must be achieved. These data may be needed even for an AM that is approved for use for therapeutic purposes if it is being used in a manner inconsistent with its intended use or labeling or if the route of administration or dosage level of the AM may present risks not previously encountered or considered.

## CONCLUSION

While many types of AMs are used during the manufacture of cell, gene, and tissue-engineered products, they have received less emphasis than the final products. However, the importance of AM quality to the quality of the final product cannot be overstated. Good quality AMs should perform as intended in a consistent manner, batch-to-batch, if they are carefully selected and appropriately used. AMs of
insufficient quality will affect the quality and the effectiveness of the final product and endanger the health of patients. Thus, implementing an AM qualification program that addresses the risks associated with the AM, the stage of manufacture at which it is used, and the amount of the AM used during manufacture will ensure the safety and effectiveness of the final product.

## APPENDIX

AMs used in cell, gene, and tissue-engineered products will be regulated in the context of the manufacturing process of the cell, gene, and tissue-engineered products. Certain AMs may already be approved for uses other than for cell, gene, and tissue-engineered product manufacture. It is preferable to source AMs that are approved therapeutic products when they are available because they are wellcharacterized with an established toxicological profile and are manufactured according to controlled and documented procedures. The following list of documents should provide relevant regulatory guidance and a description of best practices in product and process development, manufacturing, quality control, and quality assurance:
Biological Reactivity Tests, In Vitro $\langle 87\rangle$
Biological Reactivity Tests, In Vivo $\langle 88\rangle$
Biotechnology-Derived Articles $\langle 1045\rangle$
Cell and Gene Therapy Products $\langle 1046\rangle$
Biotechnology-Derived Articles-Tests $\langle 1047\rangle$
21 CFR 211 Subpart E, 211.80 through 211.94 and 211.101
21 CFR 312
21 CFR 314

21 CFR 801.109 (b) (1)
21 CFR 807.81 through 21 CFR 807.97
21 CFR 812
21 CFR 814
FDA Center for Biologics Evaluation (CBER) "Draft Guidance for Monoclonal Antibodies Used as Reagents in Drug Manufacturing" (1999)

FDA Center for Biologics Evaluation (CBER) "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals" (1993)

FDA Center for Devices and Radiological Health (CDRH) "Class II Special Controls Guidance Document: Tissue Culture Media for Human ex vivo Tissue and Cell Culture Processing Applications; Final Guidance for Industry and FDA Reviewers" (May 16, 2001)

CDRH Blue Book Memorandum G95-1
ISO 10993-1: 1997 "Biological Evaluation of Medical Devices-Part 1: Evaluation and Testing"

International Conference on Harmonization (ICH) Q5A "Guidance for Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human and Animal Origin"

International Conference on Harmonization (ICH) Q5D "Guidance on Quality of Biotechnological/Biological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products"

Public Health Service Guideline on Infectious Diseases Issues in Xenotransplantation (October 18, 2000) $\mathbf{\Delta U S P 2 8}^{\text {© }}$

## REAGENTS, INDICATORS, AND SOLUTIONS

## Reagent Specifications

## Briefing

Acetal. This new reagent is used as a component of Standard solution $C$ in the test for Volatile impurities under the harmonized monograph for Alcohol, which appears in the Harmonization section of this PF.
(HDQ: M. Marques) RTS-40773-1

## Add the following:

${ }^{\boldsymbol{4}}$ Acetal, $\mathrm{C}_{6} \mathrm{H}_{14} \mathrm{O}_{2}$ - 118.2-Use a suitable grade. $\Delta$ USP28

## BriEfing

Bacterial Alkaline Protease Preparation. This new reagent is specified in the test for Content of all-E-lycopene, 5Z-lycopene, and related compounds, and the test for Content of lycopene under Lycopene Preparation, appearing elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-40413-2

## Add the following:

${ }^{\text {4 }}$ Bacterial Alkaline Protease Preparation-Use a suitable grade. ${ }^{116}{ }_{\Delta U S P 28}$

## Briefing

Benzamidine Hydrochloride Hydrate. This new reagent is used in the test for Fibroblast growth factor-2 content in the proposed new monograph for Small Intestinal Submucosa Wound Matrix, appearing elsewhere in this number of $P F$.
(HDQ: M. Marques) $\quad$ RTS-40758-2

## Add the following:

${ }^{\text {© }}$ Benzamidine Hydrochloride Hydrate, $\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{~N}_{2}$. $\mathrm{HCl}-156.6$ [1670-14-0]—White to off-white powder. Use a suitable grade. ${ }^{10}{ }_{\Delta U S P 28}$

## BRIEFING

Bovine Collagen. This new reagent is used in the test for Glycosaminoglycan content in the proposed new monograph for Small Intestinal Submucosa Wound Matrix, appearing elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-40758-4

## Add the following:

${ }^{\Delta}$ Bovine Collagen-Use a suitable grade that contains less than $1 \mu \mathrm{~g}$ glycosaminoglycan per $\mathrm{mg} .{ }^{10}{ }_{\Delta}{ }^{\text {USP28 }}$

## BRIEFING

Rat Tail Collagen. This new reagent is used in the Bioactivity test in the proposed new monograph for Small Intestinal Submucosa Wound Matrix, appearing elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-40758-12

## Add the following:

${ }^{\boldsymbol{\Delta}}$ Rat Tail Collagen-Use a suitable grade. ${ }^{102} \mathbf{\Delta U S P 2 8}^{\text {— }}$

## BRIEFING

Cyclohexylmethanol. This new reagent is used in the preparation of the Standard solutions in the test for Related compounds in the draft monograph for Benzyl Alcohol, which appears in the Harmonization section of this $P F$.
(HDQ: M. Marques) RTS-40773-8

## Add the following:

${ }^{\Delta}$ Cyclohexylmethanol, $\mathrm{C}_{7} \mathrm{H}_{14} \mathrm{O}-\mathbf{1 1 4 . 1 9}$ —Use a suitable grade. $\triangle U S P 28$

## Briefing

Dicyclohexyl. This new reagent is used in the preparation of the Dicyclohexyl solution in the test for Related compounds in the draft monograph for Benzyl Alcohol, which appears in the Harmonization section of this PF.

$$
\text { (HDQ: M. Marques) } \quad \text { RTS }-40773-8
$$

## Add the following:

$$
\begin{aligned}
& \mathbf{\Delta} \text { Dicyclohexyl, } \mathrm{C}_{12} \mathrm{H}_{22}-\mathbf{1 6 6 . 3 1} \text { —Use a suitable } \\
& \text { grade. } \Delta U S P 28
\end{aligned}
$$

## BRIEFING

1,9-Dimethyl-Methylene Blue. This new reagent is used in the test for Glycosaminoglycan content in the proposed new monograph for Small Intestinal Submucosa Wound Matrix, appearing elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-40758-6

## Add the following:

© $\mathbf{1}$,9-Dimethyl-Methylene Blue, $\mathrm{C}_{36} \mathrm{H}_{46} \mathrm{Cl}_{4} \mathrm{~N}_{6} \mathrm{OS}_{2} \mathrm{Zn}$ -
850.1 [23481-50-7]—Dark green powder. Use a suitable grade. ${ }^{10}{ }_{\Delta U S P 28}$

## BRIEFING

3-(Dodecyldimethylammonio)propanesulfonate. This new reagent is used to prepare the Medium in the Dissolution test under Mephobarbital Tablets, appearing elsewhere in this number of $P F$.

## Add the following:

> s3-(Dodecyldimethylammonio)propanesulfonate (Lauryl sulfobetaine, $N, N$-dimethyl- $N$-dodecyl-N-(3-sulfopropyl) ammonium betaine), $\mathrm{C}_{17} \mathrm{H}_{37} \mathrm{NO}_{3} \mathrm{~S}-\mathbf{3 3 5 . 5 4}$
> [14933-08-5]-Use a suitable grade. $\mathbf{\Delta U S P 2 8}$

## BRIEFING

Ethylbenzene. This new reagent is used in the preparation of the Ethylbenzene solution in the test for Related compounds in the draft monograph for Benzyl Alcohol, which appears in the Harmonization section of this $P F$.
(HDQ: M. Marques) RTS-40773-8

## Add the following:

©thylbenzene, $\mathrm{C}_{8} \mathrm{H}_{10}-\mathbf{1 0 6 . 1 7}-$ Not less than $99.5 \%$. $\mathbf{\Delta S P 2 8}$

## Briefing

Fibroblast Growth Factor-2. This new reagent is used in the Bioactivity test in the proposed new monograph for Small Intestinal Submucosa Wound Matrix, appearing elsewhere in this number of $P F$.
(HDQ: M. Marques) $\quad$ RTS-40758-8

## Add the following:

©Fibroblast Growth Factor-2—Use a suitable grade. ${ }^{114}{ }_{\Delta U S P 28}$

## Briefing

Lauryl Dimethyl Amine Oxide. This new reagent is specified in the Dissolution Medium in the monograph for Isradipine Capsules, which appears elsewhere in this number of $P F$.

$$
\text { (HDQ: M. Marques) } \quad \text { RTS-40548-11 }
$$

## Add the following:

${ }^{4}$ Lauryl Dimethyl Amine Oxide (N,N-Dimethyldodecy-lamine-N-oxide), $\mathrm{C}_{14} \mathrm{H}_{31} \mathrm{NO}$, [1643-20-5]-229.41—Use a suitable grade. ${ }^{115}{ }_{\Delta U S P 28}$

## Briefing

Methanol, Aldehyde-Free. This new reagent is used in the section Suitability for determination of aldehydes under the reagent methylbenzothiazolone hydrazone hydrochloride that is specified in the test for Aldehyde in the draft monograph for Ethylcellulose, which appears in the Harmonization section of this $P F$.
(HDQ: M. Marques) RTS-40768-1

## Add the following:

${ }^{\Delta}$ Methanol, Aldehyde-Free, $\mathrm{CH}_{3} \mathrm{OH}$ - 32.04-Dissolve 25 g of iodine in 1 L of methanol and pour the solution, with constant stirring, into 400 mL of 1 N sodium hydroxide. Add 150 mL of water, and allow to stand for 16 hours. Filter, and boil under a reflux condenser until the odor of iodoform disappears. Distill the solution by fractional distillation. It contains not more than $0.001 \%$ of aldehydes and ketones. $\Delta$ USP28

## BRIEFING

Methylbenzothiazolone Hydrazone Hydrochloride, page 1599 of PF 28(5) [Sept.-Oct. 2002]. This new reagent is used as a specified component of the Acetaldehyde test in the draft monograph for Ethylcellulose, which appears in the Harmonization section of this $P F$.
(HDQ: M. Marques) RTS-40768-1

## Add the following:

${ }^{4}$ Methylbenzothiazolone Hydrazone Hydrochloride, $\mathrm{C}_{8} \mathrm{H}_{10} \mathrm{CIN}_{3} \mathrm{~S} \cdot \mathrm{H}_{2} \mathrm{O}-\mathbf{2 3 3} .7$ [38894-11-0] Use a stitable grade. An almost white or yellowish, crystalline powder.

Melting point $\langle 741\rangle$ : about $270^{\circ}$.

Suitability for determination of adehydes-To 2 mL of aldehyde-free methanol add $60 \mu \mathrm{~L}$ of a 1 g per L solution of propionaldehyde in aldehyde-free methanol and 5 mL of a 4 g per L solution of methylbenzothiazolone hydrazone hydrochloride. Mix, and allow to stand for 30 minutes. Prepare a blank omitting the propionaldehyde solution. Add 25.0 mL of a 2 g per L solution of ferric chloride to the test solution and to the blank, dilute with acetone to 100.0 mL , and mix. The absorbance of the test solution, measured at 660 nm using the blank as compensation liquid, is not less than 0.62. UUSP28 $^{\text {. }}$

## BRIEFING

4-Methylpentan-2-ol. This new reagent is used as a component of Test solution B in the test for Volatile impurities under the harmonized monograph for Alcohol, which appears in the Harmonization section of this PF.
(HDQ: M. Marques) RTS-40773-1

## Add the following:

44-Methylpentan-2-ol, $\mathrm{C}_{6} \mathrm{H}_{14} \mathrm{O}-\mathbf{1 0 2} .2$ - Use a suitable grade. $\triangle U S P 28$

## BRIEFING

Oxygen-Helium Certified Standard, USP 27 page 2699. The reagent Oxygen-Helium Certified Standard is being proposed for deletion. It is being replaced by the new USP Oxygen-Helium RS, appearing elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-40629-10

## Delete the following:

${ }^{4}$ Oxygen-Helium-Certified Standard- A mixture of 1.0\% exygen in industrial grade helium. It is available from mest suppliers of specialty fostes. $\mathbf{A U S P 2 8}$

## BRIEFING

Phenylmethylsulfonyl Fluoride. This new reagent is used in the test for Fibroblast growth factor- 2 content in the proposed new monograph for Small Intestinal Submucosa Wound Matrix, appearing elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-40758-10

## Add the following:

${ }^{\text {© }}$ Phenylmethylsulfonyl Fluoride, $\mathrm{C}_{7} \mathrm{H}_{7} \mathrm{FO}_{2} \mathrm{~S}-\mathbf{1 7 4 . 2}$ [329-98-6]-White to faint yellow powder. Use a suitable grade. ${ }^{10}{ }_{\Delta U S P 28}$

## BRIEFING

Propionaldehyde. This new reagent is used to prepare the reagent, methylbenzotiazolone hydrazone hydrochloride, specified in the test for Aldehyde in the Ethylcellulose monograph, which appears in the Harmonization section of this PF.
(HDQ: M. Marques) RTS-40768-1

## Add the following:

${ }^{\wedge}$ Propionaldehyde, $\mathrm{C}_{3} \mathrm{H}_{6} \mathrm{O}-\mathbf{5 8 . 0 8}$-Use a suitable grade. $\triangle$ USP28

## BRIEFING

Sodium 1-Heptanesulfonate, Monohydrate. This new reagent is used in the test for Chromatographic purity and in the Assay under Homatropine Hydrobromide, which appears elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS—37240-2

## Add the following:

${ }^{\text {4 }}$ Sodium 1-Heptanesulfonate Monohydrate, $\mathrm{C}_{7} \mathrm{H}_{15}$ $\mathrm{NaO}_{3} \mathrm{~S} \cdot \mathrm{H}_{2} \mathrm{O}-\mathbf{2 2 0 . 2 6}$ [22767-50-6]—Use a suitable grade. $\Delta$ USP28

## Briefing

Tritirachium Album Proteinase K. This new reagent is used in the test for Glycosaminoglycan content in the proposed new monograph for Small Intestinal Submucosa Wound Matrix, appearing elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-40758-14

## Add the following:

${ }^{\Delta}$ Tritirachium Album Proteinase K—Use a suitable grade. ${ }^{113} \mathbf{\Delta U S P 2 8}^{\text {U }}$

## Briefing

Tropine. This new reagent is used in the test for Limit of tropine under Homatropine Hydrobromide, which appears elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS—37240-3

## Add the following:

${ }^{\Delta}$ Tropine, $\mathrm{C}_{8} \mathrm{H}_{15} \mathrm{NO}-\mathbf{1 4 1 . 2}$ [120-29-6]-Use a suitable grade. $\mathbf{\Delta S P 2 8}$

## Briefing

Reagent Footnotes, USP 27 page 2738, page 1133 of $P F$ 26(4) [July-Aug. 2000], page 3373 of $P F 27(6)$ [Nov.-Dec. 2001], page 266 of $P F$ 29(1) [Jan.-Feb. 2003], page 508 of $P F$ 29(2) [Mar.-Apr. 2003], page 1257 of PF 29(4) [July-Aug. 2003], and page 317 of PF 30(1) [Jan.-Feb. 2004]. The following new reagents reference Footnote 10 : Bovine collagen; Benzamidine hydrochloride hydrate; 1,9-Dimethyl-methylene blue; and Phenylmethylsulfonyl fluoride. The new reagent Rat tail collagen references Footnote 102 . Footnotes $113,114,115$, and 116 are added to provide information regarding the commercial availabil-
ity of Tritirachium album proteinase K, Fibroblast growth factor-2, Lauryl dimethyl amine oxide, and Bacterial alkaline protease preparation, respectively.
(HDQ: M. Marques) RTS-37456-2

## Change to read:

${ }^{10}$ A suitable grade is available from Regis Chemieal Co., 1101 N . Franklin-St., Chiengo, H60610.

■Sigma-Aldrich, www.sigma-aldrich.com.■1S (USP27)

## Add the following:

■102 A suitable grade is available from BD Biosciences,
Elontech, 1020-East Meadow Cirele, Palo Alto, CA 94303-4230. www.bdbiosciences.com.■1S (USP27)

## Add the following:

$\boldsymbol{\Delta}_{113}$ A suitable grade can be obtained from Qiagen, Inc., www.qiagen.com. $\mathbf{U S P 2 8}$

## Add the following:

$\boldsymbol{\Delta}_{114}$ A suitable grade can be obtained from Roche Diagnostics Corporation, www.roche-diagnostics.com. $\Delta$ USP28

## Add the following:

$\boldsymbol{\Delta}_{115}$ A suitable grade is available from Fluka, catalog number 40234, www.sigma-aldrich.com. $\Delta$ USP28

## Add the following:

$\boldsymbol{\Delta}_{116}$ A suitable grade is commercially available as "Protext
6L" from Genencor, www.genencor.com. $\Delta$ USP28

## REFERENCE TABLES

## BRIEFING

Container Specifications for Capsules and Tablets, USP 27 page 2741, and page 2055 of $P F$ 29(6) [Nov.-Dec. 2003].
(HDQ) RTS-40598-1; 40774-1

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the Packaging and storage requirements set forth in the individual monographs. It lists the capsules and tablets that are, or will be, official in the United States Pharmacopeia and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

| Monograph Title | Container <br> Specification |
| :--- | :--- |
| Change to read: | W |
| Acepromazine Maleate Tablets | LT, |
|  | LR (USP27) |

## Change to read:

| Acetaminophen, Aspirin, and Caffeine Tablets | W |
| :---: | :---: |
|  | $\mathrm{T}_{\mathbf{m}_{1 S}(\text { USP27) }}$ |
| Change to read: |  |
| Acetazolamide Tablets | W |
|  | $\mathrm{T}_{\mathbf{m}_{1 S}(\text { USP27) }}$ |

Change to read:
Acetohexamide Tablets
H
${ }^{-1}{ }^{\text {2S }}$ (USP27)
Add the following:

| - Alendronate Sodium Tablets | $\mathrm{T}_{\mathbf{L} 2 \mathrm{~S} \text { (USP27) }}$ |
| :---: | :---: |
| Change to read: |  |
|  |  |
|  | $\mathrm{T}_{\mathbf{M} 2 \mathrm{~S}}$ (USP27) |

Change to read:
Alumina and Magnesia Tablets


| Monograph Title | Container <br> Specification | Monograph Title | Container <br> Specification |
| :---: | :---: | :---: | :---: |
| Change to read: |  |  |  |
| Alumina, Magnesia, and Calcium Carbonate Tablets | W | Add the following: |  |
|  | $\mathrm{T}^{\text {m2S }}$ (USP27) | -Irbesartan Tablets | $\mathrm{W}_{\mathbf{M 2 S}}$ (USP27) |
| Change to read: <br> Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets |  | Add the following: |  |
|  | W $\mathbf{D}^{\mathrm{T}} \mathbf{m S}_{2}\left(U S P_{27}\right)$ | -Irbesartan and Hydrochlorothiazide |  |
| Add the following: |  | Tablets | $W_{\text {2S (USP27) }}$ |
| -Benazepril Tablets | $W_{\text {M2S (USP27) }}$ | Add the following: |  |
| Add the following: |  | -Isosorbide Mononitrate Tablets | $\mathrm{T}_{\text {2S }}^{\text {(USP27) }}$ |
| -Bisoprolol Fumarate Tablets | T, LR $\mathrm{MIS}_{\text {(USP27) }}$ | Add the following: |  |
| Add the following: |  | -Isosorbide Mononitrate Tablets, |  |
| -Bisoprolol Fumarate and Hydrochlorothiazide Tablets |  | Extended-Release | $\mathrm{T}_{\text {2S }}$ (USP27) |
|  | $\mathrm{W}_{\text {IS }}$ (USP27) | Add the following: |  |
| Add the following: |  | - Isradipine Capsules | $\mathrm{T}_{\text {L2S (USP27) }}$ |
| -Cefaclor Tablets | $\mathrm{T}_{\text {LSS (USP27) }}$ | Add the following: |  |
| Add the following: |  | -Loratadine Tablets | $\mathrm{T}_{\text {IS }}^{\text {(USP27) }}$ |
| -Clarithromycin Tablets, Extended- |  | Add the following: |  |
| Release | $\mathrm{W}_{\text {(2S }}$ (USP27) | -Metformin Hydrochloride Tablets | $\mathrm{T}_{\text {2S }}$ (USP27) |
| Add the following: |  | Add the following: |  |
| -Black Cohosh Tablets | T, LR $\mathrm{m}_{\text {2S }}$ (USP27) | -Metolazone Tablets | T, LR $\mathbf{\\|} 2$ (USP27) |
| Add the following: |  | Add the following: |  |
| - Desogestrel and Ethinyl Estradiol |  | -Misoprostol Tablets | $\mathrm{T}_{\text {2S }}$ (USP27) |
| Tablets | $\mathrm{W}_{\mathbf{M 2 S}}$ (USP27) | Add the following: |  |
| Add the following: |  | -Naratriptan Tablets | $\mathrm{T}_{\text {IS }}^{\text {(USP27) }}$ |
| -Fluoxetine Capsules, Delayed-Release | $\mathrm{T}_{\text {2S }}$ (USP27) | Add the following: |  |
| Add the following: |  | -Norgestimate and Ethinyl Estradiol |  |
| - Gabapentin Capsules | $\mathrm{W}_{\text {-2S (USP27) }}$ | Tablets | $\mathrm{W}_{\mathbf{1 2 S} \text { (USP27) }}$ |
| Add the following: |  | Add the following: |  |
| - Ginkgo Capsules | T, LR $\mathbf{m}_{\text {2S }}$ (USP27) | -Oxaprozin Tablets | $\mathrm{T}, \mathrm{LR}_{\mathbf{1 2 S}}{ }_{\text {(USP27) }}$ |
| Add the following: |  | Add the following: |  |
| - Ginkgo Tablets |  | -Paroxetine Hydrochloride Tablets | $W_{\text {L2S (USP27) }}$ |
| Change to read: <br> Asian Ginseng Capsules |  | Add the following: |  |
|  | T, ŁR | -Quinapril Tablets | $W_{\text {2S (USP27) }}$ |
|  |  | Add the following: |  |
| Add the following: |  |  |  |
| ${ }^{\text {A }}$ Indinavir Sulfate Capsules | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ | -Rimantadine Hydrochloride Tablets | P27) |


| Monograph Title | Container <br> Specification |
| :--- | :--- |
| Add the following: |  |
| -Valsartan Capsules | ${\mathrm{T}, \mathrm{LR}_{\mathbf{2 S}} \text { (USP27) }}^{\text {Add the following: }}$ |
| -Valsartan and Hydrochlorothiazide | $\mathrm{W}_{\mathbf{2 S}}$ (USP27) |
| Tablets |  |

## BRIEFING

Description and Relative Solubility of USP and NF Articles, USP 27 page 2747, page 5310 of $P F 23(6)$ [Nov.-Dec. 1997], page 7017 of $P F 24(5)$ [Sept.-Oct. 1998], page 8282 of $P F 25(3)$ [MayJune 1999], page 8589 of $P F$ 25(4) [July-Aug. 1999], page 8917 of PF 25(5) [Sept.-Oct. 1999], page 9254 of PF 25(6) [Nov.-Dec. 1999], page 837 of $P F$ 26(3) [May-June 2000], page 1135 of $P F$ 26(4) [July-Aug. 2000], page 1385 of $P F$ 26(5) [Sept.-Oct. 2000], page 1907 of PF 27(1) [Jan.-Feb. 2001], page 2281 of $P F$ 27(2) [Mar.-Apr. 2001], page 2839 of $P F$ 27(4) [July-Aug. 2001], page 3374 of PF 27(6) [Nov.-Dec. 2001], page 554 of $P F$ 28(2) [Mar.Apr. 2002], page 1236 of $P F$ 28(4) [July-Aug. 2002], page 1542 of $P F$ 28(5) [Sept.-Oct. 2002], page 1953 of $P F$ 28(6) [Nov.-Dec. 2002], page 266 of $P F$ 29(1) [Jan.-Feb. 2003], page 509 of $P F$ 29(2) [Mar.-Apr. 2003], page 812 of $P F$ 29(3) [May-June 2003], page 1262 of $P F$ 29(4) [July-Aug. 2003], page 1684 of PF 29(5) [Sept.-Oct. 2003], page 2057 of PF 29(6) [Nov.-Dec. 2003], and page 317 of $P F 30$ (1) [Jan.-Feb. 2004].
(HDQ) RTS—37240-1; 40209-1; 40209-2; 40209-3; 402094; 40209-5; 40773-2; 40773-4; 40773-6; 40814-1; 40814-2; 40862-1; 40862-2; 40864-1

## Add the following:

${ }^{\Delta}$ Acesulfame Potassium: A white, crystalline powder or colorless crystals. Soluble in water; very slightly soluble in acetone and in alcohol. NF category: Sweetening agent. $\Delta$ USP28

## Add the following:

${ }^{4}$ Adipic Acid: A white, crystalline powder. Freely soluble in alcohol and in methanol; soluble in boiling water and in acetone; slightly soluble in water. NF category: Buffering agent. $\Delta U S P 28$

## Add the following:

${ }^{\Delta}$ Cellulose Acetate Butyrate:- Cellaburate: Fine white or almost white powder or granules. Available in a range of viscosities, acetyl and butyl contents. Slightly hygroscopic; soluble in acetone, in methylene chloride, in pyridine, and in dimethyl sulfoxide; practically insoluble in water and in alcohol. NF category: Coating agent; polymer membranes. $\triangle$ USP28

## Delete the following:

Citric Acid: Colerless, translueent erystals, or white, granular to fine, erystalline pewder. The hydreus formisefflorescent in dry air. The anhydreus form melts at abeut $153^{\circ}$, with decempesition. Very soluble in water; freely soluble in aleehel; very slightly selut ble in ether. NF eategory: Acidifying agent; buffering agent._USP28

## Add the following:

${ }^{\wedge}$ Anhydrous Citric Acid: Colorless, translucent crystals, or white, granular to fine, crystalline powder. in dry air. Melts at about $153^{\circ}$, with decomposition. Very soluble in water; freely soluble in alcohol; very slightly soluble in ether. NF category: Acidifying agent; buffering agent. $\Delta$ USP28

## Add the following:

${ }^{\Delta}$ Citric Acid Monohydrate: Colorless, translucent crystals, or white, granular to fine, crystalline powder. Efflorescent in dry air. Very soluble in water; freely soluble in alcohol; very slightly soluble in ether. NF category: Acidifying agent; buffering agent. $\triangle$ USP28

## Add the following:

${ }^{\boldsymbol{4}}$ Galactose: A white, crystalline or finely granulated powder. Soluble in water; very slightly soluble in alcohol.
NF category: Sweetening agent._USP28

## Change to read:

Homatropine Hydrobromide: White crystals, or white, crystalline powder. Is affected by light.
${ }^{4}$ Slowly darkens on exposure to light. $\triangle$ USP28
Freely soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; insoluble in ether.
${ }^{\mathbf{4}}$ Melts between $214^{\circ}$ and $217^{\circ}$, with slight decomposition. $\mathbf{\Delta}$ USP28

## Add the following:

${ }^{\Delta}$ Maleic Acid: White, crystalline powder. Freely soluble in water and in alcohol; sparingly soluble in ether. _USP28 $^{\text {U }}$

## Add the following:

${ }^{4}$ Sodium Sulfite: Colorless crystals. Freely soluble in water, very slightly soluble in alcohol. NF category: Antioxidant. $\triangle$ USP28

## Add the following:

${ }^{4}$ Sodium Tartrate: Transparent, colorless, odorless crystals. Freely soluble in water; insoluble in alcohol. NF category: Sequestering agent. $\triangle$ USP28

## Add the following:

${ }^{\Delta}$ Corn Starch: Irregular, angular, white masses or fine powder. Is odorless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. NF category: Tablet and/or capsule diluent; tablet disintegrant; tablet binder; suspending and/or viscosity-increasing agent. $\Delta$ USP28

## Add the following:

${ }^{\Delta}$ Potato Starch: Irregular, angular, white masses or fine powder. Is odorless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. NF category: Tablet and/or capsule diluent; tablet disintegrant; tablet binder; suspending and/or viscosity-increasing agent._ USSP28 $^{\text {. }}$

## Add the following:

${ }^{4}$ Wheat Starch: Irregular, angular, white masses or fine powder. Is odorless and has a slight, characteristic taste. Insoluble in cold water and in alcohol. NF category: Tablet and/or capsule diluent; tablet disintegrant; tablet binder; suspending and/or viscosity-increasing agent. $\triangle$ USP28

## Add the following:

${ }^{4}$ Succinic Acid: White, odorless crystals. Soluble in water, in alcohol, and in glycerin; freely soluble in boiling water. NF category: Neutralizing agent. $\triangle U S P 28$

Items from Earlier Numbers of PF that Have Not Yet Appeared in a Supplement, and are Therefore Candidates for Subsequent Supplements.

## GENERAL NOTICES AND REQUIREMENTS

"Official" and "Official Articles"-See PF Vol. 29 No. 6, page 1823.

Significant Figures and Tolerances-See PF Vol. 29 No. 6, page 1824.

General Chapters-See PF Vol. 29 No. 6, page 1825.
Ingredients and Processes-See PF Vol. 29 No. 6, page 1825.
Tests and Assays-See PF Vol. 29 No. 6, page 1826.
Preservation, Packaging, Storage, and Labeling-See PF Vol. 29 No. 6, page 1829.

## USP MONOGRAPHS

Acebutolol Hydrochloride Capsules-See PF Vol. 27 No. 1, page 1743.

Acepromazine Maleate-See PF Vol. 29 No. 6, page 1832.
Acepromazine Maleate Injection-See PF Vol. 27 No. 3, page 2494.

Acepromazine Maleate Tablets-See PF Vol. 27 No. 3, page 2494.
Acetaminophen-See PF Vol. 27 No. 3, page 2494.
Acetaminophen Capsules-See PF Vol. 27 No. 3, page 2494.
Acetaminophen for Effervescent Oral Solution-See PF Vol. 27 No. 3, page 2495.
Acetaminophen Oral Solution-See PF Vol. 30 No. 1, page 40.
Acetaminophen Oral Suspension-See PF Vol. 30 No. 1, page 40.
Acetaminophen Suppositories-See PF Vol. 27 No. 3, page 2495.
Acetaminophen Tablets-See PF Vol. 27 No. 3, page 2495.
Acetaminophen and Aspirin Tablets-See PF Vol. 30 No. 1, page 41.

Acetaminophen, Aspirin, and Caffeine Tablets-See PF Vol. 27 No. 3, page 2495.
Capsules Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 43.
Oral Powder Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 44.
Oral Solution Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 44.
Tablets Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine-See PF Vol. 30 No. 1, page 42.
Tablets Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 44.
Acetaminophen and Codeine Phosphate Capsules-See PF Vol. 30 No. 1, page 45.
Acetaminophen and Codeine Phosphate Oral Solution-See PF Vol. 30 No. 1, page 46.
Acetaminophen and Codeine Phosphate Oral Suspension-See PF Vol. 30 No. 1, page 46.
Acetaminophen and Codeine Phosphate Tablets-See PF Vol. 29 No. 3, page 602.
Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solu-tion-See PF Vol. 30 No. 1, page 46.
Acetaminophen and Diphenhydramine Citrate Tablets-See PF Vol. 30 No. 1, page 47.
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets-See PF Vol. 30 No. 1, page 47.
Acetaminophen and Pseudoephedrine Hydrochloride TabletsSee PF Vol. 30 No. 1, page 48.
Acetazolamide-See PF Vol. 27 No. 3, page 2500.

Acetazolamide for Injection-See PF Vol. 27 No. 3, page 2500.
Acetazolamide Tablets-See PF Vol. 27 No. 3, page 2501.
Glacial Acetic Acid-See PF Vol. 27 No. 3, page 2501.
Acetic Acid Irrigation-See PF Vol. 27 No. 3, page 2501.
Acetic Acid Otic Solution-See PF Vol. 27 No. 3, page 2501.
Acetohexamide Tablets-See PF Vol. 27 No. 3, page 2501.
Acetohydroxamic Acid Tablets-See PF Vol. 30 No. 1, page 49.
Acetylcholine Chloride-See PF Vol. 27 No. 3, page 2502.
Acetylcholine Chloride for Ophthalmic Solution-See PF Vol. 27 No. 3, page 2502.
Acetylcysteine-See PF Vol. 27 No. 3, page 2503.
Acetylcysteine Solution-See PF Vol. 27 No. 3, page 2503.
Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solu-tion-See PF Vol. 27 No. 3, page 2503.
Acyclovir-See PF Vol. 29 No. 6, page 1833.
Acyclovir Capsules-See PF Vol. 29 No. 3, page 602.
Acyclovir for Injection-See PF Vol. 29 No. 3, page 602.
Acyclovir Ointment-See PF Vol. 29 No. 3, page 604.
Acyclovir Oral Suspension-See PF Vol. 29 No. 6, page 1833.
Acyclovir Tablets-See PF Vol. 29 No. 3, page 604.
Adenosine-See PF Vol. 29 No. 6, page 1834.
Albendazole-See PF Vol. 27 No. 3, page 2505.
Albendazole Oral Suspension-See PF Vol. 29 No. 4, page 991.
Albendazole Tablets-See PF Vol. 27 No. 3, page 2505.
Albumin Human-See PF Vol. 29 No. 4, page 992.
Albuterol-See PF Vol. 27 No. 3, page 2505.
Albuterol Sulfate-See PF Vol. 27 No. 3, page 2506.
Albuterol Tablets-See PF Vol. 30 No. 1, page 50.
Alclometasone Dipropionate-See PF Vol. 27 No. 3, page 2506.
Alclometasone Dipropionate Cream-See PF Vol. 27 No. 3, page 2507.

Alclometasone Dipropionate Ointment-See PF Vol. 27 No. 3, page 2507.
Dehydrated Alcohol Injection-See PF Vol. 27 No. 3, page 2507.
Rubbing Alcohol-See PF Vol. 27 No. 3, page 2507.
Alcohol in Dextrose Injection-See PF Vol. 27 No. 3, page 2508.
Alendronate Sodium-See PF Vol. 28 No. 3, page 737.
Alendronate Sodium Tablets-See PF Vol. 28 No. 3, page 740.
Alendronic Acid Tablets-See PF Vol. 29 No. 4, page 997.
Alfentanil Hydrochloride-See PF Vol. 29 No. 6, page 1834.
Allopurinol Oral Solution-See PF Vol. 29 No. 4, page 1000.
Allopurinol Tablets-See PF Vol. 29 No. 3, page 604.
Alprazolam Tablets-See PF Vol. 30 No. 1, page 51.
Alprostadil-See PF Vol. 29 No. 5, page 1412.
Alteplase-See PF Vol. 29 No. 6, page 1835.
Altretamine-See PF Vol. 27 No. 3, page 2514.
Altretamine Capsules-See PF Vol. 27 No. 3, page 2514.
Potassium Alum-See PF Vol. 27 No. 3, page 2515.
Alumina and Magnesia Oral Suspension-See PF Vol. 27 No. 3, page 2515 .
Alumina and Magnesia Tablets-See PF Vol. 27 No. 3, page 2515.
Alumina, Magnesia, and Calcium Carbonate Oral SuspensionSee PF Vol. 27 No. 6, page 3241.
Alumina, Magnesia, and Calcium Carbonate Tablets-See PF Vol. 29 No. 6, page 1835.
Alumina, Magnesia, and Calcium Carbonate Chewable TabletsSee PF Vol. 29 No. 6, page 1836.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tab-lets-See PF Vol. 29 No. 6, page 1837.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets-See PF Vol. 29 No. 6, page 1837.
Alumina, Magnesia, and Simethicone Tablets-See PF Vol. 29 No. 6 , page 1841 .
Alumina, Magnesia, and Simethicone Chewable Tablets-See PF Vol. 29 No. 6, page 1842.
Amantadine Hydrochloride Capsules-See PF Vol. 30 No. 1, page 51.

Amifostine-See PF Vol. 30 No. 1, page 52.
Amiloride Hydrochloride and Hydrochlorothiazide Tablets-See PF Vol. 29 No. 3, page 605.
Aminocaproic Acid-See PF Vol. 29 No. 5, page 1414.

Aminopentamide Sulfate-See PF Vol. 29 No. 6, page 1844.
Aminophylline-See PF Vol. 29 No. 5, page 1414.
Aminosalicylate Sodium Tablets-See PF Vol. 30 No. 1, page 53.
Amitriptyline Hydrochloride-See PF Vol. 29 No. 6, page 1844.
Ammonium Chloride-See PF Vol. 29 No. 5, page 1415.
Ferric Ammonium Citrate for Oral Solution-See PF Vol. 29 No. 6 , page 1845 .
Ammonium Molybdate-See PF Vol. 29 No. 5, page 1416.
Amobarbital Sodium-See PF Vol. 29 No. 6, page 1845.
Amoxicillin Tablets-See PF Vol. 29 No. 1, page 48.
Amoxicillin and Clavulanate Potassium for Oral Suspension-See PF Vol. 30 No. 1, page 53.
Amoxicillin and Clavulanate Potassium Tablets-See PF Vol. 29 No. 3, page 605.
Amphetamine Sulfate Tablets-See PF Vol. 30 No. 1, page 54.
Ampicillin-See PF Vol. 28 No. 6, page 1766.
Ampicillin Capsules-See PF Vol. 30 No. 1, page 55.
Ampicillin Tablets-See PF Vol. 30 No. 1, page 56.
Amprolium Oral Solution-See PF Vol. 29 No. 3, page 606.
Anileridine-See PF Vol. 29 No. 6, page 1846.
Anthrax Vaccine Adsorbed-See PF Vol. 29 No. 4, page 1002.
Antithrombin III Human-See PF Vol. 30 No. 1, page 56.
Ascorbic Acid Tablets-See PF Vol. 30 No. 1, page 60.
L-Asparagine-See PF Vol. 29 No. 3, page 687.
Aspirin and Codeine Phosphate Tablets-See PF Vol. 29 No. 3, page 606.
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules-See PF Vol. 30 No. 1, page 60.
Atenolol-See PF Vol. 29 No. 5, page 1416.
Atenolol Oral Solution-See PF Vol. 29 No. 4, page 1001.
Atenolol Tablets-See PF Vol. 29 No. 1, page 49.
Atenolol and Chlorthalidone Tablets-See PF Vol. 29 No. 3, page 606.

Atovaquone Oral Suspension-See PF Vol. 29 No. 6, page 1846.
Atracurium Besylate-See PF Vol. 29 No. 6, page 1846.
Atracurium Besylate Injection-See PF Vol. 29 No. 4, page 1008.
Atropine Sulfate-See PF Vol. 29 No. 6, page 1847.
Aurothioglucose-See PF Vol. 29 No. 6, page 1847.
Azaperone-See PF Vol. 29 No. 6, page 1847.
Azithromycin-See PF Vol. 29 No. 5, page 1417.
Azithromycin Capsules-See PF Vol. 27 No. 6, page 3394.
Aztreonam-See PF Vol. 30 No. 1, page 61.
Baclofen-See PF Vol. 29 No. 6, page 1848.
Baclofen Tablets-See PF Vol. 30 No. 1, page 61.
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$\dagger$ New cancellations in 30(2).

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## HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps (Stages).

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In $P F$, this stage appears as OFFICIAL INQUIRY STAGE 4 in the Harmonization section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

## Stage 5: Consensus

## A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

## B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.
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# MONOGRAPHS (USP) 

## BRIEFING

Alcohol, USP 27 page 59 and page 1699 of PF 29(5) [Sept.Oct. 2003]. The European Pharmacopoeia is the coordinating pharmacopoeia for the international harmonization of compendial standards for the Alcohol monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Identification A | + | + | + |
| Identification B | + | + | + |
| Appearance | + | + | + |
| Acidity or alkalinity | + | + | + |
| Relative density | + | + | + |
| Absorbance | + | + | + |
| Volatile impurities | + | + | + |
| Residue on evapo- <br> ration | + | + | + |
| Storage | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters.
Definition and Relative density: Each pharmacopeia specifies a different range for the content; the values for relative density vary accordingly and, in addition, are expressed at different temperatures.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Differences between the ADOPTION STAGE 6 document and the current USP monograph include the following:
(1) Definition-No change.
(2) Packaging and storage-Storage conditions to protect from light are added.
(3) USP Reference standards-A reference standard for Alcohol is added for use in the Identification test.
(4) Identification-Tests $A$ and $B$ are replaced with a more definitive IR absorption test, and the test for specific gravity is moved under Identification.
(5) Clarity of solution-This test is added to comply with EP standards.
(6) Color of solution-This test is added to comply with EP standards.
(7) Specific gravity-No change.
(8) Acidity-This test is replaced by a test for Acidity or alkalinity to comply with EP standards.
(9) Limit of nonvolatile residue-The sample size is increased from 40 to 100 mL .
(10) Water-insoluble substances-This test is deleted. Because the monograph contains tests for Nonvolatile residue and Volatile impurities, this test is no longer needed.
(11) Aldehydes and other foreign organic substances-This test is replaced with a Volatile impurities test.
(12) Amyl alcohol and nonvolatile, carbonizable substancesThis test is replaced with a Volatile impurities test.
(13) Ultraviolet absorbance-This test is added to comply with EP standards.
(14) Limit of acetone and isopropyl alcohol-This test is replaced with a Volatile impurities test.
(15) Methanol-This test is replaced with a Volatile impurities test.
(16) Volatile impurities-This chromatographic test is added to limit a wide array of volatile impurities within a single test method.
(EMC: J. Lane) RTS-40773-1

## Change to read:

## Aleohel


$\mathrm{C}_{2} \mathrm{H}_{6} \mathrm{O}$
Ethenel.
Ethyl aleohel_ $\quad[64-17.5]$.
\#- Alcohol contains not less than 92.3 percent and not more than 93.8 percent, by weight, corresponding to not less than 94.9 pereent and not more than 96.0 pereent, by volume, at $15.56^{\circ}$, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Packaging and-storage- Preserve-in tight containers, remete frem flire.

## Identifieation-

A: Mix 5 drops in a small beaker with 1 mL of potassimm per manginate solution ( 1 in 100 ) and 5 -drops of 2 N sulfuric acid, and eover the beaker immediately with a filter paper meistened with - a selution recently prepared by dissolving 0.1 g of sodium nitrofer rieyanide and 0.25 g of piperazine in 5 mL of water: an intense blue eoler is produced on the filter paper, the coler becoming paler after $a$ few minuter.
B: To 5 mL of a solution ( 1 in 10 ) add 1 mL of 1.0 N soditm hydroxide, then slowly (over a period of 3 minutes) add 2 mL of 0.1 N iodine: the odor of iodoform develops, and a yellow preeipitate is formed within 30 mintutes.
Speeific gravity $\langle 844\rangle$ - between 0.812 and 0.816 at $15.56^{\circ}$, indieating between $92.3 \%$ and $93.8 \%$, by weight, or between $94.9 \%$ and $96.0 \%$, by velume, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.
Acidity Tb 50 mL , in a glass stoppered flask, add 50 mL of re eently beiled water. Add phenelphthalein TS, and titrate with 0.020 N sodium hydroxide to a pink color that persists for 30 seconds: not more than 0.90 mL of 0.020 N sodium hydroxide is required for neutralization.
Limit of nonvolatile residue-Evaporate 40 mL in a tared dish on a water bath, and dry at $105^{\circ}$ for 1 hour: the weight of the residue does not exeed 1 mg.
Water insoluble substanees- Dilute it with an equal volume of water: the mixture is clear and remains clear for 30 minutes after eooling to $10^{\circ}$.
Aldehydes and other foreign organie substanees-Place 20 mL in a glass-stoppered cylinder that has been thoroughly cleaned with hydrochloric acid, then rinsed with water and finally with the At
eohol to be tested. Cool the contents to approximately $15^{\circ}$, and add, by means of a carefully cleaned pipet, 0.10 mL of 0.10 N pe tassium permanganate, noting aceurately the time of addition. Mix at one by inveriting the stoppered eylinder, and allow it to stand at $15^{\circ}$ for 5 minutes: the pink color dees not entirely disappear.
Amylaleoholand nonvolatile, carbonizable substanees Allow 25 mL to vaperate spentaneously from a pereelain dish, carefully protect from dust, until the suface of the dish is barely meist: ne redor brown color is produced immediately upon the addition of a few dreps of sulfuric acid.
Limit of acetone and isopropylaleohol To 1.0 mL add 1.0 mL of water, 1.0 mL of a saturated solution of dibasic sodium pherphate, and 3.0 mL of a satrated solution of potassium permangafate. Warm the mixture to $45^{\circ}$ to $50^{\circ}$, and allow to stand until the permanganate color is discharged. Add 3.0 mL of 2.5 N sodium hydroxide, and filter, without washing, through a sintered glass fil ter. Prepare a control by mixing 1.0 mL of the saturated solution of dibasic sodium phesphate, 3.0 mL of 2.5 N sodium hydroxide, 80 He of acetone, and 5.0 mL of water. To ach solution add 1 mL of furfural solution ( 1 in 100 ), allow to stand for 10 minutes, then to 1.0 mL of each solution add 3 mL of hydrechloric acid: any pink evler produced in the test solution is net more intense than that in the control.
Methanol To 1 drep add 1 drep of water, 1 drep of dilute phos phoric acid ( 1 in 20), and 1 drep of potassium permangenate-solur tion ( 1 in 20). Mix, allow to stand for 1 minute, and add sodium metabisulfte solution ( 1 in 20), drepwise, until the permanganate evlor is discharged. If a brewn color remains, add 1 drop of the dilute phosphoric acid. To the colorless solution add 5 mL of freshly prepared chromotropic acid TS, and heat on a water bath at $60^{\circ}$ for 10 minutes: any violet coler should not exeed that produred by 0.04 mg of methanel in 1 mL of water, treated in the same way as the sample.

AAlcohol
$\mathrm{C}_{2} \mathrm{H}_{6} \mathrm{O} \quad 46.07$
Ethanol.
Ethyl alcohol [64-17-5].
» Alcohol contains not less than 92.3 percent and not more than 93.8 percent, by weight, corresponding to not less than 94.9 percent and not more than 96.0 percent, by volume, at $15.56^{\circ}$, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Packaging and storage-Preserve in tight containers, protected from light. ind remole from heat, sparks, or open flames.

USP Reference standards $\langle 11\rangle$ —USP Alcohol RS.
Clarity of solution-[NOTE-The Test solution is to be compared to Reference suspension $A$ and to water in diffused daylight 5 minutes after preparation of Reference suspension A.]

Hydrazine solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Methenamine solution-Transfer 2.5 g of methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension-[NOTE-This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of Hydrazine solution to the Methenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE-This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension A. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension $B$.

Test solution $A$-The substance to be examined.
Test solution B-Dilute 1.0 mL of Test Solution $A$ to 20 mL with water, and allow to stand for 5 minutes before testing.

Procedure-Transfer a sufficient portion of Test solution $A$ and Test solution $B$ to separate test tubes of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Reference suspension A, Reference suspension $B$, and water to separate matching test tubes. Compare Test solution A, Test solution B, Reference suspension $A$, Reference suspension $B$, and water in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). [NOTE-The diffusion of light must be such that Reference suspension $A$ can readily be distinguished from water, and that Reference suspension $B$ can readily be distinguished from Reference suspension A.] Test solution $A$ and Test solution $B$ show the same clarity as that of water or their opalescence is not more pronounced than that of

## Reference suspension $A$.

## Color of solution-

Standard stock solution-Combine 3.0 mL of ferric chloride $\mathrm{CS}, 3.0 \mathrm{~mL}$ of cobaltous chloride $\mathrm{CS}, 2.4 \mathrm{~mL}$ of cupric sulfate CS , and 1.6 mL of dilute hydrochloric acid ( 10 g per L).

Standard solution-[NOTE—Prepare the Standard solution immediately before use.] Transfer 1.0 mL of Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix.

Test solution-The substance to be examined.
Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Standard solution and water to separate, matching test tubes. Compare the Test solution, Standard solution, and water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophoto-
metry and Light-Scattering $\langle 851\rangle$ ). The Test solution has the appearance of water or is not more intensely colored than the Standard solution.

## Identification-

A: It complies with the test for Specific gravity.
B: Infrared Absorption $\langle 197 \mathrm{~F}\rangle$ or $\langle 197 \mathrm{~S}\rangle$ neat.
Specific gravity $\langle 841\rangle$ : between 0.812 and 0.816 at $15.56^{\circ}$, indicating between $92.3 \%$ and $93.8 \%$, by weight, or between $94.9 \%$ and $96.0 \%$, by volume, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

## Acidity or alkalinity-

Phenolphthalein solution-Dissolve 0.1 g of phenolphthalein in 80 mL of alcohol, and dilute with water to 100 mL .

Procedure-To 20 mL of alcohol, add 20 mL of freshly boiled and cooled water and 0.1 mL of Phenolphthalein solution. The solution is colorless. Add 1.0 mL of 0.01 N sodium hydroxide. The solution is pink ( 30 ppm , expressed as acetic acid).

Ultraviolet absorption—Record the UV absorption spectrum of the test material from 200 to 400 nm in a $1-\mathrm{cm}$ cell: maximum absorbance 0.40 at $240 \mathrm{~nm}, 0.30$ between 250 and 260 nm , and 0.10 between 270 and 340 nm . Examine between 235 and 340 nm , in a $5-\mathrm{cm}$ cell, using water as the compensation liquid. The absorption curve is smooth.

## Volatile impurities-

Test solution $A$-The substance to be examined.
Test solution B—Add $150 \mu \mathrm{~L}$ of 4-methylpentan-2-o1 to 500.0 mL of the substance to be examined.

Standard solution A-Dilute $100 \mu \mathrm{~L}$ of methanol to 50.0 mL with the substance to be examined. Dilute 5.0 mL of the solution to 50.0 mL with the substance to be examined.

Standard solution B-Dilute $50 \mu \mathrm{~L}$ of methanol and 50 $\mu \mathrm{L}$ of acetaldehyde to 50.0 mL with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 10.0 mL with the substance to be examined.

Standard solution C-Dilute $150 \mu \mathrm{~L}$ of acetal to 50.0 mL with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 10.0 mL with the substance to be examined.

Standard solution D-Dilute $100 \mu \mathrm{~L}$ of benzene to 100.0 mL with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 50.0 mL with the substance to be examined.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector, maintained at about $280^{\circ}$, and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ fused silica capillary column bonded with a $1.8-\mu \mathrm{m}$ layer of phase G43. The carrier gas is helium with a linear velocity of about 35 cm per second and a split ratio of 1:20. The column is maintained at $40^{\circ}$ for the first 12 minutes after an injection is made and is increased from $40^{\circ}$ to $240^{\circ}$ from 12 to 32 minutes after injection. During the period of 32 to 42 minutes after an injection is made the column is maintained at $240^{\circ}$. The injector port is maintained at $200^{\circ}$.

Procedure-Inject about $1.0 \mu \mathrm{~L}$ of Standard solution B into a suitable gas chromatograph, and record the chromatogram. The resolution, $R$, between the first major peak (acetaldehyde) and the second major peak (methanol) is not less than 1.5. Separately inject equal volumes $(1.0 \mu \mathrm{~L})$ of Test solution $A$ and Test solution $B$ into the chromatograph, record the chromatograms, and measure the major peaks. Calculate the concentration of methanol in Test solution A: not more than half the area of the corresponding peak in the chromatogram obtained with Standard solution A (200 $\mathrm{ppm})$.

Calculate the sum of the contents of acetaldehyde and acetal, expressed as acetaldehyde, using the following expression:

$$
\left[\left(10 \times A_{E}\right) /\left(A_{T}-A_{E}\right)\right]+\left[\left(30 \times C_{E}\right) /\left(C_{T}-C_{E}\right)\right]
$$

where $A_{E}$ is the area of the acetaldehyde peak in the chromatogram obtained with the Test solution $A ; A_{T}$ is the area of the acetaldehyde peak in the chromatogram obtained with Standard solution B; $C_{E}$ is the area of the acetal peak in the chromatogram obtained with Test solution $A$; and $C_{T}$ is the area of the acetal peak in the chromatogram obtained with Standard solution $C$ : not more than 10 ppm , expressed as acetaldehyde.

Calculate the content of benzene using the following expression:

$$
\left(2 B_{E}\right) /\left(B_{T}-B_{E}\right),
$$

where $B_{E}$ is the area of the benzene peak in the chromatogram obtained with Test solution $A$; and $B_{T}$ is the area of the benzene peak in the chromatogram obtained with Standard solution $D$ : not more than 2 ppm . If necessary, the identity of benzene can be confirmed using another suitable chromatographic system (stationary phase with a different polarity).

The total of all other impurities in the chromatogram obtained with Test solution B: not more than the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with Test solution B (300 ppm).
Disregard any peaks that are 0.03 times the area of the peak corresponding to 4-methylpentan-2-ol in the chromatogram obtained with Test solution $B(9 \mathrm{ppm})$.

Limit of nonvolatile residue-Evaporate 100 mL in a tared dish on a water bath, and dry at $100^{\circ}$ to $105^{\circ}$ for 1 hour: the weight of the residue does not exceed 2.5 mg . $\Delta U S P 28$

## BRIEFING

Dehydrated Alcohol, USP 27 page 60 and page 1702 of $P F$ $29(5)$ [Sept.-Oct. 2003]. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of compendial standards for the Dehydrated Alcohol monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Identification B | + | + | + |
| Appearance | + | + | + |
| Acidity or alkalinity | + | + | + |
| Relative density | + | + | + |
| Absorbance | + | + | + |
| Volatile impurities | + | + | + |
| Residue on evapo- <br> ration | + | + | + |
| Storage | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters.
Relative density: The values for relative density are expressed at different temperatures in the three pharmacopeias.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications

Differences between the ADOPTION STAGE 6 document and the current $U S P$ monograph include the following:
(1) Definition-No change.
(2) Packaging and storage-Storage conditions to protect from light are added.
(3) USP Reference standards-A reference standard for alcohol is added for the Identification test.
(4) Identification-Tests $A$ and $B$ are replaced with a more definitive Infrared absorption test, and the test for Specific gravity is moved under Identification.
(5) Clarity of solution-This test is added to comply with EP standards.
(6) Color of solution-This test is added to comply with EP standards.
(7) Specific gravity-No change.
(8) Acidity-This test is replaced by a test for Acidity or alkalinity to comply with EP standards.
(9) Limit of nonvolatile residue-The sample size is increased from 40 to 100 mL .
(10) Water-insoluble substances-This test is deleted. Because the monograph contains tests for Nonvolatile residue and Volatile impurities, this test is no longer needed.
(11) Aldehydes and other foreign organic substances-This test is replaced with a Volatile impurities test.
(12) Amyl alcohol and nonvolatile, carbonizable substancesThis test is replaced with a Volatile impurities test.
(13) Ultraviolet absorbance-The standards have been modified to comply with EP standards.
(14) Limit of acetone and isopropyl alcohol-This test is replaced with a Volatile impurities test.
(15) Methanol-This test is replaced with a Volatile impurities test.
(16) Volatile impurities-This chromatographic test is added to limit a wide array of volatile impurities within a single test method.
(EMC: J. Lane)
RTS-40773-7

## Change to read:

## Dehydrated Aleohol


\# Dehydrated Aleohol contains not less than 99.2 pereent, by weight, corresponding to not less than 99.5 pereent, by voltame, at $15.56^{\circ}$, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Packaging and-storage Preserve in tight containers, remote frem fire.

## Identifiention-

A: Mix 5 dreps in a small beaker with 1 mL of petassium per manganate solution ( 1 in 100) and 5 drops of 2 N sulfuric acid, and eover the beaker immediately with a filter paper moistened with a solution recently prepared by dissolving 0.1 gof sodium nitrofer ricyanide and 0.25 gof piperazine in 5 mL of water: an intense blue evlor is produced on the flter paper, the color beeoming pater after a few mintutes.

B: To 5 mL of a solution ( 1 in 10) add 1 mL of 1.0 N sodium hydroxide, then slowly (over a period of 3 mintes) add 2 mL of $\theta .1 \mathrm{~N}$ iodine: the odor of iodeform develops, and a yellow preei pitate is formed within 30 minutes.
Speeifie gravity $\langle 844\rangle:$ not more than 0.7962 at $15.56^{\circ}$, indieating not less than $99.2 \%$ of $_{2} \mathrm{H}_{5} \mathrm{OH}$ by weight.
Acidity $\mathrm{To}-50 \mathrm{~mL}$, in a glass stoppered flask, add 50 mL of re eently boiled water. Add phenolphthalein TS, and titrate with 0.020 N sodium hydroxide to a pink coler that persists for 30 seconds: not mere than 0.90 mL of 0.020 N sodium hydroxide is required for neutralization.
Limit of nonvolatile residue-Evaporate 40 mL in a tared dishon a water bath, and dry at $105^{\circ}$ for 1 hour: the weight of the residue does not exceed 1 ms.
-Water-insoluble substances-Dilute it with an equal volume of water: the mixture is clear and remains clear for 30 minutes after eoveling to $10^{\circ}$.
Aldehydes and other foreign organie substanees-Place 20 mL in a glass-stoppered eylinder that has been thoroughly cleaned with hydrechlorie acid, then rinsed with water and finally with the Dehydrated Aleohel to be tested. Cool the contents to approximately $15^{\circ}$, and add, by means of a carefally cleaned pipet, 0.10 mL of 0.10 N petassitum permanganate, noting aecurately the timeof ad dition. Mix at once by inverting the stoppered cylinder, and allow it to stand $15^{\circ}$ for 5 minntes: the pink color does not entirely disарреат.

Amylalcohol and nonvolatile, carbonizable substances Allow 25 mL to evaporate spontaneously from a poreelain dish, carefully protected from dust, until the surface of the dish is barely moist: $\mathrm{n} \theta$ red or brewn color is produced immediately upen the addition of a few drops of sulfuric acid.
Utraviolet absorbanee Record the UVabsorption spectrmbe tween 340 nm and 235 nm in a $1-\mathrm{cm}$ cell, with water in a matehed eell in the reference beam: the absorbance is not more than 0.08 at 240 nm , and 0.02 between 270 nm and 340 nm , and the eurve drawn threugh these peints is smooth.
Limil of acetone and isopropylaleohol.To 1.0 mL add 1 mL of water, 1 mL of a saturated solution of dibasic sodium phosphate, and 3 - mL of a saturated solution of potassitm permancanate. Warm the mixture to $45^{\circ}$ to $50^{\circ}$, and allow to stand until the per mangenate color is diseharged. Add 3 mL of 2.5 N sodimm hydrox ide, and filter, without washing, through a sintered glass filter. Prepare a control containing 1 mL of the saturated solution of di basic sodium phosphate, 3 mL of 2.5 N sodium hydroxide, and 80 He of acetone in 9 mL . To each solution add 1 mL of furfural solut tion ( 1 in 100), and allow to stand for 10 minutes, then to 1.0 mL of each solution add 3 mL of hydrochloric acid: any pink color produred in the test solution is not more intense than that in the control.
Methanol- To 1 drep add 1-drop of water, 1 drop of dilute phos phoric acid ( 1 in 20), and 1 drop of potassium permanganate solut tion ( 1 in 20). Mix, allow to stand for 1 minute, and add sodium metabisulfte solution ( 1 in 20), drepwise, until the permanganate coler is diseharged. If a brewn color remains, add 1 drep of the dilute phosphoric acid. To the colorless solution add 5 mL of freshly prepared chromotropic acid TS, and heat on a water bath at $60^{\circ}$ for 10 minttes: no violet color appears.

## ©Dehydrated Alcohol

$\mathrm{C}_{2} \mathrm{H}_{6} \mathrm{O} \quad 46.07$
Ethanol.
Ethyl alcohol [64-17-5].
» Dehydrated Alcohol contains not less than 99.2 percent, by weight, corresponding to not less than 99.5 percent, by volume, at $15.56^{\circ}$, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Packaging and storage-Preserve in tight containers, protected from light. from fire.

USP Reference standards $\langle 11\rangle$ —USP Dehydrated Alcohol $R S$.

Clarity of solution-[NOTE-Test solution is to be compared to Reference suspension $A$ and to water in diffused daylight 5 minutes after preparation of Reference suspension $A$.]

Hydrazine solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in water, dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Methenamine solution-Transfer 2.5 g of methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension-[NOTE-This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of Hydrazine solution to the Methenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE-This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension A. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension B.

Test solution $A$-The substance to be examined.
Test solution B-Dilute 1.0 mL of Test solution $A$ to 20 mL with water and allow to stand for 5 minutes before testing.

Procedure-Transfer a sufficient portion of Test solution $A$ and Test solution $B$ to separate test tubes of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Simi-
larly transfer portions of Reference suspension A, Reference suspension $B$, and water to separate, matching test tubes. Compare Test solution $A$, Test solution B, Reference suspension $A$, Reference suspension $B$, and water in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and LightScattering $\langle 851\rangle$ ). [NOTE-The diffusion of light must be such that Reference suspension $A$ can readily be distinguished from water, and Reference suspension $B$ can readily be distinguished from Reference suspension A.] Test solution $A$ and Test solution $B$ show the same clarity as that of water, or their opalescence is not more pronounced than that of Reference suspension A.

## Color of solution-

Standard stock solution-Combine 3.0 mL ferric chloride CS, 3.0 mL cobaltous chloride CS, 2.4 mL cupric sulfate CS , and 1.6 mL dilute hydrochloric acid ( 10 g per L ).

Standard solution-[NOTE-Prepare the Standard solution immediately before use.] Transfer 1.0 mL of Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix.

Test solution-The substance to be examined.
Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Standard solution and water to separate matching test tubes. Compare the Test solution, Standard solution, and water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). The Test solution has the appearance of water or is not more intensely colored than the Standard solution.

## Identification-

A: It complies with the test for Specific gravity.
B: Infrared Absorption $\langle 197 \mathrm{~F}\rangle$ or $\langle 197 \mathrm{~S}\rangle$ neat.
Specific gravity $\langle 841\rangle$ : not more than 0.7962 at $15.56^{\circ}$, indicating not less than $99.2 \%$ of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$, by weight.

Acidity or alkalinity-To 20 mL of alcohol, add 20 mL of freshly boiled and cooled water and 0.1 mL of Phenolphthalein solution. The solution is colorless. Add 1.0 mL of 0.01 N sodium hydroxide. The solution is pink ( 30 ppm , expressed as acetic acid).
Phenolphthalein solution-Dissolve 0.1 g of phenolphthalein in 80 mL of alcohol and dilute to 100 mL with water.

Ultraviolet absorption-Record the UV absorption spectrum of the test material from 200 to 400 nm in a $1-\mathrm{cm}$ cell: maximum absorbance 0.40 at $240 \mathrm{~nm}, 0.30$ between 250 and 260 nm , and 0.10 between 270 and 340 nm . Examine between 235 and 340 nm , in a $5-\mathrm{cm}$ cell, using water as the compensation liquid. The absorption curve is smooth.

## Volatile impurities-

Test solution $A$-The substance to be examined.
Test solution B-Add $150 \mu \mathrm{~L}$ of 4-methylpentan-2-ol to 500.0 mL of the substance to be examined.

Standard solution A-Dilute $100 \mu \mathrm{~L}$ of methanol to 50.0 mL with the substance to be examined. Dilute 5.0 mL of the solution to 50.0 mL with the substance to be examined.

Standard solution B-Dilute $50 \mu \mathrm{~L}$ of methanol and 50 $\mu \mathrm{L}$ of acetaldehyde to 50.0 ml with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 10.0 mL with the substance to be examined.

Standard solution C-Dilute $150 \mu \mathrm{~L}$ of acetal to 50.0 mL with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 10.0 mL with the substance to be examined.

Standard solution D—Dilute $100 \mu \mathrm{~L}$ of benzene to 100.0 mL with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 50.0 mL with the substance to be examined.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame ionization detector, maintained at about $280^{\circ}$, and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ fused silica capillary column bonded with a $1.8 \mu \mathrm{~m}$ layer of phase G43. The carrier gas is helium with a linear velocity of about 35 cm per second and a split ratio of 1:20. The column is maintained at $40^{\circ}$ for the first 12 minutes after an injection is made and is increased from $40^{\circ}$ to $240^{\circ}$ from 12 to 32 minutes after injection. During the period of 32 to 42 minutes after an injection is made the column is maintained at $240^{\circ}$. The injector port is maintained at $200^{\circ}$.
Procedure-Inject about $1.0 \mu \mathrm{~L}$ of Standard solution B into a suitable gas chromatograph, and record the chromatogram. The resolution, $R$, between the first major peak (acetaldehyde) and the second major peak (methanol) is not less than 1.5. Separately inject equal volumes ( $1.0 \mu \mathrm{~L}$ ) of Test solution $A$ and Test solution $B$ into the chromatograph, record the chromatograms, and measure the major peaks. Calculate the concentration of methanol in Test solution A: not more than half the area of the corresponding peak in the chromatogram obtained with Standard solution A (200 ppm).

Calculate the sum of the contents of acetaldehyde and acetal, expressed as acetaldehyde, using the following expression:

$$
\left[\left(10 \times A_{E}\right) /\left(A_{T}-A_{E}\right)\right]+\left[\left(30 \times C_{E}\right) /\left(C_{T}-C_{E}\right)\right],
$$

where $A_{E}$ is the area of the acetaldehyde peak in the chromatogram obtained with the Test solution; $A_{T}$ is the area of
the acetaldehyde peak in the chromatogram obtained with Standard solution B; $C_{E}$ is the area of the acetal peak in the chromatogram obtained with Test solution $A$; and $C_{T}$ is the area of the acetal peak in the chromatogram obtained with Standard solution $C$ : not more than 10 ppm , expressed as acetaldehyde.
Calculate the content of benzene using the following expression:

$$
\left(2 B_{E}\right) /\left(B_{T}-B_{E}\right),
$$

where $B_{E}$ is the area of the benzene peak in the chromatogram obtained with Test solution $A$, and $B_{T}$ is the area of the benzene peak in the chromatogram obtained with Standard solution $D$ : not more than 2 ppm . If necessary, the identity of benzene can be confirmed using another suitable chromatographic system (stationary phase with a different polarity).

The total of all other impurities in the chromatogram obtained with Test solution $B$ is not more than the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with Test solution $B$ ( 300 ppm ). Disregard any peaks that are 0.03 times the area of the peak corresponding to 4 -methylpentan-2-ol in the chromatogram obtained with Test solution B (9 ppm).

Limit of nonvolatile residue-Evaporate 100 mL in a tared dish on a water bath, and dry at $100^{\circ}$ to $105^{\circ}$ for 1 hour: the weight of the residue does not exceed 2.5 mg . $\mathbf{U} U S P 28$

## BRIEFING

Citric Acid, USP 27 page 461 and page 872 of PF 28(3) [MayJune 2002]. It is proposed to delete the monograph. See briefings under Citric Acid, Anhydrous and Citric Acid, Monohydrate.
(EMC: J. Lane) RTS-40769-4

## Delete the following:

## © Citric Acid


$\mathrm{G}_{6} \mathrm{H}_{8} \Theta_{7} \quad 192.12$
$1,2,3$ Prepanetriearbexylic acid, 2 hydroxy -
Gitric acid [77-92 9$]$.
Menohydrate 210.14 [5949-29-1].
\#Citric Acid is anhy drous or contains one molecule of water of hydration. It contains not less than 99.5 per cent and not more than 100.5 percent of $\mathrm{G}_{6} \mathrm{H}_{8} \mathrm{O}_{7}$, cal eulated on the anhydrous basis.

Paekaging and-storage-Preserve in tight containers.
Labeling Label it to indiente whether it is anhydreus or hydrous. Identifiention A solution respends to the tests for Citrate $\langle 194$ ) : Water, Method $I\langle 924\rangle \div$ not more than $0.5 \%$ (anhydrous form) and net more than $8.8 \%$ (hydrous form).
Readily carbonizable substances Transfer 1.0-g, powdered for the test, to a $22 \times 175 \mathrm{~mm}$ test ube previeusly rimsed with 10 mL of sulfuric acid TS and allowed to drain for 10 minutes. Add 10 mL of sulfuric acid TS, agitate until- solution is complete, and immerse in a water bath at $90 \pm 1^{\circ}$ for $60 \pm 0.5$ minutes, keeping the level of the acid below the level of the water during the entire period. Gool the tube in rumning water, and tramsfer the acid to a color eomparison tube: the color of the acid is not darker than that of a similar volume of Matching Fluid K (see Color and Achromicim $\langle 634\rangle$ ) in a matehing tube, the tubes being observed vertically against a white background.
Residtue on-ignition- $\langle 284\rangle$ : not more than- $0.05 \%$.
Sulfate-To 10 mL of a solution ( 1 in 100) add 1 mL of barium ehloride TS to which has been added 1 drep of hydrechlorie acid: ne turbidity is produeed.
Arsenic, Meth $I\langle z 14\rangle \div 3$ Ppm.
Heary metals- $\langle 234\rangle \div 0.001 \%$.
Limit of oxalate-Neutralize 10 mL of a solution ( 1 in 10) with 6 N ammenium hydroxide, add 5-drops of 3 N hydrochloric acid, eool, and add 2 mL of ealeimm chloride TS: no tarbidity is produeed.
Organie volatile imptrities, Methat $I V\langle 467\rangle$ : meets the requirements.
Assay Place about 3 g of Citric Acid in a tared flask, and weigh aceurately. Dissolve in 40 mL of water, add phenolphthatein TS, and titrate with 1 N sodimm hydroxide VS . Each mL of 1 N sodimm hydroxide is equivalent to 64.04 mg of $\mathrm{C}_{6} \mathrm{H}_{8} \Theta_{7^{-}} \mathbf{\Delta}$ USP28

## BRIEFING

Citric Acid, Anhydrous, page 872 of $P F$ 28(3) [May-June 2002]. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Citric Acid, Anhydrous monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based on the corresponding monograph for Citric Acid, Anhydrous that was prepared by the European Pharmacopoeia. The European Pharmacopoeia draft was based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia. The current USP monograph for Citric Acid will be replaced with two separate monographs for Anhydrous Citric Acid and Citric Acid Monohydrate.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Appearance of solu- <br> tion | + | + | + |
| Readily carbonizable <br> substances | + | + | + |
| Oxalic acid | + | + | + |
| Sulfates | + | + | + |
| Aluminium | + | - | + |
| Water | + | + | + |
| Sulphated ash | + | + | + |
| Assay | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Identification, Heavy metals, Characters, Labeling, Bacterial endotoxins, Sterility, Storage.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Differences between the European Pharmacopoeia Adoption Stage 6 document and the current USP monograph include the following:
(1) Definition-Changed to include only Anhydrous Citric Acid in order to conform to the individual monograph for Anhydrous Citric Acid.
(2) Packaging-No change.
(3) Labeling-The indication of anhydrous or hydrous is deleted in order to conform to the individual monograph for Anhydrous Citric Acid. A requirement that the label indicates where it is intended for use in dialysis solutions is added. Considerations for bacterial endotoxins and sterility are added.
(4) USP Reference standards-A USP Citric Acid Reference Standard that is used in the Identification test is added.
(5) Clarity of solution-This test is added in order to conform with EP standards.
(6) Color of solution-This test is added in order to conform with EP standards.
(7) Identification-The test for citrate is deleted, and a more definitive infrared absorption test is added.
(8) Bacterial endotoxins-Statements are added that refer to the limits under the appropriate dosage form monograph. Specific requirements have been omitted.
(9) Sterility-Statements are added that refer to the limits under the appropriate dosage form monograph.
(10) Water-The standard for this test is increased from $0.5 \%$ to $1.0 \%$ in order to conform with EP standards.
(11) Residue on ignition-The standard for this test is increased from $0.05 \%$ to $0.1 \%$ in order to conform with JP standards.
(12) Readily carbonizable substances-No change.
(13) Sulfate-The test procedure is changed to a quantitative test in order to conform to EP standards.
(14) Arsenic-This test is deleted because the Heavy metals test sufficiently accounts for arsenic.
(15) Heavy metals-No change.
(16) Limit of oxalic acid-The test procedure is changed to a quantitative test in order to conform to EP standards.
(17) Limit of aluminum-This test is added in order to conform with EP standards concerning usage in dialysis. This requirement is similar to the Limit of aluminum in the USP Calcium Acetate monograph.
(18) Organic volatile impurities-No change.
(19) Assay-The sample size is decreased from 3 g in 40 mL of water to 0.55 g in 50 mL of water. The amount of Anhydrous Citric Acid that is equivalent to 1 mL of 1 N sodium hydroxide is changed to specify a more accurate quantity (i.e., from 64.04 mg to 64.03 mg ).
(EMC: J. Lane) RTS-40769-2

## Add the following:

## ©Citric Acid, Anhydrous Anhydrous Citric Acid

$\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7} \quad 192.13$
1,2,3-Propanetricarboxylic acid, 2-hydroxy-.
Citric acid [77-92-9].
» Anhydrous Citric Acid contains not less than 99.5 percent and not more than 100.5 percent of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7}$, calculated on the anhydrous basis.

Packaging and-storage-Preserve in tight containers.
Labeling-Where it is intended for use in dialysis solutions, it is so labeled. Where Anhydrous Citric Acid must be subjected to further processing during the preparation
 be subjected to further processing during the preparation
of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled. Where Anhydrous Citric Acid is sterile, it is so labeled.

USP Reference standards $\langle 11\rangle — U S P$ Citric Acid RS.
Clarity of solution-[NOTE-The Test solution is to be compared to Reference suspension $A$ in diffused daylight 5 minutes after preparation of Reference suspension A.]
Hydrazine sulfate solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours before use.

## Hexmethyle solution Methenamine solu-

 tion-Transfer 2.5 g of Hewnethye Methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.Primary opalescent suspension-[NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of Hydrazine sulfate solution to the Hexmen Methenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000mL volumetric flask, dilute with water to volume, and mix.
Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension A. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension B.
Test solution-Dissolve 2.0 g of Anhydrous Citric Acid in about 5 mL of water, dilute with water to 10 mL , and mix.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Reference suspension $A$, Reference suspension $B$, and water to separate matching test tubes. Compare the Test solution, Reference suspension $A$, Reference suspension $B$, and water in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and LightScattering $\langle 851\rangle$ ). [NOTE-The diffusion of light must be such that Reference suspension $A$ can readily be distinguished from water, and that Reference suspension $B$ can readily be distinguished from Reference suspension A.] The Test solution shows the same clarity as that of water.

## Color of solution-

Standard stock solutions-Prepare three solutions, $A, B$, and $C$, containing, respectively, the following parts of ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and dilute hydrochloric acid ( 10 g per L ):
$A-2.4: 0.6: 0: 7.0$.
$B-2.4: 1.0: 0.4: 6.2$.
C-9.6:0.2:0.2:0.
Standard solutions-[NOTE—Prepare the Standard solutions immediately before use.] Transfer 2.5 mL of Standard stock solution $A$ to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix to obtain Standard solution A. Transfer 2.5 mL of Standard stock solution $B$ to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix to obtain Standard solution B. Transfer 0.75 mL of Standard stock solution $C$ to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix to obtain Standard solution C.

Test solution-Use the Test solution prepared as directed in the test for Clarity of solution.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Standard solution A, Standard solution B, Standard solution C, and water to separate matching test tubes. Compare the Test solution, Standard solution A, Standard solution B, Standard solution $C$, and water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). The Test solution is not more intensely colored than Standard solutions $A, B$, or water.

Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$-Dry the substance to be examined at $105^{\circ}$ for 2 hours.

Bacterial endotoxins $\langle 85\rangle$-If inted for use in the manufacturing of parenteral dosage forms, without a futher appropriate procedure for the removal-of bacterial endotoxins, not more that 0.5 I . U. of en milligram. The level of bacterial endotoxins are such that the requirement under the relevant dosage form monograph(s) in which Anhydrous Citric Acid is used can be met. Where the label states that Anhydrous Citric Acid must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins are such that the requirement under the relevant dosage form monograph(s) in which Anhydrous Citric Acid is used can be met.

Sterility $\langle 71\rangle$ - Where the label states that Anhydrous Citric Acid is sterile, it meets the requirements for Sterility $\langle 71\rangle$ under the relevant dosage form monograph(s) in which Anhydrous Citric Acid is used.

Water, Method $I\langle 921\rangle$ : not more than $1.0 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on 1.0 g .

Readily carbonizable substances-Transfer 1.0 g of powdered Anhydrous Citric Acid to a $22-\times 175-\mathrm{mm}$ test tube previously rinsed with 10 mL of sulfuric acid TS and allowed to drain for 10 minutes. Add 10 mL of sulfuric acid TS, agitate until solution is complete, and immerse in a water bath at $90 \pm 1^{\circ}$ for $60 \pm 0.5$ minutes, keeping the level of the acid below the level of the water during the entire period. Cool the tube in running water, and transfer the acid to a color-comparison tube: the color of the acid is not darker than that of a similar volume of Matching Fluid K (see Color and Achromicity $\langle 631\rangle$ ) in a matching tube, the tubes being observed vertically against a white background.

## Sulfate-

Standard sulfate solution A-To 181 mg of dibasic potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of 30 percent alcohol, swirl to dissolve, dilute with 30 percent alcohol to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a $1000-\mathrm{mL}$ volumetric flask, dilute with 30 percent alcohol to volume, and mix. This solution contains $10 \mu \mathrm{~g}$ of sulfate per mL .

Standard sulfate solution B-To 181 mg of dibasic potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of water, swirl to dissolve, dilute with water to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a $1000-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. This solution contains $10 \mu \mathrm{~g}$ of sulfate per mL .

Citric acid solution-Dissolve 2.0 g of Anhydrous Citric Acid in about 10 mL of water, dilute with water to 30 mL , and mix.

Procedure-To 4.5 mL of Standard sulfate solution $A$ add 3 mL of a barium chloride solution (1 in 4), shake, and allow to stand for 1 minute. To 2.5 mL of the resulting suspension, add 15 mL of the Citric acid solution and 0.5 mL of 5 N acetic acid, and mix (test solution). Prepare the Standard
solution in the same manner, except use 15 mL of Standard sulfate solution B instead of the Citric acid solution: any turbidity produced in the test solution after 5 minutes standing is not greater than that produced in the Standard solution (0.015\%).

Heavy metals $\langle 231\rangle: 0.001 \%$.
Limit of oxalic acid-Prepare a citric acid solution by dissolving 800 mg of Anhydrous Citric Acid in 4 mL of water. Add 3 mL of hydrochloric acid and 1 g of granular zinc, boil for 1 minute, and allow to stand for 2 minutes. Transfer the supernatant to a test tube containing 0.25 mL of a phenylhydrazine hydrochloride solution (1 in 100), and heat to boiling. Cool rapidly, transfer to a graduated cylinder, and add an equal volume of hydrochloric acid and 0.25 mL of a potassium ferricyanide solution (1 in 20). Shake, and allow to stand for 30 minutes (test solution). Concomitantly prepare a control solution in the same manner, except use 4 mL of an oxalic acid solution containing 0.10 mg per mL , equivalent to 0.0714 mg of anhydrous oxalic acid per mL , instead of the citric acid solution: any pink color produced in the test solution is not more intense than that produced in the control solution ( $0.036 \%$ ).

Limit of aluminum (where it is labeled as intended for use in dialysis)-

Standard aluminum solution-To 352 mg of aluminum potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of water, swirl to dissolve, add 10 mL of diluted sulfuric acid, dilute with water to volume, and mix. Immediately before use, transfer 1.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.
pH 6.0 Acetate buffer-Dissolve 50 g of ammonium acetate in 150 mL of water, adjust with glacial acetic acid to a pH of 6.0 , dilute with water to 250 mL , and mix.

Test solution-Dissolve 20.0 g of Anhydrous Citric Acid in 100 mL of water, and add 10 mL of pH 6.0 Acetate buffer. Extract this solution with successive portions of 20, 20, and 10 mL of a $0.5 \%$ solution of 8-hydroxyquinoline in chloroform, combining the chloroform extracts in a $50-\mathrm{mL}$ volumetric flask. Dilute the combined extracts with chloroform to volume, and mix.
Standard solution-Prepare a mixture of 2.0 mL of Standard aluminum solution, 10 mL of pH 6.0 Acetate buffer, and 98 mL of water. Extract this mixture as described for the Test solution, dilute the combined extracts with chloroform to volume, and mix.
Blank solution-Prepare a mixture of 10 mL of pH 6.0 Acetate buffer and 100 mL of water. Extract this mixture as described for the Test solution, dilute the combined extracts with chloroform to volume, and mix.
Procedure-Determine the fluorescence intensities of the Test solution and the Standard solution in a fluorometer set at an excitation wavelength of 392 nm and an emission wavelength of 518 nm , using the Blank solution to set the instrument to zero. The fluorescence of the Test solution does not exceed that of the Standard solution ( $0.2 \mu \mathrm{~g} \mathrm{per} \mathrm{g}$ ).
Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

Assay—Place about 0.550 g of Anhydrous Citric Acid in a tared flask, and weigh accurately. Dissolve in 50 mL of water, add 0.5 mL of phenolphthalein TS, and titrate with 1 N sodium hydroxide VS. Each mL of 1 N sodium hydroxide is equivalent to 64.03 mg of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7 \cdot \mathbf{\Delta} U S P 28}$

## Briefing

Citric Acid Monohydrate, page 876 in PF 28(3) [May-June 2002]. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Citric Acid, Monohydrate monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based on the corresponding monograph for Citric Acid, Monohydrate that was prepared by the European Pharmacopoeia. The European Pharmacopoeia draft was based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia. The current USP monograph for Citric Acid will be replaced with two separate monographs for Anhydrous Citric Acid and Citric Acid Monohydrate.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Appearance of solu- <br> tion | + | + | + |
| Readily carbonizable <br> substances | + | + | + |
| Oxalic acid | + | + | + |
| Sulfates | + | + | + |
| Aluminium | + | - | + |
| Water | + | + | + |
| Sulphated ash | + | + | + |
| Assay |  |  | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Identification, Heavy metals, Characters, Labeling, Bacterial endotoxins, Sterility, Storage.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Differences between the European Pharmacopoeia Adoption Stage 6 document and the current $U S P$ monograph for Citric Acid include the following:
(1) Definition-Changed to include only Citric Acid Monohydrate in order to conform to the individual monograph for Citric Acid Monohydrate.
(2) Labeling-The indication of anhydrous or hydrous is deleted in order to conform to the individual monograph for Citric Acid Monohydrate. A requirement that the label indicate where it is intended for use in dialysis solutions is added. Considerations for bacterial endotoxins and sterility are added.
(3) USP Reference standards-A USP Citric Acid Reference Standard that is used in the Identification test is added.
(4) Clarity of solution-This test is added in order to conform with EP standards.
(5) Color of solution - This test is added in order to conform with EP standards.
(6) Identification-The test for Citrate is deleted and a more definitive infrared absorption test is added.
(7) Packaging-No change.
(8) Bacterial endotoxins-Statements are added that refer to the limits under the appropriate dosage form monograph. Specific requirements have been omitted.
(9) Sterility-Statements are added that refer to the limits under the appropriate dosage form monograph.
(10) Water-The standard for this test is changed from not more than $8.8 \%$ to a range of $7.5 \%$ to $9.0 \%$ in order to conform with EP standards.
(11) Residue on ignition-The standard for this test is increased from $0.05 \%$ to $0.1 \%$ in order to conform with JP standards.
(12) Readily carbonizable substances-No change.
(13) Sulfate-The test procedure is changed to a quantitative test in order to conform to EP standards.
(14) Arsenic-This test is deleted because the Heavy metals test sufficiently accounts for arsenic.
(15) Heavy metals-No change.
(16) Limit of oxalic acid-The test procedure is changed to a quantitative test in order to conform to EP standards.
(17) Limit of aluminum - This test is added in order to conform with EP standards concerning usage in dialysis. This requirement is similar to the Limit of aluminum in the USP Calcium Acetate monograph.
(18) Organic volatile impurities-This test is deleted because it is not necessary.
(19) Assay-The sample size is decreased from 3 g in 40 mL of water to 0.55 g in 50 mL of water. The amount of Citric Acid Monohydrate that is equivalent to 1 mL of 1 N sodium hydroxide is changed to specify a more accurate quantity (i.e., from 64.04 mg to 64.03 mg ).
(EMC: J. Lane) RTS-40769-3

## Add the following:

## ${ }^{\Delta}$ Citric Acid Monohydrate


$\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7} \cdot \mathrm{H}_{2} \mathrm{O} \quad 210.14$
1,2,3-Propanetricarboxylic acid, 2-hydroxy-, monohy-
drate $\quad[5949-29-1]$. drate [5949-29-1].
» Citric Acid Monohydrate contains one molecule of water of hydration. It contains not less than 99.5 percent and not more than 100.5 percent of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7}$, calculated on the anhydrous basis.

Packaging and-storage-Preserve in tight containers.
Labeling-Where it is intended for use in dialysis solutions, it is so labeled. Where Citric Acid Monohydrate must be subjected to further processing during the preparation of
injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled. Where Citric Acid Monohydrate is sterile, it is so labeled.

USP Reference standards $\langle 11\rangle$ —USP Citric Acid RS
Clarity of solution-[NOTE-The Test solution is to be compared to Reference suspension $A$ in diffused daylight 5 minutes after preparation of Reference suspension A.]
Hydrazine sulfate solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours before use.

Methenamine solution-Transfer 2.5 g of methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension-[NOTE-This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of Hydrazine sulfate solution to the Methenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension A. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension $B$.

Test solution-Dissolve 2.0 g of Citric Acid Monohydrate in about 5 mL of water, dilute with water to 10 mL , and mix.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Reference suspension $A$, Reference suspension $B$, and water to separate matching test tubes. Compare the Test solution, Reference suspension $A$, Reference suspension $B$, and water in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and LightScattering $\langle 851\rangle$ ). [NOTE-The diffusion of light must be such that Reference suspension $A$ can readily be distinguished from water, and that Reference suspension $B$ can readily be distinguished from Reference suspension A.] The Test solution shows the same clarity as that of water.

## Color of solution-

Standard stock solutions-Prepare three solutions, $A, B$, and $C$, containing, respectively, the following parts of ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and dilute hydrochloric acid ( 10 g per L ):
$A-2.4: 0.6: 0: 7.0$
$B-2.4: 1.0: 0.4: 6.2$
C-9.6:0.2:0.2:0
Test solution-Use the Test solution prepared in the Clarity of solution test.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Standard solution A, Standard solution B, Standard solution C, and water to separate matching test tubes. Compare the Test solution, Standard solution A, Standard solution B, and Standard solution C, and water in diffused daylight, viewing vertically against a white background (see Visual Com-
parison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). The Test solution is not more intensely colored than Standard solutions $A, B$, and $C$ or water.

Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$ — Dry the substance to be examined at $105^{\circ}$ for 2 hours.

Bacterial endotoxins $\langle 85\rangle$ - If intended for use in the man ufacturing of parenteral dosage forms, withent a futher ap propriate procedure for the removal of bacterial endotoxins, not mere that $0.5 \mathrm{I} . \mathrm{U}$. of entoxin per milligram. The level of bacterial endotoxins are such that the requirement under the relevant dosage form monograph(s) in which Citric Acid Monohydrate is used can be met. Where the label states that Citric Acid Monohydrate must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins are such that the requirement under the relevant dosage form monograph(s) in which Citric Acid Monohydrate is used can be met.

Sterility $\langle 71\rangle$-Where the label states that Citric Acid Monohydrate is sterile, it meets the requirements for Sterility $\langle 71\rangle$, under the relevant dosage form monograph(s) in which Citric Acid Monohydrate is used.

Water, Method $I\langle 921\rangle$ : between $7.5 \%$ and $9.0 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on 1.0 g .

Readily carbonizable substances-Transfer 1.0 g of powdered Citric Acid Monohydrate, to a $22-\times 175-\mathrm{mm}$ test tube previously rinsed with 10 mL of sulfuric acid TS, and allow to drain for 10 minutes. Add 10 mL of sulfuric acid TS, agitate until solution is complete, and immerse in a water bath at $90 \pm 1^{\circ}$ for $60 \pm 0.5$ minutes, keeping the level of the acid below the level of the water during the entire period. Cool the tube in running water, and transfer the acid to a color-comparison tube: the color of the acid is not
darker than that of a similar volume of Matching Fluid $K$ (see Color and Achromicity $\langle 631\rangle$ ) in a matching tube, the tubes being observed vertically against a white background.

## Sulfate-

Standard sulfate solution A-To 181 mg of dibasic potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of 30 percent alcohol, swirl to dissolve, dilute with 30 percent alcohol to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a $1000-\mathrm{mL}$ volumetric flask, dilute with 30 percent alcohol to volume, and mix. This solution contains $10 \mu \mathrm{~g}$ of sulfate per mL .

Standard sulfate solution B-To 181 mg of dibasic potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of water, swirl to dissolve, dilute with water to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a $1000-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. This solution contains $10 \mu \mathrm{~g}$ of sulfate per mL .
Citric acid solution-Dissolve 2.0 g of Citric Acid Monohydrate in about 10 mL of water, dilute with water to 30 mL , and mix.

Procedure-To 4.5 mL of Standard sulfate solution $A$ add 3 mL of a barium chloride solution (1 in 4), shake, and allow to stand for 1 minute. To 2.5 mL of the resulting suspension, add 15 mL of the Citric acid solution and 0.5 mL of 5 N acetic acid, and mix (test solution). Prepare the Standard solution in the same manner, except use 15 mL of Standard sulfate solution B instead of the Citric acid solution: any turbidity produced in the test solution after 5 minutes standing is not greater than that produced in the Standard solution (0.015\%).

Heavy metals $\langle 231\rangle$ : $0.001 \%$.
Limit of oxalic acid—Prepare a citric acid solution by dissolving 800 mg of Citric Acid Monohydrate in 4 mL of water. Add 3 mL of hydrochloric acid and 1 g of granular
zinc, boil for 1 minute, and allow to stand for 2 minutes. Transfer the supernatant to a test tube containing 0.25 mL of a phenylhydrazine hydrochloride solution (1 in 100), and heat to boiling. Cool rapidly, transfer to a graduated cylinder, and add an equal volume of hydrochloric acid and 0.25 mL of a potassium ferricyanide solution (1 in 20). Shake, and allow to stand for 30 minutes (test solution). Concomitantly prepare a control solution in the same manner, except use 4 mL of an oxalic acid solution containing 0.10 mg per mL , equivalent to 0.0714 mg of anhydrous oxalic acid per mL, instead of the citric acid solution: any pink color produced in the test solution is not more intense than that produced in the control solution ( $0.036 \%$ ).

Limit of aluminum (where it is labeled as intended for use in dialysis)-
Standard aluminum solution-To 352 mg of aluminum potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of water, swirl to dissolve, add 10 mL of diluted sulfuric acid, dilute with water to volume, and mix. Immediately before use, transfer 1.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.
pH 6.0 Acetate buffer-Dissolve 50 g of ammonium acetate in 150 mL of water, adjust with glacial acetic acid to a pH of 6.0 , dilute with water to 250 mL , and mix.
Test solution-Dissolve 20.0 g of Citric Acid Monohydrate in 100 mL of water, and add 10 mL of pH 6.0 Acetate buffer. Extract this solution with successive portions of 20, 20 , and 10 mL of a $0.5 \%$ solution of 8 -hydroxyquinoline in chloroform, combining the chloroform extracts in a $50-\mathrm{mL}$ volumetric flask. Dilute the combined extracts with chloroform to volume, and mix.

Standard solution-Prepare a mixture of 2.0 mL of Standard aluminum solution, 10 mL of pH 6.0 Acetate buffer, and 98 mL of water. Extract this mixture as described for the Test solution, dilute the combined extracts with chloroform to volume, and mix.
Blank solution-Prepare a mixture of 10 mL of pH 6.0 Acetate buffer and 100 mL of water. Extract this mixture as described for the Test solution, dilute the combined extracts with chloroform to volume, and mix.

Procedure-Determine the fluorescence intensities of the Test solution and the Standard solution in a fluorometer set at an excitation wavelength of 392 nm and an emission wavelength of 518 nm , using the Blank solution to set the instrument to zero. The fluorescence of the Test solution does not exceed that of the Standard solution ( $0.2 \mu \mathrm{~g}$ per g ).

Assay—Place about 0.550 g of Citric Acid Monohydrate in a tared flask, and weigh accurately. Dissolve in 50 mL of water, add 0.5 mL of phenolphthalein TS, and titrate with 1 N sodium hydroxide VS. Each mL of 1 N sodium hydroxide is equivalent to 64.03 mg of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7 \cdot \mathbf{\Delta}}$ USP28

Sodium Chloride, USP 27 page 1699 and page 1249 of $P F$ 28(4) [July-Aug. 2002]. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Sodium Chloride monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based on the corresponding monograph for Sodium Chloride that was prepared by the European Pharmacopoeia. The European Pharmacopoeia draft was based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Identification B | + | + | + |
| Acidity or alkalinity | + | + | + |
| Bromides | + | + | + |
| Ferrocyanides | + | + | + |
| Iodides | + | + | + |
| Nitrites | + | + | + |
| Phosphates | + | + | + |
| Sulfates | + | + | + |
| Aluminum | + | + | + |
| Barium | + | + | + |
| Iron | + | + | + |
| Magnesium and alka- <br> line-earth metals | + | + | + |
| Potassium | + | + | + |
| Loss on drying | + | + | + |
| Assay | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Appearance of solution, Arsenic, Bacterial endotoxins, Heavy metals, Characters, Labeling, Sterility, Storage.
Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Differences between the European Pharmacopoeia Adoption Stage 6 document and the current USP monograph include the following:

1. Definition-No change.
2. Labeling-Considerations have been made for Bacterial endotoxins and Sterility.
3. Appearance of solution-No change.
4. Packaging-No change.
5. Identification-The test for Chloride is modified to comply with EP standards.
6. Bacterial endotoxins-This test is added to comply with parenteral dosage use.
7. Sterility-This test is added to comply with parenteral dosage use.
8. Acidity or alkalinity-No change.
9. Loss on drying-A sample weight of 1.000 g is added.
10. Limit of bromides-No change.
11. Limit of phosphates-No change.
12. Limit of potassium - The test is changed to a method of direct calibration to comply with EP standards.
13. Iodides-No change.
14. Aluminum-This test is added to conform to EP standards concerning usage in dialysis. This requirement is similar to the Limit of aluminum test in the USP Calcium Acetate monograph.
15. Magnesium and alkaline-earth metals-No change.
16. Arsenic-No change.
17. Iron-The limit prescribed by the USP is retained. The general method is modified to create better conditions of evaluation.
18. Barium-Solution concentrations are altered.
19. Ferrocyanides-No change.
20. Sulfate-The test is modified to comply with EP standards.
21. Nitrites-No change.
22. Assay-This test is modified to comply with EP standards.
(EMC: J. Lane) RTS-40769-7

## Change to read:

## Sodium Chloride

$\mathrm{NaCl}-58.44$
Sodium chleride-
Sodium chleride [7647 14-5].
\#-Sodium Chloride contains not less than-99.0 percent and not more than 100.5 percent of NaCl , caleulateden the dried basis. It contains no added substance.

Packaging and storage- Preserve in well closed containers.
Labeling Where Sodium-Chloride is intended for use in the manufacture of injectable dosage forms, peritoneal dialysis solu tions, hemodialysis solutions, or hemefiltration solutions, it is so tabeled.
Appearance of solution- Dissolve 20.0 g of it in carben dioxidefree water, and dilute with the same solvent 100.0 mL . This solutien is clear and colerless.
Identifiention A solution (1 in 20) respends to the tests for SO ditur $\langle 194\rangle$-and for Chloride $\langle 191\rangle$ :
Acidity or alkalinity To 20 mL of the solution prepared for the test for Appearance of solution, add 0.1 mL of bremothymol blue TS: not more than 0.5 mL of 0.01 N hydrochloric acid or 0.01 N soditm hydroxide is required to change the color of this solution. Loss ondrying (734) - Dry itat $105^{\circ}$ for 2 heurs: it loses not more than $0.5 \%$ of its weight.
Iodides Meisten 5- of it by the drepwise addition of a freshly prepared mixture of 0.15 mL of sodimm nitrite solution ( 1 in 10 ), 2 mL of 1 N sulfurie acid, 25 mL of iodide freestareh TS, and 25 mL of water. After 5 minutes, examine the substance in naturat light. No blue coler is observed.
Aluminum- $\langle\mathbf{2 0 6}\rangle$ (where it is labeled as intended for use in the manufacture of peritoneal dialysis solutions, hemodialysis solutions, or hempfiltration solutions). Proceed as directed using 10.0 g of Sodime Chloride to prepare the Test Preparation: the limit is 0.2 Hy pers.
Magnesitm andalkaline-earth metals To 200 mL of water add 0.1 s of hydroxylamine hydrochloride, 10 mL of pH 10.0 amme nia ammonium chloride buffer (prepared by dissolving 5.4 g of ammenium chloride in 20 mL of water, adding 20 mL of ammo nium hydroxide and diluting to 100 mL ), 1 mL of 0.1 M zine sul fate, and about 0.2 g of eriochrome black $T$ trituration. Heat to about $40^{\circ}$. Titrate this solution with 0.01 M edetate disodium VS until the violet color changes to deep blue. To this solution add 10.0 g of Sodium Chloride dissolved in 100 mL of water. If the eoler changes to violet, titrate the solution with 0.01 M edetate disodium VS to a deep blue endpoint. The volume of 0.01 M edetate disodium consumed in the second titration does not exceed 2.5 mb ( $0.01 \%$, ealeulated as Ca ).
Arsenie, Method $I\langle z 14\rangle \div 1 \mu \mathrm{sper}$ ह.

Barium Dissolve 4.0 g in 20 mL of water, filter if necessary, and divide the solution into portions. To one pertion add 2 mL of 2 N sulfuric acid, and to the other add 2 mL of water: the solutions are equally clear after standing for 2 hours.
Ferrocyanides Dissolve 2.0 g in 6 mL of water. Add 0.5 mL of a mixture of 5 mL of ferric ammenimm-sulfate solution ( 1 g g in 100 mL of 0.1 N sulfuric acid) and 95 mL of ferrous sulfate solution ( 1 in 100): No blue coler develops in 10 mintes.
Sulfate- $\langle z 21\rangle$ - 1.0 g pertion shows no more sulfate than correspends to 0.20 mL of 0.020 N sulfuric acid ( $0.020 \%$ ).
Iron $\langle 244\rangle$-Dissolve 5.0 g in 45 mL of water and 2 mL of hydroehloric acid: the limit is $2 \mu \mathrm{~g}$ per of.
Nitrites To 10 mL of the solution prepared in the test for Appeat ane of solution, add 10 mL of water, and measure the absorbance of the solution in a 1 em cell at 354 mm . The absorbanee is not greater than 0.01 .
Heary metats, Meth $I\langle 234\rangle: 5 \mathrm{ppm}$.
Limit of bromides To 0.5 mL of the solution prepared for the test for Appearane of shltion, add 4.0 mL of water, 2.0 mL of pH-4.7 phenel red TS, and 1.0 mL of chloramine $T$ solution ( 0.1 mos per mL), and mix immediately. After 2 minutes, add 0.15 mL of 0.1 N sodium thiosulfate, mix, dilute with water to 10.0 mL , and mix. The absorbance of this solution mearured at 590 nm, using water as the comparisen liguid, is not greater than that of a Stan dard solution, conemitantly prepared, using 5.0 mL of a solution eontaining 3.0 mg of petassitm bromide per liter and preee ding as above, starting with the addition of 2.0 mL of pH 4.7 phenol red TS ( $0.010 \%$ ).
Limil of phosphates-Dilute 2 mL of the solution prepared in the test for Appear of solution to 100 mL with water. Add 4 mL of sulfomolybdic acid TS, and add 0.1 mL of a mixtme of 1 mL of strenger acid stannous chloride TS and 10 mL of 2 N hydrechlorie acid. Concemitantly prepare a Standard solution using a mixture of $Z \mathrm{~mL}$ of a freshly prepared 1 to 100 dilution of a stock solution eontaining 0.716 mg of monobasic potassium phosphate per mL and 98 mL of water. After 10 minutes compare the colors of 20 mL of each solution. Any color in the test solution is not more in tense than that in the Standard solution ( $0.0025 \%$ ).
Limil of potassium. (where it is labeled as intended for use in the manufacture of injectable dosage forms, peritoneal dialysis solutions, hemodialysis solutions, or hemofiltration solutions)

Stock test solution Transfer 10.0 ह of Sodimm-Chloride to a 100 mL volumetric flask, add water and swinl to dissolve, dilute with water to volume, and mix.

Standerd solution [NOTE-The Standerd solution-and Test si hutions may be modified, if necessary, to obtain solutions of suit able coneentrations adaptable to the linear or working range of the instrument.] Dissolve 1.144 . 5 of potassium chloride, previously dried at $105^{\circ}$ for 3 heurs, in water, dilute with water to 1000 mL , and mix. This solution contains the equivalent of $600 \mathrm{\mu} \mathrm{~g}$ of petassium per mL. Dilute quantitatively with water to obtain a solution containing the equivalent of 50 - 5 g of potascium per mL .

Test solutions. To three 25 mL volumetric flacks add 10.0 mL ef Stock est solutivn. To two of the flasks add 5.0 mL and 10.0 mL of Standed solution, respectively. Dilute all three flasks with water to volume, and mix.

Proedure Using atomic abserption-spectrophotometry (see Spectrophometyy and Light Seattering $(851\rangle$ ), analyze the Test solutions by the method of standard addition analysis using an air acetylene flame and a wavelength of 766.5 nm . The limit is $0.05 \%$.
Assay Dissolve about 200 mg of Sodium Chloride, aceurately weighed, in 10 mL of water, and add 10 mL of glacial acetic acid, 75 mL of methamel, and 3-dreps of eosin Y TS. Titrate, with shak ing, with 0.1 N silver nitrate VS to a pink endpoint. Each mL of 0.1 $N$ silver nitrate is equivalent to 5.844 mg of NaCl .

## ©Sodium Chloride

NaCl
58.44

Sodium Chloride
Sodium Chloride [7647-14-5].
» Sodium Chloride contains not less than 99.0 percent and not more than 100.5 percent of NaCl , calculated on the dried basis.

Packaging and-storage-Preserve in well-closed containers.

Labeling-Where Sodium Chloride is intended for use in the manufacture of injectable dosage forms, peritoneal dialysis solutions, hemodialysis solutions, or hemofiltration solutions, it is so labeled. Where Sodium Chloride must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of Bacterial endotoxins, it is so labeled. Where Sodium Chloride is sterile, it is so labeled.

Appearance of solution-Dissolve 20.0 g of Sodium Chloride in carbon dioxide-free water, and dilute with the same solvent to 100.0 mL . This solution is clear and colorless.

Identification-It responds to the tests for Sodium $\langle 191\rangle$ and for Chloride.

Chloride—Dissolve about 3 mg of Sodium Chloride in 2 mL of water. Acidify with diluted nitric acid and add 0.4 mL of silver nitrate TS. Shake and allow to stand. A curdled, white precipitate is formed. Centrifuge and wash the precipitate with three 1-mL portions of water, and discard the washings. Carry out this operation rapidly in subdued light, disregarding the fact that the supernatant may not become perfectly clear. Suspend the precipitate in 2 mL of water
and add 1.5 mL of 10 N ammonium hydroxide. The precipitate dissolves easily with the possible exception of a few large particles, which dissolve more slowly.

## Bacterial endotoxins $\langle 85\rangle$-If intended for use in the

 manufacture of parenteral dosage forms, it contains net more than 5 I.U. of ere gram. The level of Bacterial endotoxins are such that the requirement under the relevant dosage form monograph(s) in which Sodium Chloride is used can be met. Where the label states that Sodium Chloride must be subjected to further processing during the preparation of injectable dosage forms, the level of Bacterial endotoxins are such that the requirement under the relevant dosage form monograph(s) in which Sodium Chloride is used can be met.Sterility $\langle 71\rangle$ —Where the label states that Sodium Chloride is sterile, it meets the requirements for Sterility, under the relevant dosage form monograph(s) in which Sodium Chloride is used.

Acidity or alkalinity-To 20 mL of the solution prepared for the test for Appearance of solution, add 0.1 mL of bromothymol blue TS: not more than 0.5 mL of 0.01 N hydrochloric acid or 0.01 N sodium hydroxide is required to change the color of this solution.

Loss on drying $\langle 731\rangle$-Dry the test material at $105^{\circ}$ for 2 hours: it loses not more than $0.5 \%$ of its weight, determined on a 1.000 g sample.

Limit of bromides-To 0.5 mL of the solution prepared for the test for Appearance of solution, add 4.0 mL of water, 2.0 mL of pH 4.7 phenol red TS , and 1.0 mL of chloramine T solution ( 0.1 mg per mL ), and mix immediately. After 2 minutes, add 0.15 mL of 0.1 N sodium thiosulfate, mix, dilute with water to 10.0 mL , and mix. The absorbance of this solution measured at 590 nm , using water as the comparison liquid, is not greater than that of a Standard solution, concomitantly prepared, using 5.0 mL of a solution containing
3.0 mg of potassium bromide per L and proceeding as above, starting with the addition of 2.0 mL of pH 4.7 phenol red TS ( $0.010 \%$ ).

Limit of phosphates-Dilute 2 mL of the solution prepared in the test for Appearatre of solution to 100 mL with water. Add 4 mL of sulfomolybdic acid TS, and add 0.1 mL of a mixture of 1 mL of stronger acid stannous chloride TS and 10 mL of 2 N hydrochloric acid. Coneomitantly prepare a Standed solution in the same manner, using a mixture of $Z \mathrm{~mL}$ of a freshly prepared 1 to 100 dilution of a stock solution containing 0.716 mg of menobasic potassitm phesphate per mL and 98 mL of water. After 10 minutes empare the colers of 20 mL of each solution. Any color in the test solution is not more intense than that in the Stanlad solum (0.0025\%, or 25 ppm$)$.

Phosphate stock standard solution-Dissolve an accurately weighed quantity of monobasic potassium phosphate in water to obtain a solution with a concentration of about 0.716 mg per mL .

Phosphate standard solution-Dilute 1 mL of the Stock standard solution with water to 100 mL . Prepare this solution fresh.

Standard solution-Dilute 2 mL of the Phosphate standard solution with water to 100 mL .

Test solution-Dilute 2 mL of the solution prepared in the test for Appearance of solution with water to 100 mL .

Procedure-To the Standard solution and the Test solution, add 4 mL of sulfomolybdic acid TS, and add 0.1 mL of a mixture of 1 mL of stronger acid stannous chloride TS and 10 mL of 2 N hydrochloric acid. After 10 minutes, compare the colors of 20 mL of each solution: any color in the Test solution is not more intense than that in the Standard solution ( $0.0025 \%$ ).

Limit of potassium (where it is labeled as intended for use in the manufacture of injectable dosage forms, peritoneal dialysis solutions, hemodialysis solutions, or hemofiltration solutions)-

Test solution-Transfer 1.00 g of Sodium Chloride to a $100-\mathrm{mL}$ volumetric flask, add water and swirl to dissolve, dilute with water to volume, and mix.

Standard solution-[NOTE-The Standard solution and the Test solution may be modified, if necessary, to obtain solutions of suitable concentrations adaptable to the linear or working range of the instrument.] Dissolve 1.144 g of potassium chloride, previously dried at $105^{\circ}$ for 3 hours, in water, dilute with water to 1000 mL , and mix. This solution contains the equivalent of $600 \mu \mathrm{~g}$ of potassium per mL . Dilute as required to obtain not fewer than three solutions at concentrations that span the expected value in the Test solution.

Procedure-Using atomic absorption spectrophotometry (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ), measure, at least three times, the emission intensity of the Test solution and the Standard solution using an air-acetylene flame and a wavelength of 766.5 nm . Prepare a calibration curve from the mean of the readings obtained with the Standard solution, and determine the concentration of potassium in the Test solution. The limit is $0.05 \%$.

Iodides-Moisten 5 g of Sodium Chloride by the dropwise addition of a freshly prepared mixture of 0.15 mL of sodium nitrite solution ( 1 in 10), 2 mL of 1 N sulfuric acid, 25 mL of iodide-free starch TS, and 25 mL of water. After 5 minutes, examine the substance in natural light. No blue color is observed.

Aluminum (where it is labeled as intended for use in the manufacture of peritoneal dialysis solutions, hemodialysis solutions, or hemofiltration solutions)-

Standard aluminum solution-To 352 mg of aluminum potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of water, swirl to dissolve, add 20 mL of diluted sulfuric acid, dilute with water to volume, and mix. Immediately before use, transfer 1.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.
pH 6.0 Acetate buffer-Dissolve 50 g of ammonium acetate in 150 mL of water, adjust with glacial acetic acid to a pH of 6.0 , dilute with water to 250 mL , and mix.

Test solution-Dissolve 20.0 g of Sodium Chloride in 100 mL of water, and add 10 mL of pH 6.0 Acetate buffer. Extract this solution with successive portions of 20,20 , and 10 mL of a $0.5 \%$ solution of 8 -hydroxyquinoline in chloroform, combining the chloroform extracts in a $50-\mathrm{mL}$ volumetric flask. Dilute the combined extracts with chloroform to volume, and mix.

Standard solution-Prepare a mixture of 2.0 mL of Standard aluminum solution, 10 mL of pH 6.0 Acetate buffer, and 98 mL of water. Extract this mixture as described for the Test solution, dilute the combined extracts with chloroform to volume, and mix.

Blank solution-Prepare a mixture of 10 mL of pH 6.0 Acetate buffer and 100 mL of water. Extract this mixture as described for the Test solution, dilute the combined extracts with chloroform to volume, and mix.

Procedure-Determine the fluorescence intensities of the Test solution and the Standard solution in a fluorometer set at an excitation wavelength of 392 nm and an emission wavelength of 518 nm , using the Blank solution to set the instrument to zero. The fluorescence of the Test solution does not exceed that of the Standard solution $(0.2 \mu \mathrm{~g}$ per g$)$.

Magnesium and alkaline-earth metals-To 200 mL of water add 0.1 g of hydroxylamine hydrochloride, 10 mL of pH 10.0 ammonia-ammonium chloride buffer (prepared by dissolving 5.4 g of ammonium chloride in 20 mL of water, adding 20 mL of ammonium hydroxide and diluting to 100 mL ), 1 mL of 0.1 M zinc sulfate, and about 0.2 g of eriochrome black T trituration. Heat to about $40^{\circ}$. Titrate this solution with 0.01 M edetate disodium VS until the violet color changes to deep blue. To this solution add 10.0 g of Sodium Chloride dissolved in 100 mL of water. If the color changes to violet, titrate the solution with 0.01 M edetate disodium VS to a deep blue endpoint. The volume of 0.01 $M$ edetate disodium consumed in the second titration does not exceed $2.5 \mathrm{~mL}(0.01 \%$, calculated as Ca$)$.

Arsenic, Method $I\langle 211\rangle: 1 \mu \mathrm{~g}$ per g.

## Iron-

Test solution-Use a $10-\mathrm{mL}$ portion of the solution prepared for the test for Appearance of solution.

Standard solution-Immediately before use, dilute Standard iron solution (see Iron $\langle 241\rangle$ ) 1 to 10 with water. This solution contains the equivalent of $1 \mu \mathrm{~g}$ of iron per mL . Combine 4 mL of this solution and 6 mL of water.

Procedure-To each of the solutions, add 2 mL of a 200 g per L solution of citric acid and 0.1 mL of thioglycolic acid. Mix, make alkaline with stronger ammonia water, and dilute with water to 20 mL . After 5 minutes, any pink color in the Test solution is not more intense than that from the Standard solution. The limit is $2 \mu \mathrm{~g}$ per g .

Barium-To 5 mL of the solution prepared for the test for Appearance of solution, add 2 mL of 2 N sulfuric acid and 5 mL of water. To another 5 mL of the solution prepared for the test for Appearance of solution, add 7 mL of water. The solutions are equally clear after standing for 2 hours.

Ferrocyanides-Dissolve 2.0 g in 6 mL of water. Add 0.5 mL of a mixture of 5 mL of ferric ammonium sulfate solution ( 1 g in 100 mL of 0.1 N sulfuric acid) and 95 mL of ferrous sulfate solution (1 in 100): no blue color develops in 10 minutes.

## Sulfate-

Standard sulfate solution A-To 181 mg of potassium sul-
fate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of $30 \%$ alcohol, swirl to dissolve, dilute with $30 \%$ alcohol to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a $1000-\mathrm{mL}$ volumetric flask, dilute with $30 \%$ alcohol to volume, and mix. This solution contains 10 $\mu \mathrm{g}$ of sulfate per mL .

Standard sulfate solution B-To 181 mg of potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of water, swirl to dissolve, dilute with water to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a $1000-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. This solution contains $10 \mu \mathrm{~g}$ of sulfate per mL .

Sodium chloride solution-Dissolve 2.5 g of Sodium Chloride in 50 mL of water.
Procedure-To 1.5 mL of Standard sulfate solution $A$ add 1 mL of a barium chloride solution ( 1 in 4), shake, and allow to stand for 1 minute. To 2.5 mL of the resulting suspension, add 15 mL of the Sodium Chloride solution and 0.5 mL of 5 N acetic acid, and mix (Test solution). Prepare the Standard solution in the same manner, except use 15 mL of Standard sulfate solution B instead of the Sodium Chloride solution: any turbidity produced in the Test solution after 5 minutes standing is not greater than that produced in the Standard solution ( $0.020 \%$ ).

Nitrites-To 10 mL of the solution prepared in the test for Appearance of solution, add 10 mL of water, and measure the absorbance of the solution in a $1-\mathrm{cm}$ cell at 354 nm . The absorbance is not greater than 0.01 .

Heavy metals, Method I $\langle 231\rangle$ : 5 ppm .
Assay—Dissolve 50 mg of Sodium Chloride, accurately weighed, in water and make 50 mL . Titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically (see Titrimetry $\langle 541\rangle$ ). Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of $\mathrm{NaCl}_{\mathbf{\perp}}$ USP28 $^{\text {U }}$

## MONOGRAPHS (NF)

## BRIEFING

Benzyl Alcohol, NF 22 page 2830 and page 879 of $P F$ 28(3) [May-July 2002]. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for Benzyl Alcohol, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following draft monograph represents the ADOPTION STAGE 6 draft, which has been accepted by the members of the Pharmacopeial Discussion Group.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification | + | + | + |
| Appearance of solu- <br> tion | + | + | + |
| Refractive index | + | + | + |
| Acidity | + | + | + |
| Benzaldehyde and <br> other related sub- <br> stances | + | + | + |
| Peroxide value | + | + | + |
| Residue on evapo- <br> ration | + | + | + |
| Assay | + | + |  |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Labeling, Storage.
Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Proposed changes to the current $N F$ monograph include the following:
(1) Definition-The lower limit is changed from 97.0 percent to 98.0 percent based on the argument that this quality is easily obtainable and that the tight limits of the Related compounds test justify a tighter limit for the Assay.
(2) Packaging-No change.
(3) Labeling-Requirements for injectable dosage forms are added.
(4) USP Reference standards-A new reference standard for benzyl alcohol is added to comply with the proposed IR test.
(5) Clarity of solution - This test is added because of the possible use of benzyl alcohol in parenteral dosage forms.
(6) Color of solution-This test is added because of the possible use of benzyl alcohol in parenteral dosage forms.
(7) Identification-In light of comments received, the use of infrared absorption spectrophotometry is adopted for this test.
(8) Specific gravity-This test has been deleted from the monograph and added to the Benzyl Alcohol entry under Description and Solubility.
(9) Peroxide value-This test is added to conform to EP standards.
(10) Refractive index - The lower limit is changed to reflect EP standards.
(11) Acidity-Minor editorial changes are made.
(12) Residue on ignition-This test is deleted. Inorganic compounds are not likely to be present because distillation procedures are used during the production of this substance.
(13) Limit of nonvolatile residue-The sample weight is increased from 2 g to 10 g to ensure greater accuracy.
(14) Halogenated compounds and halides-This test is deleted. The GC method adequately controls benzyl chloride, and inorganic halogenated compounds are not likely to be present because distillation procedures are used during the production of this substance.
(15) Related compounds-The Benzaldehyde test is renamed as a Related compounds test. The test is revised to specify a G16 column based on analyses performed with a DB-Wax column, to reduce solution volumes and to widen the limits for the impurities under test.
(16) Organic volatile impurities-This test is deleted, as it is not necessary.
(17) Assay-The phenolphthalein solution preparation is changed to conform to EP methods.
(EMC: J. Lane) RTS-40773-8

## Change to read:

## Benzyl Aleohol


$\mathrm{E}_{7} \mathrm{H}_{8} \mathrm{O}-108.14$
Benzenemethanel.
Benzyl aleehel [100-51-6].
\#Benzyl Aleohol contains not less than-97.0 pereent and not more than 100.5 pereent of $\mathrm{C}_{7} \mathrm{H}_{8} \Theta$.
Packaging and storage-Preserve in tight containers, and prevent expestre to light.

Identification Add 2 or 3 drops of it to 5 mL of potassimm per manganate solution ( 1 in 20), and acidify with 2 N sulfuric acid: the odor of benzaldehyde is perceptible.
Specifie gravity $\langle 844\rangle$ : between 1.042 and 1.047.
Refractive index- $\langle 834\rangle$ :- 1.539 and 1.541 at $20^{\circ}$.
Aeidity Neutralize 50 mL of aleohol containing 1 mL of phenolphthatein TS with 0.10 N sodium hydroxide. Dissolve 10 mt of Benzyl Aleohel in 10 mL of the neutralized aleohel, and titrate with 0.10 N sodium hydroxide: not more than 1.0 mL is consumed.
Residtreon-ignition- $\langle z 81\rangle$ - Evaporate 25 mL in a suitablecrut eible, and ignite constant weight: not more than $0.005 \%$ is found.
Nonvolatile residte- Evaporate 2.0 of of it to dryness on a water bath, and dry the residue at $105^{\circ}$ for one hour. Cool in a desiecator, and weigh: not more than $1-\mathrm{mg}$ is found.
Halogenated compounds and-halides [NOTE-All glassuare used for this proeedure must be chloride free and may be prepared by soaking overnight in a mixture consisting of water and nitric acid ( $1: 1$ ), rinsing with water, and storing full of water.]

Standard preparation Dissolve an aceurately weighedquantity of sodium chleride in water, and dilute quantitatively, and stepwise if neeessary, with water to obtain a solution having a known eon eentration of 0.0132 mg of NaCl per mL .

Fest preparation Dissolve 6.7 g in 50 mL of aleohel, dilute with water to 100.0 mL , and mix. To 10.0 mL of this solution add 7.5 mL of 2 N sodium hydroxide and 0.125 g of niekel alumifum catalyst, and heat this mixttre in a conieal flask on a water bath for 10 minutes. Allow to eool to room temperature and filter, eellecting the filtrate in a 25 mL volumetrie flack. Wash with three $z \mathrm{~mL}$ pertions of aleohol, dilute the combined filtrate and washings with water to volume, and mix.

Blank preparation Prepare as directed for Test preparation, emitting the Benzyl Aleohel.

Ferric anmanimenlfate solution Shake 30.0. g of ferrie ammonium sulfate with 40 mL of nitric acid, dilute with water to 100 mL , and mix. Centrifuge or filter, if necessary, to obtain a-clear solution.

Proedure-To four 25 mL velumetric flacks separately transfer 10.0 mL of the Test preparation, 10.0 mL of the Statert prept Fation, 10.0 mL of the Blank preparation, and 10.0 mL of water. To each flask add 5.0 mL of Ferric ammenneme solution, mix, and add dropwise and with swirling 2 mL of nitric acideand 5.0 mL of a solution of mereuric thiocyanate in anhydrous alcohol ( 0.3 in 100). Shake, dilute the eonents of each flack with water to volume, and let the solutions stand in a water bath at $20^{\circ}$ for 15 mimutes. Measure the absorbanee at 460 nm of the solution made from the Fest preparation against the solution from the Blank preparation, and measure the absorbance at 460 nm of the solution from the Standard preparation against the solution from water. The former is not greater than the latter $(0.03 \%$ as Cl $)$.

## Benzaldehyde-

Internal standard solution-Prepare a solution-in acetonitrile eontainimg about 0.2 mg of methylparaben per mL.
Mobile phase-Prepare a suitable degassed and filtered mixture of water and acenitrile ( $62: 38$ ). Make adjustments if necessary (see-Chrematograyly $\langle 624$ ).

Stada solution Prepare a solution in ace anitrile eontaining 0.200 mg of benzaldehyde per mL.

Standtard preparation Transfer 5.0 mL of Standerd solution and 5.0 mL of Intern standed solution to a 50 mL volumetric flask, add ace mitrile to volume, and mix.

Fest preparation Pipet 2 mL of Benzyl Aleohel and 10 mL of
 with acenitrile volume, and mix.

Chromatographie syistem (see-Chromatography $\langle 624$ ) The tiquid chromatograph is equipped with - 282 nm detector and a $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}$ column that contains packing L 7 . The flow rate is about 1.0 mL per minute. Chromatograph the Test preparation, and record the peak respenses as directed under Precedtre: the
resolution, $R$, between the benzyl alcehol and methylparaben peaks is not less than 2.0. Chromatograph the Standard preparation, and record the peak respenses as directed mider Procedure: the relative standard deviation of the ratio of the peak respenses for replieate injections is not more than $2.0 \%$.

Proedtre- Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Stand preparation and the Test preparation inte the chromatograph, record the chrematograms, and measure the respenses for the major peaks. The relative retention times are about 0.6 for benzyl aleohol, 0.7 for methylparaben, and 1.0 for benzaldehydeGaleulate the percentage of benzaldehyde taken by the formula:

$$
0.1\left(R_{t}+R_{s}\right)
$$

in which $R_{\downarrow}$ and $R_{f}$ are the response ratios of benzaldehyde to methylparaben obtained for the Test preparation and the-Standard preparition, respectively: net mere than- $0.20 \%$ is fount.
Organie volatile impurities, Method $V\langle 467\rangle \div$ meets the requirements.
Assay Te about 900 mg of Benzyl Aleehel, aeeurately weighed, add 15.0 mL of a mixture of pyridine and acetic anhydride (7:1), and heat on a water bath under reflux for 30 minutes. Coel, add 25 mL of water, add 5 dreps of a 1 in 100 solation of phenelphthalein in pyridine, and titrate with 1 N soditum hydroxide VS. Perform a blank determination. Caleulate the pereentage-of $\mathrm{C}_{7} \mathrm{H}_{8} \Theta$ taken by the fermata:-

$$
10.81 N\left(Y_{p}-Y_{t}\right) / H,
$$

in which $Y_{L}$ and $Y_{B}$ are the number of mL of 1 N sodium hydroxide tosed for the Benzyl Aleohel and the blank, respectively; and $W$ is the weight, in of, of Benzyl Aleohel taken.

## ©Benzyl Alcohol

20024-26
$\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{O} \quad 108.14$
Benzenemethanol.
Benzyl alcohol [100-51-6].
» Benzyl Alcohol contains not less than 98.0 percent and not more than 100.5 percent of $\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{O}$.

Packaging and-storage - Preserve in tight containers, and prevent exposure to light.

Labeling-Where Benzyl Alcohol is intended for use in the manufacture of injectable dosage forms, it is so labeled.

USP Reference standards $\langle 11\rangle$ —USP Benzyl Alcohol RS. Clarity of solution-[NOTE-The Test solution is to be compared to Reference suspension 1 in diffused daylight 5 minutes after preparation of Reference suspension 1.]

Hydrazine solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand 4 to 6 hours before use.

Methenamine solution-Transfer 2.5 g of methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension-[NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of Hydrazine solution to the Methenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension 1. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension 2.

Test solution-Dissolve 2.0 g of Benzyl Alcohol in 60 mL of water, and mix.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm , to obtain a depth of 40 mm . Similarly transfer portions of Reference suspension 1, Reference suspension 2, and water to separate matching test tubes. Compare the Test solution, Reference suspension 1, Reference suspension 2, and water in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). [NOTE-The diffusion of light
must be such that Reference suspension 1 can readily be distinguished from water, and that Reference suspension 2 can readily be distinguished from Reference suspension 1.] The Test solution shows the same clarity as that of water, or its opalescence is not more pronounced than that of Reference suspension 1.

## Color of solution-

Test solution-Use the Test solution prepared in the test for Clarity of solution.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm , to obtain a depth of 40 mm . Similarly transfer a portion of water to a separate matching test tube. Compare the color of the Test solution with that of water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle)$. The Test solution has the color of water.

Identification-Infrared Absorption $\langle 197 \mathrm{~F}\rangle$, on undried specimen.

Peroxide value $\langle 401\rangle$ : not more than 5 .
Refractive index $\langle 831\rangle$ : between 1.538 and 1.541 at $20^{\circ}$.
Acidity-Neutralize 50 mL of alcohol containing 1 mL of phenolphthalein TS with 0.10 N sodium hydroxide. Dissolve 10 mL of Benzyl Alcohol in 10 mL of the neutralized alcohol, and titrate with 0.10 N sodium hydroxide to the first appearance of a pink color that persists for not less than 30 seconds: not more than 1.0 mL is consumed.

Limit of nonvolatile residue-[NOTE-Ensure that the Benzyl Alcohol to be examined complies with the test for Peroxide value $\langle 401\rangle$ before performing this test.] Evaporate 10.0 g of Benzyl Alcohol on a water bath to dryness, and dry the residue at $105^{\circ}$ for 1 hour. Cool in a desiccator, and weigh. The residue weighs not more than 5 mg : not more than $0.05 \%$ of nonvolatile residue is found.

## Related compounds-

Test solution-Use the Benzyl Alcohol specimen under examination.

Ethylbenzene solution-Transfer 100 mg of ethylbenzene, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Test solution to volume, and mix. Transfer 1.0 mL of this solution to a $10-\mathrm{mL}$ volumetric flask, dilute with Test solution to volume, and mix.

Dicyclohexyl solution-Transfer 2.0 g of dicyclohexyl to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Test solution to volume, and mix. Transfer 1.0 mL of this solution to a $10-\mathrm{mL}$ volumetric flask, dilute with Test solution to volume, and mix.

Standard solution 1-Transfer 750 mg of benzaldehyde, accurately weighed, and 500 mg of cyclohexylmethanol, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Test solution to volume, and mix. Transfer 0.5 mL of this solution to a $10-\mathrm{mL}$ volumetric flask, add 1.0 mL of Ethylbenzene solution and 1.5 mL of Dicyclohexyl solution, dilute with Test solution to volume, and mix.
Standard solution 2 (where the Benzyl Alcohol under test is intended for use in the manufacture of injectable dosage forms)—Transfer about 250 mg of benzaldehyde, accurately weighed, and about 500 mg of cyclohexylmethanol, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Test solution to volume, and mix. Transfer 0.5 mL of this solution to a $10-\mathrm{mL}$ volumetric flask, add 1.0 mL of Ethylbenzene solution and 1.0 mL of Dicyclohexyl solution, dilute with Test solution to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ column coated with a $0.5-$ $\mu \mathrm{m}$ film of G16. Helium is used as the carrier gas flowing at a rate of 1.2 mL per minute at $50^{\circ}$. The injection port and
detector temperatures are maintained at about $200^{\circ}$ and $310^{\circ}$, respectively. The column temperature is programmed to increase linearly from $50^{\circ}$ to $220^{\circ}$ at a rate of $5^{\circ}$ per minute, and is maintained at $220^{\circ}$ for 35 minutes. Chromatograph the appropriate Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.28 for ethylbenzene, 0.59 for dicyclohexyl, 0.68 for benzaldehyde, 0.71 for cyclohexylmethanol, and 1.0 for benzyl alcohol; and the resolution, $R$, between benzaldehyde and cyclohexylmethanol is not less than 3.0.

Procedure-Separately inject equal volumes (about 0.1 $\mu \mathrm{L}$ ) of the appropriate Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. [NOTE-Disregard any peak having an area less than 0.01 times the area of the ethylbenzene peak in the chromatogram of the appropriate Standard solution. In the chromatogram of the Test solution, verify that there are no peaks with the same retention times as those of ethylbenzene or dicyclohexyl.]

In the chromatogram of the Test solution, the area of any peak corresponding to benzaldehyde is not greater than the difference between the area of the peak due to benzaldehyde in the chromatogram of Standard solution $1(0.15 \%)$ or in the chromatogram of Standard solution $2(0.05 \%)$ and the area of the peak due to benzaldehyde in the chromatogram of the Test solution.

In the chromatogram of the Test solution, the area of any peak corresponding to cyclohexylmethanol is not greater than the difference between the area of the peak due to cyclohexylmethanol in the chromatogram of Standard solution $1(0.10 \%)$ or in the chromatogram of Standard solution $2(0.10 \%)$ and the area of the peak due to cyclohexylmethanol in the chromatogram of the Test solution.

In the chromatogram of the Test solution, the sum of the areas of any peaks with retention times less than that of benzyl alcohol, excluding the peaks due to benzaldehyde and cyclohexylmethanol, is not greater than four times the area of the ethylbenzene peak in the chromatogram of Standard solution $1(0.04 \%)$ or is not greater than two times the area of the ethylbenzene peak in the chromatogram of Standard solution 2 ( $0.02 \%$ ).
In the chromatogram of the Test solution, the sum of the areas of any peaks with retention times greater than that of benzyl alcohol is not greater than the area of the dicyclohexyl peak in the chromatogram of Standard solution 1 ( $0.3 \%$ ) or in the chromatogram of Standard solution 2 ( $0.2 \%$ ).

Organie volatile impurities, Method $V\langle 467\rangle$ :-meets the requirements.

Assay-To about 900 mg of Benzyl Alcohol, accurately weighed, add 15.0 mL of a freshly prepared mixture of pyridine and acetic anhydride (7:1), and boil under reflux for 30 minutes. Cool, add 25 mL of water, add 0.25 mL of a phenolphthalein solution prepared by dissolving 100 mg of phenolphthalein in 80 mL of alcohol and diluting with water to 100 mL , and titrate with 1 N sodium hydroxide VS. Perform a blank determination (see Titrimetry $\langle 541\rangle$ ). Calculate the percentage of $\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{O}$ taken by the formula:

$$
10.81 N\left(V_{B}-V_{U}\right) / W,
$$

in which $V_{U}$ and $V_{B}$ are the number of mL of 1 N sodium hydroxide used for the Benzyl Alcohol and the blank, respectively; and $W$ is the weight, in g, of Benzyl Alcohol taken. ${ }^{N F 23}$

## BRIEFING

Carboxymethylcellulose Calcium, $N F 22$ page 2841 and page 1252 of PF 28(4) [July-Aug. 2002]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of compendial standards for this article. The revisions presented in this proposal, which represents the ADOPTION STAGE 6 draft, reflect the Committee of Revision's results in this harmonization effort and have been accepted by the members of the Pharmacopeial Discussion Group.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Identification B | + | + | + |
| Identification C | + | + | + |
| Identification D | + | + | + |
| Alkalinity | + | + | + |
| Loss on drying | + | + | + |
| Residue on ignition | + | + | + |
| Limit of chloride | + | + | + |
| Limit of sulfate | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Heavy metals, Packaging and storage

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications

Proposed changes from the current $N F$ monograph include the following:

1. Definition-No change.
2. Packaging-No change.
3. Identification-No change.
4. Alkalinity-No change.
5. Loss on drying-No change.
6. Residue on ignition-Default ignition temperatures are employed.
7. Heavy metals-No change.
8. Limit of chloride-No change.
9. Limit of sulfate-The limit has been modified to $1.0 \%$ from $0.96 \%$.
10. Silicate-Deleted, based on comments that this test is unnecessary since silicate is not added to the article of commerce.
11. Starch-Deleted, based on comments that this test is unnecessary since starch is not added to the article of commerce.
12. Organic volatile impurities-Deleted, based on information that no organic solvents are used in the manufacture of the article of commerce.
(EMC: J. Lane) RTS-40769-6

## Change to read:

## Carboxymethyleellulose Caleium

Gellulese, earboxymethylether, caleium salt.
Cellulese carboxymethyl ether calcium salt. [9050-04-8].
\#Carboxymethyleellulose Caleitm is the caleium salt of a polyeaboxymethyl ether of cellulose.

Packaging and-storage- Preserve in tight containers.
Identifiention-
A: Shake theroughly 0.1 g with 10 mL of water, followed by $z$ mL of 1 N soditm hydroxide, allow to stand for 10 mintutes, and use 1 mL of this solution as the test solution, retaining the remain der of it for Identification tests $B$ and $C$. To 1 mL of the test solution add water to make 5 mL , then to 1 drop of the resulting solution add 0.5 mL of chromotropic acid TS, and heat in a wath bath for 10 minutes: a red purple coler develops.
B: Shake 5 mL of the test solution obtained in Identifieation test $A$ with $10-\mathrm{mL}$ of acetone: a white, floeculent precipita is formed.

C: Shake 5 mL of the test solution obtained in Identifieation test A with 1 mL of ferric chloride TS: a brown, floceulent precipi tate is formed.

Đ: Ignite 1 g to ash, dissolve the residue in 10 mL of water and 5 mL of 6 N aeetic acid, and filter, if neeessary. Boil the filtrate, eool, and neutralize with 6 N ammenium hydroxide: the solution respends to the tests for Calcium- $\langle 19\rangle\rangle$ :
Atkalinity Shak thereughly 1.0 g with 50 mL of freshly beiled and cooled water, and add 2 drops of phenolphthatein TS: no red color develops.
Less on drying $\left\langle 734\right.$ - Dry it at $105^{\circ}$ for 4 heurs: it loses not more than $10.0 \%$ of its weight.
Residue on ignition- $\left\langle\frac{284\rangle}{}\right.$ : between 10.0\% and 20.0\%, about 0.5 g, previously dried, being used for the test, and an ignition tem perature of $450^{\circ}$ to $550^{\circ}$ being used.
Chloride-$\langle z 24\rangle$ Shake heroughly 0.80 g with 50 mb of water, dissolve in 10 mL of 1 N sodium hydroxide, add water to make 100 mL , and use 20 mL of this solution as the test solution, retainime the remainder of it for the test for sulfate. Heat 20 mL of the test solution with 10 mL of 2 N nitric acid in a water bath until a floc eulent precipitate is formed, cool, centrifuge, and remove the supernatant liquid. Wash the precipitate with three $10-\mathrm{mL}$ pertions of water by centrifuging each time, combine the supernatant liquid and the washings, add water to make 100 mL , and mix: a 25 mL pertion of this solution shous ne more chloride than is contained in 0.20 mL of 0.020 N hydrechleric acid ( $0.36 \%$ ).

Silieate- Weigh aceurately about $1-\frac{g}{5}$, ignite in a platinmm dish, add 20 mL of 3 N hydrochloric acid, cover with a wateh glass, and boil gently for 30 minutes. Remove the wateh glass, andera perate in a water bath, with the aid of a current of air, to dryness. Continte heating for 1 hour, add 10 mL of hot water, stir well, and filter through quantitative filter paper. Wash the residue with her water, dry it together with the filter paper after no turbidity is pro dured on the addition of silver nitrate TS to the last washing, then ignite to constant weight: not more than $1.5 \%$ of residue is ob tained.
Sulfate $\langle 224\rangle$-Heat 10 mL of the test solution obtained in the test for Chterite with 1 mL of hydrochloric acid in a water bath untila floculent preeipitate is formed, cool, centrifuge, and remove the supernatant liquid. Wash the precipitate with three 10 mL pertions of water by centriftging each time, combine the supernatant liguid and the washings, add wate to make 100 mL , and mix: a 25 mL pertion of this solution shows ne meresulfate than is contained in 0.20 mL of 0.020 N sulfuric acid ( $0.96 \%$ ).

Heary metats- $\langle$ z31 $\rangle$ - Determine as directed in the test for Heawy metals under Methyleellullose, except to use only 1 gof Carboxy methylcellulose Caleium. The limit is $0.002 \%$.
Stareh Heat 0.10 with 10 mL of water, cool, and add 2 dreps of iodine TS: no blue color develops.
Organie volatile impurities, Methad $I K\langle 467\rangle \div$ meets the requirements.

## ©Carboxymethylcellulose Calcium

Cellulose, carboxymethyl ether, calcium salt.
Cellulose carboxymethyl ether calcium salt
[9050-04-8].
» Carboxymethylcellulose Calcium is the calcium salt of a polycarboxymethyl ether of cellulose.

Packaging and-storage-Preserve in tight containers.

## Identification-

A: Shake thoroughly 0.1 g with 10 mL of water, followed by 2 mL of 1 N sodium hydroxide, allow to stand for 10 minutes, and use 1 mL of this solution as the test solution, retaining the remainder of it for Identification tests $B$ and $C$. To 1 mL of the test solution add water to make 5 mL , then to 1 drop of the resulting solution add 0.5 mL of chromotropic acid TS, and heat in a water bath for 10 minutes: a red-purple color develops.

B: Shake 5 mL of the test solution obtained in Identification test $A$ with 10 mL of acetone: a white flocculent precipitate is formed.

C: Shake 5 mL of the test solution obtained in Identification test $A$ with 1 mL of ferric chloride TS: a brown, flocculent precipitate is formed.

D: Ignite 1 g to ash, dissolve the residue in 10 mL of water and 5 mL of 6 N acetic acid, and filter, if necessary. Boil the filtrate, cool, and neutralize with 6 N ammonium hydroxide: the solution responds to the tests for Calcium $\langle 191\rangle$.

Alkalinity—Shake thoroughly 1.0 g with 50 mL of freshly boiled and cooled water, and add 2 drops of phenolphthalein TS: no red color develops.

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 4 hours: it loses not more than $10.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : between $10.0 \%$ and $20.0 \%$, about 1.0 g , previously dried, being used for the test. an-ignition temperature of $450^{\circ}$ to $550^{\circ}$ being used.

Heavy metals $\langle 231\rangle$-Determine as directed in the test for Heavy metals under Methylcellulose, except to use only 1 g of Carboxymethylcellulose Calcium. The limit is $0.002 \%$.

Limit of chloride $\langle 221\rangle$ - Shake thoroughly 0.80 g with 50 mL of water, dissolve in 10 mL of 1 N sodium hydroxide, add water to make 100 mL , and use 20 mL of this solution as the test solution, retaining the remainder of it for the test for Limit of sulfate. Heat 20 mL of the test solution with 10 mL of 2 N nitric acid in a water bath until a flocculent precipitate is formed, cool, centrifuge, and remove the supernatant. Wash the precipitate with three $10-\mathrm{mL}$ portions of water by centrifuging each time, combine the supernatant and the washings, add water to make 100 mL , and mix: a $25-\mathrm{mL}$ portion of this solution shows no more chloride than is contained in 0.20 mL of 0.020 N hydrochloric acid (0.36\%).

Limit of sulfate $\langle 221\rangle$ —Heat 10 mL of the test solution obtained in test for Limit of chloride with 1 mL of hydrochloric acid in a water bath until a flocculent precipitate is formed, cool, centrifuge, and remove the supernatant. Wash the precipitate with three $10-\mathrm{mL}$ portions of water by centrifuging each time, combine the supernatant and the washings, add water to make 100 mL , and mix: a $25-\mathrm{mL}$ portion of this solution shows no more sulfate than is contained in 0.21 mL of 0.020 N sulfuric acid $(1.0 \%) \cdot \mathbf{\Delta N F 2 3}^{\text {N }}$

## BriEfing

Cellacefate, $N F 22$ page 2845 and page 1253 of $P F$ 28(4) [JulyAug. 2002]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of compendial standards for this article. The revisions presented in this proposal, which represents the ADOPTION STAGE 6 draft, reflect the Committee of Revision's results in this harmonization effort and have been accepted by the members of the Pharmacopoeial Discussion Group.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Packaging and stor- <br> age | + | + | + |
| Identification | + | + | + |
| Viscosity | + | + | + |
| Water | + | + | + |
| Residue on ignition | + | + | + |
| Limit of free acid | + | + | + |
| Phthalyl content | + | + | + |
| Content of acetyl | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Heavy metals, Organic volatile impurities.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Proposed changes from the current $N F$ monograph include the following:

1. Definition-No change.
2. Packaging-No change.
3. USP Reference standards--No change.
4. Identification-Test $B$ is deleted, because it is not needed, as the polymeric character of Cellacefate can be identified by the viscosity determination.
5. Viscosity-No change.
6. Water-No change.
7. Residue on ignition-No change.
8. Heavy metals-No change.
9. Limit of free acid-No change.
10. Organic volatile impurities-No change.
11. Phthalyl content-The strength of sodium hydroxide is corrected to be constant throughout the test.
12. Content of acetyl-No change.
(EMC: J. Lane) RTS-40875-2

## Change to read:

## Cellacefate

Gellulese, acetate, 1,2 benzenediearbexylate.
Cellulese [9004-38 0].
\# Cellacefate is a reaction product of phthalic anhydride and a partial acetate ester of cellulose. It contains not less than 21.5 percent and not more than 26.0 per eent of acetyl $\left(\mathrm{C}_{2} \mathrm{H}_{3} \theta\right)$ groups and not less than 30.0 percent and not more than 36.0 percent of phthalyl(oearboxy benzoyl, $\mathrm{G}_{8} \mathrm{H}_{5} \mathrm{O}_{3}$ ) groups, caleulated on the anhydrous, acid free basis.

Paekaging and-storage- Preserve in tight containers.
USP Referenee standards- $\langle H\rangle$ USP Cellutese Aeetate Phthat ters

## Ifentifieation-

A: Infrat Abserption $\langle 197 \mathrm{~K}\rangle$-Do not dry specimens.
B: Dissolve abert 150 mg in 1 mL of acene, and perriontoa elear slass plate in an area good difflow: a glossy, clear film is depesited as the acene evaporates.
Viseosity $\langle 914\rangle$ - Dissolve 15 -g, caleulated on the anhydrous ba sis, in 85 g of a mixture of 249 parts of anhydreus acetone and 4 part of water, by weight: the apparent viseosity (see Procedure for Methyleellules wher IViscosity $\langle 914\rangle$ ) is between- 45 and 90 cen tipeises, determined at $25 \pm 0.2^{\circ}$.
Water, Methad $I\langle 924\rangle$ : net mere than $5.0 \%$, a mixture of dehy drated aleohol and methylene-chloride (3:2) being used instead of methand as the solvent.
Residue-on ignition- $\langle 284\rangle \div$ net mere than $0.1 \%$.
Heary metals, Method $I\langle z 31\rangle \div 0.001 \%$.
Himit of free acid. Transfer 3.0 g , aceurately weighed, to glass stoppered flask, add 100 mL of dilute methanel (1 in 2), insert the stopper in the flask, and shake for 2 hours. Filter, and wash the flask and the filter with 10 mL pertions of the methanol solution, adding the washings to the filtrate. Titrate the combined filtrate and washings with 0.1 N sodium hydroxide VS to a phenolphtha tein endpeint. Perform a blank determination on 120 mL of the dilute methanol ( 1 in 2). Caleulate the pereentage of free acid, $B$, by the formula:-

$$
0.83064 / H
$$

in which $A$ is the velume, in mL, of 0.1 N sodium hydroxideconstmed, corrected for the blank, and $W$ is the weight, in go, of the Gellacefate, caleulated on the anhydrous basis. Not more that $3.0 \%$, caleulated as phthalic acid, is found.
Organic volatile impurities, Method $I V\langle 467\rangle$ : meets the requirements.
Phthalyl content Transfer about 1-8, aceurately weighed, to a eonical flask, dissolve in 50 mL of a mixture of aleohol and ace one (3:2), add phenolphthalein TS, and titrate with 0.1 N sodium hy droxide VS. Perform a blank determination, and make any neeessary correction. Caleulate the pereentage of phthalyl, on the acid free basis, by the formula:

$$
100[(1.4914 / \text { H) } \quad 1.795 B] /(100-B)
$$

in which 4 is the volume, in mL, of 0.1 N sodimm hydroxide consumed after correction for the blank, $W$ is the weight, in $g$, of Cet tacefate taken, calculated on the anhydrous basis, and $B$ is the pereentage of acid found in the test for Limit of free acid.

Content of acetyl Transfer about 500 mg , aceurately weighed, to a glass stoppered flask, and add 50 mL of water and 50.0 mL of 0.5 N soditm hydroxide VS. Connect the flask to a reflux condenser, and reflux for 60 minutes. Cool, add 5 drops of phenelphthalein TS, and titrate with 0.5 N hydrechloric acid VS. Perform a blank determination. Caleulate the free and combined acids, as acetyl, taken by the formmat:-

$$
2.152(A / H)
$$

in which 4 is the volume, in mL , of 0.5 N soditm hydroxide con sumed after correction for the blank, and $W$ is the weight, ing, of Gellacefate aken, on the anhydrous basis. Caleulate the pereentage of acetyl, on the acid free basis, taken by the formula:
$[100(P-0.5182 B) /(100-B)]-0.5772 C$,
in whieh $P$ is the free and combined acids, as aeetyl, $B$ is the per eentage of acid found in the test for Free aeid, and $C$ is the pereen tage of phthalyl found in the test for Phthaly/ content.

## ${ }^{\Delta}$ Cellacefate

Cellulose, acetate, 1,2-benzenedicarboxylate.
Cellulose acetate phthalate [9004-38-0].
» Cellacefate is a reaction product of phthalic anhydride and a partial acetate ester of cellulose. It contains not less than 21.5 percent and not more than 26.0 percent of acetyl $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}\right)$ groups and not less than 30.0 percent and not more than 36.0 percent of phthalyl(o-carboxybenzoyl) $\left(\mathrm{C}_{8} \mathrm{H}_{5} \mathrm{O}_{3}\right)$ groups, calculated on the anhydrous, acid-free basis.

Packaging-and-storage - Preserve in tight containers.
USP Reference standards $\langle 11\rangle —$ USP Cellulose Acetate Phthalate RS.

Identification, Infrared absorption $\langle 197 \mathrm{~K}\rangle$ —Do not dry specimens.

Viscosity $\langle 911\rangle$-Dissolve 15 g , calculated on the anhydrous basis, in 85 g of a mixture of 249 parts of anhydrous acetone and 1 part of water, by weight: the apparent viscosity (see Procedure for Methylcellulose under Viscosity $\langle 911\rangle$ ) is between 45 and 90 centipoises, determined at 25 $\pm 0.2^{\circ}$.

Water, Method I $\langle 921\rangle$ : not more than $5.0 \%$, a mixture of dehydrated alcohol and methylene chloride (3:2) being used instead of methanol as the solvent.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$. Ignition temperature $600 \pm 50^{\circ}$.

Heavy metals, Method II $\langle 231\rangle$ : $0.001 \%$.
Limit of free acid—Transfer 3.0 g , accurately weighed, to a glass-stoppered flask, add 100 mL of dilute methanol ( 1 in 2), insert the stopper in the flask, and shake for 2 hours. Filter, and wash the flask and the filter with two $10-\mathrm{mL}$ portions of the methanol solution, adding the washings to the filtrate. Titrate the combined filtrate and washings with 0.1 N sodium hydroxide VS to a phenolphthalein endpoint. Perform a blank determination on 120 mL of the dilute methanol (1 in 2). Calculate the percentage of free acid, $B$, by the formula:

$$
0.8306 A / W,
$$

in which $A$ is the volume, in mL , of 0.1 N sodium hydroxide consumed, corrected for the blank; and $W$ is the weight, in g , of the Cellacefate, calculated on the anhydrous basis. Not more than $3.0 \%$, calculated as phthalic acid, is found.

Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

Phthalyl content-Transfer about 1 g , accurately weighed, to a conical flask, dissolve in 50 mL of a mixture of alcohol and acetone (3:2), add phenolphthalein TS, and titrate with
0.1 N sodium hydroxide VS. Perform a blank determination, and make any necessary correction. Calculate the percentage of phthalyl, on the acid-free basis, by the formula:

$$
100[(1.491 A / W)-1.795 B] /(100-B),
$$

in which $A$ is the volume, in mL , of 0.1 N sodium hydroxide consumed after correction for the blank; $W$ is the weight, in g , of Cellacefate taken, calculated on the anhydrous basis; and $B$ is the percentage of acid found in the test for Limit of free acid.

Content of acetyl-Transfer about 100 mg , accurately weighed, to a glass-stoppered flask, and add 25.0 mL of 0.1 N sodium hydroxide VS. Connect the flask to a reflux condenser, and reflux for 30 minutes. Cool, add 5 drops of phenolphthalein TS, and titrate with 0.1 N hydrochloric acid VS. Perform a blank determination. Calculate the free and combined acids, as acetyl, taken by the formula:

$$
0.4305(A / W)
$$

in which $A$ is the volume, in mL , of 0.1 N sodium hydroxide consumed after correction for the blank; and $W$ is the weight, in g , of Cellacefate taken, on the anhydrous basis. Calculate the percentage of acetyl, on the acid-free basis, taken by the formula:

$$
[100(P-0.5182 B) /(100-B)]-0.5772 C,
$$

in which $P$ is the free and combined acids, as acetyl; $B$ is the percentage of acid found in the test for Limit of free acid; and $C$ is the percentage of phthalyl found in the test for Phthalyl content. $\mathbf{A N F 2 3}^{\text {N }}$

## Briefing

Cellulose Acetate, NF 22 page 2847 and page 1255 of $P F 28$ (4) [July-Aug. 2002]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of compendial standards for this article. The revisions presented in this proposal, which represents the ADOPTION STAGE 6 draft, reflect the Committee of Revision's results in this harmonization effort and have been accepted by the members of the Pharmacopeial Discussion Group.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | - | + |
| Packaging and stor- <br> age | + | - | + |
| Labeling | + | - | + |
| Identification | + | - | + |
| Loss on drying | + | - | + |
| Residue on ignition | + | - | + |
| Free acid | + | - | + |
| Content of acetyl | + | - | + |

JP will not include this monograph and has not therefore participated in harmonization.

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Microbial contamination, Heavy metals.

Specific local attributes: Organic volatile impurities.
Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Proposed changes from the current $N F$ monograph include the following:

1. Definition-This section is clarified with the indication that the acetyl group limits are to be calculated on the dried basis. 2. Packaging-No change.
2. Labeling-Requirements are added that the labeling indicate nominal or targeted acetyl content value.
3. USP Reference standards-No change.
4. Identification-No change.
5. Loss on drying-No change.
6. Residue on ignition-No change.
7. Heavy metals-No change.
8. Free acid-The requirement that the material be previously dried is deleted.
9. Organic volatile impurities-No change.
10. Content of acetyl-The requirement that the material be previously dried is deleted.
(EMC: J. Lane) RTS-40769-5

## Change to read:

## Cellulose Acetate

| Gellulese aceate. |  |
| :---: | :---: |
| Gellulose, acetate | [9004-35 |
| Gellulose, diaceta | [9035-69-2]. |
| Gellulose, triacet | [9012 09 |

\#Cellulose Acetate is partially or completely acety tated cellulose. It contains not less than 29.0 pereent and not more than 44.8 percent, by weight, of acety $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}\right)$ groups. Its acetyl content is not less than 90.0 pereent and not more than 110.0 percent of that indicated on the label.

Paekaging and-storage - Preserve in tight containers.
Labeling The label stater the neminal pereentage entent of aceyly
USP Referenee standards- $\langle H\rangle$-USP Cellutose Aeetate RS.
Identifieation- Prepare a - 1 in 10 solution of Cellulose Acetate, previously dried, in dioxane. Spread 1 drep of the solution on a sodium chloride plate, place a second sodium chloride plate over it, and spread the specimen between the plates. Separate the plates, heat them both at $105^{\circ}$ for 1 hemr, and reassemble the dried plates: the IR absorption speetrum exhibits maxima only at the same wavelengths as that of a similar preparation of USP Cellulase Acetate RS, treate in the same manner.
Less endrying $\left\langle 734\right.$ ) - Dry it at $105^{\circ}$ for 3 heurs: it loses net mere than $5.0 \%$ of its weight.
Residue on ignition- $\langle z 81\rangle \div$ not more than $0.1 \%$.
Heary metals, Method $I T\langle 231\rangle \div 0.001 \%$.
Free acid- Transfer about 5-o, previously dried and aceurately weighed, to 250 mL flask. Add 150 mL of freshly beiled, cooled water, insert the stopper in the flack, swirl the suspension gently, and allow it to stand for 3 hours. Filter through paper, and wash the flask and the filter with water, adding these washings to the filtrateAdd phenelphthalein-TS, and titrate the combined filtrate and washings with 0.01 N soditm hydroxide VS. Each mL of 0.04 N sodium hydroxide is equivalent to 0.6005 mg of acetic acid: not mere than $0.1 \%$ is found, on the dried basis.
Organic volatile impurities, Method $I K\langle 467\rangle$ :meets the require ments.

## Content of neetyl-

FOR CELLLLOSE ACETATE LABELED TOCONTAIN NOT MORE THAN 42.0\%OF ACETYL GROUPS- Transfer about 2 of, previously dried and aceurately weighed, to 500 mL flack. Add 100 mL of acetene and 5 mL to 10 mL of water to the flask, imsert the stopper in the flask, and stir with a magnetic stimrer until solution is complete. Add 30 mL , aceurately measured, of 1.0 N sodimm hydroxide VS to the solution, with constant stirring. $\Lambda$ finely divided precipitate of regenerated cellulese, free frem lumps, is obtained. Insert the stopper in the flack, and stir with a magnetic stirrer for 30 minutes. Add 100 mL of hot water, washing down the sides of the flask, and stir for 4 to 2 minutes. Titrate the exeess sodium hydrexide solution with 1.0 A sulfuric acid VS to a phenelphthatein endpeint. Treat a blank in the same manner. Caleulate the percentage of acetyl taken by the formmat:-

$$
4.305(B-A) / W
$$

in which $B$ and $A$ are the volumes, in mL , of 1.0 N sulfuric acid consumed by the blank and the Cellulese Acetate, respectively, and Whis the weight, in of, of Cellulose-Acetate taken.

FOR-GELLULOSE ACETATE LABELED-TOCONTAIN MORETHAN-42.0\% OF ACETYL GROUPS - Transfer about 2 g, previeusly dried and ac eurately weighed, to a 500 mL conieal flask. Add 30.0 mL of dimethylsulfoxide and 100 mL of aeetene, and stir for 16 hours with the aid of a magnetic stirrer. Pipet 30 mL of 1 N sodium hydroxide VS slewly inte the flask, with censtant stiming. Insert the stepper in the flask, and stir for 6 minutes. Allow to stand without stirrimg for 60 minates. Restmestiming, and add $100-\mathrm{mL}$ of water that has been preheated to $80^{\circ}$, washing down the sides of the flask. Stir for 2 minutes, and coel toreom temperature. Add-4 to 5-drops of phenelphthalein TS, and titrate the exeess soditm hydroxide with 0.5 N hydrechlerie acid VS. Ade an aceurately meastred ex eess of about 0.5 mL of 0.5 N hydrechloric acid VS. Stir for 5 min utes. Allow to stand for 30 minutes. Titrate with 0.5 N sedium hydrexide $V S$ to a persistent pink endpeint, using a magnetic stir fer for agitation. Caleulate the net number of milliequivalents of sodium hydroxide consumed, and correet this value by use of the average of two blank determinations run concomitantly through the entire procedure. Caleulate the pereentage of acetyl taken by the fermula:

$$
4.305 n+H 2
$$

in which $n$ is the corrected value of the net number of milliequiven lents of sedium hydrexide consumed, and $M$ is the weight, in gi, of Cellulese-Acetate taken.

## ©Cellulose Acetate

Cellulose acetate.
$\begin{array}{ll}\text { Cellulose, diacetate } & {[9035-69-2] .} \\ \text { Cellulose, triacetate } & {[9012-09-3] .}\end{array}$
» Cellulose Acetate is partially or completely acetylated cellulose. It contains not less than 29.0 percent and not more than 44.8 percent, by weight, of acetyl $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}\right)$ groups, calculated on the dried basis. Its acetyl content is not less than 90.0 percent and not more than 110.0 percent of that indicated on the label.

Packaging storage-Preserve in tight containers.
Labeling-The tabeling states the nominal percentage content of acetyl.

USP Reference standards $\langle 11\rangle$ —USP Cellulose Acetate $R S$.

Identification-Prepare a solution of Cellulose Acetate (1 in 10), previously dried, in dioxane. Spread 1 drop of the solution on a sodium chloride plate, place a second sodium chloride plate over it, and spread the specimen between the plates. Separate the plates, heat them both at $105^{\circ}$ for 1 hour, and reassemble the dried plates: the IR absorption spectrum exhibits maxima only at the same wavelengths as that of a similar preparation of USP Cellulose Acetate RS, treated in the same manner.

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 3 hours: it loses not more than $5.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $0.001 \%$.
Free acid-Transfer about 5 g , accurately weighed, to a $250-\mathrm{mL}$ flask. Add 150 mL of freshly boiled, cooled water, insert the stopper into the flask, swirl the suspension gently, and allow it to stand for 3 hours. Filter through paper, and wash the flask and the filter with water, adding these washings to the filtrate. Add phenolphthalein TS, and titrate the combined filtrate and washings with 0.01 N sodium hydroxide VS. Calculate the percentage of free acid in the portion of Cellulose Acetate taken by the formula:

$$
0.06005 A / W,
$$

in which $A$ is the volume, in mL , of 0.01 N sodium hydroxide consumed; and $W$ is the weight, in g , of the Cellulose Acetate taken, calculated on the dried basis. Not more than $0.1 \%$, calculated as acetic acid, is found.

Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

## Content of acetyl-

FOR CELLULOSE ACETATE LABELED TO CONTAIN NOT MORE THAN $42.0 \%$ OF ACETYL GROUPS-Transfer about 2 g , accurately weighed, to a $500-\mathrm{mL}$ flask. Add 100 mL of acetone and 5 mL to 10 mL of water to the flask, insert the
stopper into the flask, and stir with a magnetic stirrer until solution is complete. Add 30 mL , accurately measured, of 1.0 N sodium hydroxide VS to the solution, with constant stirring. A finely divided precipitate of regenerated cellulose, free from lumps, is obtained. Insert the stopper into the flask, and stir with a magnetic stirrer for 30 minutes. Add 100 mL of water that has been preheated to $80^{\circ}$, washing down the sides of the flask, stir for 2 minutes, and cool to room temperature. Titrate the excess sodium hydroxide solution with 1.0 N sulfuric acid VS to a phenolphthalein endpoint. Treat a blank in the same manner. Calculate the percentage of acetyl in the portion of Cellulose Acetate taken by the formula:

$$
4.305(B-A) / W,
$$

in which $B$ and $A$ are the volumes, in mL , of 1.0 N sulfuric acid consumed by the blank and the Cellulose Acetate, respectively; and $W$ is the weight, in g , of Cellulose Acetate taken, calculated on the dried basis.

## FOR CELLULOSE ACETATE LABELED TO CONTAIN MORE

THAN $42.0 \%$ OF ACETYL GROUPS-Transfer about 2 g , accurately weighed, to a $500-\mathrm{mL}$ conical flask. Add 30.0 mL of dimethylsulfoxide and 100 mL of acetone, and stir for 16 hours with the aid of a magnetic stirrer. Pipet 30 mL of 1 N sodium hydroxide VS slowly into the flask, with constant stirring. Insert the stopper into the flask, and stir for 6 minutes. Allow to stand without stirring for 60 minutes. Resume stirring, and add 100 mL of water that has been preheated to $80^{\circ}$, washing down the sides of the flask. Stir for 2 minutes, and cool to room temperature. Add 4 to 5 drops of phenolphthalein TS, and titrate the excess sodium hydroxide solution with 0.5 N hydrochloric acid VS. Add an accurately measured excess of about 0.5 mL of 0.5 N hydrochloric acid VS. Stir for 5 minutes. Allow to stand for 30 minutes. Titrate with 0.5 N sodium hydroxide VS to a persistent pink endpoint, using a magnetic stirrer for
agitation. Calculate the net number of milliequivalents of sodium hydroxide consumed, and correct this value by use of the average of two blank determinations run concomitantly through the entire procedure. Calculate the percentage of acetyl in the portion of Cellulose Acetate taken by the formula:

$$
4.305 n / W,
$$

in which $n$ is the corrected value of the net number of milliequivalents of sodium hydroxide consumed; and $W$ is the weight, in g , of Cellulose Acetate taken, calculated on the dried basis. ^NF $^{\text {F2 }}$

## Briefing

Croscarmellose Sodium, NF 22 page 2856 and page 1567 of PF 28(5) [Sept.-Oct. 2002]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of compendial standards for the Croscarmellose Sodium monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The revisions presented in this proposal, which represents the ADOPTION STAGE 6 draft , are based on comments received in response to the Official Inquiry Stage 4 draft, which appeared in Pharmacopeial Previews on page 4007 of PF 23(3) [May-June 1997].

The following Harmonization Stage 6 draft is present for regional implementation. The table below illustrates which attributes of the draft are agreed upon by EP, JP, and USP, and which attributes are not.
Pharmacopeial Discussion Group Sign-Off
Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Packaging and stor- <br> age | + | + | + |
| Identification A | + | + | + |
| Identification B | + | + | + |
| Identification C | - | + | + |
| pH | + | + | + |
| Loss on drying | + | + | + |
| Residue on ignition | + | + | + |
| Degree of substitu- <br> tion | + | + | + |
| Settling volume | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Identification of sodium, Microbial limits, Heavy metals, Sodium chloride and sodium blycolate, Water-soluble substances, Organic volatile impurities.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Differences between this Adoption Stage 6 document and the current $N F$ monograph include the following:
(1) Definition-Revisions are made to make the definition more specific.
(2) Packaging-The container type is changed from tight to wellclosed.
(3) Identification-No change.
(4) Microbial limits-This section is added to strengthen the monograph. The proposed limits are consistent with those proposed for oral solids.
(5) pH -The volume of water used is changed to 100 mL , and the mixing time is changed from 1 hour to 5 minutes, based on comments received.
(6) Loss on drying - The drying time is changed to 6 hours, based on data indicating that an equilibrium loss on drying value is obtained after 6 hours.
(7) Sodium chloride and sodium glycolate-No change.
(8) Residue on ignition-This section is added as a test separate from Degree of substitution.
(9) Heavy metals-No change.
(10) Degree of substitution-The Residue on ignition test is deleted, having become a separate test.
(11) Content of water-soluble material-No change.
(12) Settling volume-No change.
(13) Organic volatile impurities-No change.
(EMC: J. Lane) RTS-40875-1

## Change to read:

## Crosearmellose Sodium

## \#-Crosearmellose Sodimm is across-linked polymer of

 earboxymethyleellulese sodium.
## Paekaging and-storage-Preserve in tight containers.

## Identifieation-

A: Mix 1 g of it with 100 mL of methylene blue solution ( 1 im 250,000 ), stir the mixture, and allow it to settle: the Croscarmellose Sodium absorbs the methylene blue and settles as a blue, fibrous mass.
B: Mix 1 g of it with 50 mL of water. Transfer 1 mL of the mix ture to small test tube, and add 1 mL of water and 5 drops of 1 naphthel TS. Ineline the test tube, and carefully add 2 mL of sulfuric acid down the side-so that it forms a lower layer: a red purple coler develops at the interface.

C: A portion of the mixture of it with water, prepared as direc ted in Identification test $B$, respends to the tests for Sodium-〈194): $\mathbf{p H}\langle 794\rangle$ - Mix 1 g of it with 99 mL of water for 1 hourr: the pH of the dispersion is between 5.0 and 7.0 .
Loss-0n-drying $\left\langle 734\right.$ ) Dry it at $105^{\circ}$ to constant weight: it leses tot mere than $10.0 \%$ of its weight.

## Sodium-chloride and-sodium-glyeolate-

SODHM CHLORIDE-Weigh aceurately about 5 g of it into 250 mL beaker, add 50 mL of water and 5 mL of $30 \%$ hydrogen per oxide, and heat on a steam bath for 20 minutes, stirring oceasionally to ensure hydration. Cool, add 100 mL of water and 10 mL of
nitric acid, and titrate with 0.05 N silver nitrate VS , determining the endpoint potentiometrieally, using a silver based indientor elecrode and a double junction reference electrode containing $10 \%$ petassium nittate filling solution in the outer jacket and a standard filling solution in the inner jacket, and stiming constantly (see Titrimetry (544) ). Caleulate the pereentage of sodium chloride in the specimen taken by the formula:

$$
584.4 \mathrm{VNH}(100-b) H 4,
$$

in which $V$ and $N$ represent the volume, in mL , and the nommality, respectively, of the-silver nitrate, $b$ is the pereentage of Loss ont drying, determine separately, Wis the weight, in of, of the speci men, and 584.4 is an equivalence factor for sodium chloride.
sodum glycolate Transfer about 500 mg of it, aceurately weighed, into a 100 mL beaker, meisten thoreughly with 5 mL of glacial acetic acid, followed by 5 mL of water, and stir with a glass rod to ensure proper hydration (usually about 15 minutes). Slowly add 50 mL of acetone, with stirring, then add 1 gof sodium ehleride, and stir for several minthes to ensure complete precipita tion of the earboxymethyleellulose. Filter through a soft, open tex tured paper, previously wetted with a small amount facetone, and eellect the filtrate in a 100 mL volumetric flask. Use an additional 30 mL of ace 0 ne facilitate the transfer of the solids and to wash the filter cake, then dilute with acetene to volume, and mix.

Prepare a series of standard solutions as follows. Transfer 100 mg of ghyeolic acid, previously dried in a desiecator at room tem-perature-overnight and aceurately weighed, to a 100 mL volumetric flask, dissolve in water, dilute with water to volume, and mix. Use this solution within 30 days. Transfer $1.0,2.0,3.0$, and 4.0 mL pertions of the solution, respectively, to separate 100 mL velumetric flasks, add water to each flask to make 5 mL , then add 5 mL of glacial acetic acid, dilute with acetone to volume, and mix.

Fransfer 2.0 mL of the test solution and 2.0 mL of each standard selution to separate 25 mL volumetric flacks, and prepare a blank flask eontaining 2.0 mL of a solution eontaining 5\% ach of glacial acetic acid and water in acetone. Place the uncovered flasks in a boiling water bath for 20 -minutes, aceurately timed, to remove the acetone, remove from the bath, and cool. Add to each flack 5.0 mL of 2,7 dihydroxynaphthatene TS, mix, add an additionat 15 mL , and again mix. Cover the mouth of each flack with a small piece of alumintm foil. Place the flasks upright in a beiling water bath for 20 minutes, then remove from the bath, cool, dilute with sulftric acid to volume, and mix.

Determine the absorbance of each solution at 540 nm, with a suitable spectrophotemeter, against the blank, and prepare a standard eurve using the abserbance obtained from the standard solur tions. From the standard eurve and the absorbance of the test specimen, determine the weight (w), in me, of glyeolic acid in the-sperimen, and caleulate the pereentage of soditm glyeolate in the specimen taken by the formetla:

$$
12.9 w /(100-b) H 4,
$$

in which 12.9 is a fator converting glyeolic acid to sodimm glyeo tate, $b$ is the pereentage of Less on drying, determined separately, and $W$ is the weight, in g, of the specimen. The sum of the pereen tages of sodium chloride and sodium slycolate is not more than $0.5 \%$.
Heary metats, Methed $I\langle\langle z 3\rangle) \div 0.001 \%$.
Degree of substitution- Transfer about 1-of it, aceurately weighed, to a glass stoppered, 500 mL conieal flask, add- 300 mL of sodium chloride solution ( 1 in 10 ), then add 25.0 mL of 0.1 N soditm hydroxide VS. Insert the stopper, and allow to stand for 5 minates with intermittent shaking. Add 5 -drops of m-eresel purple TS, and from a buret add about 15 mL of 0.1 N hydrochloric acid VS. Insert the stopper in the flask, and shake. If the solution is purple, add 0.1 N hydrochloric acid VS in 1 mL peritions until the
solution becomes yellow, shaking after each addition. Titrate with 0.1 N sodium hy droxide VS to a purple endpoint. Caleulate the net number of milliequivalents, $M$, of base required for the neutraliza tion of 1 g of Creseamellose Sodium, on the dried basis. Deter mine the percentage of residue on ignition, $C$, of the Gresearmellose Soditm on the dried basis as directed under Resi due on Ignition $\langle 284\rangle$, using sufficient sulfuric acid to meisten the entire residue after the initial charring step, and additional sulfurie acid if an excessive amount of carbonaceous material remains after the initial complete volatilization of white fumes.

Galeulate the degree of acid earboxymethyl substitution, $A$, at ken by the formula:

$$
1150 M H(7102-412 M-80 C)
$$

Galeulate the degree of sodium earboxymethyl substitution, $S$, ta ken by the formula:

$$
(162+584) C /(7102 \quad 80 C)
$$

The degree of substitution is the sum- of $A+S$. It is between 0.60 and 0.85 , caleulated on the dried basis.
Content of water soluble material Disperse about 10- s, at eurately weighed, in 800 mL of water, cucurately meacured, and stir for 1 minate every 10 minutes durimg the farst 30 minutes. A1 low tostand for an additional hour, or centrifuge, if neeessary. Deeant about 200 mL of the aqueous-slumy onto a rapid filtering fllter paper in a vacuum filtration fanmel, apply vacuum, and collect about 150 mL of the filtrate. Pour the filtrate into a tared 250 mL beaker, weigh aceurately, and caleulate the weight, in of, of the fit trate, $\mathrm{H}_{3}$, by difference. Coneentrate on a hot plate to a small wot tume, but not to dryness, dry at $105^{\circ}$ for 4 hours, again weigh, and ealeulate the weight, in g, of residue $H_{4}$, by difference. Caleulate the pereentage of water soluble material in the specimen, on the Aried basis, taken by the formula:

$$
100 H_{4}\left(800+W_{2}\right) /\left[H_{2} H_{3}(1-0.01 b)\right]
$$

in whieh $\mathrm{H}_{2}$ is the weight, in g, of the specimen taken, and $b$ is the pereentage Loss on drying of the-specimen taken. It is between $1.0 \%$ and $10.0 \%$

Settling voltme To 75 mL of water in a 100 mL graduated ey tinder add $1.5-\frac{g}{}$ of it in -0.5 - 5 pertions, shaking vigoreusly after each addition. Add water to make 100 mL , shake again until all of the pewder is hemegeneeusly distributed, and allow to stane for 4 heurs. Note the volume of the settled mass. It is between 10.0 and 30.0 mL .

Organie volatile imptrities, Method $H\langle\langle 467\rangle \div$ meets the requirements.

## ${ }^{\Delta}$ Croscarmellose Sodium

## » Croscarmellose Sodium is the sodium salt of a

 cross-linked, partly $O$-(carboxymethylated) cellulose.Packaging and-storage-Preserve in well-closed containers.

## Identification-

A: Mix 1 g of it with 100 mL of methylene blue solution ( 1 in 250,000 ), stir the mixture, and allow it to settle: the Croscarmellose Sodium absorbs the methylene blue and settles as a blue, fibrous mass.

B: Mix 1 g of it with 50 mL of water. Transfer 1 mL of the mixture to a small test tube, and add 1 mL of water and 5 drops of 1-naphthol TS. Incline the test tube, and carefully add 2 mL of sulfuric acid down the side so that it forms a lower layer: a reddish-violet color develops at the interface.

C: A portion of the mixture of it with water, prepared as directed in Identification test $B$, responds to the flame test for Sodium $\langle 191\rangle$.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed 1000 per g , the total combined molds and yeasts count does not exceed 100 per g , and it meets the requirements of the tests for absence of Escherichia coli. $\mathbf{p H}\langle 791\rangle$-Mix 1 g of it with 100 mL of water for 5 min utes: the pH of the dispersion is between 5.0 and 7.0.

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 6 hours: it loses not more than $10.0 \%$ of its weight.

## Sodium chloride and sodium glycolate-

SODIUM CHLORIDE-Weigh accurately about 5 g of it into a $250-\mathrm{mL}$ beaker, add 50 mL of water and 5 mL of $30 \%$ hydrogen peroxide, and heat on a steam bath for 20 minutes, stirring occasionally to ensure hydration. Cool, add 100 mL of water and 10 mL of nitric acid, and titrate with 0.05 N silver nitrate VS, determining the endpoint potentiometrically, using a silver-based indicator electrode and a dou-ble-junction reference electrode containing $10 \%$ potassium
nitrate filling solution in the outer jacket and a standard filling solution in the inner jacket, and stirring constantly (see Titrimetry $\langle 541\rangle$ ). Calculate the percentage of sodium chloride in the specimen taken by the formula:

$$
584.4 V N /[(100-b) W]
$$

in which $V$ and $N$ represent the volume, in mL , and the normality, respectively, of the silver nitrate; $b$ is the percentage of Loss on drying, determined separately; $W$ is the weight, in g , of the specimen; and 584.4 is the equivalence factor for sodium chloride.

SODIUM GLYCOLATE-Transfer about 500 mg of it, accurately weighed, into a $100-\mathrm{mL}$ beaker, moisten thoroughly with 5 mL of glacial acetic acid, followed by 5 mL of water, and stir with a glass rod to ensure proper hydration (usually about 15 minutes). Slowly add 50 mL of acetone, with stirring, then add 1 g of sodium chloride, and stir for several minutes to ensure complete precipitation of the carboxymethylcellulose. Filter through a soft, opentextured paper, previously wetted with a small amount of acetone, and collect the filtrate in a $100-\mathrm{mL}$ volumetric flask. Use an additional 30 mL of acetone to facilitate the transfer of the solids and to wash the filter cake, then dilute with acetone to volume, and mix.

Prepare a series of standard solutions as follows. Transfer 100 mg of glycolic acid, previously dried in a desiccator at room temperature overnight and accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in water, dilute with water to volume, and mix. Use this solution within 30 days. Transfer $1.0-\mathrm{mL}, 2.0-\mathrm{mL}, 3.0-\mathrm{mL}$, and $4.0-\mathrm{mL}$ portions of the solution, respectively, to separate $100-\mathrm{mL}$ volumetric flasks, add water to each flask to make 5 mL , then add 5 mL of glacial acetic acid, dilute with acetone to volume, and mix.

Transfer 2.0 mL of the test solution and 2.0 mL of each standard solution to separate $25-\mathrm{mL}$ volumetric flasks, and prepare a blank flask containing 2.0 mL of a solution containing $5 \%$ each of glacial acetic acid and water in acetone. Place the uncovered flasks in a boiling water bath for 20 minutes, accurately timed, to remove the acetone, remove from the bath, and cool. Add to each flask 5.0 mL of $2,7-$ dihydroxynaphthalene TS, mix, add an additional 15 mL , and again mix. Cover the mouth of each flask with a small piece of aluminum foil. Place the flasks upright in a boiling water bath for 20 minutes, then remove from the bath, cool, dilute with sulfuric acid to volume, and mix.

Determine the absorbance of each solution at 540 nm , with a suitable spectrophotometer, against the blank, and prepare a standard curve using the absorbances obtained from the standard solutions. From the standard curve and the absorbance of the test specimen, determine the weight (w), in mg, of glycolic acid in the specimen, and calculate the percentage of sodium glycolate in the specimen taken by the formula:

$$
12.9 w /[(100-b) W]
$$

in which 12.9 is a factor converting glycolic acid to sodium glycolate; $b$ is the percentage of Loss on drying, determined separately; and $W$ is the weight, in g , of the specimen. The sum of the percentages of sodium chloride and sodium glycolate is not more than $0.5 \%$.

Residue on ignition $\langle 281\rangle$ : between $14.0 \%$ and $28.0 \%$, calculated on the dried basis, about 1.0 g being used for the test, using sufficient sulfuric acid to moisten the entire residue after the initial charring step, and additional sulfuric acid if an excessive amount of carbonaceous material remains after the initial complete volatilization of white fumes. Ignition temperature $600 \pm 50^{\circ}$.

Heavy metals, Method II $\langle 231\rangle$ : $0.001 \%$.

Degree of substitution-Transfer about 1 g of it, accurately weighed, to a glass-stoppered, $500-\mathrm{mL}$ conical flask, add 300 mL of sodium chloride solution (1 in 10), then add 25.0 mL of 0.1 N sodium hydroxide VS. Insert the stopper, and allow to stand for 5 minutes with intermittent shaking. Add 5 drops of $m$-cresol purple TS, and from a buret add about 15 mL of 0.1 N hydrochloric acid VS. Insert the stopper in the flask, and shake. If the solution is purple, add 0.1 N hydrochloric acid VS in 1-mL portions until the solution becomes yellow, shaking after each addition. Titrate with 0.1 N sodium hydroxide VS to a purple endpoint. Calculate the net number of milliequivalents, $M$, of base required for the neutralization of 1 g of Croscarmellose Sodium, on the dried basis.

Calculate the degree of acid carboxymethyl substitution, $A$, by the formula:

$$
1150 M /(7102-412 M-80 C)
$$

where $C$ is the percentage of residue on ignition of the Croscarmellose Sodium as determined in the test for Residue on ignition $\langle 281\rangle$.

Calculate the degree of sodium carboxymethyl substitution, $S$, by the formula:

$$
(162+58 A) C /(7102-80 C)
$$

The degree of substitution is the sum of $A+S$. It is between 0.60 and 0.85 , calculated on the dried basis.

Content of water-soluble material-Disperse about 10 g , accurately weighed, in 800 mL of water, accurately measured, and stir for 1 minute every 10 minutes during the first 30 minutes. Allow to stand for an additional hour, or centrifuge, if necessary. Decant about 200 mL of the aqueous slurry onto a rapid-filtering filter paper in a vacuum filtration funnel, apply vacuum, and collect about 150 mL of the filtrate. Pour the filtrate into a tared $250-\mathrm{mL}$ beaker, weigh accurately, and calculate the weight, in g , of the filtrate, $W_{3}$, by
difference. Concentrate on a hot plate to a small volume, but not to dryness, dry at $105^{\circ}$ for 4 hours, again weigh, and calculate the weight, in g , of residue $W_{l}$, by difference. Calculate the percentage of water-soluble material in the specimen, on the dried basis, taken by the formula:

$$
100 W_{1}\left(800+W_{2}\right) /\left[W_{2} W_{3}(1-0.01 b)\right],
$$

in which $W_{2}$ is the weight, in g , of the specimen taken; and $b$ is the percentage Loss on drying of the specimen taken: not more than $10.0 \%$ is found.

Settling volume-To 75 mL of water in a $100-\mathrm{mL}$ graduated cylinder add 1.5 g of it in $0.5-\mathrm{g}$ portions, shaking vigorously after each addition. Add water to make 100 mL , shake again until all of the powder is homogeneously distributed, and allow to stand for 4 hours. Note the volume of the settled mass. It is between 10.0 and 30.0 mL .

Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements. $\boldsymbol{\Delta N F 2 3}^{\text {N }}$

## Briefing

Ethylcellulose, NF 21 page 2865 and page 1568 of $P F$ 28(5) [Sept.-Oct. 2002]. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Ethylcellulose monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based on the corresponding monograph for Ethylcellulose prepared by the European Pharmacopoeia. The European Pharmacopoeia draft was based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Acidity/alkalinity | + | + | + |
| Viscosity | + | + | + |
| Acetaldehyde | + | + | + |
| Chlorides | + | + | + |
| Sulphated ash | + | + | + |
| Assay | + | + | + |
| Labeling |  | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Heavy metals, Loss on drying.
Specific local attributes: Identification B (EP) i.e. "it complies with the limits of assay."

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Differences between the Adoption Stage 6 document and the current $N F$ monograph include the following:
(1) Definition-Revisions are made to make the definition more specific.
(2) Packaging-No change.
(3) Labeling-The requirement that ethoxy content be stated on the label is deleted.
(4) USP Reference standards-No change.
(5) Identification-The identification test is replaced with a more definitive IR absorption test.
(6) Viscosity-This test is modified to comply with EP and JP standards.
(7) Acidity or alkalinity-This test is added to comply with EP standards.
(8) Loss on drying-No change.
(9) Residue on ignition-The standards for this test are modified to comply with those of EP.
(10) Lead-This test is deleted, based on comments received that the test is not needed.
(11) Heavy metals-No change.
(12) Organic volatile impurities-This test is deleted, based on comments received that the test is not needed.
(13) Acetaldehyde-This test is added to comply with EP standards.
(14) Chlorides-This test is added to comply with EP standards.
(15) Assay-The current NF test is replaced with a more specific chromatographic procedure, in part to comply with EP standards.
(EMC: J. Lane) RTS—37582-1

## Change to read:

## Ethyleellulose

Gellulese, ethyl ether.
Gellulese ethyl ether. [9004-573].
\# Ethyleellulese is an ethyl ether of cellulese. When dried at $105^{\circ}$ for 2 hours, it contains not less that 44.0 percent and not more than 51.0 percent of ethoxy $\left(-\mathrm{OC}_{2} \mathrm{H}_{5}\right)$ sromps.

Packaging and storage-Preserve in well closed containers.
Labeling Label it to indieate its viseosity (under the conditions specified herein) and its ethoxy content.
USP Referenee-standards- $\langle H\rangle$ USP Ethyteellutose RS.
Identifieation Dissolve 5 - 5 in 95 g of a mixtrre of 80 parts of toluene and 20 parts of alcohol, by weight: a clear, stable, slightly yellow solution recults. Pour a few mL of this solution onto a sodium chloride plate, and allow the solvent to evaporate: a thin, fough, contintreus, clear film remains. The IR absorption spectrum of the film so obtained exhibits maxima only at the-same wavelengths as that of a similar preparation of USP Ethyleellulose RS. The film, prepared from the test specimen and removed from the plate, is flammable-
Viseosity
Solvent syistems For Ethyleellulese containing less than 46.5 pereent of ethoxy groups, prepare a-solvent system consisting of 69 pats of toluene and 40 parts of aleohel, by weight. Otherwise, prepare a solvent system consisting of 80 parts of toltene and 20 parts of aleohol, by weight.

Proedure Place a quatity of undried Ethyleellulose, ac eurately weighed and equivalent to 5.0 g of solids on the dried ba sis, in a bottle containing $95 \pm 0.05$ go of the appropriate solvent system. Shake or tumble the bottle until the sample is completely dissolved. Adjust the temperature of the solution to $25 \pm 0.1^{\circ}$, and determine the viseosity as deseribed in the section Procedure for Gellulose Derivatives under Iiseosity $\langle 914$, but make all determi fations at $25^{\circ} / 25^{\circ}$ insted of $20^{\circ} / 20^{\circ}$ as directed therein. The vis eosity is net less than $90.0 \%$ and net mere than $110.0 \%$ of that stated on the label for a labeled viscosity of 10 centipoises or more; not less than $80.0 \%$ and not more than $120.0 \%$ of that stated on the tabel for a labeled viseosity of less than 10 centipeises but more than 6 eentipeises; and not less than $75.0 \%$ and not more than $140.0 \%$ of that stated on the label for a labeled viseosity of 6 een tiperises or less.
Less ondrying $\left\langle 734\right.$ ) - Dry it at $105^{\circ}$ for 2 hemrs: it leses net mere than 3.0\% of its weight.
Residue on ignition $\langle z 84\rangle \div$ net mere than $0.4 \%$.
Head- $\langle 254\rangle \div 10 \mathrm{ppm}$.
Heary metals, Method $I\left\langle\langle 234\rangle: 20\right.$ per per $\frac{1}{8}$.
Organic volatile impurities, Method $I V\langle 467\rangle$ : meets the require ments.
Assay Proeed as directed under Methoxy Determination- $\langle 431$ ); using about 50 mg of Ethyleellulese, previously dried and aceurately weighed. Each mL of 0.1 N seditm thiesulfate-is equiver lent to 0.7510 mg of $\left(\mathrm{OC}_{2} \mathrm{H}_{5}\right)$.

## © Ethylcellulose

Cellulose, ethyl ether.
Cellulose ethyl ether [9004-57-3].
» Ethylcellulose is a partly $O$-ethylated cellulose. It contains not less than 44.0 percent and not more than 51.0 percent of ethoxy $\left(-\mathrm{OC}_{2} \mathrm{H}_{5}\right)$ groups, calculated with reference to the dried substance.

Packaging and-storage-Preserve in well-closed containers.

Labeling-Label it to indicate its nominal viscosity in millipascal seconds for a 5 percent $\mathrm{m} / \mathrm{m}$ solution.

USP Reference standards $\langle 11\rangle$ —USP Ethylcellulose RS.
Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
Viscosity $\langle 911\rangle$-Shake a quantity of ethylcellulose equivalent to 5.00 g of the dried substance with 95 g of a mixture of 20 g of alcohol and 80 g of toluene until the substance is dissolved. Determine the viscosity using a capillary viscometer. The viscosity, determined at $25^{\circ}$ and expressed in $\mathrm{mPa} \cdot \mathrm{s}$, is not less than $80.0 \%$ and not more than $120.0 \%$ of that stated on the label for a nominal viscosity greater than $6 \mathrm{mPa} \cdot \mathrm{s}$; and not less than $75.0 \%$ and not more than $140.0 \%$ of that stated on the label for a nominal viscosity not greater than $6 \mathrm{mPa} \cdot \mathrm{s}$.

Acidity or alkalinity-To 0.5 g of ethylcellulose, accurately weighed, add 25 mL of carbon dioxide-free water and shake for 15 minutes. Pass through a sintered-glass filter (40) with a maximum diameter of pores between $16 \mu \mathrm{~m}$ and $40 \mu \mathrm{~m}$. To 10 mL of this solution, add 0.1 mL of Phenolphthalein solution and 0.5 mL of 0.01 N sodium hydroxide. The solution is pink. To 10 mL of this solution, add 0.1 mL of Methyl red solution and 0.5 mL of 0.01 N hydrochloric acid. The solution is red.

Phenolphthalein solution-Dissolve 100 mg of phenolphthalein in 80 mL of alcohol, and dilute with water to 100 mL .

Methyl red solution-Dissolve 50 mg of methyl red in a mixture of 1.86 mL of 0.1 N sodium hydroxide and 50 mL of alcohol, and dilute with water to 100 mL .

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 2 hours: it loses not more than $3.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.5 \%$, determined on 1.0 g .

Heavy metals, Method II $\langle 231\rangle: 20 \mu \mathrm{~g}$ per g.
Acetaldehyde-Introduce 3.0 g into a $250-\mathrm{mL}$ conical flask with a ground-glass stopper, add 10 mL of water, and stir by mechanical means for 1 hour. Allow to stand for 24 hours, filter, and dilute the filtrate with water to 100.0 mL . Transfer 5.0 mL to a 25 mL volumetric flask, add 5 mL of a 0.5 g per L solution of methylbenzothiazolone hydrazone hydrochloride, and heat in a water bath at $60^{\circ}$ for 5 minutes. Add 2 mL of Ferric chloride-sulfamic acid reagent, and heat again at $60^{\circ}$ for 5 minutes. Cool, and dilute with water to 25.0 mL . The solution is not more intensely colored than a standard prepared at the same time and in the same manner using, instead of the 5.0 mL of the filtrate, 5.0 mL of a reference solution prepared by diluting 3.0 mL of Acetaldehyde standard solution with water ( 100 ppm ) to 100.0 mL .

Ferric chloride-sulfamic acid reagent-Prepare a solution containing 10 g per L of ferric chloride and 10 g per L of sulfamic acid.

Acetaldehyde standard solution-Dissolve 1.0 g of acetaldehyde in 2-propanol, and dilute with the same solvent to 100.0 mL . Dilute 5.0 mL of the solution with water to 500.0 mL . Prepare immediately before use.

Chlorides-Disperse 250 mg in 50 mL of water, heat to boiling, and allow to cool, shaking occasionally. Filter, and discard the first 10 mL of the filtrate. Dilute 10 mL of
the filtrate with water to 15 mL . Add 1 mL of Dilute nitric acid, and pour the mixture as a single addition into a test tube containing 1 mL of 0.1 N silver nitrate VS. Prepare a standard in the same manner using 10 mL of Chloride standard solution and 5 mL of water. Examine the tubes laterally against a black background. After standing for 5 minutes protected from light, any opalescence in the test solution is not more intense than that in the standard ( $0.1 \%$ ).
Dilute nitric acid-Dilute 20 mL of nitric acid with water to 100 mL .

Chloride standard solution-Immediately before use, dilute with water to 100 times its volume a solution containing sodium chloride equivalent to 0.824 g per L of sodium chloride.

## Assay-

NOTE-Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps of the Test solution preparation and the Reference solution preparation in a properly functioning hood.

Internal standard solution-Dilute $120 \mu \mathrm{~L}$ of toluene with $o$-xylene to 10 mL .
Test solution-Transfer 50.0 mg of ethylcellulose, 50 mg of adipic acid, and 2.0 mL of the Internal standard solution into a suitable 5 mL thick-walled reaction vial, with a pres-sure-tight septum closure. Cautiously add 2.0 mL of hydriodic acid, immediately close the vial tightly, and weigh the contents and the vial accurately. Shake the vial for 30 seconds, heat to $125^{\circ}$ for 10 minutes, allow to cool for 2 minutes, shake again for 30 seconds, and heat to $125^{\circ}$ for 10 minutes. Afterwards allow to cool for 2 minutes, and repeat shaking and heating for a third time. Allow the vial to cool for 45 minutes, and reweigh. If the loss is greater than 10 mg , discard the mixture and prepare another. Use the upper layer for analysis.

Reference solution-Transfer 100.0 mg of adipic acid, 4.0 mL of the Internal standard solution and 4.0 mL of hydriodic acid into a suitable 10 mL thick-walled reaction vial with a pressure-tight septum closure. Close the vial tightly, and weigh the vial and contents accurately. Afterwards inject $50 \mu \mathrm{~L}$ of the iodoethane through the septum with a syringe, weight the vial again, and calculate the mass of iodoethane added, by difference. Shake well, and allow the layers to separate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and a $2-\mathrm{mm} \times 5.0-\mathrm{m}$ stainless steel column packed with $3 \% \mathrm{G} 2$ on $150-\mu \mathrm{m}$ to $180-\mu \mathrm{m}$ mesh support S1A. The carrier gas is nitrogen, flowing at a rate of about 15 mL per minute. The injection port and detector temperatures are both maintained at $200^{\circ}$. The column temperature is maintained at $80^{\circ}$.
Procedure-Inject $1 \mu \mathrm{~L}$ of the upper layer of the Reference solution into the chromatograph, record the chromatogram, and record the areas of the peaks. The relative retention times are as follows: iodoethane 0.6 , toluene 1.0 , and $o$-xylene 2.3. Adjust the sensitivity of the system so that the heights of the two principal peaks are at least $50 \%$ of the full scale of the recorder. The test is not valid unless the resolution between the peaks corresponding to iodoethane and toluene is at least 2.0. Inject $1 \mu \mathrm{~L}$ of the Test solution into the chromatograph, and record the chromatogram as directed for Reference solution. Use the retention
times observed in the chromatogram of the Reference solution to identify the peaks in the chromatogram of the Test solution. Calculate the percentage of ethoxy groups by the formula:

$$
[451000 / 312]\left[Q_{1} m_{2}\right] /\left[Q_{2} m_{1}(100-d)\right],
$$

where $Q_{1}$ is the ratio of the iodoethane peak area to the toluene peak area in the chromatogram obtained with the Test solution; $Q_{2}$ is the ratio of the iodoethane peak area to the toluene peak area in the chromatogram obtained with the Reference solution; $m_{1}$ is the mass of ethylcellulose used in the Test solution in mg ; $m_{2}$ is the mass of iodoethane used in the Reference solution in mg ; and $d$ is the loss on drying as a percentage. $\mathbf{\Delta N F 2 3}^{\text {N }}$

## Briefing

Hydroxyethyl Cellulose, NF 22 page 2877. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Hydroxyethyl Cellulose monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the Revised OFFICIAL INQUIRY STAGE 4 document, is based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia. The harmonization draft sections proposed for the $N F$ monograph have been editorially styled. Readers are urged to review these In-Process Revision proposals carefully and to respond to USP no later than May 1, 2004.

Major changes proposed include:
(1) In the opening paragraph (the Definition)-A more simple definition is used.
(2) Packaging-No change.
(3) Labeling-A style change is added to specify apparent viscosity.
(4) Identification-Tests $B$ and $C$ are replaced by three different tests to comply with EP and JP standards.
(5) Viscosity-The EP method for Apparent viscosity has been adopted.
(6) pH -The lower limit is expanded from 6.0 to 5.5 .
(7) Loss on drying-No change.
(8) Residue on ignition-The EP standard of not more than 4.0\% has been adopted.
(9) Chlorides-This test is added to comply with EP standards.
(10) Nitrates-This test is added to comply with EP standards.
(11) Limit of glyoxal-This test is added to comply with EP standards. Technical grades of hydroxyethyl cellulose are frequently treated with glyoxal to improve their processing properties. Carry over to pharmaceutical grade materials cannot be excluded. Glyoxal is a highly reactive impurity that warrants limiting.
(12) Limit of ethylene oxide-This test is added to comply with EP standards. Ethylene oxide can be a starting material in the manufacture of hydroxyethyl cellulose and is a highly toxic substance.
(13) Limit of 2-chloroethanol-This test is added to comply with EP standards.
(14) Organic volatile impurities-No change.
(15) Heavy metals-No change.
(EMC: J. Lane) RTS-40798-1

## Add the following:

## Hydroxyethyl Cellulose

Cellulose, 2-hydroxyethyl ether [9004-62-0].
» Hydroxyethyl Cellulose is a partially $O$-(2-hydroxyethylated) cellulose.

Packaging-Preserve in well-closed containers.
Labeling-The labeling indicates the apparent viscosity, in millipascal seconds for a $2 \%$ solution.

## Identification-

A: Stir about 1 g into 100 mL of water: After about 10 minutes, dilute with water to 100 mL , and stir to dissolve.

B: To 10 mL of the solution obtained from Identification test $A$, add 0.3 mL of dilute acetic acid (contains not less than 115 g per L and not more than 125 g per L of $\mathrm{C}_{2} \mathrm{H}_{4} \mathrm{O}_{2}$ ) and 2.5 mL of a 100 g per L solution of tannic acid. A yel-lowish-white, flocculent precipitate is formed which dissolves in ammonia TS.

C: In a test tube about 160 mm in length, thoroughly mix 1 g of it with 2 g of finely powdered manganese sulfate. Introduce to a depth of 2 cm into the upper part of the tube a strip of filter paper impregnated with a freshly prepared mixture of 1 volume of a 200 g per L solution of diethanolamine and 11 volumes of a 50 g per L solution of sodium nitroprusside, adjust with 1 N hydrochloric acid to a pH of about 9.8. Insert the tube 8 cm into a silicone oil bath, and heat at $190^{\circ}$ to $200^{\circ}$. The filter paper becomes blue within 10 minutes. Carry out a blank test.

D: Dissolve 0.2 g of it completely, without heating, in 15 mL of a 700 g per L solution of sulfuric acid. Pour the solution with stirring into 100 mL of iced water, and dilute with iced water to 250 mL . In a test tube, mix thoroughly while cooling in iced water 1 mL of the solution with 8 mL of sulfuric acid, added dropwise. Heat on a water bath for exactly 3 minutes, and immediately cool in iced water. While the mixture is cold, carefully add 0.6 mL of Ninhydrin solution, and mix well. Allow to stand at $25^{\circ}$. A pink color is produced immediately and does not become violet within 100 minutes.

Ninhydrin solution-Dissolve 3 g of ninhydrin in 100 mL of a 45.5 g per L solution of sodium bisulfite.

Apparent viscosity $\langle 911\rangle: 75 \%$ to $140 \%$ of the value is stated on the label. While stirring, introduce a quantity of the substance to be examined equivalent to 2.00 g of the dried substance into 50 g of water. Dilute with water to 100.0 g , and stir to dissolve. Determine the viscosity using a rotating viscometer at $25^{\circ}$ and at a shear rate of $100 \mathrm{~s}^{-1}$ for substances with an expected viscosity up to $100 \mathrm{mPa} \cdot \mathrm{s}$, at a shear rate of $10 \mathrm{~s}^{-1}$ for substances with an expected viscosity between $100 \mathrm{mPa} \cdot \mathrm{s}$ an $20,000 \mathrm{mPa} \cdot \mathrm{s}$ and at a shear rate of $1 \mathrm{~s}^{-1}$ for substances with an expected viscosity above $20,000 \mathrm{mPa} \cdot \mathrm{s}$.

If it is impossible to obtain a shear rate of exactly $1 \mathrm{~s}^{-1}, 10$ $\mathrm{s}^{-1}$, or $100 \mathrm{~s}^{-1}$ respectively, use a rate slightly higher and a rate slightly lower, and interpolate.
$\mathbf{p H}\langle 791\rangle$ : between 5.5 and 8.5. Use the solution obtained from Identification test $A$.

Loss on drying $\langle 731\rangle$ —Dry a 1.000 g sample at $100^{\circ}$ to $105^{\circ}$ for 3 hours: it loses not more than $10.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $4.0 \%$, determined on a 1.0 g sample.

## Chlorides-

Test solution-Disperse a quantity of the substance to be examined equivalent to 1.0 g of the dried substance in 50 mL of water that has been previously boiled and cooled. After 10 minutes, dilute with water to 100 mL that has been previously boiled and cooled, and stir to dissolve. Dilute 1 mL of this solution with water to 30 mL .

Chloride standard solution ( 5 ppm Cl )—Immediately before use, dilute with water to 100 times its volume a solution containing sodium chloride equivalent to 0.824 g in 1000.0 mL .

Standard solution-Mix 10 mL of Chloride standard solution ( 5 ppm Cl ) and 5 mL of water.

Procedure-Add 1 mL of a dilute nitric acid solution (125 g per L ) to the Test solution, and pour the mixture as a single addition into a test tube, containing 1 mL of silver nitrate solution ( 17 g per L). Prepare a standard in the same manner, using the Standard solution in place of the Test solution. Examine the tubes laterally against a black background. After standing for 5 minutes protected from light, any opalescence in the Test solution is not more intense than that in the Standard solution.

Nitrates-[NOTE-Prepare all solutions immediately before use.]

Buffer solution-To a mixture of 50 mL of 2 N sulfuric acid and 800 mL of water, add 135 g of potassium phosphate, monobasic, and dilute with water to 1000 mL .

Buffered water-Dilute 80 mL of Buffer solution with water to 2000 mL .

Nitrate standard solution (500 ppm NO 3 )—Dissolve 0.8154 g of potassium nitrate in 500 mL of Buffered water, and dilute with the same solvent to 1000.0 mL .

Test solution-Dissolve 0.50 g of the substance to be examined in Buffered water, and dilute with the same solvent to 100.0 mL .

Reference solutions-If hydroxyethyl cellulose has an apparent viscosity of $1000 \mathrm{mPa} \cdot \mathrm{s}$ or less, dilute $10.0 \mathrm{~mL}, 20.0$ mL , and 40.0 mL of Nitrate standard solution (500 ppm $\mathrm{NO}_{3}$ ) to 100.0 mL with Buffered water, and mix. If hydroxyethyl cellulose has an apparent viscosity of more than $1000 \mathrm{mPa} \cdot \mathrm{s}$, dilute $1.0 \mathrm{~mL}, 2.0 \mathrm{~mL}$, and 4.0 mL of Nitrate standard solution ( $500 \mathrm{ppm} \mathrm{NO} \mathrm{N}_{3}$ ) with Buffered water, to 100.0 mL , and mix.

Procedure-Carry out the measurements for each solution, potentiometrically (see Titrimetry $\langle 541\rangle$ ), using as an indicator, a nitrate selective electrode and a silver-silver chloride electrode with a 0.1 M ammonium sulfate as a reference electrode. Calculate the concentration of nitrates using a calibration curve: maximum of $3.0 \%$ (dried substance), if hydroxyethyl cellulose has an apparent viscosity of $1000 \mathrm{mPa} \cdot \mathrm{s}$ or less and a maximum of $0.2 \%$ (dried substance), if hydroxyethyl cellulose has an apparent viscosity of more than $1000 \mathrm{mPa} \cdot \mathrm{s}$.

## Limit of glyoxal-

Standard solution-In a 100 mL graduated flask, weigh a quantity of glyoxal solution ( $40 \%(\mathrm{w} / \mathrm{w})$ ) corresponding to 0.200 g of $\mathrm{C}_{2} \mathrm{H}_{2} \mathrm{O}_{2}$, and make up with alcohol to volume.

Immediately before use dilute the solution with the same solvent to 100 times its volume. Immediately before use, dilute the solution above with alcohol to 10 times its volume.

Test solution-Introduce 1.0 g of it into a test tube with a ground glass stopper, and add 10.0 mL of alcohol. Stopper the tube, and stir by mechanical means for 30 minutes. Centrifuge, and retain the supernatant.

Procedure-To 2 mL of the Test solution, add 5.0 mL of a 4 g per L solution of methylbenzothiazolone hydrazone hydrochloride in an $80 \%(\mathrm{v} / \mathrm{v})$ solution of glacial acetic acid in water. Shake to homogenize. After 2 hours, the solution is not more intensely colored than a standard prepared at the same time and in the same manner using 2.0 mL of the Standard solution instead of the 2.0 mL of the Test solution: not more than 20 ppm .

Limit of ethylene oxide-[NOTE-All vials must be closed immediately with a butyl rubber membrane stopper, coated with aluminum or polytetrafluoroethylene and secured with an aluminum crimped cap.]

Polyethylene glycol 200 preparation-Introduce 500 mL of polyethylene glycol 200 into a 1000 mL round-bottom flask. Using a rotation evaporator remove any volatile components applying for 6 hours at a temperature of $60^{\circ}$ and in a vacuum with a pressure of 1.5 kPa to 2.5 kPa .
Ethylene oxide stock solution-[NOTE-All operations carried out in the preparation of these solutions must be conducted in a fume-hood. The operator must protect both hands and face by wearing polyethylene protective gloves and an appropriate face mask. Store all solutions in an airtight container in a refrigerator at $4^{\circ}$ to $8^{\circ}$. Carry out all determinations three times.]

Ethylene oxide solution-Weigh 1.00 g of cold Ethylene oxide stock solution (equivalent to 2.5 mg of ethylene oxide) into a cold flask containing 40.0 g of cold Polyethylene glycol 200 preparation. Mix and determine the exact mass, and
dilute to a calculated mass to obtain a solution containing 50 $\mu \mathrm{g}$ of ethylene oxide per g of solution. Weigh 10.00 g into a flask containing about 30 mL of water, mix, and dilute with water ( $10 \mu \mathrm{~g}$ per mL of ethylene oxide) to 50.0 mL . Prepare immediately before use.

Standard preparation A-Accurately weigh, and transfer 1.00 g of the substance to be examined into an identical 5 mL vial. Add 0.2 mL of cooled Ethylene oxide solution and 0.8 mL of water. It swells in water but does not dissolve.

Standard preparation B-To 0.1 mL of Ethylene oxide solution in a 5 mL vial add 0.1 mL of a freshly prepared 10 mg per L solution of acetaldehyde.
Test preparation-Accurately weigh and transfer 1.00 g of the substance to be examined to a 5 mL vial (other sizes may be used depending on the operating conditions), and add 1 mL of water. It swells in water but does not dissolve.

Into a dry, clean test tube, cooled in a mixture of 1 part of sodium chloride and 3 parts of crushed ice, introduce a slow current of ethylene oxide gas, allowing condensation onto the inner wall of the test tube. Using a glass syringe, previously cooled to $-10^{\circ}$, inject about $300 \mu \mathrm{~L}$ (corresponding to about 0.25 g ) of liquid ethylene oxide into 50 mL of Polyethylene glycol 200 preparation. Determine the absorbed quantity of ethylene oxide by weighing before and after absorption ( $M_{e o}$ ). Dilute with Polyethylene glycol 200 preparation to 100.0 mL . Mix well before use. To 10 mL of a 500 g per L suspension of magnesium chloride in ethanol, add 20.0 mL of 0.1 N alcoholic hydrochloric acid VS (dilute 5.0 mL of 1 N hydrochloric acid VS with alcohol to 500.0 mL ) in a flask. Stopper, shake to obtain a saturated solution, and allow to stand overnight to equilibrate. Weigh 5.00 g of Ethylene oxide stock solution into the flask, and allow to stand for 30 minutes. Titrate with 0.1 N alcoholic potassium hydroxide VS determining the endpoint potentiometrically (see Titrimetry $\langle 541\rangle$ ). Carry out a blank titration, replacing
the substance to be examined with the same quantity of Polyethylene glycol 200 preparation. Calculate the content of ethylene oxide in mg per g by the formula:

$$
\left(\left(V_{0}-V_{1}\right) \times f \times 4.404\right) / m
$$

where $V_{0}$ and $V_{1}$ are the volumes of alcoholic potassium hydroxide used respectively for the blank titration and the assay; $f$ is the factor of the alcoholic potassium hydroxide solution; and $m$ is the mass of the sample taken (g).

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The gas chromatograph is equipped with a flame-ionization detector, maintained at about $250^{\circ}$, and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ fused silica capillary column bonded with a $1.0-\mu \mathrm{m}$ layer of phase G2. The carrier gas is helium with a linear velocity of about $20 \mathrm{~cm} / \mathrm{s}$ and a split ratio of 1:20. The column temperature is maintained at $50^{\circ}$ for the first 5 minutes after an injection is made, than the temperature is increased at a rate of $30^{\circ}$ to $230^{\circ}$, and maintained at $230^{\circ}$ for 5 minutes. The injection port temperature is maintained at $150^{\circ}$. Static head space conditions are used that include an equilibration temperature of $70^{\circ}$, an equilibration time of 45 minutes, and use a pressurization time of 30 seconds. Maintain the transfer line temperature at $75^{\circ}$. Inject about 1.0 mL of the gaseous phase of Standard preparation B into a suitable gas chromatograph, and record the chromatogram. Adjust the sensitivity of the system so that the heights of the two principal peaks in the chromatogram obtained are not less than $15 \%$ of the full scale of the recorder. The resolution, $R$, between the peaks corresponding to acetaldehyde and ethylene oxide is at least 2.0.

Procedure-Separately inject equal volumes ( 1.0 mL ) of the gaseous phase of the Test preparation and Standard preparation $A$ into the chromatograph, record the chromatograms, and measure the major peaks. In the chromatogram obtained with the Test preparation, the area of any peak cor-
responding to ethylene oxide is not greater than half the area of the peak due to ethylene oxide in the chromatogram obtained with Standard preparation $A$ : not more than 1 ppm .

The content of ethylene oxide in ppm can be calculated by the formula:

$$
\left(A_{T} \times M_{E O} \times C\right) /\left(0.25\left(A_{R} \times M_{T}-A_{T} \times M_{\mathrm{R}}\right)\right),
$$

where $C=C_{E O} /\left(M_{E O} \times 10\right)$, and where $A_{T}$ is the area of the peak corresponding to ethylene oxide in the chromatrogram obtained with the Test preparation; $A_{R}$ is the area of the peak corresponding to ethylene oxide in the chromatogram obtained with Standard preparation $A ; M_{E O}$ is the mass of absorbed ethylene oxide (used for preparing the Ethylene oxide solution) in $\mathrm{g} ; M_{T}$ is the mass of the substance to be examined in g in the Test preparation; $M_{R}$ is the mass of the substance to be examined in g in the Standard preparation $A ; C$ is the correction factor to be determined from the formula; $C_{E O}$ is the ethylene oxide content in mg per mL , determined by titration.

Limit of 2-chloroethanol- [NOTE-All vials must be closed immediately with a butyl rubber membrane stopper, coated with aluminum or polytetrafluoroethylene, and secured with an aluminum crimped cap.]

Test preparation-Transfer 50 mg of the substance to be examined to a 10 mL vial (other sizes maybe used depending on the operating conditions), add $2 \mu \mathrm{~L}$ of isopropyl alcohol. Seal the vial, and mix.

Standard preparation A-Accurately weigh and dissolve 0.125 g of 2-chloroethanol, and dilute with isopropyl alcohol to 50.0 mL . Dilute 1.0 mL of the solution with 2-propanol to 10.0 mL .

Standard preparation B-Transfer 50 mg of it to an identical 10 mL vial, add $2 \mu \mathrm{~L}$ of Standard preparation A, seal the flask, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector, maintained at about $250^{\circ}$, and a $0.32-\mathrm{mm} \times 50-\mathrm{m}$ fused silica capillary column bonded with a $1.2-\mu \mathrm{m}$ layer of phase G2. The carrier gas is helium with a linear velocity of about 25 to $35 \mathrm{~cm} / \mathrm{s}$ and a split ratio of 1:10. The column temperature is maintained at $60^{\circ}$ for the first 6 minutes after an injection is made, increased from $60^{\circ}$ to $110^{\circ}$ from 6 minutes to 16 minutes after injection, and increased from $110^{\circ}$ to $230^{\circ}$ from 16 minutes to 31 minutes after injection. The temperature is then maintained at $230^{\circ}$ for 5 minutes. The injection port temperature is maintained at $150^{\circ}$. Static head space conditions are used that include an equilibration temperature of $110^{\circ}$, an equilibration time of 20 minutes. Maintain the transfer line temperature at $115^{\circ}$.

Procedure-Separately inject about 2.0 mL of the gaseous phase of Standard preparation B, and the Test preparation into a suitable gas chromatograph, and record the chromatogram. The retention time of 2-chloroethanol is about 7.8 minutes. In the chromatogram obtained with the Test preparation, the area of any peak corresponding to 2chloroethanol is not greater than 0.5 times the area of the peak due to 2-chloroethanol in the chromatogram obtained with Standard preparation B: not more than 10 ppm .

Heavy metals, Method II $\langle 231\rangle: 20 \mu \mathrm{~g}$ per g.
Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

## BRIEFING

Starch, NF 22 page 2939. Because monographs for Corn Starch, Potato Starch, and Wheat Starch are being addressed for Harmonization ADOPTION STAGE 6, the Starch monograph is proposed for deletion, as it is no longer needed.
(EMC: J. Lane) RTS-40769-1

## Delete the following:

## $\Delta$ Stareh

## Stareh. <br> Stareh [ 0095 25-8].

\#-Stareh consists of the gramules separated from the mature grain of corn [Zea mays Linné (Fum. Grami neae)] or of wheat [Triticum aestivum Linné (Fam. Gramineae)], or from tubers of the potato [Solammetuberosum Linmé (Fam. Solanaceae)].
NOTE-Starches obtained from-different botanieal sources may not have identical properties with respect to their use for specific pharmaceutical purposes, e.g., as a tablet-disintegrating agent. Therefore, types of stareh should not be interehanged unless performance equivalency has been aseentained.

Packaging and-storage Preserve in well clesed containers. Labeling Label it to indieate the botanieal source from which it was derived.
Botanie-characteristies-
Corn-starch Pelygonat, reunded or sphereidal grantles up-te about $35 \mathrm{\mu m}$ in diameter and usually having a cireular or sev eral rayed central cleft.

Wheat stareh Two distinet ypesef granales aresimple lentieut tar large granules 20 to 25 - mm or up to 50 - mm in diameter, and small spherieal gramules 5 to 10 km in diameter. Striations are faintly marked and coneentric.

Potatostarch Simple-granules, irregularly oveid or spherical, 30 to $100 \mathrm{\mu m}$ in diameter, and subspherieal gramules 10 to $35 \mathrm{\mu m}$ in diameter. Striations are well marked and concentric.

## Identifieation-

A: Prepare a smooth mixture of 1 g of it with 2 mL of cold water, stir it into 15 mL of boiling water, boil gently for 2 minutes, and cool: the product is a translucent, whitish jelly.

B: A water slumy of it is colered reddish violet to deep blue by dine TS.
Mierobial limits $\langle 64\rangle$-It meets the requirements of the tests for absenee of Salmenella species and Escherichia ooli.
 Stareh, transferring to a suitable nommetallic container, and adding 100 mL of water. Agitate continuously at a moderate rate for 5 min utes, then stop agitation, and immediately determine the pH to the fearest 0.1 unit: the pH , determined potentiometrieally, is between 4.5 and 7.0 for Corn starch and Wheat starch, and is between 5.0 and 8.0 for $P$ otato starel.
Lessondrying $\left\langle 734\right.$ ) - Dry itat $120^{\circ}$ for 4 heurs: it leses net mere than $14.0 \%$ of its weight.
Residue-on-ignition- $\langle z 81\rangle \div$ not more than $0.5 \%$, determined on a 2.0 gest specimen.

Iren- $\langle z 44\rangle$ - Dissolve the residtue obtained in the test for Residtue en ignition in 8 mL of hydrochloric acid with the aid of gentle heat ing, dilute with water to 100 mL , and mix. Dilute 25 mL of this solution with water to -47 mL : the limit is $0.002 \%$.
Oxidizing substances Transfer 4.0-5 to a glass-stoppered, 125 mL conieal flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 mintues. Deeant into a glass stoppered, 50 mL centri fuge tube, andeentifuge toclarify. Transfer 30.0 mL of clear super matant liguid to a glass stoppered, 125 mL conical flack. Add 1 mL ef ghacial acetic acid and 0.5 g to 1.0 of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minntes in the dark. Add 4 mL of stareh TS, and titrate with 0.002 N sodirm thiosulfate VS to the disappearance of the stareh iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to 34 Hg of oxidant, ealeulated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate is required ( $0.002 \%$ ).
Sulfur dioxide Mix 20 g with 200 mL of water until a smoeth suspension is obtained, and filter. To 100 mL of the clear filtrate add 3 mL of stareh TS, and titrate with 0.010 N iodine

to the first permanent blue color: not more than 2.7 mL is con stmed (0.008\%).
Organic volatile impurities, Method $I K\langle 467\rangle$ :- meets the requir ements..nN23

## BRIEFING

Corn Starch, page 882 of PF 28(3) [May-June 2002]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Corn Starch monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based on the corresponding monograph for Starch that was prepared by the United States Pharmacopeia. The USP draft was based in part on comments from the Japanese Pharmacopoeia and the European Pharmacopoeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by USP. The current $N F$ monograph for Starch will be proposed for deletion, to be replaced by new monographs for Corn Starch, Potato Starch, and Wheat Starch.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Identification B | + | + | + |
| Identification C | + | + | + |
| pH | + | + | + |
| Loss on drying | + | + | + |
| Residue on ignition | + | + | + |
| Limit of iron | + | + | + |
| Limit of oxidizing <br> substances | + | + | + |
| Sulfur dioxide <br> determination | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Microbial contamination, Storage, Labeling.
Specific local attributes: Foreign matter (EP).
Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.
Differences between the International Harmonization Adoption Stage 6 document for Corn Starch and the current NF Starch monograph include the following:
(1) Definition-Changed to include only Corn Starch, as to conform to the individual monograph for Corn Starch.
(2) Identification test $C$-The test is modified to use 1 mL of mucilage, instead of 10 mL , and a new, less concentrated test solution is added.
(3) Packaging-No change.
(4) Labeling-A requirement that the label indicate where it is intended for use in preparing Absorbable Dusting Powder is added to ensure that microbial limits are met.
(5) Botanical characteristics-This test has been modified and moved to the Identification section.
(6) Identification-A microscopic test is added that is similar to the Botanical characteristics section. The other two tests are modified slightly for clarification.
(7) Microbial limits-The revised limit for the total combined molds and yeasts count in the test is based on comments received. The addition of the requirements for Absorbable Dusting Powder are based on specific microbial requirements for Absorbable Dusting Powder.
(8) pH -The lower limit is expanded in order to conform with EP standards.
(9) Loss on drying-The revised test conditions reportedly correspond to ISO 1666 and are preferred by users of starches because of reduced testing time.
(10) Residue on ignition-The standard for this test is increased from $0.5 \%$ to $0.6 \%$ in order to conform with EP standards.
(11) Limit of iron-The test procedure is changed in order to conform to EP standards.
(12) Limit of oxidizing substances-No change.
(13) Limit of sulfur dioxide-The change in the standard reflects the corresponding limits proposed by the EC food laws.
(14) Organic volatile impurities-This test is deleted, as it is not necessary.
(EMC: J. Lane) RTS-40773-4

## Add the following:

## ©Corn Starch

» Corn Starch consists of the starch granules separated from the mature grain of corn [Zea mays Linné (Fam. Gramineae)].

Packaging and-storage-Preserve in well-closed containers.

Labeling-Where Corn Starch is intended for use in preparing Absorbable Dusting Powder, it is so labeled and the label states that it must be subjected to further processing during the preparation of Absorbable Dusting Powder.

## Identification-

A: Under a microscope, using not less than $20 \times$ magnification and using a mixture of glycerin and water (1:1) as a mounting agent, it appears as either angular polyhedral granules of irregular sizes with diameters ranging from about $2 \mu \mathrm{~m}$ to about $23 \mu \mathrm{~m}$ or as rounded or spheroidal granules of irregular sizes with diameters ranging from about $25 \mu \mathrm{~m}$ to about $35 \mu \mathrm{~m}$. The central hilum consists of a distinct cavity or two- to five-rayed cleft, and there are no concentric striations. Between crossed nicol prisms, the starch granules show a distinct black cross intersecting at the hilum.

B: Suspend 1 g of it in 50 mL of water, boil for $1 \mathrm{~min}-$ ute, and cool: a thin, cloudy mucilage is formed.

C: Te 10 mL of the mucilage obtained in Identification test $B$, add 0.04 mL of iodine and potassium iodide TS: an erange red to dark blue color is produced, which disappears

## en heating.

C: To 1 mL of the mucilage obtained in Identification test $B$, add 0.05 mL of Iodine solution: an orange-red to dark blue color is produced, which disappears on heating.

Iodine solution-Dissolve 12.7 g of iodine and 20 g of potassium iodide in water, and dilute with water to 1000.0 mL . To 10.0 mL of this solution, add 0.6 g of potassium iodide, and dilute with water to 100.0 mL . Prepare immediately before use.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed $100010^{3}$ per g , the total combined molds and yeasts count does not exceed $10010^{2}$ per g , and it meets the requirements of the test for the absence of Escherichia coli. Where it is intended for use in preparing Absorbable Dusting Powder, it also meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.
$\mathbf{p H}\langle 791\rangle$ —Prepare a slurry by weighing 5.0 g of Corn Starch, transferring to a suitable nonmetallic container, and adding 25.0 mL of freshly boiled and cooled water. Agitate continuously at a moderate rate for 1 minute. Stop the agitation, and allow to stand for 15 minutes. Determine the pH to the nearest 0.1 unit: the pH , determined potentiometrically, is between 4.0 and 7.0.

Loss on drying $\langle 731\rangle$ - Dry about 1 g , accurately weighed, at $130^{\circ}$ for 90 minutes: it loses not more than $15.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.6 \%$, determined on a $1.0-\mathrm{g}$ test specimen. Ignition temperature $600 \pm 50^{\circ}$.

Limit of iron-Shake 1.5 g of Corn Starch with 15 mL of 2 N hydrochloric acid, and filter. Transfer 10 mL of the filtrate to a test tube, add 2 mL of citric acid solution (2 in 10), 0.1 mL of thioglycolic acid, and mix. Add 10 N ammonium hydroxide until the solution is distinctly alkaline to litmus, dilute with water to 20 mL , and mix (Test Solution). Prepare a Standard Iron Solution containing the equivalent of $10 \mu \mathrm{~g}$ of iron per mL as directed under Iron $\langle 241\rangle$. Immediately before use, quantitatively dilute an accurately measured volume of this solution with water to obtain a Diluted

Standard Iron Solution containing the equivalent of $1 \mu \mathrm{~g}$ of iron per mL. Prepare the Standard Solution by transferring 10 mL of the Diluted Standard Iron Solution to a test tube and proceeding in the same manner as directed for the preparation of the Test Solution, beginning with "add 2 mL of citric acid solution (2 in 10)." After 5 minutes, any pink color in the Test Solution is not more intense than that in the Standard Solution, corresponding to a limit of $10 \mu \mathrm{~g}$ of iron per $g$.

Limit of oxidizing substances-Transfer 4.0 g to a glassstoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate is required ( $20 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ).

Limit of sulfur dioxide-Not more than $50 \mu \mathrm{~g}$ per g .

## Reagents-

Carbon dioxide-Use carbon dioxide, with a flow regulator that will maintain a flow of $100 \pm 10 \mathrm{~mL}$ per minute.

Bromophenol blue indicator solution-Dissolve 100 mg of bromophenol blue in 100 mL of dilute alcohol (1 in 5), and filter if necessary.

Hydrogen peroxide solution-Dilute $30 \%$ hydrogen peroxide with water to obtain a $3 \%$ solution. Just before use, add 3 drops of Bromophenol blue indicator solution, and neutralize to a violet-blue endpoint with 0.01 N sodium hydroxide. Do not exceed the endpoint.
Apparatus-In this test, the sulfur dioxide is released from the test specimen in a boiling acid medium and is removed by a stream of carbon dioxide. The separated gas is collected in a dilute hydrogen peroxide solution where the sulfur dioxide is oxidized to sulfuric acid and titrated with standard alkali. The apparatus consists essentially of a 500mL three-neck, round-bottom, boiling flask, a separatory funnel having a capacity of 100 mL or greater, a gas inlet tube of sufficient length to permit introduction of the carbon dioxide within 2.5 cm of the bottom of the boiling flask, a reflux condenser having a jacket length of 200 mm , and a delivery tube connecting the upper end of the reflux condenser to the bottom of a receiving test tube. Apply a thin film of stopcock grease to the sealing surfaces of all of the joints except the joint between the separatory funnel and the boiling flask, and clamp the joints to ensure tightness.

Procedure-Add 150 mL of water to the boiling flask. Close the stopcock of the separatory funnel, and begin the flow of carbon dioxide at a rate of $100 \pm 5 \mathrm{~mL}$ per minute through the Apparatus. Start the condenser coolant flow. Add 10 mL of Hydrogen peroxide solution to a receiving test tube. After 15 minutes, without interrupting the flow of carbon dioxide, remove the separatory funnel from the boiling flask, and transfer 25.0 g of test specimen into the boiling flask with the aid of 100 mL of water. Apply stopcock grease to the outer joint of the separatory funnel, and replace the separatory funnel in the boiling flask. Close the stopcock of the separatory funnel, and add 80 mL of 2 N hydrochloric acid to the separatory funnel. Open the stopcock of the separatory funnel to permit the hydrochloric acid
solution to flow into the boiling flask, guarding against the escape of sulfur dioxide into the separatory funnel by closing the stopcock before the last few mL of hydrochloric acid drain out. Position the Apparatus in a water bath, and Boil the mixture for 1 hour. Remove the receiving test tube, and transfer its contents to a $200-\mathrm{mL}$ wide-necked, conical flask. Rinse the receiving test tube with a small portion of water, add the rinsing to the $200-\mathrm{mL}$ conical flask, and mix. Heat on a water bath for 15 minutes, and allow to cool. Add 0.1 mL of Bromophenol blue indicator solution, and titrate the contents with 0.1 N sodium hydroxide VS until the color changes from yellow to violet-blue, with the color change lasting for at least 20 seconds. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Calculate the content, in $\mu \mathrm{g}$ per g , of sulfur dioxide in the test specimen taken by the formula:

$$
1000(32.03) \mathrm{VN} / W,
$$

in which 32.03 is the milliequivalent weight of sulfur dioxide; $V$ is the volume, in mL , of titrant consumed; $N$ is the normality of the titrant; and $W$ is the weight, in g , of test specimen taken.

Organic volatile imptrities, Meth $H\langle\langle 467\rangle$ :-meets the requirements. $\mathbf{A N F}^{\text {NF }}$

BRIEFING

Potato Starch, page 885 of $P F 28(3)$ [May-June 2002]. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Potato Starch monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph represents the ADOPTION STAGE 6 document. The EP draft was based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by EP. The current NF monograph for Starch will be proposed for deletion, to be replaced by Corn Starch, Potato Starch, and Wheat Starch.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Identification B | + | + | + |
| Identification C | + | + | + |
| pH | + | + | + |
| Iron | + | + | + |
| Oxidizing substances | + | + | + |
| Sulfur dioxide | + | + | + |
| Loss on drying | + | + | + |
| Sulphated ash | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Microbial contamination, Storage.
Specific local attributes: Foreign matter (EP).
Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.
Differences between the International Harmonization Adoption Stage 6 document for Potato Starch and the current NF Starch monograph include the following:
(1) Definition-Changed to include only Potato Starch, as to conform to the individual monograph for Potato Starch.
(2) Packaging-No change.
(3) Labeling-Deleted.
(4) Botanical characteristics-This test has been modified and moved to the Identification section.
(5) Identification-A microscopic test is added that is similar to the Botanical characteristics section. The other two tests are modified slightly for clarification.
(6) Microbial limits-The revised limit for the total combined molds and yeasts count in the test is based on comments received.
(7) $\mathrm{pH}-\mathrm{No}$ change.
(8) Loss on drying-The revised test conditions reportedly correspond to ISO 1666 and are preferred by users of starches because of reduced testing time.
(9) Residue on ignition-The standard for this test is increased from $0.5 \%$ to $0.6 \%$ in order to conform with EP standards.
(10) Limit of iron-The test procedure is changed in order to conform to EP standards.
(11) Limit of oxidizing substances-No change.
(12) Limit of sulfur dioxide-The change in the standard reflects the corresponding limits proposed by the EC food laws.
(13) Organic volatile impurities-This test is deleted because it is unnecessary.
(EMC: J. Lane) RTS-40773-6

## Add the following:

## $\Delta$ Potato Starch

## » Potato Starch is obtained from the tuber of Solanum tuberosum $L$.

Packaging and-storage-Preserve in well-closed containers.

## Identification-

A: Under a microscope, using a mixture of glycerin and water (1:1) as a mounting agent, it presents granules, either irregularly shaped, ovoid, or pear-shaped, usually $30 \mu \mathrm{~m}$ to $100 \mu \mathrm{~m}$ in size, but occasionally exceeding $100 \mu \mathrm{~m}$, or rounded, $10 \mu \mathrm{~m}$ to $35 \mu \mathrm{~m}$ in size. There are occasional compound granules having two or four components. The ovoid and pear-shaped granules have an eccentric hilum and the rounded granules acentric or slightly eccentric hilum. All granules show clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum.

B: Suspend 1 g of it in 50 mL of water, boil for $1 \mathrm{~min}-$ ute, and cool: a thin, cloudy mucilage is formed.

C: To 1 mL of the mucilage obtained in Identification test $B$, add 0.05 mL of iodine and potassium iodide TS: a dark blue color is produced, which disappears on heating.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed $100010^{3}$ per g , the total combined molds and yeasts count does not exceed $10010^{2}$ per g , and it meets the requirements of the test for the absence of Escherichia coli.
$\mathbf{p H}\langle 791\rangle$ —Prepare a slurry by weighing 5.0 g of Potato Starch, transferring to a suitable nonmetallic container, and adding 25.0 mL of freshly boiled and cooled water. Agitate continuously at a moderate rate for 1 minute. Stop the agitation, and allow to stand for 15 minutes. Determine the pH to the nearest 0.1 unit: the pH , determined potentiometrically, is between 5.0 and 8.0.

Loss on drying $\langle 731\rangle$-Dry about 1 g , accurately weighed, at $130^{\circ}$ for 90 minutes: it loses not more than $20.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.6 \%$, determined on a $1.0-\mathrm{g}$ test specimen. Ignition temperature $600 \pm 50^{\circ}$.

Limit of iron-Shake 1.5 g of Potato Starch with 15 mL of 2 N hydrochloric acid, and filter. Transfer 10 mL of the filtrate to a test tube, add 2 mL of citric acid solution (2 in 10), 0.1 mL of thioglycolic acid, and mix. Add 10 N ammonium hydroxide until the solution is distinctly alkaline to litmus, dilute with water to 20 mL , and mix (Test Solution). Prepare a Standard Iron Solution containing the equivalent of $10 \mu \mathrm{~g}$ of iron per mL as directed under Iron $\langle 241\rangle$. Immediately before use, quantitatively dilute an accurately measured volume of this solution with water to obtain a Diluted Standard Iron Solution containing the equivalent of $1 \mu \mathrm{~g}$ of iron per mL . Prepare the Standard Solution by transferring 10 mL of the Diluted Standard Iron Solution to a test tube and proceeding in the same manner as directed for the preparation of the Test Solution, beginning with "add 2 mL of citric acid
solution (2 in 10)." After 5 minutes, any pink color in the Test Solution is not more intense than that in the Standard Solution, corresponding to a limit of $10 \mu \mathrm{~g}$ of iron per g .

Limit of oxidizing substances-Transfer 4.0 g to a glassstoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate is required ( $20 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ).

Limit of sulfur dioxide: not more than $50 \mu \mathrm{~g}$ per g .

## Reagents-

Carbon dioxide-Use carbon dioxide, with a flow regulator that will maintain a flow of $100 \pm 10 \mathrm{~mL}$ per minute.

Bromophenol blue indicator solution-Dissolve 100 mg of bromophenol blue in 100 mL of dilute alcohol (1 in 5), and filter if necessary.
Hydrogen peroxide solution-Dilute 30\% hydrogen peroxide with water to obtain a $3 \%$ solution. Just before use, add 3 drops of Bromophenol blue indicator solution, and neutralize to a violet-blue endpoint with 0.01 N sodium hydroxide. Do not exceed the endpoint.

Apparatus-In this test, the sulfur dioxide is released from the test specimen in a boiling acid medium and is removed by a stream of carbon dioxide. The separated gas is collected in a dilute hydrogen peroxide solution where the sulfur dioxide is oxidized to sulfuric acid and titrated with
standard alkali. The apparatus consists essentially of a 500mL three-neck, round-bottom boiling flask, a separatory funnel having a capacity of 100 mL or greater, a gas inlet tube of sufficient length to permit introduction of the carbon dioxide within 2.5 cm of the bottom of the boiling flask, a reflux condenser having a jacket length of 200 mm , and a delivery tube connecting the upper end of the reflux condenser to the bottom of a receiving test tube. Apply a thin film of stopcock grease to the sealing surfaces of all of the joints except the joint between the separatory funnel and the boiling flask, and clamp the joints to ensure tightness.

Procedure-Add 150 mL of water to the boiling flask. Close the stopcock of the separatory funnel, and begin the flow of carbon dioxide at a rate of $100 \pm 5 \mathrm{~mL}$ per minute through the Apparatus. Start the condenser coolant flow. Add 10 mL of Hydrogen peroxide solution to a receiving test tube. After 15 minutes, without interrupting the flow of carbon dioxide, remove the separatory funnel from the boiling flask, and transfer 25.0 g of test specimen into the boiling flask with the aid of 100 mL of water. Apply stopcock grease to the outer joint of the separatory funnel, and replace the separatory funnel in the boiling flask. Close the stopcock of the separatory funnel, and add 80 mL of 2 N hydrochloric acid to the separatory funnel. Open the stopcock of the separatory funnel to permit the hydrochloric acid solution to flow into the boiling flask, guarding against the escape of sulfur dioxide into the separatory funnel by closing the stopcock before the last few mL of hydrochloric acid drain out. Position the Apparatus in a bath, and Boil the mixture for 1 hour. Remove the receiving test tube, and transfer its contents to a $200-\mathrm{mL}$ wide-necked, conical flask. Rinse the receiving test tube with a small portion of water, add the rinsing to the $200-\mathrm{mL}$ conical flask, and mix. Heat on a water bath for 15 minutes, and allow to cool. Add 0.1 mL of Bromophenol blue indicator solution, and titrate the
contents with 0.1 N sodium hydroxide VS until the color changes from yellow to violet-blue, with the color change lasting for at least 20 seconds. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Calculate the content, in $\mu \mathrm{g}$ per g , of sulfur dioxide in the test specimen taken by the formula:

$$
1000(32.03) \mathrm{VN} / W,
$$

in which 32.03 is the milliequivalent weight of sulfur dioxide; $V$ is the volume, in mL , of titrant consumed; $N$ is the normality of the titrant; and $W$ is the weight, in g , of test specimen taken.

Organic volatile impurities, Methed $I H(467)$ : meets the requirements._NF23

## Briefing

Rice Starch. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Rice Starch monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the revised OFFICIAL INQUIRY STAGE 4 document, is based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts. The text presented is similar to the harmonization drafts for Corn, Wheat, and Potato Starch that appear in this issue of Pharmacopeial Forum.
(EMC: J. Lane) RTS-40773-3

## Add the following:

## Rice Starch

» Rice Starch is obtained from the caryopsis of Oryza sativa $L$.

Packaging-Preserve in well-closed containers.

## Identification-

A: Examined under a microscope using a mixture of equal volumes of glycerin and water, it presents polyhedral, simple grains $1 \mu \mathrm{~m}$ to $10 \mu \mathrm{~m}$, mostly $4 \mu \mathrm{~m}$ to $6 \mu \mathrm{~m}$, in size. These simple grains often gather in ellipsoidal, compound grains $50 \mu \mathrm{~m}$ to $100 \mu \mathrm{~m}$ in diameter. The granules have a poorly visible central hilum and there are no concentric striations. Between crossed nicol prisms, the starch granules show a distinct black cross intersecting at the hilum.

B: Suspend 1 g of it in 50 mL of water, boil for $1 \mathrm{~min}-$ ute, and cool: a thin, cloudy mucilage is formed.

C: To 1 mL of the mucilage obtained in Identification test $B$, add 0.05 mL of Iodine and potassium iodide solution: an orange-red to dark blue color is produced, which disappears on heating.

Iodine and potassium iodide solution-To 10.0 mL of 0.05 M iodine, add 0.6 g of potassium iodide and dilute to 100.0 mL with water. Prepare immediately before use.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed $10^{3}$ cfu per g , the total combined molds and yeasts count does not exceed $10^{2}$ cfu per g , and it meets the requirements of the test for the absence of Escherichia coli.
$\mathbf{p H}\langle 791\rangle$ —Prepare a slurry by weighing 5.0 g of Rice Starch, transferring to a suitable nonmetallic container, and adding 25.0 mL of freshly boiled and cooled water. Agitate continuously at a moderate rate for 1 minute. Stop the agitation and allow to stand for 15 minutes. Determine the pH to the nearest 0.1 unit: the pH , determined potentiometrically, is between 5.0 and 8.0.

Loss on drying $\langle 731\rangle$-Dry about 1 g , accurately weighed, at $130^{\circ}$ for 90 minutes: it loses not more than $15.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.6 \%$, determined on a $1.0-\mathrm{g}$ test specimen.

Foreign matter-Examine under a microscope using a mixture of equal volumes of glycerin and water: not more than traces of matter other than starch granules are present. No starch grains of any other origin are present.

Limit of iron-Shake 1.5 g of Rice Starch with 15 mL of 2 $N$ hydrochloric acid, and filter. Transfer 10 mL of the filtrate to a test tube, add 2 mL of citric acid solution (2 in 10), 0.1 mL of thioglycolic acid, and mix. Add 10 N ammonium hydroxide until the solution is distinctly alkaline to litmus, dilute with water to 20 mL , and mix (Test Solution). Prepare a Standard Iron Solution containing the equivalent of $10 \mu \mathrm{~g}$ of iron per mL as directed under Iron $\langle 241\rangle$. Immediately before use, dilute an accurately measured volume of this solution quantitatively with water to obtain a Diluted Standard Iron Solution containing the equivalent of $1 \mu \mathrm{~g}$ of iron per mL . Prepare the Standard Solution by transferring 10 mL of the Diluted Standard Iron Solution to a test tube and proceeding in the same manner as directed for the preparation of the Test solution, beginning with "add 2 mL of citric acid solution (2 in 10)." After 5 minutes, any pink color in the Test Solution is not more intense than that in the Standard Solution, corresponding to a limit of $10 \mu \mathrm{~g}$ of iron per g .

Limit of oxidizing substances-Transfer 4.0 g to a glassstoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant liquid to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of $0.002 N$ sodium thiosul-
fate VS is equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate VS is required ( $20 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ).

Limit of sulfur dioxide-Not more than $50 \mu \mathrm{~g}$ per g .
Reagents-
Carbon dioxide - Use carbon dioxide, with a flow regulator that will maintain a flow of $100 \pm 10 \mathrm{~mL}$ per minute.

Bromophenol blue indicator solution-Dissolve 100 mg of bromophenol blue in 100 mL of dilute alcohol (1 in 5), and filter if necessary.

Hydrogen peroxide solution-Dilute $30 \%$ hydrogen peroxide with water to obtain a $3 \%$ solution. Just before use, add 3 drops of Bromophenol blue indicator solution, and neutralize to a violet-blue endpoint with 0.01 N sodium hydroxide. Do not exceed the endpoint.
Apparatus-In this test, the sulfur dioxide is released from the test specimen in a boiling acid medium and is removed by a stream of carbon dioxide. The separated gas is collected in a dilute hydrogen peroxide solution where the sulfur dioxide is oxidized to sulfuric acid and titrated with standard alkali. A suitable apparatus for sulfur dioxide determination is shown in the accompanying diagram (Figure $1)$. The apparatus consists essentially of a $500-\mathrm{mL}$ threeneck, round-bottom, boiling flask, $A$, a separatory funnel, $B$, having a capacity of 100 mL or greater, a gas inlet tube, of sufficient length to permit introduction of the carbon dioxide within 2.5 cm of the bottom of the boiling flask, a reflux condenser, $C$, having a jacket length of 200 mm , and a delivery tube, $E$, connecting the upper end of the reflux condenser to the bottom of a receiving test tube, $D$. Apply a thin film of stopcock grease to the sealing surfaces of all of the joints except the joint between the separatory funnel and the boiling flask, and clamp the joints to ensure tightness.


Fig. 1.

Procedure—Add 150 mL of water to the boiling flask $(A)$. Close the stopcock of the separatory funnel, and begin the flow of carbon dioxide at a rate of $100 \pm 5 \mathrm{~mL}$ per minute through the Apparatus. Start the condenser coolant flow. To 10 mL of Hydrogen peroxide solution, add 0.15 mL of Bromophenol blue indicator solution. Add 0.1 N sodium hydroxide until a violet-blue color is obtained, without exceeding the end-point. Place the solution in the test tube $(D)$. After 15 minutes, without interrupting the flow of carbon dioxide, remove the separatory funnel $(B)$ from the boiling flask and transfer 25.0 g of test specimen into the boiling flask with the aid of 100 mL of water. Apply stopcock grease to the outer joint of the separatory funnel, and replace the separatory funnel in the boiling flask. Close the stopcock of the separatory funnel, and add 80 mL of 2 N hydrochloric acid to the separatory funnel. Open the stopcock of the separatory funnel to permit the hydrochloric acid solution to flow into the boiling flask. Boil the mixture for 1 hour. Open the stopcock of the funnel and stop the flow of carbon diox-
ide and also the heating and the cooling water. Remove the receiving test tube, and transfer its contents to a $200-\mathrm{mL}$ wide-necked, conical flask. Rinse the receiving test tube with a small portion of water, add the rinsing to the 200mL conical flask, and mix. Heat on a water bath for 15 minutes and allow to cool. Add 0.1 mL of Bromophenol blue indicator solution, and titrate the contents with 0.1 N sodium hydroxide VS until the color changes from yellow to violet-blue. Perform a blank determination and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Calculate the content, in $\mu \mathrm{g}$ per g , of sulfur dioxide in the test specimen taken by the formula:

$$
1000(32.03) V N / W
$$

in which 32.03 is the milliequivalent weight of sulfur dioxide, $V$ is the volume, in mL , of titrant consumed, $N$ is the normality of the titrant, and $W$ is the weight, in g , of test specimen taken.

Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

## BRIEFING

Wheat Starch, page 888 of $P F$ 28(3) [May-June 2002]. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Wheat Starch monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph represents the ADOPTION STAGE 6 document. The EP draft was based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by EP. The current $N F$ monograph for Starch will be proposed for deletion, to be replaced by Corn Starch, Potato Starch, and Wheat Starch.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Identification B | + | + | + |
| Identification C | + | + | + |
| pH | + | + | + |
| Iron | + | + | + |
| Total protein | + | - | + |
| Oxidizing substances | + | + | + |
| Sulfur dioxide | + | + | + |
| Loss on drying | + | + | + |
| Sulphated ash | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Microbial contamination, Storage.

Specific local attributes: Foreign matter (EP).
Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Differences between the International Harmonization Adoption Stage 6 document for Wheat Starch and the current NF Starch monograph include the following:
(1) Definition-Changed to include only Wheat Starch, as to conform to the individual monograph for Wheat Starch.
(2) Packaging-No change.
(3) Labeling-Deleted.
(4) Identification test $C$-The iodine test solution preparation is added.
(5) Botanical characteristics-This test has been modified and moved to the Identification section.
(6) Identification-A microscopic test is added that is similar to the Botanical characteristics section. The other two tests are modified slightly for clarification.
(7) Microbial limits-The revised limit for the total combined molds and yeasts count in the test is based on comments received.
(8) pH -No change.
(9) Loss on drying-The revised test conditions reportedly correspond to ISO 1666 and are preferred by users of starches because of reduced testing time.
(10) Residue on ignition-The standard for this test is increased from $0.5 \%$ to $0.6 \%$ in order to conform with EP standards.
(11) Total Protein-This test is added to conform with EP.
(12) Limit of iron-The test procedure is changed in order to conform to EP standards.
(13) Limit of oxidizing substances-No change.
(14) Limit of sulfur dioxide-The change in the standard reflects the corresponding limits proposed by the EC food laws.
(15) Organic volatile impurities-This test is deleted, as it is not necessary.
(EMC: J. Lane) RTS-40773-2

## Add the following:

## © Wheat Starch

» Wheat Starch is obtained from the caryopsis of Triticum aestivum L. (T. vulgare Vill.).

Packaging and-storage-Preserve in well-closed containers.

## Identification-

A: Under a microscope, using a mixture of glycerin and water (1:1) as a mounting agent, it presents large and small granules, and very rarely, intermediate sizes. The large granules, usually $10 \mu \mathrm{~m}$ to $60 \mu \mathrm{~m}$ in diameter, are discoid or, more rarely, reniform when seen face-on. The central hilum and striations are invisible or barely visible and the granules sometimes show cracks on the edges. Seen in profile, the granules are elliptical and fusiform and the hilum appears as a slit along the main axis. The small granules, rounded or polyhedral, are $2 \mu \mathrm{~m}$ to $10 \mu \mathrm{~m}$ in diameter. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum.

B: Suspend 1 g of it in 50 mL of water, boil for $1 \mathrm{~min}-$ ute, and cool: a thin, cloudy mucilage is formed.

C: Te 1 mL of the mucilage obtained in Identificution

## test $B$, add 0.05 mL of iodine and petassium iodide $\mathrm{TS}:$ a

## dark blue color is produced, which disappears on heating.

C: To 1 mL of the mucilage obtained in Identification test $B$, add 0.05 mL of Iodine solution: an orange-red to dark blue color is produced, which disappears on heating.

Iodine solution-Dissolve 12.7 g of iodine and 20 g of potassium iodide in water, and dilute with water to 1000.0 mL . To 10.0 mL of this solution, add 0.6 g of potassium iodide, and dilute with water to 100.0 mL . Prepare immediately before use.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed $100010^{3}$ per g , the total combined molds and yeasts count does not exceed $10010^{2}$ per g , and it meets the requirements of the test for the absence of Escherichia coli.
$\mathbf{p H}\langle 791\rangle$ —Prepare a slurry by weighing 5.0 g of Wheat Starch, transferring to a suitable nonmetallic container, and adding 25.0 mL of freshly boiled and cooled water. Agitate continuously at a moderate rate for 1 minute. Stop the agitation, and allow to stand for 15 minutes. Determine the pH to the nearest 0.1 unit: the pH , determined potentiometrically, is between 4.5 and 7.0.

Loss on drying $\langle 731\rangle$ —Dry about 1 g , accurately weighed, at $130^{\circ}$ for 90 minutes: it loses not more than $15.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.6 \%$, determined on a $1.0-\mathrm{g}$ test specimen. Ignition temperature $600 \pm 50^{\circ}$.

Total protein: not more than $0.3 \%$ of total protein (corresponding to $0.048 \% \mathrm{~N}_{2}$, conversion factor: 6.25).
Procedure-Accurately weigh 6.0 g of test substance containing about 2 mg of nitrogen, transfer to a combustion flask, and add 4 g of a powdered mixture of 100 g of potassium sulfate, 5 g of cupric sulfate, and 2.5 g of selenium, and three glass beads. Wash any adhering particles from the neck into the flask with 5 mL of sulfuric acid, allowing it to run down the sides of the flask, and mix the contents by rotation. Close the mouth of the flask loosely, for example by means of a glass bulb with a short stem, to avoid excessive loss of sulfuric acid. Heat gradually at first, then increase the temperature until there is vigorous boiling with
condensation of sulfuric acid in the neck of the flask; precautions should be taken to prevent the upper part of the flask from becoming overheated. Continue the heating for 30 minutes, unless otherwise prescribed. Cool, dissolve the solid material by cautiously adding to the mixture 25 mL of water, cool again, and place in a steam distillation apparatus. Add 30 mL of sodium hydroxide solution (42 in 100), and distil immediately by passing steam through the mixture. Collect about 40 mL of distillate in 20.0 mL of 0.01 N hydrochloric acid and enough water to cover the tip of the condenser. Towards the end of the distillation, lower the receiver so that the tip of the condenser is above the surface of the acid. Take precautions to prevent any water on the outer surface of the condenser from reaching the contents of the receiver. Titrate the distillate with 0.01 N sodium hydroxide, using methyl purple TS as indicator ( $\mathrm{n}_{1} \mathrm{~mL}$ of 0.01 N sodium hydroxide).
Repeat the test using about 50 mg of glucose in place of the substance to be examined ( $\mathrm{n}_{2} \mathrm{~mL}$ of 0.01 N sodium hydroxide).

$$
\text { Content of nitrogen }=\left(0.01401\left(\mathrm{n}_{2}-\mathrm{n}_{1}\right)\right) / \mathrm{m}
$$

where $m$ is the amount of test substance weighed, in $g$.
Limit of iron-Shake 1.5 g of Wheat Starch with 15 mL of 2 N hydrochloric acid, and filter. Transfer 10 mL of the filtrate to a test tube, add 2 mL of citric acid solution (2 in 10), 0.1 mL of thioglycolic acid, and mix. Add 10 N ammonium hydroxide until the solution is distinctly alkaline to litmus, dilute with water to 20 mL , and mix (Test Solution). Prepare a Standard Iron Solution containing the equivalent of $10 \mu \mathrm{~g}$ of iron per mL as directed under Iron $\langle 241\rangle$. Immediately before use, quantitatively dilute an accurately measured volume of this solution with water to obtain a Diluted Standard Iron Solution containing the equivalent of $1 \mu \mathrm{~g}$ of iron per mL . Prepare the Standard Solution by transferring 10 mL of the Diluted Standard Iron Solution to a test tube and pro-
ceeding in the same manner as directed for the preparation of the Test Solution, beginning with "add 2 mL of citric acid solution (2 in 10)." After 5 minutes, any pink color in the Test Solution is not more intense than that in the Standard Solution, corresponding to a limit of $10 \mu \mathrm{~g}$ of iron per g .

Limit of oxidizing substances-Transfer 4.0 g to a glassstoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS , and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate is required ( $20 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ).

Limit of sulfur dioxide: not more than $50 \mu \mathrm{~g}$ per g .

## Reagents-

Carbon dioxide—Use carbon dioxide, with a flow regulator that will maintain a flow of $100 \pm 10 \mathrm{~mL}$ per minute.

Bromophenol blue indicator solution-Dissolve 100 mg of bromophenol blue in 100 mL of dilute alcohol (1 in 5 ), and filter if necessary.

Hydrogen peroxide solution-Dilute $30 \%$ hydrogen peroxide with water to obtain a $3 \%$ solution. Just before use, add 3 drops of Bromophenol blue indicator solution, and neutralize to a violet-blue endpoint with 0.01 N sodium hydroxide. Do not exceed the endpoint.

Apparatus-In this test, the sulfur dioxide is released from the test specimen in a boiling acid medium and is removed by a stream of carbon dioxide. The separated gas is
collected in a dilute hydrogen peroxide solution where the sulfur dioxide is oxidized to sulfuric acid and titrated with standard alkali. The apparatus consists essentially of a 500mL three-neck, round-bottom, boiling flask, a separatory funnel having a capacity of 100 mL or greater, a gas inlet tube of sufficient length to permit introduction of the carbon dioxide within 2.5 cm of the bottom of the boiling flask, a reflux condenser having a jacket length of 200 mm , and a delivery tube connecting the upper end of the reflux condenser to the bottom of a receiving test tube. Apply a thin film of stopcock grease to the sealing surfaces of all of the joints except the joint between the separatory funnel and the boiling flask, and clamp the joints to ensure tightness.

Procedure-Add 150 mL of water to the boiling flask. Close the stopcock of the separatory funnel, and begin the flow of carbon dioxide at a rate of $100 \pm 5 \mathrm{~mL}$ per minute through the Apparatus. Start the condenser coolant flow. Add 10 mL of Hydrogen peroxide solution to a receiving test tube. After 15 minutes, without interrupting the flow of carbon dioxide, remove the separatory funnel from the boiling flask, and transfer 25.0 g of test specimen into the boiling flask with the aid of 100 mL of water. Apply stopcock grease to the outer joint of the separatory funnel, and replace the separatory funnel in the boiling flask. Close the stopcock of the separatory funnel, and add 80 mL of 2 N hydrochloric acid to the separatory funnel. Open the stopcock of the separatory funnel to permit the hydrochloric acid solution to flow into the boiling flask, guarding against the escape of sulfur dioxide into the separatory funnel by closing the stopcock before the last few mL of hydrochloric acid drain out. Position the Apparatus in a water bath, and Boil the mixture for 1 hour. Remove the receiving test tube, and transfer its contents to a $200-\mathrm{mL}$ wide-necked, conical flask. Rinse the receiving test tube with a small portion of water, add the rinsing to the $200-\mathrm{mL}$ conical flask, and mix. Heat
on a water bath for 15 minutes, and allow to cool. Add 0.1 mL of Bromophenol blue indicator solution, and titrate the contents with 0.1 N sodium hydroxide VS until the color changes from yellow to violet-blue, with the color change lasting for at least 20 seconds. Perform a blank determination, and make any necessary correction (see Titrimetry
$\langle 541\rangle$ ). Calculate the content, in $\mu \mathrm{g}$ per g , of sulfur dioxide in the test specimen taken by the formula:

$$
1000(32.03) V N / W,
$$

in which 32.03 is the milliequivalent weight of sulfur dioxide; $V$ is the volume, in mL , of titrant consumed; $N$ is the normality of the titrant; and $W$ is the weight, in g , of test specimen taken.

Organic volatile imptrities, Method $H(467)$ : meets the requirements. $\mathbf{\Delta N F}^{\mathrm{NF} 23}$

## PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the Staff Directory to find the contact information).

Briefings Each Preview is preceded by a Briefing in the following format:

## Briefing

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being used, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see How To Use PF), the name of the scientific staff liaison who handled this item, and the USP tracking correspondence number, as shown in the example below:
(PA5: K. Russo) RTS-55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.
PHARMACOPEIAL PREVIEWS ..... 729
MONOGRAPHS (USP) ..... 731
Methylphenidate Hydrochloride ..... 731
DIETARY SUPPLEMENTS-MONOGRAPHS ..... 734
Tomato Extract Containing Lycopene Capsules [new] ..... 734

## MONOGRAPHS (USP)

## BriEfing

Methylphenidate Hydrochloride, USP 27 page 1217 and page 1932 of PF 29(6) [Nov.-Dec.2003]. It is proposed to replace the tests for Limit of erythro $\left[\left(R^{*}, S^{*}\right)\right]$ isomer and Limit of $\alpha$-phenyl-2-piperidineacetic acid hydrochloride and the existing Assay with a new test for Related compounds and a new Assay. The liquid chromatographic procedures are performed with a Zorbax Eclipse-XDB C18 brand of L1 column. The retention time of methylphenidate is about 29 minutes. The limits for impurities are also being revised. It is also proposed to add new USP Reference Standards and to add storage conditions to the Packaging and storage section.
(PA3: S. Salado) RTS-38283-1

## Change to read:

Packaging and storage—Preserve in well-closed containers.
Store at a temperature between $15^{\circ}$ and $30^{\circ}$.

## Change to read:

USP Reference standards $\langle 11\rangle$ — USP Methylphenidate Hydrochloride RS. USP Methylphenidate Hyrochloride Eyythro Isomer RS. USP Methylphenidate Hydrochloride Erythro Isomer Solution RS. USP a Phenyl2 piperidine Aeid Hy liochloride RS.

USP Methylphenidate Related Compound B RS. USP Methylphenidate Related Compound C RS. USP Methylphenidate Related Compound D RS. USP Methylphenidate Related Compound E RS. USP Methylphenidate Related Compound F RS. USP Methylphenidate Related Compound G RS. USP Methylphenidate Related Compound H RS.

## Delete the following:

Limil of erythro $\left[\left(R^{*} *, S *\right)\right]$ isomer-
Mobile solvent Prepare a solution consisting of a mixture of ehloroform, methanol, and ammenium hydroxide (190:10:1).

Petecting reagent Dissolve 0.7 g of bismuth subnitrate in 40 mL of a mixture of water and glacial acetic acid ( $4: 1$ ). Add- 40 mL of potassium iodide solution (2 in 5), then add 120 mL of gla eial ucetic acid and 250 mL of water.

Test solution Prepare a solution in methanol containing 50 mg of Methylphenidate Hydrochloride per mL.

Proedure Prepare methanel solutions of Methylphenidate Hydrechloride and of USP Methylphenidate Hydrochloride Ery thro Isomer RS containing 50 mg per mb and 0.5 mg per mb , respectively. Apply $20 \mu \mathrm{~L}$ pertions of each-solutionApply $20 \mu \mathrm{H}$ pertions of the Test solution and USP Methylphenidate Hydroehloride Erythro-Isomer Solution RSto a suitable thin layer chromatographie plate (seeChromatography $\langle 624$ ) ) eont withan 0.25
mm layer of chromatographic silica gel. Allow the spots to dry, and develop the chromatogram, using the Mobile solvent, in a suitable ehamber, lined with absorbent paper and previously equilibrated with the Mobile solvent, until the solvent frent has moved about three fourths of the length of the plate. Remove the plate from the developing chamber, and allow the solvent to eraporate. Loeate the spots on the plate by spraying first with the Deteeting reagent and then with 1 N sulfuric acid. Any spot in the lane from the methylphenidate hydrochloride at the same $R_{F}$ as the erythro iso mer is not larger or more intense than that produced by USP Methylphenidate Hydrechloride Erythre-Isemer RS,USP Methyl phenidate-Hydrochloride Erythro Isomer Solution RS, when viewed under ordinaty lighting (1\%).

## Delete the following:

Limit of $\alpha$-phenyl-2-piperidineacetic acid hydrochloride -
Agbile solvent Mix 65 volumes of chloroform with 25 vol umes of methanel and 5 volumes of acetic acid.
Sodium hydroxide methand- Prepare a 1 in 2500 -solution-of sodium hydroxide in methanol.
Spray reagent $I . \mathrm{Mix} 850 \mathrm{mg}$ of bismuth subnitrate with 40 mL of water and 10 mL of glacial acetic acid (Solution A). Dissolve 8 s ef potassitm iodide in 20 mL of water (Selution B). Mix Selations $A$ and $B$ together to obtain the Stock solution. [NOTE-This Stock solution may be stored for several menths in a dark bottle.] Mix 10 mL of the Stock solution with 20 mL of glacial acetic acid, and dilute with water to make 100 mL to bbtain the Spray reagent.
fpray reagent II Use hydrogen peroxide solution.
Standard preparation- Dissolve a suitable quantity of USP $\alpha$ Phenyl 2 piperidineacetic Acid Hydrochloride RS in Sodium hy droxide methathol to obtain a solution having a known coneentra fion of about 240 - 4 g per mL
Test preparation Dissolve 400 mg of Methylphenidate Hydroehloride, aceurately weighed, in Sodium hydroxide methatal to make 10.0 mL . Use immediately after preparation.
Proedure Apply $10 \mu \mathrm{~L}$ pertions of the Test preparation and the Standard preparation to a suitable thin layer chromatographie plate (see-Chromatograply ( 624 )) eonted with a- 0.25 mm layer of ehrematographic siliea gel. Allow the spets to dry, and develop the ehromatogram, using the Mobile solvent, in a suitable chamber, lined with absorbent paper and previously equilibrated with Mobile solvent, until the solvent frent has moved about three fouthis of the length of the plate. Remeve the plate frem the developing ehamber, and allow the plate to dry for 30 minutes. Spray the plate with Spray reagent I followe by Spray reagent II.-NOTE-After spray ing with the Spray reagents, cover the plate with a second plate to prevent fading of the spots.] Examine the plate: any spot in the lane from the Test preparation having the same $R_{2}$ value as the prineipat spot from the Stand preparation is not larger or more intense than that produre by the Standard preparation (0.6\%).

## Add the following:

## Related compounds-

Buffer solution and Mobile phase-Prepare as directed in the Assay.

Standard solution-Dissolve accurately weighed quantities of USP Methylphenidate Hydrochloride RS, USP Methylphenidate Related Compound C RS, USP Methylphenidate Related Compound D RS, USP Methylphenidate Related Compound B RS, USP Methylphenidate Related Compound E RS, USP Methylphenidate Related Com-
pound F RS, USP Methylphenidate Related Compound H RS, and USP Methylphenidate Related Compound G RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution containing about $0.4 \mu \mathrm{~g}$ per mL of USP Methylphenidate Related Compound C RS, USP Methylphenidate Related Compound E RS, and USP Methylphenidate Related Compound H RS; about $0.8 \mu \mathrm{~g}$ per mL of USP Methylphenidate Hydrochloride RS, USP Methylphenidate Related Compound D RS, USP Methylphenidate Related Compound B RS, and USP Methylphenidate Related Compound F RS; and about $1.2 \mu \mathrm{~g}$ per mL of USP Methylphenidate Related Compound G RS.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are de-
scribed in Table 1; the resolution, $R$, between adjacent peaks is not less than 2.0 ; and the relative standard deviation for replicate injections is not more than $5.0 \%$ for each peak.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure all of the peak area responses. Calculate the percentage of each impurity in the portion of Methylphenidate Hydrochloride taken by the formula:

$$
5(C / W)\left(r_{i} / r_{S}\right),
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of each impurity in the Standard solution; $W$ is the weight, in mg, of the sample taken; $r_{i}$ is the peak area for each impurity; and $r_{S}$ is the peak area of the respective substance in the Standard solution: the impurities meet the requirements provided in Table 1. [NOTE-Compare the $\alpha$-phenyl-2-pyridylacetonitrile peak and all of the unknown peaks with the methylphenidate hydrochloride peak.]

Table 1

|  | Relative |  |
| :--- | :---: | :---: |
| Compound name | Retention | Limit |
| Methylphenidate related compound E | Time | $(\%)$ |
| Methylphenidate related compound C | about 0.18 | 0.1 |
| Methylphenidate related compound H | about 0.22 | 0.1 |
| Methylphenidate related compound F | about 0.24 | 0.1 |
| Methylphenidate related compound D | about 0.40 | 0.1 |
| Methylphenidate related compound B | about 0.45 | 0.4 |
| Methylphenidate hydrochloride | about 0.59 | 0.1 |
| Methylphenidate related compound G | 1.0 | - |
| $\alpha$-Phenyl-2-pyridylacetonitrile | about 2.0 | 0.15 |
| Unknown | about 2.4 | 0.1 |
| Total | - | 0.1 |

## Change to read:

Assay-Dissolve about 225 mg of Methylphenidate Hydroehloride, ceeurately weighed, in 50 mL of glacial acetic acid in a 125 mL conieal flask. Add 15 mL of mereuric acetate TS and 5 drops of $p$ naphtholbenzein TS, and titrate with 0.1 N perchlorie acid VS to a green endpeint. Perform a blank determination, and make any necessary eorrection. Each mLof 0.1 N perehloric acid is equivalent 26.98 mg of $\mathrm{C}_{44} \mathrm{H}_{4_{9}} \mathrm{NO}_{2} \cdots \mathrm{HCl}$.

Buffer solution-Transfer about 3.4 g of monobasic potassium phosphate and 2.0 g of sodium 1-heptanesulfonate to a 1-L volumetric flask. Dissolve in and dilute with water to volume, and mix. Add 1 mL of triethylamine, and adjust with phosphoric acid to a pH of $2.42 \pm 0.02$.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (78:22). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Standard preparation-Dissolve an accurately weighed quantity of USP Methylphenidate Hydrochloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.4 mg per mL .

Assay preparation-Transfer about 20 mg of Methylphenidate Hydrochloride, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask containing about 40 mL of Mobile phase. Sonicate for 10 minutes to dissolve, and cool to room temperature. Dilute with Mobile phase to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the Assay preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak areas for the methylphenidate hydro-
chloride peaks. Calculate the quantity, in mg , of $\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ in the portion of Methylphenidate Hydrochloride taken by the formula:

$$
50 C\left(r_{U} / r_{S}\right)
$$

in which C is the concentration, in mg per mL , of USP Methylphenidate Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## DIETARY SUPPLEMENTS MONOGRAPHS

## BRIEFING

Tomato Extract Containing Lycopene Capsules. Because there is no existing USP monograph for this article, the following new monograph is being previewed.
(DSB: G. Giancaspro) RTS—36476-1

## Add the following:

## Tomato Extract Containing Lycopene Capsules

## » Tomato Extract Containing Lycopene Capsules

 contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Extract calculated by its content of lycopene$\left(\mathrm{C}_{40} \mathrm{H}_{56}\right)$. They contain phytofluene, phytoene, beta carotene, and tocopherols in the following ratios with respect to lycopene: not less than 0.11 for the combined amount of phytofluene $\left(\mathrm{C}_{40} \mathrm{H}_{68}\right)$ and phytoene $\left(\mathrm{C}_{40} \mathrm{H}_{64}\right)$, not less than 0.03 for beta carotene $\left(\mathrm{C}_{40} \mathrm{H}_{56}\right)$, and not less than 0.14 for tocopherols $\left(\mathrm{C}_{28} \mathrm{H}_{48} \mathrm{O}_{2}\right)$.

Packaging and storage-Preserve in tight, light-resistant containers. Store at $22^{\circ}$, with excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-The label states the official name and the Latin binomial of the species from which the Extract contained in the Capsules was derived. Label them to state the content of Extract per Capsule, and the content of lycopene in percentage of the Extract contained in each Capsule.

USP Reference standards $\langle 11\rangle$ —USP Lycopene RS. USP
Tomato Extract Containing Lycopene RS.

## Identification-

A: Determine the content of the Capsules as directed for Identification test $A$ under Tomato Extract Containing Lycopene.
B: Determine the content of the Capsules as directed for Identification test $B$ under Tomato Extract Containing Lycopene. The area ratio is not more than 0.10 .

Microbial limits $\langle 2021\rangle$-It meets the requirements of the tests for absence of Salmonella species, Escherichia coli, and Pseudomonas aeruginosa. The total aerobic bacterial count does not exceed 1000 per g , and the total combined molds and yeasts count does not exceed 200 per g.

Dissolution $\langle 711\rangle$ - [To come.]
Weight variation $\langle 2091\rangle$ : meet the requirements.

## Content of lycopene-

Butylated hydroxytoluene stock solution, Diluting solution, Standard solution A, Standard solution B, and Chromatographic system-Proceed as directed in the test for Content of lycopene under Tomato Extract Containing Lycopene.

Test solution-Quantitatively transfer the weighed contents of not fewer than 8 Capsules to a $100-\mathrm{mL}$ volumetric flask using 30 to 50 mL of methylene chloride as solvent. Add 10 mL of Butylated hydroxytoluene stock solution. Sonicate the solution for 1 minute to completely dissolve the sample. Cool to room temperature, dilute with methylene chloride to volume, and mix well. Dilute with Diluting solution to obtain a solution having an expected concentration of about 0.07 mg of lycopene per mL .

Procedure-Separately inject equal volumes ( $10 \mu \mathrm{~L}$ ) of Standard solution A and the Test solution into the chromatograph, record the chromatograms, and measure the responses of the major lycopene peaks. Calculate the concentration of lycopene in Standard solution A, in ppm, by the formula:

$$
50,000 A_{X} / 345
$$

in which $A_{X}$ is the absorbance of Standard solution B, and 345 is the absorptivity of pure lycopene. Calculate the quantity, in mg, of lycopene per Capsule by the formula:

$$
0.1(C / N)\left(r_{U} / r_{S}\right)(D)
$$

in which $C$ is the concentration, in ppm, of Standard solution $A ; N$ is the number of Capsules taken to prepare the Test solution; $D$ is the dilution factor for the preparation of the Test solution using Diluting solution; and $r_{U}$ and $r_{S}$ are the areas of the lycopene peak responses obtained from the Test solution and Standard solution A, respectively.

Content of other carotenoids and tocopherols (phytofluene, phytoene, beta carotene, and tocopherols)-

Butylated hydroxytoluene stock solution, Diluting solution, Standard solution A, Standard solution B, and Test solution-Proceed as directed in the test for Content of lycopene.
Mobile phase, System suitability solution, and Chromatographic system-Proceed as directed in the test for Content of other carotenoids and tocopherols (phytofluene, phytoene, beta carotene, and tocopherols) under Tomato Extract Containing Lycopene.

Procedure-Separately inject equal volumes ( $10 \mu \mathrm{~L}$ ) of Standard solution $A$ and the Test solution into the chromatograph, and record the chromatograms. Identify the locus of the peaks for lycopene isomers, beta carotene isomers, phytofluene isomers, and phytoene by comparison with the Reference Chromatogram provided with the corresponding lot of USP Tomato Extract Containing Lycopene RS. Measure the sum of the peak responses of the lycopene isomers at 472 nm in Standard solution $A$, the sum of the peak responses of the beta carotene isomers at 450 nm , the phytofluene isomers at 350 nm , the response of the phytoene isomers at 288 nm , and the sum of the peak responses of all tocopherols at 288 nm in the Test solution.

Determine the concentration of Standard solution $A$ as directed for Procedure under Content of lycopene.

Calculate the quantity, in mg, of beta carotene per Capsule by the formula:

$$
0.1(C / N)\left(r_{U 1} / r_{S}\right)(D)(345 / 259.2)
$$

in which $C$ is the concentration, in ppm, of Standard solution $A ; N$ is the number of Capsules taken to prepare the Test solution; $D$ is the dilution factor for the preparation of the Test solution using Diluting solution; $r_{U 1}$ is the sum of the peak responses for beta carotene isomers at 450 nm obtained from the Test solution; $r_{S}$ is sum of the peak responses for
the lycopene isomers at 472 nm obtained from Standard solution A; 345 is the absorptivity of pure lycopene; and 259.2 is the absorptivity of pure beta carotene.

Calculate the quantity, in mg, of phytofluene per Capsule by the formula:

$$
0.1(C / N)\left(r_{U 2} / r_{S}\right)(D)(345 / 135)
$$

in which $C$ is the concentration, in ppm, of Standard solution $A ; N$ is the number of Capsules taken to prepare the Test solution; $D$ is the dilution factor for the preparation of the Test solution using Diluting solution; $r_{U 2}$ is the sum of the peak responses for phytofluene isomers at 350 nm obtained from the Test solution; $r_{S}$ is sum of the peak responses for the lycopene isomers at 472 nm obtained from Standard solution $A ; 345$ is the absorptivity of pure lycopene; and 135 is the absorptivity of pure phytofluene.
Calculate the quantity, in mg, of phytoene per Capsule by the formula:

$$
0.1(C / N)\left(r_{U 3} / r_{S}\right)(D)(345 / 125)
$$

in which $C$ is the concentration, in ppm, of Standard solution $A ; N$ is the number of Capsules taken to prepare the Test solution; $D$ is the dilution factor for the preparation of the

Test solution using Diluting solution; $r_{U 3}$ is the area of the phytoene peak response at 288 nm obtained from the Test solution; $r_{S}$ is the sum of the peak responses for the lycopene isomers at 472 nm obtained from Standard solution A; 345 is the absorptivity for pure lycopene; and 125 is the absorptivity for pure phytoene.
Calculate the quantity, in mg, of tocopherols per Capsule by the formula:

$$
0.1(C / N)\left(r_{U 4} / r_{S}\right)(D)(345 / 8.5)
$$

in which $C$ is the concentration, in ppm, of Standard solution $A ; N$ is the number of Capsules taken to prepare the Test solution; $D$ is the dilution factor for the preparation of the Test solution using Diluting solution; $r_{U 4}$ is the sum of the peak responses for all of the tocopherol peaks at 288 nm obtained from the Test solution; $r_{S}$ is sum of the peak responses for the lycopene isomers at 472 nm obtained from Standard solution A; 345 is the absorptivity of pure lycopene; and 8.5 is the average absorptivity of tocopherols.

## STIMULI TO THE REVISION PROCESS

This section may contain the following:

- reports or statements of authoritative committees
- original research reports
- evaluations of new and existing pharmacopeial methods
- commentaries
- articles relevant to compendial issues

These items are published to stimulate discussion and continual review of Pharmacopeial standards. Generally, if an Expert Committee publishes an article on which they are specifically seeking comment, this will be clearly stated in the article. Readers may submit comments on issues raised in this section, but comment is not as critical as that for the In-Process Revision and Pharmacopeial Previews sections. Readers interested in submitting comments should see Instructions to Authors.
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Instructions to Authors ..... 739

## Instructions to Authors

Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to $U S P-N F$ revision will be considered for publication in the Pharmacopeial Forum under the section Stimuli to the Revision Process. Manuscripts are received with the explicit understanding that they have not been published previously and that they are not simultaneously under consideration by any other publication.

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Abstract-Include an abstract of not more than 250 words stating the purpose and the results or conclusions of the article.
References-Consult a current copy of the Pharmacopeial Forum and the ACS Style Guide for assistance with reference style.

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Submission Instructions-Manuscripts must be submitted both as an electronic file and as a printed copy of the electronic file. Submit the text in Microsoft ${ }^{\circledR}$ Word or another current word-processing application. The preferred format for graphics submitted electronically is tagged image file format (TIFF). Graphics that cannot be submitted electronically must be cameraready, of easily reproducible quality and size, and clearly labeled. Photocopies are not acceptable. Manuscripts submitted for publication should be addressed to:

Pharmacopeial Forum
Executive Secretariat, USP
12601 Twinbrook Pkwy.
Rockville, MD 20852


## NOMENCLATURE

This section includes supplements to the latest edition of the USP Dictionary of USAN and International Drug Names that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

## USP Dictionary of USAN and International Drug Names 2003 USP DICTIONARY SUPPLEMENT 6

IMPORTANT-Save this Supplement. This and all supplements appearing in $P F$ are needed to keep the 2003 edition of the USP Dictionary (USPD) up to date. The cumulative contents of the supplements to the current (2003) edition will be included in the next complete edition of the Dictionary.

## New United States Adopted Names (USAN)

No newly established United States Adopted Names (USAN) are available for publication at this time. See preceding and succeeding numbers of $P F$ for other new USAN to supplement the Dictionary main volume.

## Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

## Dextiopronin

## Change the chemical structure to read:



Eniporide
Change the chemical structure to read:


Esonarimod
Change the chemical structure to read:


Fenoprofen
Change the chemical structure to read:


Iosulamide Meglumine
Change the chemical structure to read:



Iosumetic Acid
Change the chemical structure to read:


Iotasul
Change the chemical structure to read:


## Josamycin

Change the chemical structure to read:


## Kainic Acid

Change the chemical structure to read:


Lotrafiban Hydrochloride
Add the following chemical structure:


## Maridomycin

Change the chemical structure to read:


## Mazaticol

Change the chemical structure to read:


## Pemetrexed Disodium

Add the following to be the first chemical name:
L-Glutamic acid, $N$-[4-[2-(2-amino-4,7-dihydro-4-oxo-1 $H$-pyrro-lo[2,3-d] pyrimidin-5-yl)ethyl]benzoyl]-, disodium salt (9CI)

## Proposed and Recommended International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO).

Under its charter, the WHO is empowered simply to recommend specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as proposals ("Proposed International Nonproprietary Names"). A period of four months from the date of publication in WHO Drug Information is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested par-
ties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as recommendations ("Recommended International Nonproprietary Names'"), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

## Recommended International Nonproprietary Names

The following 43 nonproprietary names have been selected by the World Health Organization (WHO) as Recommended International Nonproprietary Names. This list, with chemical names or
descriptions and the molecular formulae, appears in WHO Drug Information, Vol 17, No. 4, 2003.

| Recommended INN | Recommended INN | Recommended INN | Recommended INN |
| :--- | :--- | :--- | :--- |
| Alvocidib | Bertilimumab | Fipamezole | Oxeglitazar |
| Anatibant | Bortexomib | Gemcabene | Posizolid |
| Ardenermin | Cinacalcet | Ibrolipim | Rafabegron |
| Arimoclomol | Darunavir | Iclaprim | Rupintrivir |
| Arundic Acid | Dexmethylphenidate | Iosimenol | Salcaprozic Acid |
| Aselizumab | Disufenton Sodium | Latidectin | Sorafenib |
| Asoprisnil Ecamate | Dofequidar | Lurasidone | Squalamine |
| Ataciguat | Doramapimod | Mantabegron | Tacedinaline |
| Atazanavir | Etiprednol Dicloacetate | Matuzumab | Telbivudine |
| Barixibat | Etravirine | Meclinertant | Tolevamer |
| Barusiban | Etriciguat | Mitratapide |  |

## Suggested United States Adopted Names

The United States Adopted Names (USAN) program is the specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs while the drugs are still in the investigational stages. The American Medical Association (AMA), the American Pharmaceutical Association (APhA), and the United States Pharmacopeial Convention (USPC) jointly sponsor the USAN program with representation from the FDA.

Each U.S. Adopted Name is chosen with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official United States Pharmacopeia or National Formulary. A measure of the prestige and recognition of the value of the USAN program can be found in the following regulations published by the Commissioner of Food and Drugs and the Secretary of Health and Human Services in the Federal Register of February 1988.

All who are concerned with the prescription, dispensing, use, sale or manufacture of drugs may, in the absence of the designation of an official name by the FDA, rely on the current compendial name or the U.S. Adopted Name (USAN) listed in this volume as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act.
A formal procedure ${ }^{1}$ is followed by the USAN Council in selecting an established name for a drug. The USAN Council Secretary is also an ex officio member of the International Nonproprietary Names (INN) Committee. USAN Guiding Principles are concordant with World Health Organization (WHO) principles, and all

| Suggested USAN | Category |
| :--- | :--- |
| Abatacept Alfa | Treatment of juvenile arthritis <br> Abatapcept Alfa <br> abd autoimmune diseases <br> Abatapcim Alfa |
| Abatapfusim Alfa |  |
| Signatapcim Alfa |  |
| Signatapcimus Alfa |  |
| Abrimostim |  |
| Lanimostim |  |
| Antineoplastic |  |
| Abtumumab |  |
| Aclatumumab |  |
| Atumumab |  |
| Hutumumab |  |
| Panitumumab |  |
| Paritumumab |  |
| Ulatumumab |  |
| Aclogrel Hydrochloride | Platelet aggregation inhibitor |
| Cicloflugrel Hydrochloride |  |
| Flosulagrel Hydrochloride |  |
| Losulagrel Hydrochloride |  |
| Prasugrel Hydrochloride |  |
| Prasulagrel Hydrochloride |  |
| Prosulagrel Hydrochloride |  |
| Prosulgrel Hydrochloride |  |

[^79]USANs for substances also named by the INN Committee are systematically processed through the INN Committee. This ensures that, with very rare exceptions, USANs are identical to INNs and available for world-wide use.
A suggestion for a USAN originates usually from a firm or an individual who has developed a substance of potential therapeutic utility to the point where there is a distinct possibility of its being marketed in the United States of America. Occasionally, the initiative is taken by the USAN Council in the form of a request to parties interested in a substance for which a nonproprietary name appears to be lacking.
Submissions to the USAN Council are expected to conform to the established Guiding Principles ${ }^{2}$ and to be reasonably free from conflict with other names, including both trademarks and nonproprietary names. An effort is made to discourage the occasional, undesirable practice of incorporating in trademarks the syllables used in an established nonproprietary name, or syllables recommended for USAN. Such trademarks may act as a bar to the subsequent adoption of appropriate nonproprietary names for closely related drugs.

The suggested nonproprietary names for the drugs described in the following list are under consideration by the USAN Council. The name(s) being considered for each drug substance, and the applicable category, are separated by double spacing from the name(s) and category for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.
Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Suggested USAN | Category |
| :--- | :--- |
| Acrimustivir Dihydrochloride | ex-vivo Blood Bank process for <br> Acromustine Dihydrochloride <br> inactivation of viruses, bacter- |
| Acromustrale Dihydrochloride |  |
| ia, parasites, and leukocytes |  |
| Afralemust Dihydrochloride | in red blood cells (nucleic acid |
| Amustaline Dihydrochloride | alkylator) |
| Amustalino Dihydrochloride |  |
| Cloracrilink Dihydrochloride |  |
| Crilomustine Dihydrochloride |  |
| Linomustine Dihydrochloride |  |
|  |  |
| Adafaxine Hydrochloride | Antidepressant; antianxiety |
| Aldafaxine Hydrochloride |  |
| Atafaxine Hydrochloride |  |
| Edanfaxine Hydrochloride |  |
| Efdanfaxine Hydrochloride |  |
| Radafaxine Hydrochloride |  |
| Sunefaxine Hydrochloride |  |
| Vadafaxine Hydrochloride |  |
| Zunefaxine Hydrochloride |  |
|  | Rigid gas permeable contact |
| Adfilcon H | lens material with a poly |
| Alifilcon H | HEMA soft skirt |

[^80]| Suggested USAN | Category | Suggested USAN | Category |
| :---: | :---: | :---: | :---: |
| Adv-2,5-huE1B-deleted-2 | Antineoplastic | Asterbulin | Treatment of solid tumors |
| Adv-2,5-hup53-2 |  | Atrobulin |  |
| Ixadusugene (E1B deleted) |  | Mivobulin |  |
| Ixadusugene (p53) |  | Taltobulin |  |
| Lontucirev (Replicating Ade- |  | Tubulastin |  |
| novirus) |  | Xenobulin |  |
| Padtucirev (Replicating Adenovirus) |  | Atilmotrec Prozomotin | Stimulation of gastrointestinal motility |
| Afglucosidase Alfa | Treatment of Pompe's disease | Zilmotisin |  |
| Aglucosidase Alfa |  |  |  |
| Alglucosidase Alfa |  | Atugabrin | Treatment of insomnia (sleepenhancing agent) |
| Alglucosidase Beta |  | Elesiclogab |  |
|  |  | Iriquigab |  |
| Alkarginine Acetate | Treatment of cardiogenic shock complicating acute myocardial infarction |  |  |
| Monarginine Acetate |  | Avanafil | Treatment of erectile dysfunction |
| Targinine Acetate |  | Tyanafil |  |
|  |  | Vatanafil |  |
| Alsufatase | Treatment of Maroteaux-Lamy syndrome (Mucopolysaccharidosis [MPS] VI) | Vitanafil |  |
| Alsulibase |  | Xyanafil |  |
| Sultaminase |  |  |  |
| Sultamitase |  | Avicurium Chloride | Neuromuscular blocker |
|  |  | Bantacurium Chloride |  |
| Anisotriasorb | Topical sunscreen active ingredient for OTC use | Benecurium Chloride |  |
| Bemotrizine |  | Bravacurium Chloride |  |
| Bisotrizine |  | Brevicurium Chloride |  |
| Bisoxtrizine |  | Brosacurium Chloride |  |
| Bisoxyzine |  | Gantacurium Chloride |  |
| Triasorb |  | Nexicurium Chloride |  |
|  |  | Revacurium Chloride |  |
| Anretinib | Antineoplastic | Vantacurium Chloride |  |
| Arcutinib |  | Velocurium Chloride |  |
| Palrotinib |  | Zelacurium Chloride |  |
| Panretinib |  |  |  |
| Pelitinib |  | Bectapitant Mesylate | Antiemetic |
| Pelritinib |  | Vestipitant Mesylate |  |
| Ramotinib |  | Vintapitant Mesylate |  |
| Recetinib |  |  |  |
|  |  | Bectcarin | Antineoplastic |
| Apaselag |  | Treat acute myocardial infarction and deep vein thrombosis | Effectecarin |  |
| Apselagon Alfa | Neotecarin |  |  |
| Domaselag |  |  |  |
| Epselagon Alfa | Belocitabine |  | Treatment of HIV-1 and HIV-2 infection |
| Ipselagon Alfa | Revacitabine |  |  |
| Nimapsel | Revcitavir |  |  |
| Paltaselag | Tesacitabine |  |  |
| Sifusapsel | Tesrevir |  |  |
| Sipapsel |  |  |  |  |
| Torapsel |  |  | Bendamustine Hydrochloride | Treatment of hematologic cancer with initial focus on nonHodgkin's lymphoma |
| Torfusapsel |  |  |  |  |
| Apilimumab | Treatment of oncology disease and HIV infection |  |  |  |
| Palimumab |  | Bepisermin Cobasermin | Antidiabetic |  |
| Apoptaxel | Antineoplastic | Derasermin |  |  |
| Azetaxel |  | Mecasermin Infabate |  |  |
| Milataxel |  | Mecasermin Rinfabate Obasermin |  |  |
| Aptusugen | Treatment of refractory of locally recurrent cancer of the head and neck | Obisatrizole |  |  |
| Oncotusugen |  | Bisatrizole Bisoctrizole | Topical sunscreen active ingredient for OTC use |  |
|  |  | Bistriazole |  |  |
| Armodafinil | Wakefulness promoting agent | Bitrisorb |  |  |
|  |  | Microtriazol |  |  |
|  |  | Mirometrizole |  |  |



[^81]| Suggested USAN | Category |
| :---: | :---: |
| Latistaurib | Selective tyrosine kinase inhib- |
| Lestaurtinib | itor (neurotrophin trkA) in- |
| Litratinib | tended for use in the treatment |
| Trakindole | of tumors such as prostate and |
| Trakizole | pancreatic carcinomas |
| Lemuteporfin | Photodynamic therapy |
| Lemuxaporfin |  |
| Leranaporfin |  |
| Luxaporfin |  |
| Ranaporfin |  |
| Seraporfin |  |
| Sertaporfin |  |
| Tuxaporfin |  |
| Linxotecan | Antineoplastic |
| Pegbetotecan |  |
| Pegcamotecan |  |
| Pegcamtecan |  |
| Peglinxotecan |  |
| Lumiliximab | Treatment of allergic asthma, |
| $\begin{array}{ll}\text { Riliximab } \\ \text { Veriliximab } & \text { allergic rhinitis, chronic lym- } \\ \text { phocytic leukemia }\end{array}$ |  |
|  |  |
| Metazamulin | Topical antibiotic for secondar- |
| Prusarimulin | ily infected traumatic lesions |
| Retapamulin | (SITL) and secondarily infected |
| Retazamulin | dermatoses (SID) or impetigo |
| Retezamulin |  |
| Tezapimulin |  |
| Zapimulin |  |
| Papahisperin | Treatment of diseases caused |
| Papifutespen | by human papilloma virus |
| Procarogammadex | Reversal agent for neuromus- |
| Pronagammadex | cular blocking agent |
| Sunagammadex |  |


| Suggested USAN | Category |
| :---: | :---: |
| Produlestan | Appetite suppression |
| Trodulamine |  |
| Trodulespan |  |
| Trodulesqual |  |
| Trodulestamine |  |
| Trodulestane |  |
| Troduspemol |  |
| Trodusqualine |  |
| Trodusquemine |  |
| Remofovir Mesylate | Antiviral |
| Soliglitia | Treatment of Type 2 diabetes mellitus |
| Soliglitian |  |
| Soliglixian |  |
| Stabaczumab | Treatment of Staphylococcus aureus infections |
| Stafabaczumab |  |
| Staphbaczumab |  |
| Stefbaczumab |  |
| Stefibaczumab |  |
| Tefibazumab |  |
| Synthadotin | Treatment of patients with advanced refractory neoplasms |
| Tesaglitazar | Treatment of Type 2 diabetes mellitus and insulin resistance syndrome |
| Tiplactinib | Treatment of fibrinolytic impairment |
| Tiplactinin |  |
| Tiplagtinin |  |
| Tiplastinin |  |
| Tiplaxtinin |  |
| Tiplaxtinor |  |
| Vatalanib | Treatment of tumors |
| Yttrium Y90 Lecratuzumab | Tumor eradication |
| Yttrium Y90 Tacatuzumab |  |
| Yttrium Y90 Tactuzumab |  |
| Yttrium Y90 Vintuzumab |  |

## Suggested International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO). INNs for substances originating within the United States are applied for through the USAN Council. INN and USAN Guiding Principles are concordant, which assures that, with very few exceptions, INNs and USANs are identical.

Under its charter, the WHO is empowered simply to recommend specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as proposals ("Proposed International Nonproprietary Names"). A period of four months from the date of publication in WHO Drug Information is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event
that no objection is received, the WHO proceeds with listing and publishing the names so devised as recommendations ("Recommended International Nonproprietary Names"), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

The names for the drugs that are categorized in the following list are under consideration for the selection of new Proposed International Nonproprietary Names. The name(s) being considered for each drug substance, and the applicable category, are separated by double spacing from the name(s) and category for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Suggested INN | Category |
| :---: | :---: |
| Ceftobasidril Daloxate Ceftobasitol Daloxate Ceftrobipirol Daloxate Ceftrotapirol Daloxate | Broad spectrum cephalosporin antibiotic |
| Cenalidomide Lenalidomide | Treatment of multiple myeloma, myelodysplastic syndromes, solid tumors including glioma and metastatic melanoma, Crohn's disease, and congestive heart failure |
| Combotide Endotide Tetratide | Anticancer |
| Dasantafil | Treatment of erectile dysfunction |
| Denufosol | Treatment of rhinitis, URI and lung disease, including Cystic Fibrosis. Also, retinal detachment and edema |
| Depelestat Epelestat | Treatment of bronchopulmonary inflammatory damage, specifically Cystic Fibrosis |
| Dirlotapide | Treatment of obesity in companion animals (dogs) |
| Emglumegad Eglumetad | Antianxiety; smoking cessation |
| Emporide Meporide Oriporide | Treatment of ischemic heart disease and chronic heart failure |
| Eslansoprazole Levoprazole Solansoprazole | Treatment of reflux esophagitis, GERD, duodenal ulcer and gastric ulcer (proton pump inhibitor) |
| Fidexaban | Anticoagulant |


| Suggested INN | Category |
| :---: | :---: |
| Flumethrin | Ectoparasiticide for topical use on dogs, cattle, sheep, goats, horses, and honey bees |
| Gadobrinic Acid Gadophenoxetic Acid Gadorinic Acid Gadotrexic Acid Gadoxetic Acid | Diagnostic aid |
| Gantacurium Chloride | Induce muscle paralysis as surgical adjunct; neuromuscular blocker |
| Golimumab Rolimumab | Treatment of rheumatoid arthritis, uvetis, asthma, and Crohn's disease |
| Idroequol Idronoxil | Antineoplastic |
| Ilapezil <br> Ladopezil <br> Ladostigil <br> Lavopezil <br> Lavostigmine | Treatment of Alzheimer's disease |
| Lanimostim | Antineoplastic; anti-infective growth factor that acts on both progenitor and mature cells of the macrophage line |
| Latistaurib <br> Lestaurtinib <br> Litratinib | Treatment of tumors such as prostate and pancreatic carcinomas (selective inhibitor of tyrosine kinase) |
| Lemuteporfin Lemuxaporfin | Photosensitivity agent with applications of photodynamic therapy |
| Lumiliximab | Treatment of allergic asthma, allergic rhinitis, and chronic lymphocytic leukemia |
| Mecasermin Obasermin | Antidiabetic |
| Metasentan Renasentan Renosentan | Treatment of cardiovascular diseases (endothelin receptor antagonist) |
| Milataxel | Antineoplastic |
| Papifutespen | Treatment of diseases caused by human papilloma virus |
| Paritumumab | Antineoplastic; treatment of EGF expressing tumors |
| Pegcamotecan | Treatment of small cell lung cancer, and gastric adenocarcinoта |
| Pelitinib Pelritinib | Antineoplastic |


| Suggested INN | Category |
| :---: | :---: |
| Perzinfotel | Treatment of neuropathic pain |
| Prasugrel | Inhibition of platelet aggregation; platelet ADPP 2 Y12 antagonist |
| Procarogammadex Pronagammadex Sunagammadex | A cyclodextrin determined for the termination of steroid muscle relaxants (such as rocuronium and vecuronium) |
| Radafaxine | Anti-depressant; treatment of anxiety disorders |
| Regadenoson | Adenosine $A_{2 A}$ agonist; use as an adjunctive pharmacologic agent in cardiac perfusion imaging studies |
| Retapamulin Retazamulin | Topical antibiotic for secondarily infected traumatic lesions (SITL) and secondarily infected dermatoses (SID) or impetigo |
| Selodenoson | Management of atrial fibrillation and atrial flutter |
| Stefbaczumab Tefibazumab | Treatment of Staphylococcus aureus infections |
| Stenavancin Telavancin | Antibacterial agent active against gram-positive pathogens |
| Taltobulin | Treatment of solid tumors |
| Tandutinib | Treatment of acute myelogenous leukemia |
| Tiplactinin Tiplastinin Tiplaxtinin | Treatment of fibrinolytic impairment diseases |
| Torapsel | Treatment of acute myocardial infarction ( $P$-Selectin antagonist) |
| Tredulamine Trodulamine Trodusqualine Trodusquemine | Appetite suppression |
| Valamycin Valimycin Valomycin | Antibiotic for use in the treatment of bacterial infections in animals |
| Vatalanib | Antineoplastic |
| Vestipitant | Anti-depressant; anti-anxiety; prevention of nausea and vomiting; used in the treatment of functional dyspepsia, irritable bowel syndrome, and GERD |
| Yttrium Y 90 Tacatuzumab | Tumor eradication |

## INDEX

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## New Items at a Glance

See what's new in USP Reference Standards. For your convenient and quick reference, here's a list of Reference Standards released by USP over the past year.

This list is continuously updated with the newest Reference Standards released within the past 12 months.

| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1002505 | Acesulfame Potassium (200 mg) | F0C136 | \$260 |
| 1012939 | Allantoin (200 mg) | F0C169 | \$156 |
| 1019417 | Amifostine Disulfide (25 mg) | F0C152 | \$487 |
| 1029953 | Ammonium Chloride (200 mg) | F0C134 | \$156 |
| 1043750 | Aspartame Acesulfame (200 mg) | F0C137 | \$156 |
| 1048619 | Benazepril Hydrochloride (125 mg) | F0C250 | \$156 |
| 1048620 | Benazepril Related Compound A ( 15 mg ) | F0C252 | \$487 |
| 1048630 | Benazepril Related Compound B ( 15 mg ) | F0C256 | \$487 |
| 1065618 | Betahistine Hydrochloride (200 mg) | F0C105 | \$156 |
| 1078733 | Bupropion Hydrochloride (200 mg) | F0C123 | \$208 |
| 1097636 | Cefepime Hydrochloride (500 mg) | F0C063 | \$156 |
| 1097647 | Cefepime Hydrochloride System Suitability ( 25 mg ) | F0C095 | \$156 |
| *1098118 | Cefpiramide ( 300 mg ) | F0C203 | \$156 |
| 1111001 | Chlorhexidine (200 mg) | F0C306 | \$156 |
| 1111103 | Chlorhexidine Acetate ( 500 mg ) | F0C281 | \$156 |
| 1133536 | Choline Bitartrate (200 mg) | F0C057 | \$156 |
| 1133547 | Choline Chloride (200 mg) | F0C058 | \$156 |
| 1140247 | Clomipramine Hydrochloride ( 200 mg ) | F0C075 | \$156 |
| 1140349 | Clonazepam Related Compound C ( 25 mg ) | F0C340 | \$487 |
| *1140393 | Clonidine (200 mg) | F0C401 | \$156 |
| 1140418 | Clonidine Related Compound A ( 25 mg ) | F0C373 | \$487 |
| 1148500 | Copovidone (100 mg) | F0C194 | \$156 |
| *1152701 | Cyclandelate ( 200 mg ) | F0C384 | \$156 |
| 1171900 | Desflurane ( 0.5 mL ) | F0C187 | \$156 |
| 1171910 | Desflurane Related Compound A ( 0.1 mL ) | F0C031 | \$487 |
| 1179708 | Dextran 40 (50 mg) | F0C247 | \$156 |
| 1179741 | Dextran 70 (50 mg) | F0C260 | \$156 |
| 1224959 | Dolasetron Mesylate (200 mg) | F0C319 | \$156 |
| 1224960 | Dolasetron Mesylate Related Compound A ( 25 mg ) | F0C321 | \$487 |
| 1225292 | Dorzolamide Hydrochloride Related Compound A (20 mg) | F0C068 | \$487 |
| 1225419 | Doxazosin Mesylate (200 mg) | F0C079 | \$156 |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | \$520 |
| 1234806 | Emedastine Difumarate (100 mg) | F0C059 | \$156 |
| 1269458 | Fenoldopam Mesylate (200 mg) | F0C125 | \$156 |
| 1269469 | Fenoldopam Related Compound A ( 20 mg ) | F0C124 | \$487 |
| 1269470 | Fenoldopam Related Compound B ( 20 mg ) | F0C126 | \$487 |
| *1272204 | Fludarabine Phosphate ( 300 mg ) | F0C374 | \$156 |
| 1273808 | Flumazenil (200 mg) | F0C305 | \$780 |
| 1279837 | Fluoxetine Related Compound C ( 15 mg ) | F0C352 | \$487 |
| 1286060 | Formononetin ( 50 mg ) | F0C196 | \$520 |
| 1286366 | Fosphenytoin Sodium (250 mg) | F0C156 | \$156 |


| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1287675 | Gadoversetamide (200 mg) | F0C172 | \$156 |
| 1287686 | Gadoversetamide Related Compound A ( 200 mg ) | F0C173 | \$487 |
| 1288306 | Ganciclovir (200 mg) | F0C287 | \$364 |
| 1288317 | Ganciclovir Related Compound A ( 15 mg ) | F0C288 | \$624 |
| 1288510 | Gemfibrozil Related Compound A ( 20 mg ) | F0C101 | \$487 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 | \$156 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) | F0C214 | \$513 |
| 1348907 | Isoflupredone Acetate (200 mg) | F0C109 | \$156 |
| 1349014 | Isoflurane Related Compound A ( 0.1 mL ) | F0C232 | \$487 |
| *1349025 | Isoflurane Related Compound B ( 0.1 mL ) | F0C233 | \$487 |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 | \$260 |
| 1355753 | Kawain (200 mg) | F0C160 | \$208 |
| 1356020 | Ketamine Related Compound A ( 50 mg ) | F0C118 | \$487 |
| 1356836 | Lamivudine (200 mg) | F0C361 | \$156 |
| *1370270 | Loratadine ( 200 mg ) | F0C414 | \$260 |
| 1392454 | Meropenem ( 300 mg ) | F0C201 | \$182 |
| 1396309 | Metformin Hydrochloride (200 mg) | F0C209 | \$182 |
| 1396310 | Metformin Related Compound A ( 50 mg ) | F0C210 | \$487 |
| 1441232 | Metoprolol Related Compound A ( 20 mg ) | F0C343 | \$520 |
| *1441243 | Metoprolol Related Compound B ( 50 mg ) | F0C377 | \$520 |
| 1441254 | Metoprolol Related Compound C ( 20 mg ) | F0C344 | \$520 |
| *1441265 | Metoprolol Related Compound D ( 50 mg ) | F0C378 | \$520 |
| 1449518 | Nabumetone (200 mg) | F0C072 | \$156 |
| 1471914 | Norgestimate ( 200 mg ) | F0C086 | \$156 |
| 1478582 | Ondansetron Hydrochloride ( 300 mg ) | F0C222 | \$208 |
| 1478593 | Ondansetron Related Compound A ( 50 mg ) | F0C191 | \$487 |
| 1478618 | Ondansetron Related Compound C ( 50 mg ) | F0C251 | \$487 |
| 1478629 | Ondansetron Related Compound D ( 50 mg ) | F0C226 | \$487 |
| 1482207 | Oxaprozin (200 mg) | F0C115 | \$156 |
| 1483301 | Oxfendazole (200 mg) | F0C128 | \$156 |
| 1491332 | Paclitaxel (200 mg) | F0C180 | \$1,508 |
| 1491343 | Paclitaxel Related Compound A ( 20 mg ) | F0C179 | \$754 |
| 1491354 | Paclitaxel Related Compound B ( 20 mg ) | F0C181 | \$754 |
| 1500251 | Paroxetine Related Compound D ( 15 mg ) | F0C228 | \$487 |
| 1535019 | Phenytoin Related Compound A ( 50 mg ) | F0C155 | \$487 |
| 1535020 | Phenytoin Related Compound B ( 50 mg ) | F0C157 | \$487 |
| 1593412 | Quinapril Related Compound A ( 50 mg ) | F0C114 | \$487 |
| 1593423 | Quinapril Related Compound B ( 50 mg ) | F0C116 | \$487 |

## New Items at a Glance (Continued)

| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1596807 | Quinine Hydrochloride Dihydrate ( 1 g ) | F0C108 | \$156 |
| 1598303 | Ramipril ( 200 mg ) | F0C099 | \$156 |
| 1598314 | Ramipril Related Compound A (20 mg) | FOC100 | \$487 |
| 1599500 | Powdered Red Clover Extract ( 500 mg ) | F0C188 | \$260 |
| 1604508 | Rimantadine Hydrochloride ( 300 mg ) | F0C266 | \$156 |
| 1610090 | Scopoletin (20 mg) | F0C329 | \$156 |
| 1612540 | Sevoflurane (1 mL) | F0C219 | \$156 |
| 1612550 | $\begin{aligned} & \text { Sevoflurane Related Compound A } \\ & (0.2 \mathrm{~mL}) \end{aligned}$ | F0C261 | \$487 |
| 1614669 | Sodium Starch Glycolate ( 400 mg ) | F0C087 | \$156 |
| 1617408 | Sotalol Hydrochloride ( 300 mg ) | F0C234 | \$182 |
| 1617419 | Sotalol Related Compound A ( 50 mg ) | F0C235 | \$487 |
| 1617420 | Sotalol Related Compound B ( 50 mg ) | F0C236 | \$487 |
| 1617430 | $\begin{aligned} & \text { Sotalol Related Compound C } \\ & (50 \mathrm{mg}) \end{aligned}$ | F0C237 | \$487 |
| 1621507 | $\begin{aligned} & \text { Stearoyl Polyoxyglycerides } \\ & (100 \mathrm{mg}) \end{aligned}$ | F0C286 | \$156 |
| 1642154 | Sumatriptan ( 50 mg ) | F0C220 | \$208 |
| 1642201 | Sumatriptan Succinate ( 200 mg ) | F0C231 | \$208 |
| 1642212 | Sumatriptan Succinate Related Compound A (15 mg) | F0C221 | \$624 |
| 1642223 | Sumatriptan Succinate Related Compound C ( 50 mg ) | F0C230 | \$624 |
| 1642700 | Tacrine Hydrochloride ( 500 mg ) | F0C119 | \$156 |
| 1643361 | Taurine ( 100 mg ) | FOC104 | \$156 |


| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1643452 | Terazosin Hydrochloride (200 mg) | F0C244 | \$156 |
| 1643463 | Terazosin Related Compound A ( 50 mg ) | F0C245 | \$487 |
| 1643474 | Terazosin Related Compound B ( 50 mg ) | F0C218 | \$487 |
| 1643485 | Terazosin Related Compound C ( 25 mg ) | F0C257 | \$487 |
| 1652500 | Thalidomide ( 200 mg ) | F0C107 | \$182 |
| 1667290 | Tiamulin Fumarate ( 250 mg ) | F0C327 | \$156 |
| 1667337 | Tiamulin Related Compound A ( 50 mg ) | F0C328 | \$494 |
| 1667520 | Tinidazole ( 200 mg ) | F0C093 | \$156 |
| 1667530 | $\begin{aligned} & \text { Tinidazole Related Compound A } \\ & (100 \mathrm{mg})\end{aligned}$ | F0C091 | \$487 |
| 1706701 | Urea C 13 (100 mg) | F0C078 | \$182 |
| 1708773 | ```Valsartan Related Compound A (20 mg)``` | F0C215 | \$624 |
| 1708795 | Valsartan Related Compound C ( 10 mg ) | F0C208 | \$624 |
| *1711155 | Vecuronium Bromide ( 60 mg ) | F0C367 | \$156 |
| 1711461 | Verteporfin ( 200 mg ) | FOC166 | \$156 |
| 1711472 | Verteporfin Related Compound A ( 50 mg ) | F0C167 | \$487 |
| 1714506 | Vinorelbine Tartrate ( 200 mg ) | F0C243 | \$156 |
| 1714528 | Vinorelbine Related Compound A ( 25 mg ) | F0C242 | \$487 |
| 1717708 | Vitexin ( 30 mg ) | FOC142 | \$520 |
| 1724656 | Zileuton (150 mg) | F0C062 | \$156 |

## USP CATALOG

## USING AND ORDERING USP REFERENCE STANDARDS

## Official Reference Standards

USP Reference Standards are required for use in pharmacopeial assays and tests in the official standards publication, the United States Pharmacopeia-National Formulary (USP-NF). USP Reference Standards help to ensure compliance with the official, FDA-enforceable quality requirements in the $U S P-N F$. The Reference Standards also lend themselves to many other applications, including measurements required to attain accurate and reproducible results in modern chromatographic and spectrophotometric methods.

## Rigorous Testing and Quality Control

USP Reference Standards are selected for their high purity, critical characteristics, and suitability for the intended purpose. Unless a USP Reference Standard label states a specific potency or content, the USP Reference Standard is taken as being $100 \%$ pure for the USP purposes for which it is provided.

Heterogeneous substances, of natural origin, are also designated "Reference Standards" where needed. Usually these are the counterparts of international standards.

USP Reference Standards are established through a process of rigorous testing, evaluation, and quality control (See page 6 for a process overview). They are independently tested in three or more laboratories-USP, FDA, and academic and industrial laboratories throughout the United States. The Reference Standards are released under the authority of USP's Board of Trustees, on the recommendation of the USP Reference Standards Expert Committee, which approves selection and suitability of each lot.

## Reference Standards Categories

USP offers more than 1,519 Reference Standards for pharmaceuticals, excipients, and dietary supplements. On pages 12-50 of this catalog, you'll find a full list of available USP and NF Reference Standards, with information updated through Dec. 2003. The list includes:

- Reference Standards required by the current official edition of $U S P-N F$.
- Reference Standards not required in the current $U S P-N F$, but for which sufficient demand remains.
- Reference Standards specified in the current edition of the Food Chemicals Codex (FCC).
- Authentic Substances (AS)—highly purified samples of chemicals, including substances of abuse, required by analytical, clinical, pharmaceutical, and research laboratories.

The distribution of controlled substances is subject to the regulations and licensing provisions of the Drug Enforcement Administration (DEA) of the U.S. Department of Justice.

USP also collaborates with the World Health Organization in its program to provide international biological standards and chemical reference materials for antibiotics, biologicals, and chemotherapeutic agents. Some USP Reference Standards are standardized in terms of the corresponding international standards.

## Proper Use of USP Reference Standards

USP Reference Standards are provided primarily for quality control use in conducting the pharmacopeial assays and tests described in the $U S P-N F$. Neither Reference Standards nor Authentic Substances are intended for use as drugs, dietary supplements, or medical devices.

To serve its intended purpose, each USP Reference Standard must be properly stored, handled, and used. Users of USP Reference Standards should refer to General Chapter $\langle 11\rangle$ in the $U S P-N F$ :

## Listing and directions in USP-NF

- Refer to the list of revisions, additions, and deletions of individual USP Reference Standards in USP 27-NF 22. Individual $U S P$ or $N F$ monographs specify the USP Reference Standard(s) required for assay and test procedures. The USP 27-NF 22 General Test Chapter $\langle 11\rangle$ USP Reference Standards provides additional information and instructions for proper use and storage. Note that if specific instructions for use appearing on the label of a USP Reference Standard differ from the instructions in Chapter $\langle 11\rangle$, the instructions on the label take precedence.
- Consult the cumulative updates to Reference Standards information provided in USP-NF Supplements and also in $U S P-N F$ Interim Revision Announcements, which are published in USP's bimonthly journal, Pharmacopeial Forum.


## Suitability for use

- The user must ascertain that the Reference Standards they are using are an official lot.
- The user must determine the suitability of Reference Standards for applications and uses not in the $U S P-N F$.


## USING AND ORDERING USP REFERENCE STANDARDS

## Storing

- Ensure that the USP Reference Standards are stored in their original stoppered containers, according to any special label directions, away from heat and humidity, and protected from light.


## Weighing

- Ensure that Reference Standard substances are accurately weighed-taking due account of relatively large errors potentially associated with weighing small masses-where it is directed that a standard solution or a standard preparation be prepared for a quantitative determination. See USP 27-NF 22 General Chapters $\langle 41\rangle$ Weights and Balances and $\langle 31\rangle$ Volumetric Apparatus, and USP-NF General Notices, for information regarding appropriate use of USP Reference Standards.


## Drying

- Use a clean and dry vessel, and not the original container, as the drying vessel where a USP Reference Standard is required to be dried before use.
- Make sure not to dry a specimen repeatedly at temperatures above 25 degrees.
- Follow any special drying requirements specified on the Reference Standards label or in specific sections of USP or NF monographs (note that any specific instructions on the label or in the monograph supersede the usual instructions in Procedures under Tests and Assays in USP-NF General Notices).
- Follow Method I under $U S P-N F$ General Chapter $\langle 921\rangle$ Water Determination where the titrimetric determination of water is required at the time a Reference Standard is to be used.
Instrumental or microanalytical methods are acceptable for this purpose. When using typical amounts, users must titrate about 50 mg of the Reference Standard with a fourfold dilution of the reagent.


## ORDERING USP REFERENCE STANDARDS

## Four convenient ways to order

1. Phone: Call USP with your requirements: (800) 227-8772 from the U.S. or Canada and (301) 881-0666 from other countries. Please note that DEA controlled substances cannot be placed over the phone.

Hours of operation:
Monday-Friday
8:30AM-5:00PM

Fax: Fax your orders to (301) 816-8148.
Online: Order through the World Wide Web at
http://www.usp.org/products. Please note that DEA controlled substances cannot be ordered online.
Mail: Send all mail orders to:
U.S. Pharmacopeia

Customer Service Department
12601 Twinbrook Parkway
Rockville, MD 20852, USA

## Important Order/Policy Information

For fax and mail orders, please use the order form at the back of this catalog. Official purchase orders on company letterhead may also be used to order USP Reference Standards. The purchase orders must have billing and shipping addresses and should include the catalog number, the name of the official Reference Standard, and the number of units ordered. Lot numbers need not be specified on written purchase orders as USP only ships current official lots. Confirmation orders may be sent and must clearly be designated as such. The USP does not assume responsibility for duplication of orders not clearly marked as confirmation orders.

## Pricing

USP Reference Standards must be ordered in whole units. Please note that one unit may include several individual containers.

Reference Standards unit prices included in the product listings from pages $12-50$ of this catalog are effective until December 31, 2004. Please note that prices and package sizes are subject to change without notice.

## No Returns or Exchanges

USP Reference Standards may not be returned or exchanged for refund.

## Quantity Discounts

A 5\% discount is allowed for 5-24 units of any one Reference Standard in a single order, and a $10 \%$ discount for 25 or more units of any one Reference Standard in a single order. These discounts are subject to change without notice.

## Shipping

- Reference Standards orders can only be shipped to a street address and not to P.O. boxes.


## USING AND ORDERING USP REFERENCE STANDARDS

- Orders to the U.S. and Ontario, Canada are shipped via air courier of USP's choice at a charge of $\$ 11$ or via air courier of the customer's choice at an additional $\$ 25$ charge.
- Non-controlled substance orders to Canadian provinces other than Ontario are shipped via air courier of USP's choice at a charge of U.S. $\$ 70$. Carriers of the customer's choice incur an additional $\$ 25$ charge.
- Non-controlled substance orders to be shipped outside the U.S. and Canada are accepted directly by USP only when customs forms related to export are not required. They are shipped via air courier of USP's choice at a charge of U.S. $\$ 70$. Carriers of the customer's choice incur an additional $\$ 25$ charge.
- Shipping in cold pack can be done at customer request for an extra charge of $\$ 25$.
- Controlled substance orders to anywhere outside the U.S. are shipped via air courier of USP's choice with a charge of U.S. $\$ 220$.
- An additional shipping charge may be assessed for dangerous goods shipments.
- An additional shipping charge of $\$ 75$ will be assessed for rush/ same-day shipments.
- Customers may provide their shipping account numbers to have shipping charged directly.


## Payment

- Full payment in advance, in U.S. dollars, is required for all U.S. orders unless open account status has been granted by USP's Finance Department. To apply for open account status, an application can be requested by calling (301) 816-8177.
- Full payment in advance, in U.S. dollars, is required for all non-U.S. orders.
- Payment may be made by check, money orders, credit cards (VISA, MasterCard, American Express), and electronic wire transfer (please call (301) 816-8177 to get bank information for wire transfers). The customer is responsible for any bank fees and must include it in the payment. The customer is also responsible for any other fees such as customs duties, taxes, or tariffs.


## List Chemicals

The following Reference Standards are "List Chemicals":
Dihydroergotamine Mesylate
*Ephedrine Sulfate
Ergonovine Maleate

[^82]Ergotamine Tartrate<br>Methylergonovine Maleate<br>Phenylpropanolamine Bitartrate<br>Phenylpropanolamine HCl<br>Pseudoephedrine HCl<br>Pseudoephedrine Sulfate

An organization in the United States seeking to purchase a List Chemical Reference Standard for resale to another customer must have a DEA registration (either a controlled substance or List Chemical registration). If an organization in the United States is purchasing the List Chemical Reference Standard for its own analytical use, it must provide USP with a letter on company letterhead describing the reason for the purchase.

## CONTROLLED DRUG SUBSTANCE ORDER

## DEA Requirements (U.S. Orders)

For all orders for controlled drug substances-regulated by the U.S. Drug Enforcement Administration (DEA)- to be shipped within the U.S., a copy of the customer's current DEA Registration Certificate must be on file with USP. To order Schedule I and II standards, customers must submit, with their order forms or purchase orders, a DEA Form 222-C, properly completed. In addition, customers ordering DEA Schedules III and IV must provide appropriate DEA registration numbers for those schedules on their order forms or purchase orders.

## DEA Requirements (International Orders)

For all international controlled drug substance orders, please contact Julie Smith at (301) 816-8164 or foreigncontrols@ usp.org.

All orders for controlled drug substances-regulated by the U.S. Drug Enforcement Administration (DEA)-to be shipped outside the U.S. must be accompanied by:

1. Full payment.
2. An import permit (in English or with an English translation attached) valid at least 6 months from the date of its receipt by USP Customer Service.
3. A statement of non-reexport and use for medical or scientific purposes (in English or with an English translation attached).
4. Purchase Order or Price Quote given by USP.

## USING AND ORDERING USP REFERENCE STANDARDS

On receiving the order, USP takes 2-3 business days to:

- Review all documents to make sure they are adequate and appropriate.
- Complete and legally approve the required DEA forms.
- Forward the forms to the DEA office to obtain the necessary Export Permits.

USP cannot ship items without an Export Permit. While it typically takes 6-10 weeks to get the permit from the DEA, USP has no control over the time in which permits are issued. On receiving the Export Permit, USP completes processing of the order in 1-3 days and ships out the materials through its freight forwarder.

Controlled substances (CI, CII, CIII, CIV, CV) and List Chemicals shipped to an international address, including Canada, add $\$ 25$ per unit.

For controlled substance orders to be shipped to Mexico, in addition to the DEA processing period, an additional week is required to obtain a certificate from the Mexican Embassy, authorizing the shipment to enter the country. Customers will pay an additional $\$ 114$ to cover the fee charged by the Mexican Embassy per import permit.

## Back Orders

USP will ship a back-ordered item if that item becomes available within 30 days of the date the order is placed if there is a valid open P.O. or payment for the item. If the order is more than 30 days old when the item becomes available, the customer will receive a Notice of Availability (NOA), indicating that the item is available. Such items will be shipped only after USP receives written authorization by the customer. The order will be canceled if the Reference Standard does not become available within six months of the original order. NOAs not replied to within 45 days of generation will be cancelled, and the customer account will be credited appropriately.

Customers may send confirmation orders for back-ordered Reference Standards that subsequently become available. They must clearly designate the confirmation orders as such-USP is not responsible for duplication of orders not clearly designated.

## HOW TO READ PRODUCT LISTINGS

Column 1 (Catalog Number): Catalog number currently assigned to each Reference Standard and Authentic Substance. Please include this number in your orders.

Column 2 (Former Catalog Number): Catalog numbers assigned prior to July 2002. These numbers are provided for your convenience so you can easily cross-reference current numbers against your earlier orders.

Column 3 (Description): Product description as designated in $U S P-N F$, the product label, and / or the Drug Enforcement Administration Control Schedule, as applicable. The quantity of material per container follows the name in parentheses (all materials are in single containers unless otherwise specified).

Column 4 (Current Lot): Current lot designation of each official item being distributed as of the date of this catalog. If the current lot is blank, the item is not in distribution.

Column 5 (Change Code): Codes that identify any change in USP Reference Standards status or information since the Nov./Dec. 2003, official Catalog. Code interpretations are as follows:

| Change <br> Code | Interpretation |
| :---: | :--- |
| 1 | New Reference Standard |
| 2 | New lot |
| 3 | Change in package size or description |
| 4 | Correction of typographical error |
| 5 | New catalog number-use for all orders |
| 6 | Previous lot no longer official; only |
| 7 | current lot to be used |
| 7 | Valid use date of previous lot extended |
| 8 | Change in catalog number and /or name, <br>  <br> 9 |
| see cross-reference section <br> Discontinued |  |

Column 6 (Previous Lot/Valid Use Date): Identifies lots no longer being distributed. The indicated month and in parenthesis indicates the date (last day of the month) through which that lot was valid as an official USP Reference Standard. (e.g. "F-1 (06/ 00 )" means lot F-1 is no longer being distributed, but was considered official through June 30, 2000.)

Column 7 (CAS Number)*: Chemical Abstracts Service number, when available, for USP Reference Standards and Authentic Substances. In case of mixtures, typically, the CAS number of the analyte of interest is listed.

Column 8 (Price) lists the price of the reference standard.

[^83]
## New Lots in Distribution

| Cat. <br> No. | Description | Curr. <br> Lot. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \hline \text { CAS } \\ \text { No. } \\ \hline \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1098118 | Cefpiramide ( 300 mg ) | F0C203 | 1 |  | [70797-11-4] | \$156 |
| 1140393 | Clonidine ( 200 mg ) | F0C401 | 1 |  | [4205-90-7] | \$156 |
| 1152701 | Cyclandelate (200 mg) | F0C384 | 1 |  | [456-59-7] | \$156 |
| 1272204 | Fludarabine Phosphate ( 300 mg ) | F0C374 | 1 |  | [75607-67-9] | \$156 |
| 1349014 | Isoflurane Related Compound A ( 0.1 mL ) (1-Chloro-2,2,2-trifluoroethyl chlorodifluoromethyl ether) | F0C232 | 1 |  | n/f | \$487 |
| 1349025 | Isoflurane Related Compound B ( 0.1 mL ) (2,2,2-Trifluoroethyldifluoromethyl ether) | F0C233 | 1 |  | n/f | \$487 |
| 1370270 | Loratadine ( 200 mg ) | F0C414 | 1 |  | [79794-75-5] | \$260 |
| 1441243 | Metoprolol Related Compound B (50 mg) ((+/-)1-chloro-2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]-propane) | F0C377 | 1 |  | n/f | \$520 |
| 1441265 | Metoprolol Related Compound D ( 50 mg ) ((+/-)N,N-bis-[2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl](1-methylethyl)amine) | F0C378 | 1 |  | n/f | \$520 |
| 1711155 | Vecuronium Bromide ( 60 mg ) | F0C367 | 1 |  | [50700-72-6] | \$156 |
| 1048222 | Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone) | H1C289 | 2 | H (11/04) | n/f | \$389 |
| 1130006 | Chlorthalidone (200 mg) | 10 C 255 | 2,3 | $\begin{aligned} & \mathrm{H}-1(11 / 04) \\ & \mathrm{H}(07 / 99) \end{aligned}$ | [77-36-1] | \$156 |
| 1150706 | Crospovidone ( 200 mg ) | G1C273 | 2 | G (12/04) | [9003-39-8] | \$156 |
| 1173235 | Desogestrel ( 50 mg ) | G0C390 | 2 | FOB282 (11/04) | [54024-22-5] | \$156 |
| 1023403 | Diazepam Related Compound B (25 mg) (3-Amino-6-chloro-1-methyl-4phenylcarbostyril) | I1C102 | 2,8 | $\begin{array}{\|l} \hline \text { I (12/04) } \\ H(04 / 01) \\ \hline \end{array}$ | [5220-02-0] | \$487 |
| 1232006 | Edetate Calcium Disodium (200 mg) | H0B272 | 2 | $\begin{aligned} & \text { G-3 }(11 / 04) \\ & \text { G-2 }(11 / 99) \\ & \hline \end{aligned}$ | [23411-34-9] | \$156 |
| 1238002 | Equilin ( 25 mg ) | 11B290 | 2 | $\begin{array}{\|l\|} \hline \text { I (11/04) } \\ \text { H-1 (05/00) } \\ \hline \end{array}$ | [474-86-2] | \$208 |
| 1242010 | Erythromycin B (150 mg) | G1C080 | 2 | $\begin{array}{\|l} \hline G(11 / 04) \\ F-1(09 / 01) \\ F(05 / 01) \\ \hline \end{array}$ | [527-75-3] | \$156 |
| 1268808 | Etoposide ( 300 mg ) | H0C315 | 2 | G (11/04) | [33419-42-0] | \$124 |
| 1270005 | Fentanyl Citrate CII (100 mg) | K0C264 | 2 | $\begin{array}{\|l\|} \hline \text { J2B227 (11/04) } \\ \mathrm{J}-1(09 / 03) \\ \mathrm{J}(05 / 02) \\ \mathrm{I}(06 / 00) \\ \hline \end{array}$ | [990-73-8] | \$207 |
| 1299200 | Griseofulvin Permeability Diameter (2 g) | J0C380 | 2 | $\begin{aligned} & 10 \mathrm{C} 138(10 / 04) \\ & \mathrm{H}(08 / 03) \end{aligned}$ | [126-07-8] | \$156 |
| 1302305 | Halazepam CIV (200 mg) (AS) | F1C224 | 2,3 | F (12/04) | [23092-17-3] | \$207 |
| 1303013 | Haloperidol Related Compound A (15 mg) (4,4-Bis[(4-p-chlorophenyl)-4-hydroxy-piperidino]-butyrophenone) | K0C362 | 2,3 | $J(12 / 04)$ | [67987-08-0] | \$487 |
| 1330005 | Hypromellose (250 mg) (Hydroxypropyl Methylcellulose) | H0C387 | 2,8 | $\begin{array}{\|l\|} \hline \text { G-1 (11/04) } \\ \text { G (02/02) } \\ \hline \end{array}$ | [9004-65-3] | \$156 |
| 1349003 | Isoflurane ( 1 mL ) | H1C199 | 2 | H (12/04) | [26675-46-7] | \$156 |
| 1371501 | L-Lysine Acetate (200 mg) | F1C027 | 2 | F (11/04) | [57282-49-2] | \$156 |
| 1375502 | Mebendazole ( 200 mg ) | G1C195 | 2 | G (11/04) | [31431-39-7] | \$156 |
| 1393005 | Mesoridazine Besylate ( $250 \mathrm{mg} \mathrm{)}$ | J0C117 | 2 | I-1 (12/04) | [32672-69-8] | \$156 |
| 1539701 | Pindolol ( 200 mg ) | IOB210 | 2 | H-1 (12/04) | [13523-86-9] | \$156 |
| 1559006 | Prednisone (250 mg) | L1B251 | 2 | $\begin{array}{\|l\|} \hline \text { L (11/04) } \\ \text { K-1 (01/02) } \\ \text { K (02/00) } \\ \hline \end{array}$ | [53-03-2] | \$156 |
| 1563320 | Probucol Related Compound A (25 mg) (2,2',6,6'-tetra-tert-butyldiphenoquinone) | F-2 | 2 | F-1 (12/04) | n/f | \$487 |

New Lots in Distribution

| Cat. No. | Description | $\begin{array}{\|l} \text { Curr. } \\ \text { Lot. } \end{array}$ | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \hline \text { CAS } \\ \text { No. } \\ \hline \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1568007 | Progesterone (200 mg) | H6C088 | 2 | $\begin{array}{\|l\|l\|} \hline \text { H-5 } & (11 / 04) \\ \text { H-4 (07/02) } \\ \hline \end{array}$ | [57-83-0] | \$124 |
| 1570304 | Propafenone Hydrochloride (200 mg) | G1C184 | 2 | $\begin{array}{\|l} \hline G(12 / 04) \\ \mathrm{F}-1(01 / 01) \\ \hline \end{array}$ | [34183-22-7] | \$156 |
| 1622000 | Stearyl Alcohol (125 mg) | H2B217 | 2 | $\begin{array}{\|l\|} \hline \text { H-1 (12/04) } \\ \text { H (09/99) } \\ \hline \end{array}$ | [112-92-5] | \$124 |
| 1623637 | Sucrose ( 100 mg ) | H1C223 | 2 | $\begin{aligned} & \text { HOB002 (11/04) } \\ & \text { G-1 (03/03) } \\ & \text { G (05/99) } \\ & \hline \end{aligned}$ | [57-50-1] | \$156 |
| 1626001 | Sulfadimethoxine (200 mg) | F4C298 | 2 | $\begin{aligned} & \hline \text { F-3 }(11 / 04) \\ & \text { F-2 (03/99) } \\ & \hline \end{aligned}$ | [122-11-2] | \$156 |
| 1628007 | Sulfamerazine ( 500 mg ) | H1C171 | 2,3 | H (12/04) | [127-79-7] | \$156 |
| 1713004 | Vinblastine Sulfate ( 50 mg ) | M0B308 | 2,3 | $\begin{array}{\|l\|} \hline \text { L (12/04) } \\ \mathrm{K}(05 / 99) \end{array}$ | [143-67-9] | \$354 |

## USP Reference Standards and Authentic Substances

| Cat. <br> No. | Description | Curr. <br> Lot. | Change Code* | Previous Lot/Valid Use Date | $\begin{aligned} & \text { CAS } \\ & \text { No. } \\ & \hline \end{aligned}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1000601 | Acebutolol Hydrochloride ( 125 mg ) | F-1 |  |  | [34381-68-5] | \$156 |
| 1001003 | Acenocoumarol (200 mg) | F |  |  | [152-72-7] | \$156 |
| 1001502 | Acepromazine Maleate ( 250 mg ) | F-2 |  | F-1 (05/02) | [3598-37-6] | \$156 |
| 1002505 | Acesulfame Potassium ( $200 \mathrm{mg} \mathrm{)}$ | F0C136 |  |  | [55589-62-3] | \$260 |
| 1003009 | Acetaminophen ( 400 mg ) | J-1 |  | $\begin{array}{\|l\|l} \hline \mathrm{J}(05 / 02) \\ \mathrm{I}(05 / 99) \\ \hline \end{array}$ | [103-90-2] | \$124 |
| 1004001 | Acetanilide Melting Point Standard (500 mg) (Approximately 114 degrees) | M0A029 |  | $\begin{array}{\|l\|} \hline \mathrm{L}(06 / 04) \\ \mathrm{K}(02 / 00) \\ \hline \end{array}$ | [103-84-4] | \$75 |
| 1005004 | Acetazolamide (2 g) | $J$ |  |  | [59-66-5] | \$156 |
| 1006007 | Acetohexamide (250 mg) | H |  | G-1 (06/99) | [968-81-0] | \$156 |
| 1006506 | Acetohydroxamic Acid ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  | F (03/03) | [546-88-3] | \$156 |
| 1007000 | Acetophenazine Maleate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [5714-00-1] | \$156 |
| 1008002 | alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane ( 125 mg ) | G-3 |  |  | n/f | \$487 |
| 1008501 | Acetylcholine Chloride ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | [60-31-1] | \$156 |
| 1009005 | Acetylcysteine (200 mg) | H1B169 |  | H (01/04) | [616-91-1] | \$156 |
| 1009901 | Acetyltributyl Citrate ( 500 mg ) | G0C120 |  | F (05/04) | [77-90-7] | \$156 |
| 1009923 | Acetyltriethyl Citrate ( 500 mg ) | F-1 |  | F (05/02) | [77-89-4] | \$156 |
| 1012065 | Acyclovir (300 mg) | J0C149 |  | 1 (06/04) | [59277-89-3] | \$197 |
| 1012101 | Adenine ( 200 mg ) | G-1 |  | G (06/00) | [73-24-5] | \$156 |
| 1012123 | Adenosine (200 mg) | F1B058 |  | F (04/03) | [58-61-7] | \$156 |
| 1012145 | Agigenin ( 25 mg ) | F |  |  | n/f | \$156 |
| 1012509 | L-Alanine ( 200 mg ) | F-2 |  | F-1 (04/01) | [56-41-7] | \$156 |
| 1012553 | Albendazole (200 mg) | G |  | F-1 (01/00) | [54965-21-8] | \$156 |
| 1012600 | Albuterol ( 200 mg ) | I |  | H (12/00) | [18559-94-9] | \$156 |
| 1012633 | Albuterol Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | J |  | $\mathrm{I}(04 / 00)$ | [51022-70-9] | \$156 |
| 1012757 | Alclometasone Dipropionate ( 300 mg ) | H |  | $\mathrm{G}(01 / 00)$ | [66734-13-2] | \$156 |
| 1012780 | Alendronate Sodium (200 mg) | F0B315 |  |  | [121268-17-5] | \$156 |
| 1012906 | Alfentanil Hydrochloride CII (500 mg) | F0B016 |  |  | [70879-28-6] | \$207 |
| 1012939 | Allantoin (200 mg) | F0C169 |  |  | [97-59-6] | \$156 |
| 1012950 | Alliin (25 mg) | F |  |  | [556-27-4] | \$1,525 |
| 1013002 | Allopurinol ( 250 mg ) | $\mathrm{I}-1$ |  | I (07/02) | [315-30-0] | \$156 |
| 1013024 | Allopurinol Related Compound A (50 mg) (3-Amino-4-carboxamidopyrazole Hemisulfate) | G |  | $\begin{aligned} & \text { F-3 (05/02) } \\ & \text { F-2 (04/99) } \\ & \hline \end{aligned}$ | n/f | \$487 |
| 1013057 | S-Allyl-L-Cysteine (25 mg) | F |  |  | n/f | \$487 |
| 1014005 | Alphaprodine Hydrochloride CII (250 mg) | F |  |  | [561-78-4] | \$207 |
| 1015008 | Alprazolam CIV (200 mg) | H |  |  | [28981-97-7] | \$207 |
| 1016000 | Alprostadil ( 25 mg ) | H |  |  | [745-65-3] | \$1,525 |
| 1017105 | Altretamine ( 500 mg ) | F |  |  | [645-05-6] | \$156 |
| 1017502 | Dried Aluminum Hydroxide Gel ( $200 \mathrm{mg} \mathrm{)}$ | F2B120 |  | F-1 (01/04) | [21645-51-2] | \$156 |
| 1018505 | Amantadine Hydrochloride ( 200 mg ) | H |  | G (04/01) | [665-66-7] | \$156 |
| 1019202 | Amcinonide (200 mg) | G0B260 |  | F-1 (03/04) | [51022-69-6] | \$156 |
| 1019417 | Amifostine Disulfide ( 25 mg ) | F0C152 |  |  | [112901-68-5] | \$487 |
| 1019508 | Amikacin (200 mg) | 1 |  | H (08/00) | [37517-28-5] | \$156 |
| 1019701 | Amiloride Hydrochloride ( 500 mg ) | H |  |  | [17440-83-4] | \$156 |
| 1019756 | Aminobenzoate Potassium (200 mg) | F-1 |  | F (06/01) | [138-84-1] | \$156 |
| 1019767 | Aminobenzoate Sodium (200 mg) | F |  |  | [55-06-6] | \$156 |

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| 1019803 | Aminobenzoic Acid (200 mg) (p-aminobenzoic acid) | H1C083 |  | $\begin{aligned} & \hline \text { H }(10 / 04) \\ & \text { G }(10 / 00) \\ & \hline \end{aligned}$ | [150-13-0] | \$156 |
| 1020008 | Aminobutanol ( 500 mg ) | G-1 |  | G (06/99) | [13054-87-0] | \$389 |
| 1021000 | Aminocaproic Acid (200 mg) | F-4 |  |  | [60-32-2] | \$156 |
| 1021703 | N -(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methylene)-amino]-glycine ( 25 mg ) | F-1 |  |  | n/f | \$487 |
| 1022808 | 2-Amino-5-chlorobenzophenone ( 25 mg ) | 1 |  | H-1 (01/03) | [719-59-5] | \$487 |
| 1025205 | Aminoglutethimide (200 mg) | F |  |  | [125-84-8] | \$156 |
| 1025307 | m -Aminoglutethimide ( $100 \mathrm{mg} \mathrm{)}$ | G |  | F (05/01) | n/f | \$487 |
| 1025351 | Aminohippuric Acid (200 mg) | F-1 |  |  | [61-78-9] | \$156 |
| 1025806 | 2-[3-Amino-5-(n-methylacetamido)-2,4,6-triiodobenzamido]-2-deoxy-dglucose ( 25 mg ) | F |  |  | n/f | \$487 |
| 1025908 | Aminopentamide Sulfate ( 200 mg ) | F0B273 |  |  | [60-46-8] | \$156 |
| 1026004 | m-Aminophenol (300 mg) | F |  |  | [591-27-5] | \$487 |
| 1026401 | Aminosalicylic Acid (125 mg) | F-1 |  | F (03/99) | [65-49-6] | \$124 |
| 1026605 | 3 -Amino-2,4,6-triodobenzoic Acid ( 50 mg ) | G |  |  | [3119-15-1] | \$487 |
| 1027007 | 5-Amino-2,4,6-triiodo-N-methylisophthalamic Acid ( 50 mg ) | F-1 |  |  | [2280-89-9] | \$487 |
| 1028000 | Amitraz (200 mg) | FOC042 |  |  | [33089-61-1] | \$156 |
| 1029002 | Amitriptyline Hydrochloride (200 mg) | J0A004 |  | I (03/03) | [549-18-8] | \$156 |
| 1029909 | Ammonio Methacrylate Copolymer Type A (100 mg) | F-1 |  | F (06/01) | [33434-24-1] | \$156 |
| 1029910 | Ammonio Methacrylate Copolymer Type B (100 mg) | F-1 |  | F (05/00) | [33434-24-1] | \$156 |
| 1029953 | Ammonium Chloride (200 mg) | F0C134 |  |  | [12125-02-9] | \$156 |
| 1030001 | Amobarbital CII (200 mg) | F-2 |  |  | [57-43-2] | \$207 |
| 1031004 | Amodiaquine Hydrochloride ( 500 mg ) | H0B238 |  | G-1 (04/03) | [6398-98-7] | \$156 |
| 1031401 | Amoxapine ( 200 mg ) | G |  | F-1 (04/02) | [14028-44-5] | \$156 |
| 1031503 | Amoxicillin (200 mg) | J0C043 |  | I (07/04) | [61336-70-7] | \$156 |
| 1032007 | Amphotericin B (125 mg) | J-2 |  | J-1 (07/02) | [1397-89-3] | \$124 |
| 1033000 | Ampicillin ( 200 mg ) | J-1 |  | $J(12 / 01)$ | [69-53-4] | \$156 |
| 1033203 | Ampicillin Sodium ( 125 mg ) | G-1 |  | G (10/99) | [69-52-3] | \$124 |
| 1033407 | Ampicillin Trihydrate (200 mg) | G |  |  | [7177-48-2] | \$156 |
| 1034002 | Amprolium ( 200 mg ) | F-1 |  | F (04/02) | [121-25-5] | \$156 |
| 1034308 | Amrinone ( 500 mg ) | G |  |  | [60719-84-8] | \$156 |
| 1034320 | Amrinone Related Compound A (100 mg) (5-carboxamide[3,4'-bipyr-idinj-6(1H)-one) | F |  |  | [62749-46-6] | \$487 |
| 1034341 | Amrinone Related Compound B ( 100 mg ) ( N -(1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-yl)-2-hydroxypropanamide) | F-1 |  | F (03/00) | n/f | \$487 |
| 1034363 | Amrinone Related Compound C (50 mg) (1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-carbonitrile) | F-1 |  | F (05/00) | n/f | \$487 |
| 1036008 | Anileridine Hydrochloride CII (250 mg) | F |  |  | [126-12-5] | \$207 |
| 1036507 | 3 -Anilino-2-(3,4,5-trimethoxybenzyl) acrylonitrile ( 25 mg ) | G-1 |  |  | [30078-48-9] | \$487 |
| 1038003 | Antazoline Phosphate (200 mg) | H |  | G-1 (04/02) | [154-68-7] | \$156 |
| 1039006 | Anthralin (200 mg) | IOB221 |  | H (11/02) | [1143-38-0] | \$156 |
| 1040005 | Antipyrine (200 mg) | G |  | F-4 (09/01) | [60-80-0] | \$156 |
| 1040708 | Apigenin-7-glucoside ( 30 mg ) | F |  |  | n/f | \$487 |
| 1041008 | Apomorphine Hydrochloride ( 250 mg ) | H |  | G (01/03) | [41372-20-7] | \$162 |
| 1041609 | Apraclonidine Hydrochloride ( 100 mg ) | H0B112 |  | G (06/03) | [73218-79-8] | \$479 |
| 1042000 | Aprobarbital CIII ( 200 mg ) (AS) | F-1 |  |  | [77-02-1] | \$207 |
| 1042500 | L-Arginine (200 mg) | G-1 |  | G (09/00) | [74-79-3] | \$156 |
| 1042601 | Arginine Hydrochloride ( 125 mg ) | G0B060 |  | F-1 (05/03) | [1119-34-2] | \$124 |
| 1042703 | Arsanilic Acid (25 mg) | F |  |  | [98-50-0] | \$156 |

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| 1043003 | Ascorbic Acid (1 g) (Vitamin C) | Q0B012 |  | P (04/03) | [50-81-7] | \$156 |
| 1043706 | Aspartame ( 200 mg ) | H1B125 |  | H (05/03) | [22839-47-0] | \$156 |
| 1043750 | Aspartame Acesulfame (200 mg) | F0C137 |  |  | [106372-55-8] | \$156 |
| 1043728 | Aspartame Related Compound A ( 75 mg ) (5-Benzyl-3,6-dioxo-2piperazineacetic Acid) | H |  | G-1 (10/99) | [5262-10-2] | \$487 |
| 1043819 | Aspartic Acid (100 mg) | F0B087 |  |  | [6899-03-2] | \$156 |
| 1044006 | Aspirin ( 500 mg ) | H |  | G-1 (11/02) | [50-78-2] | \$156 |
| 1044301 | Astemizole ( 200 mg ) | F |  |  | [68844-77-9] | \$156 |
| 1044403 | Atenolol ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G (08/01) | [29122-68-7] | \$156 |
| 1044651 | Atovaquone ( 200 mg ) | FOB190 |  |  | [95233-18-4] | \$156 |
| 1044662 | Atovaquone Related Compound A ( 25 mg ) (cis-2-[4-(4-chlorophenyl)-cyclohexyl]-3-hydroxy-1,4-naphthoquinone) | F0B188 |  |  | n/f | \$487 |
| 1044800 | Atracurium Besylate ( $100 \mathrm{mg} \mathrm{)}$ | F0B143 |  |  | [64228-81-5] | \$156 |
| 1045009 | Atropine Sulfate ( 500 mg ) | M0B098 |  | L-2 (04/03) <br> L-1 (06/02) <br> L (10/00) | [5908-99-6] | \$156 |
| 1045337 | Avobenzone ( 500 mg ) | G0B280 |  | F (09/03) | [70356-09-1] | \$156 |
| 1045508 | Aurothioglucose (100 mg) | H0B224 |  | $\begin{aligned} & G(10 / 03) \\ & F(12 / 01) \\ & \hline \end{aligned}$ | [12192-57-3] | \$156 |
| 1045600 | Azaerythromycin A (100 mg) | G |  | $\begin{aligned} & \text { F-1 (02/02) } \\ & \text { F (02/99) } \\ & \hline \end{aligned}$ | [76801-85-9] | \$156 |
| 1045756 | Azaperone ( 200 mg ) | F |  |  | [1649-18-9] | \$156 |
| 1045803 | Azatadine Maleate (200 mg) | G0B300 |  | $\begin{aligned} & \text { F-1 (04/04) } \\ & \text { F (06/00) } \\ & \hline \end{aligned}$ | [3978-86-7] | \$156 |
| 1046001 | Azathioprine (200 mg) | H |  | G-1 (02/00) | [446-86-6] | \$156 |
| 1046056 | Azithromycin (100 mg) | H0C212 |  | $\begin{aligned} & \mathrm{G}(11 / 04) \\ & \mathrm{F}(06 / 00) \\ & \hline \end{aligned}$ | [117772-70-0] | \$156 |
| 1046103 | Azlocillin Sodium (200 mg) | F |  |  | [37091-65-9] | \$156 |
| 1046147 | Azo-aminoglutethimide ( 100 mg ) | F |  |  | n/f | \$487 |
| 1046205 | Aztreonam ( 200 mg ) | G0C077 |  | F-1 (03/04) | [78110-38-0] | \$156 |
| 1046307 | Aztreonam E-Isomer ( 50 mg ) | F |  |  | n/f | \$156 |
| 1046409 | Open Ring Aztreonam ( 50 mg ) |  |  | F (12/04) | [87500-74-1] | \$156 |
| 1047300 | Bacampicillin Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G0B053 |  | F (11/02) | [37661-08-8] | \$156 |
| 1047503 | Bacitracin (1 g) (Susceptibility disk standard) | G1C254 |  | G (07/04) | [1405-87-4] | \$156 |
| 1048007 | Bacitracin Zinc (200 mg) | N0A024 |  | $\begin{aligned} & \hline \text { M-1 (11/02) } \\ & M(02 / 00) \\ & \hline \end{aligned}$ | [1405-89-6] | \$156 |
| 1048200 | Baclofen ( 500 mg ) | 1 |  |  | [1134-47-0] | \$156 |
| 1048222 | Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone) | H1C289 | 2 | H (11/04) | n/f | \$389 |
| 1048506 | Beclomethasone Dipropionate (200 mg) | K |  | J (12/00) | [5534-09-8] | \$156 |
| 1048619 | Benazepril Hydrochloride (125 mg) | F0C250 |  |  | [86541-74-4] | \$156 |
| 1048620 | Benazepril Related Compound A (15 mg) ((3R)-3-[[(1R)-1-(ethoxycar-bonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benaza-pine-1-acetic acid, monohydrochloride) | F0C252 |  |  | n/f | \$487 |
| 1048630 | Benazepril Related Compound B (15 mg) ((3S)-3-[[(1R)-1-(ethoxycar-bonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benaza-pine-1-acetic acid, monohydrochloride) | F0C256 |  |  | n/f | \$487 |
| 1049000 | Bendroflumethiazide ( $200 \mathrm{mg} \mathrm{)}$ | G-1 |  |  | [73-48-3] | \$156 |
| 1050009 | Benoxinate Hydrochloride ( 200 mg ) | F-2 |  | F-1 (10/99) | [5987-82-6] | \$124 |
| 1051001 | Benzalkonium Chloride ( 5 mL of approx. 10\% aqueous solution) | K0B151 |  | J (06/03) | [8001-54-5] | \$156 |
| 1054000 | Benzocaine ( 500 mg ) | 1 |  |  | [94-09-7] | \$156 |

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| 1055002 | Benzoic Acid (300 mg) | F6B173 |  | $\begin{aligned} & \hline \text { F-5 }(03 / 04) \\ & \text { F-4 (07/01) } \\ & \hline \end{aligned}$ | [65-85-0] | \$156 |
| 1056005 | Benzonatate (1 g) | IOB003 |  | H (01/03) | [104-31-4] | \$156 |
| 1056504 | 1,4-Benzoquinone (200 mg) | G1B145 |  | $\begin{array}{\|l\|l} \hline \text { G (01/04) } \\ \text { F-1 (11/01) } \\ \text { F (09/00) } \\ \hline \end{array}$ | [106-51-4] | \$156 |
| 1057507 | Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide) | H0B069 |  | G-4 (03/03) | [121-30-2] | \$487 |
| 1059003 | Benzphetamine Hydrochloride CIII (200 mg) (AS) | F-1 |  |  | [5411-22-3] | \$207 |
| 1060002 | Benzthiazide (200 mg) | F |  |  | [91-33-8] | \$156 |
| 1061005 | Benztropine Mesylate (200 mg) | 10 C 038 |  | H (09/04) | [132-17-2] | \$156 |
| 1061901 | Benzyl Alcohol ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | G0B306 |  | FOB106 (10/03) | [100-51-6] | \$156 |
| 1062008 | Benzyl Benzoate (5 g) | J0C060 |  | I (05/04) | [120-51-4] | \$156 |
| 1064003 | 1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride ( 25 mg ) | F-1 |  |  | n/f | \$487 |
| 1065006 | Bephenium Hydroxynaphthoate ( 500 mg ) | F |  |  | [3818-50-6] | \$156 |
| 1065618 | Betahistine Hydrochloride ( 200 mg ) | F0C105 |  |  | [5579-84-0] | \$156 |
| 1065709 | Betaine Hydrochloride ( 200 mg ) | F-1 |  | F (11/02) | [590-46-5] | \$156 |
| 1066009 | Betamethasone (200 mg) | K2C204 |  | $\begin{array}{\|l\|l\|} \hline \text { K-1 (10/04) } \\ \text { K (11/02) } \\ \hline \end{array}$ | [378-44-9] | \$156 |
| 1067001 | Betamethasone Acetate ( 500 mg ) | J0B079 |  | I (08/03) | [987-24-6] | \$156 |
| 1067307 | Betamethasone Benzoate ( 200 mg ) | F-1 |  |  | [22298-29-9] | \$156 |
| 1067704 | Betamethasone Dipropionate (125 mg) | K0C229 |  | $\begin{array}{\|l\|} \hline J(04 / 04) \\ I(03 / 99) \\ \hline \end{array}$ | [5593-20-4] | \$124 |
| 1068004 | Betamethasone Sodium Phosphate (500 mg) | J0B043 |  | $\begin{array}{\|l\|l\|} \hline \text { I-1 (02/03) } \\ \text { I (01/01) } \\ \hline \end{array}$ | [151-73-5] | \$156 |
| 1069007 | Betamethasone Valerate ( 200 mg ) | J |  | I (05/00) | [2152-44-5] | \$156 |
| 1069903 | Betaxolol Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G |  | F-1 (06/00) | [63659-19-8] | \$156 |
| 1070006 | Betazole Hydrochloride (200 mg) | H |  |  | [138-92-1] | \$156 |
| 1071009 | Bethanechol Chloride ( 200 mg ) | G |  | F-3 (07/01) | [590-63-6] | \$156 |
| 1071304 | Bile Salts (10 g) | 10C003 |  | $\begin{aligned} & \mathrm{H}-1(05 / 04) \\ & \mathrm{H}(05 / 99) \end{aligned}$ | [145-42-6] | \$124 |
| 1071508 | Biotin (200 mg) | H1B019 |  | H (04/03) | [58-85-5] | \$156 |
| 1072001 | Biperiden ( 200 mg ) | F2B080 |  | F-1 (02/04) | [514-65-8] | \$156 |
| 1073004 | Biperiden Hydrochloride (200 mg) | F-3 |  | F-2 (06/99) | [1235-82-1] | \$156 |
| 1074007 | Bisacodyl ( 125 mg ) | 11B162 |  | $\begin{aligned} & \hline \text { I (01/04) } \\ & \text { H-1 (02/99) } \\ & \hline \end{aligned}$ | [603-50-9] | \$124 |
| 1074700 | 2,5-Bis(D-arabino-1,2,3,4-tetrahydroxybutyl)pyrazine ( 25 mg ) | F |  |  | n/f | \$487 |
| 1075203 | Bis(2-ethylhexyl)maleate ( 250 mg ) | F-2 |  | F-1 (01/01) | [142-16-5] | \$487 |
| 1075509 | p-Bis(di-n-propyl)carbamylbenzenesulfonamide ( 50 mg ) | F |  |  | n/f | \$487 |
| 1075531 | Bismuth Citrate ( 100 mg ) | F |  |  | [813-93-4] | \$156 |
| 1075553 | Bismuth Subsalicylate ( 100 mg ) | F |  |  | [14882-18-9] | \$156 |
| 1075757 | Bisoprolol Fumarate ( 200 mg ) | F0B038 |  |  | [104344-23-2] | \$156 |
| 1076002 | 4,4'-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone ( 25 mg ) |  |  | G (05/03) | n/f | \$487 |
| 1076308 | Bleomycin Sulfate (15 mg) | J0B213 |  | I (01/04) | [9041-93-4] | \$307 |
| 1076352 | Bretylium Tosylate (200 mg) | F-1 |  |  | [61-75-6] | \$156 |
| 1076363 | Brinzolamide (200 mg) | F0C034 |  |  | [138890-62-7] | \$156 |
| 1076374 | Brinzolamide Related Compound A (50 mg) ((S)-(-)-4-ethylamino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide) | F0C033 |  |  | n/f | \$487 |

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| 1076385 | Brinzolamide Related Compound B (50 mg) ((R)-4-amino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide ethanedioate) | F0C035 |  |  | n/f | \$487 |
| 1076501 | Bromocriptine Mesylate ( 150 mg ) | I1C197 |  | I (09/04) | [22260-51-1] | \$156 |
| 1077005 | Bromodiphenhydramine Hydrochloride (200 mg) | F-1 |  |  | [1808-12-4] | \$156 |
| 1077708 | 8-Bromotheophylline ( 400 mg ) | G |  | F (07/02) | [10381-75-6] | \$156 |
| 1078008 | Brompheniramine Maleate (125 mg) | 11A036 |  | $\begin{array}{\|l\|} \hline \mathrm{I}(01 / 03) \\ \mathrm{H}-1(04 / 99) \\ \hline \end{array}$ | [980-71-2] | \$124 |
| 1078303 | Bumetanide (250 mg) | 10 C 111 |  | $\begin{aligned} & \text { H0B030 (05/04) } \\ & \text { G (03/03) } \end{aligned}$ | [28395-03-1] | \$156 |
| 1078325 | Bumetanide Related Compound A ( 25 mg ) (3-Amino-4-phenoxy-5sulfamoylbenzoic Acid) | F-2 |  | F-1 (05/00) | n/f | \$487 |
| 1078336 | Bumetanide Related Compound B (25 mg) (3-Nitro-4-phenoxy-5sulfamoylbenzoic Acid) | F-2 |  | F-1 (01/03) | [28328-53-2] | \$487 |
| 1078507 | Bupivacaine Hydrochloride (1 g) | H |  | $\begin{array}{ll} \text { G-2 }(03 / 03) \\ \text { G-1 } & (08 / 02) \\ \hline \end{array}$ | [14252-80-3] | \$156 |
| 1078700 | Buprenorphine Hydrochloride CIII ( 50 mg ) | F-1 |  | F (02/99) | [53152-21-9] | \$207 |
| 1078711 | Buprenorphine Related Compound A (50 mg) (21-[3-(1-propenyl)]-7-alpha-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14tetrahydrooripavine) | F1C076 |  | F (04/04) | n/f | \$487 |
| 1078733 | Bupropion Hydrochloride ( 200 mg ) | F0C123 |  |  | [31677-93-7] | \$208 |
| 1078802 | Buspirone Hydrochloride ( 200 mg ) | G |  |  | [33386-08-2] | \$156 |
| 1079000 | Butabarbital CIII ( 200 mg ) | H0C007 |  | G (03/04) | [125-40-6] | \$207 |
| 1080000 | Butacaine Sulfate (600 mg) | F |  |  | [149-15-5] | \$156 |
| 1081002 | Butalbital CIII (200 mg) | H0C054 |  | $\begin{array}{\|l\|} \hline \text { G2B077 (07/04) } \\ \text { G-2 (06/03) } \\ \text { G (05/02) } \\ \hline \end{array}$ | [77-26-9] | \$207 |
| 1081501 | Butamben ( 200 mg ) | F |  |  | [94-25-7] | \$156 |
| 1082300 | Butoconazole Nitrate (200 mg) | F1B097 |  | F (03/03) | [64872-77-1] | \$156 |
| 1082504 | Butorphanol Tartrate CIV (500 mg) | J |  | I (06/00) | [58786-99-5] | \$207 |
| 1082800 | Monotertiary-butyl-p-benzoquinone (100 mg) (FCC) | F |  |  | [3602-55-9] | \$156 |
| 1082901 | Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate ( 25 mg ) | F-1 |  |  | n/f | \$487 |
| 1083008 | 2-tert-Butyl-4-hydroxyanisole (200 mg) | L0C028 |  | K (09/03) | [88-32-4] | \$156 |
| 1083100 | 3 -tert-Butyl-4-hydroxyanisole (200 mg) | J |  | I-1 (09/01) | [121-00-6] | \$156 |
| 1084000 | Butylparaben (200 mg) | 10C139 |  | $\begin{array}{\|l\|} \hline \text { H-1 (03/04) } \\ \text { H (09/01) } \\ \hline \end{array}$ | [94-26-8] | \$156 |
| 1085003 | Caffeine ( 200 mg ) | $J$ |  | I (06/02) | [58-08-2] | \$156 |
| 1086006 | Caffeine Melting Point Standard (1 g) (Approximately 236 degrees) | JOB204 |  | I (03/04) | [58-08-2] | \$92 |
| 1086108 | Calcifediol ( 75 mg ) | G |  |  | [63283-36-3] | \$156 |
| 1086356 | Calcium Ascorbate ( 200 mg ) | F-1 |  | F (08/01) | [5743-28-2] | \$156 |
| 1086800 | Calcium Gluceptate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  | F (09/00) | [29039-00-7] | \$156 |
| 1086902 | Calcium Lactobionate (200 mg) | G0B138 |  | $\begin{array}{\|l} \hline \text { F-1 (01/04) } \\ \text { F (11/01) } \\ \hline \end{array}$ | [110638-68-1] | \$156 |
| 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) | N-1 |  | $\mathrm{N}(06 / 00)$ | [137-08-6] | \$156 |
| 1087202 | Calcium Saccharate (200 mg) | F |  |  | [5793-89-5] | \$156 |
| 1088001 | Candicidin (200 mg) | F |  |  | [1403-17-4] | \$156 |
| 1089004 | Cannabidiol CI (25 mg) (AS) | F-2 |  |  | [13956-29-1] | \$207 |
| 1090003 | Cannabinol CI (25 mg) (AS) |  |  | F-2 (05/02) | [521-35-7] | \$207 |
| 1091006 | Capreomycin Sulfate (200 mg) | G |  | F (06/01) | [1405-37-4] | \$156 |

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| 1091108 | Capsaicin (100 mg) | G-1 |  | $\begin{array}{\|l} \hline \text { G (03/02) } \\ \mathrm{F}-1(06 / 00) \\ \mathrm{F}(03 / 99) \\ \hline \end{array}$ | [404-86-4] | \$156 |
| 1091200 | Captopril (200 mg) | H |  |  | [62571-86-2] | \$156 |
| 1091221 | Captopril Disulfide ( 100 mg ) | G1B066 |  | G (01/04) | [64806-05-9] | \$487 |
| 1092009 | Carbachol (200 mg) | G |  |  | [51-83-2] | \$156 |
| 1093001 | Carbamazepine (100 mg) | J |  | I-1 (02/00) | [298-46-4] | \$156 |
| 1093205 | Carbarsone ( 200 mg ) | F |  |  | [121-59-5] | \$156 |
| 1093500 | Carbenicillin Indanyl Sodium ( 300 mg ) | G |  |  | [26605-69-6] | \$156 |
| 1094004 | Carbenicillin Monosodium Monohydrate ( $200 \mathrm{mg} \mathrm{)}$ | G-2 |  |  | n/f | \$156 |
| 1095506 | Carbidopa ( 400 mg ) | 1 |  | H (10/99) | [38821-49-7] | \$156 |
| 1095517 | Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa) | H0B121 |  | G (04/03) | n/f | \$487 |
| 1096000 | Carbinoxamine Maleate ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G-1 (11/02) | [3505-38-2] | \$156 |
| 1096407 | Carboplatin ( 100 mg ) | H0C240 |  | $\begin{aligned} & \hline G(07 / 04) \\ & F(03 / 00) \\ & \hline \end{aligned}$ | [41575-94-4] | \$159 |
| 1096509 | Carboprost Tromethamine ( 25 mg ) | F-1 |  | F (02/01) | [58551-69-2] | \$487 |
| 1096600 | Carisoprodol (1 g) | G |  | F-2 (05/02) | [78-44-4] | \$156 |
| 1096757 | Carteolol Hydrochloride (200 mg) | F-1 |  | F (11/00) | [51781-21-6] | \$156 |
| 1096804 | Cathinone Hydrochloride $\mathbf{C l}(50 \mathrm{mg})$ (alpha-Aminopropiophenone Hydrochloride) | I |  |  | [76333-53-4] | \$560 |
| 1096906 | Cefaclor ( 400 mg ) | H |  |  | [70356-03-5] | \$156 |
| 1096917 | Cefaclor, Delta-3-Isomer ( 30 mg ) | G |  | F-1 (02/00) | n/f | \$156 |
| 1097104 | Cefadroxil ( 125 mg ) | 1 |  | H (04/99) | [66592-87-8] | \$124 |
| 1097308 | Cefamandole Lithium (200 mg) | H |  |  | n/f | \$156 |
| 1097400 | Cefamandole Nafate (200 mg) | H |  |  | [42540-40-9] | \$156 |
| 1097501 | Cefamandole Sodium ( 250 mg ) | F |  |  | [30034-03-8] | \$156 |
| 1097603 | Cefazolin ( 400 mg ) | K |  | $J(06 / 00)$ | [25953-19-9] | \$156 |
| 1097636 | Cefepime Hydrochloride ( 500 mg ) | F0C063 |  |  | [123171-59-5] | \$156 |
| 1097647 | Cefepime Hydrochloride System Suitability ( 25 mg ) | F0C095 |  |  | n/f | \$156 |
| 1097658 | Cefixime ( 500 mg ) | F |  |  | [79350-37-1] | \$156 |
| 1097771 | Cefmenoxime Hydrochloride ( 350 mg ) | F |  |  | [75738-58-8] | \$156 |
| 1097782 | Cefmetazole (200 mg) | F-1 |  | F (04/02) | [56796-20-4] | \$156 |
| 1097750 | Cefonicid Sodium (1 g) | G |  |  | [61270-78-8] | \$156 |
| 1097705 | Cefoperazone Dihydrate (200 mg) | H |  | G (12/99) | [62893-19-0] | \$156 |
| 1097807 | Ceforanide ( 200 mg ) | F-1 |  | F (07/00) | [60925-61-3] | \$156 |
| 1097909 | Cefotaxime Sodium ( 250 mg ) | 1 |  |  | [64485-93-4] | \$124 |
| 1097975 | Cefotetan (500 mg) | H0C175 |  | $\begin{array}{\|l} \hline G(07 / 04) \\ F(09 / 00) \\ \hline \end{array}$ | [69712-56-7] | \$156 |
| 1098005 | Cefotiam Hydrochloride ( 325 mg ) | G0B050 |  | F (01/03) | [66309-69-1] | \$156 |
| 1098107 | Cefoxitin ( 500 mg ) | 1 |  | H (05/00) | [35607-66-0] | \$156 |
| 1098118 | Cefpiramide ( 300 mg ) | F0C203 | 1 |  | [70797-11-4] | \$156 |
| 1098049 | Cefprozil E-Isomer ( 50 mg ) | F2C284 |  | $\begin{array}{\|l\|} \hline \text { F-1 (10/04) } \\ \text { F (05/01) } \\ \hline \end{array}$ | [121123-17-9] | \$156 |
| 1098050 | Cefprozil Z-Isomer (200 mg) | G0C037 |  | F (12/03) | [121123-17-9] | \$156 |
| 1098129 | Ceftazidime, Delta-3-Isomer ( 25 mg ) | G |  | F (03/00) | n/f | \$208 |
| 1098130 | Ceftazidime Pentahydrate ( 300 mg ) | H |  | G (12/99) | [78439-06-2] | \$156 |
| 1098173 | Ceftizoxime ( 200 mg ) | H |  |  | [68401-81-0] | \$156 |
| 1098184 | Ceftriaxone Sodium ( 350 mg ) | G0B264 |  | F (08/03) | [104376-79-6] | \$156 |

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| 1098195 | Ceftriaxone Sodium E-Isomer (25 mg) | IOC190 |  | $\begin{array}{\|l\|l} \hline \text { H (07/04) } \\ \text { G (08/01) } \\ \text { F-1 }(02 / 00) \\ \hline \end{array}$ | n/f | \$208 |
| 1098209 | Cefuroxime Sodium ( 200 mg ) | H |  | G-1 (05/00) | [56238-63-2] | \$156 |
| 1098220 | Cefuroxime Axetil ( 500 mg ) | G |  | F-1 (05/02) | [64544-07-6] | \$156 |
| 1098231 | Cefuroxime Axetil Delta-3-Isomers ( 35 mg ) | H0B160 |  | G (03/03) | n/f | \$156 |
| 1098300 | Cellulose Acetate (125 mg) | F-1 |  | F (11/99) | [9004-35-7] | \$124 |
| 1098355 | Cellulose Acetate Phthalate ( 125 mg ) | F-1 |  | F (03/99) | [9004-38-0] | \$124 |
| 1098708 | Cephaeline Hydrobromide ( 200 mg ) | G-1 |  |  | n/f | \$487 |
| 1099008 | Cephalexin ( 250 mg ) | I-2 |  | I-1 (03/00) | [23325-78-2] | \$156 |
| 1102000 | Cephalothin Sodium (200 mg) | 1 |  |  | [58-71-9] | \$156 |
| 1102408 | Cephapirin Benzathine ( 100 mg ) | F |  |  | [97468-37-6] | \$156 |
| 1102500 | Cephapirin Sodium (200 mg) | I-1 |  | I (07/02) | [24356-60-3] | \$156 |
| 1102805 | Cephradine ( 200 mg ) | J |  | I (04/00) | [58456-86-3] | \$156 |
| 1103003 | Cetyl Alcohol ( 100 mg ) | 1 |  | H (03/99) | [36653-82-4] | \$156 |
| 1103105 | Cetyl Palmitate ( 50 mg ) | F0B241 |  |  | [540-10-3] | \$156 |
| 1104006 | Cetylpyridinium Chloride ( 500 mg ) | 1 |  | $\begin{array}{\|l\|l} \hline \mathrm{H}-1(06 / 01) \\ \mathrm{H}(08 / 99) \\ \hline \end{array}$ | [6004-24-6] | \$156 |
| 1106001 | Chlorambucil ( 125 mg ) | G |  | F-1 (02/99) | [305-03-3] | \$124 |
| 1107004 | Chloramphenicol (200 mg) | N1C074 |  | $\begin{array}{\|l\|} \hline N(10 / 04) \\ M(03 / 00) \\ \hline \end{array}$ | [56-75-7] | \$156 |
| 1107300 | Chloramphenicol Palmitate ( $200 \mathrm{mg} \mathrm{)}$ | G-1 |  |  | [530-43-8] | \$156 |
| 1107401 | Chloramphenicol Palmitate Nonpolymorph A (200 mg) | F-1 |  |  | [530-43-8] | \$487 |
| 1107503 | Chloramphenicol Palmitate Polymorph A (200 mg) | G |  | F (08/99) | [530-43-8] | \$487 |
| 1109000 | Chlordiazepoxide CIV (200 mg) | IOB063 |  | H-1 (03/03) | [58-25-3] | \$207 |
| 1110009 | Chlordiazepoxide Hydrochloride CIV (200 mg) | G-4 |  |  | [438-41-5] | \$207 |
| 1110020 | Chlordiazepoxide Related Compound A (25 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide) | G |  |  | [963-39-3] | \$487 |
| 1111001 | Chlorhexidine ( 200 mg ) | F0C306 |  |  | [55-56-1] | \$156 |
| 1111103 | Chlorhexidine Acetate ( 500 mg ) | F0C281 |  |  | [56-95-1] | \$156 |
| 1112503 | Chlorobutanol (200 mg) | G |  | F-3 (12/01) | [6001-64-5] | \$156 |
| 1115556 | beta-Chlorogenin (20 mg) | F |  |  | n/f | \$156 |
| 1117008 | Chloroprocaine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G0B285 |  | $\begin{array}{\|l} \hline \text { F-3 (01/04) } \\ \text { F-2 (03/99) } \\ \hline \end{array}$ | [3858-89-7] | \$156 |
| 1118000 | Chloroquine Phosphate ( 500 mg ) | 1 |  | H (10/99) | [50-63-5] | \$156 |
| 1121005 | Chlorothiazide ( 200 mg ) | H0B161 |  | G (04/03) | [58-94-6] | \$156 |
| 1122008 | Chlorotrianisene (1 g) | F |  |  | [569-57-3] | \$156 |
| 1122700 | Chloroxylenol (125 mg) | F2C259 |  | $\begin{array}{\|l} \hline \text { F-1 (07/04) } \\ \text { F (10/99) } \\ \hline \end{array}$ | [88-04-0] | \$124 |
| 1122722 | Chloroxylenol Related Compound A (25 mg) (2-chloro-3,5-dimethylphenol) | G0C275 |  | F-1 (07/04) | [5538-41-0] | \$487 |
| 1123000 | Chlorpheniramine Maleate (125 mg) | M0B020 |  | L-1 (06/03) | [113-92-8] | \$124 |
| 1123102 | Chlorpheniramine Maleate Extended-Release Tablets (Drug Release Calibrator, Single Unit) ( 60 Tablets) | G0B259 |  | F (06/03) | [113-92-8] | \$156 |
| 1124003 | Chlorphenoxamine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [562-09-4] | \$156 |
| 1125006 | Chlorpromazine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | J |  | I (04/99) | [69-09-0] | \$156 |
| 1126009 | Chlorpropamide (200 mg) | H |  |  | [94-20-2] | \$156 |
| 1127001 | Chlorprothixene (200 mg) | F-1 |  |  | [113-59-7] | \$156 |
| 1129007 | Chlortetracycline Hydrochloride ( 200 mg ) | J-1 |  | J (02/02) | [64-72-2] | \$156 |

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| 1130006 | Chlorthalidone (200 mg) | 10C255 | 2,3 | $\begin{aligned} & \mathrm{H}-1(11 / 04) \\ & \mathrm{H}(07 / 99) \\ & \hline \end{aligned}$ | [77-36-1] | \$156 |
| 1119309 | Chlorthalidone Related Compound A (25 mg) (4'-Chloro-3'-sulfamoyl-2benzophenone Carboxylic Acid) | G0C376 |  | F-3 (07/04) | n/f | \$487 |
| 1130505 | Chlorzoxazone ( 500 mg ) | 1 |  | H (07/01) | [95-25-0] | \$156 |
| 1130527 | Chlorzoxazone Related Compound A (50 mg) (2-Amino-4-chlorophenol) | G-1 |  | G (11/00) | [95-85-2] | \$487 |
| 1131009 | Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3) | M0B157 |  | $\begin{array}{\|l\|l\|} \hline L(10 / 03) \\ \text { K (09/99) } \\ \hline \end{array}$ | [67-97-0] | \$159 |
| 1131803 | Delta-4,6-cholestadienol ( 30 mg ) | F |  |  | [14214-69-8] | \$156 |
| 1132001 | Cholesteryl Caprylate (200 mg) | F |  |  | [1182-42-9] | \$156 |
| 1133004 | Cholestyramine Resin ( 500 mg ) | I |  |  | [11041-12-6] | \$124 |
| 1133503 | Cholic Acid (2 g) (AS) | F3B159 |  | F-2 (01/03) | [81-25-4] | \$156 |
| 1133536 | Choline Bitartrate ( $200 \mathrm{mg} \mathrm{)}$ | F0C057 |  |  | [87-67-2] | \$156 |
| 1133547 | Choline Chloride ( 200 mg ) | F0C058 |  |  | [67-48-1] | \$156 |
| 1133570 | Chondroitin Sulfate Sodium ( 300 mg ) | F0B256 |  |  | [39455-18-0] | \$156 |
| 1133638 | Chromium Picolinate ( 100 mg ) | F |  |  | [14639-25-9] | \$156 |
| 1134007 | Chymotrypsin ( 300 mg ) | 1 |  | H (06/01) | [9004-07-3] | \$156 |
| 1134030 | Ciclopirox Olamine ( 125 mg ) | H0C207 |  | G (05/03) | [41621-49-2] | \$124 |
| 1134051 | Cilastatin Ammonium Salt ( 100 mg ) | F-1 |  | F (07/00) | n/f | \$156 |
| 1134062 | Cimetidine ( 200 mg ) | I1C081 |  | I (05/04) | [51481-61-9] | \$156 |
| 1134073 | Cimetidine Hydrochloride ( 200 mg ) | F |  |  | [70059-30-2] | \$156 |
| 1134109 | Cinoxacin (200 mg) | F |  |  | [28657-80-9] | \$156 |
| 1134313 | Ciprofloxacin ( 125 mg ) | G-1 |  | G (05/01) | [85721-33-1] | \$124 |
| 1134324 | Ciprofloxacin Ethylenediamine Analog (25 mg) | J0A030 |  | $\begin{aligned} & \hline \text { I (01/03) } \\ & \mathrm{H}-1(02 / 99) \\ & \hline \end{aligned}$ | n/f | \$208 |
| 1134335 | Ciprofloxacin Hydrochloride ( 400 mg ) | H |  | G (04/00) | [86393-32-0] | \$156 |
| 1134357 | Cisplatin ( 100 mg ) | H |  | G (03/01) | [15663-27-1] | \$156 |
| 1134368 | Citric Acid (200 mg) | F1B092 |  | $\begin{array}{\|l\|} \hline \text { F-1 (01/04) } \\ \text { F (07/02) } \\ \hline \end{array}$ | [77-92-9] | \$156 |
| 1134379 | Clarithromycin (75 mg) | F4B183 |  | $\begin{array}{\|l\|l\|} \hline \text { F-3 (01/04) } \\ \text { F-2 (09/01) } \\ \hline \end{array}$ | [81103-11-9] | \$156 |
| 1134380 | Clarithromycin Related Compound A (50 mg) (6,11-di-O-methylerythromycin A) | G |  | F (04/01) | n/f | \$208 |
| 1134404 | Clavam-2-carboxylate Potassium (1 Pellet) | H0C089 |  | $\begin{array}{\|l} \text { GOB225 (12/03) } \\ \text { F (10/03) } \\ \hline \end{array}$ | n/f | \$487 |
| 1134426 | Clavulanate Lithium ( 200 mg ) | 1 |  | H (09/02) | n/f | \$156 |
| 1134506 | Clemastine Fumarate ( $250 \mathrm{mg} \mathrm{)}$ | 1 |  | H (10/00) | [14976-57-9] | \$156 |
| 1135000 | Clidinium Bromide ( 2 g ) | G |  |  | [3485-62-9] | \$156 |
| 1135021 | Clidinium Bromide Related Compound A ( 250 mg ) (3-Hydroxy-1methylquinuclindinium Bromide) | I |  |  | [76201-95-1] | \$487 |
| 1136002 | Clindamycin Hydrochloride (200 mg) | G4A017 |  | $\begin{aligned} & \text { G-3 (07/03) } \\ & \text { G-2 (05/99) } \end{aligned}$ | [58207-19-5] | \$428 |
| 1137005 | Clindamycin Palmitate Hydrochloride ( 200 mg ) | F-2 |  |  | [25507-04-4] | \$428 |
| 1138008 | Clindamycin Phosphate (125 mg) | IOC165 |  | $\begin{array}{\|ll} \hline \mathrm{H}-3(04 / 04) \\ \mathrm{H}-2(07 / 03) \\ \mathrm{H}-1 & (02 / 99) \\ \hline \end{array}$ | [24729-96-2] | \$214 |
| 1138201 | Clioquinol ( 500 mg ) | M |  | L-1 (01/03) | [130-26-7] | \$156 |
| 1138405 | Clobetasol Propionate ( 200 mg ) | F-1 |  | F (10/01) | [25122-46-7] | \$156 |
| 1138427 | Clobetasol Propionate Related Compound A ( 50 mg ) (9-alpha-fluoro-11-beta-hydroxy-16-beta-methyl-3-oxo-androsta-1,4-diene-17(R)-spiro-2'-[4'-chloro-5'-ethylfuran-3'(2'H)-one]) | F-1 |  | F (01/03) | n/f | \$208 |

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| 1138507 | Clocortolone Pivalate (200 mg) | G |  |  | [34097-16-0] | \$156 |
| 1138904 | Clofazimine ( 200 mg ) | F |  |  | [2030-63-9] | \$156 |
| 1139000 | Clofibrate (1 g) | I |  | H (04/01) | [637-07-0] | \$156 |
| 1140000 | Clomiphene Citrate ( 500 mg ) | H |  | G-1 (10/99) | [50-41-9] | \$156 |
| 1140101 | Clomiphene Related Compound A (100 mg) ((E,Z)-2-[4-(1,2-dipheny-lethenyl)phenoxy]-N,N-diethylethanamine Hydrochloride) | F1B206 |  | F (09/03) | n/f | \$208 |
| 1140247 | Clomipramine Hydrochloride ( 200 mg ) | F0C075 |  |  | [17321-77-6] | \$156 |
| 1140305 | Clonazepam CIV (200 mg) | G1B175 |  | $\begin{aligned} & \text { G (01/04) } \\ & \text { F-2 }(01 / 00) \\ & \hline \end{aligned}$ | [1622-61-3] | \$207 |
| 1140327 | Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophe-nyl)-6-nitrocarbostyril) | G2B110 |  | $\begin{aligned} & \text { G-1 (01/04) } \\ & \text { G (02/99) } \\ & \hline \end{aligned}$ | n/f | \$487 |
| 1140338 | Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5nitrobenzophenone) | H |  | G (04/01) | [2011-66-7] | \$487 |
| 1140349 | Clonazepam Related Compound C (25 mg) (2-Bromo-2'-(2-chloroben-zoyl)-4'-nitroacetanilide) | F0C340 |  |  | n/f | \$487 |
| 1140393 | Clonidine ( 200 mg ) | F0C401 | 1 |  | [4205-90-7] | \$156 |
| 1140407 | Clonidine Hydrochloride (200 mg) | G |  |  | [4205-91-8] | \$156 |
| 1140418 | Clonidine Related Compound A (25 mg) (Acetylclonidine) | F0C373 |  |  | [54707-71-0] | \$487 |
| 1140509 | Clorazepate Dipotassium CIV (125 mg) | G0B027 |  | $\begin{aligned} & \text { F-1 (06/03) } \\ & \text { F (12/99) } \\ & \hline \end{aligned}$ | [57109-90-7] | \$207 |
| 1140702 | Clorsulon ( 200 mg ) | F1B084 |  | F (01/04) | [60200-06-8] | \$156 |
| 1141002 | Clotrimazole (200 mg) | J |  | I (05/99) | [23593-75-1] | \$124 |
| 1141024 | Clotrimazole Related Compound A ( 25 mg ) ((0-chlorophenyl)diphenylmethanol) | I |  | $\begin{aligned} & \hline \text { H (10/01) } \\ & \text { G-1 (02/99) } \end{aligned}$ | [66774-02-5] | \$487 |
| 1141909 | Cloxacillin Benzathine (200 mg) | F-1 |  | F (03/02) | [23736-58-5] | \$156 |
| 1142005 | Cloxacillin Sodium (200 mg) | L0B086 |  | K (01/04) | [7081-44-9] | \$156 |
| 1142107 | Clozapine ( 100 mg ) | F0C032 |  |  | [5786-21-0] | \$260 |
| 1143008 | Cocaine Hydrochloride CII (250 mg) | 10B074 |  | $\begin{aligned} & \mathrm{H}-2(01 / 04) \\ & \mathrm{H}-1(02 / 99) \end{aligned}$ | [53-21-4] | \$207 |
| 1143802 | Codeine N-Oxide Cl (50 mg) | G0A034 |  | F-1 (11/02) | [3688-65-1] | \$207 |
| 1144000 | Codeine Phosphate CII (100 mg) | J0C200 |  | $\begin{aligned} & \hline 1-1(10 / 04) \\ & \mathrm{I}(09 / 02) \\ & \mathrm{H}-1(01 / 00) \\ & \hline \end{aligned}$ | [41444-62-6] | \$207 |
| 1145003 | Codeine Sulfate CII (250 mg) | H-2 |  | H-1 (01/02) | [6854-40-6] | \$207 |
| 1146006 | Colchicine ( 300 mg ) | $J$ |  | I (05/02) | [64-86-8] | \$156 |
| 1146505 | Colestipol Hydrochloride ( 200 mg ) | F-1 |  |  | [37296-80-3] | \$156 |
| 1147009 | Colistimethate Sodium ( 200 mg ) | H |  |  | [8068-28-8] | \$156 |
| 1148001 | Colistin Sulfate ( 200 mg ) | G-1 |  | G (09/99) | [1264-72-8] | \$156 |
| 1148500 | Copovidone ( 100 mg ) | FOC194 |  |  | [2586-89-9] | \$156 |
| 1149004 | Corticotropin (5.6 Units/vial; 5 vials) | M |  | L (06/99) | [9002-60-2] | \$124 |
| 1150003 | Cortisone Acetate ( 150 mg ) | 1 |  |  | [50-04-4] | \$156 |
| 1150353 | Creatinine ( 100 mg ) | F |  |  | [60-27-5] | \$156 |
| 1150502 | Cromolyn Sodium ( 500 mg ) | $J$ |  | 1 (06/00) | [15826-37-6] | \$156 |
| 1150706 | Crospovidone ( 200 mg ) | G1C273 | 2 | G (12/04) | [9003-39-8] | \$156 |
| 1151006 | Crotamiton ( 200 mg ) | H-1 |  | H (07/00) | [483-63-6] | \$156 |
| 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) | N |  | M-3 (08/99) | [68-19-9] | \$156 |
| 1152508 | Cyclacillin (200 mg) | G |  |  | [3485-14-1] | \$156 |
| 1152701 | Cyclandelate (200 mg) | F0C384 | 1 |  | [456-59-7] | \$156 |
| 1153001 | Cyclizine (1 g) DISCONTINUED |  |  | F (04/04) | [82-92-8] | \$156 |

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| 1154004 | Cyclizine Hydrochloride (200 mg) | G |  |  | [303-25-3] | \$156 |
| 1154503 | Cyclobenzaprine Hydrochloride ( 200 mg ) | G0A013 |  | F-3 (07/03) | [6202-23-9] | \$156 |
| 1154558 | Alpha Cyclodextrin ( 50 mg ) | F-1 |  | F (10/00) | [10016-20-3] | \$156 |
| 1154569 | Beta Cyclodextrin (250 mg) | G |  | F-1 (12/02) | [7585-39-9] | \$156 |
| 1154707 | Cyclomethicone 4 (200 mg) | F-2 |  | F-1 (06/02) | [69430-24-6] | \$156 |
| 1154809 | Cyclomethicone 5 ( 125 mg ) | F-2 |  | F-1 (09/99) | [69430-24-6] | \$124 |
| 1154900 | Cyclomethicone 6 (200 mg) | F2B024 |  | F-1 (03/03) | [69430-24-6] | \$156 |
| 1156000 | Cyclopentolate Hydrochloride ( $300 \mathrm{mg} \mathrm{)}$ | H |  | G (04/00) | [5870-29-1] | \$156 |
| 1157002 | Cyclophosphamide ( 500 mg ) | J |  |  | [6055-19-2] | \$124 |
| 1157501 | 2-Cyclopropylmethylamino-5-chlorobenzophenone ( 50 mg ) | F |  |  | n/f | \$487 |
| 1158005 | Cycloserine ( 200 mg ) | G |  |  | [68-41-7] | \$156 |
| 1158504 | Cyclosporine ( 50 mg ) | H-1 |  | $\begin{aligned} & \hline \text { H }(11 / 02) \\ & \text { G-2 }(03 / 00) \end{aligned}$ | [59865-13-3] | \$479 |
| 1158650 | Cyclosporine Resolution Mixture (25 mg) | F |  |  | $\begin{aligned} & {[108027-45-8]} \\ & (\mathrm{U}) \end{aligned}$ | \$412 |
| 1159008 | Cyclothiazide ( 200 mg ) | F-1 |  |  | [2259-96-3] | \$156 |
| 1161000 | Cyproheptadine Hydrochloride ( 500 mg ) | G |  | F-4 (11/02) | [41354-29-4] | \$156 |
| 1161509 | L-Cysteine Hydrochloride (200 mg) | H |  | G (05/00) | [7048-04-6] | \$156 |
| 1162002 | Cytarabine ( 250 mg ) | G-2 |  | G-1 (07/00) | [147-94-4] | \$156 |
| 1162308 | Dacarbazine ( 125 mg ) | H |  | G (01/99) | [4342-03-4] | \$124 |
| 1162320 | Dacarbazine Related Compound A ( 50 mg ) ( 5 -aminoimidazole-4carboxamide Hydrochloride) | H0C052 |  | $\begin{aligned} & \hline \text { G (03/04) } \\ & \mathrm{F}(03 / 00) \end{aligned}$ | [72-40-2] | \$487 |
| 1162330 | Dacarbazine Related Compound B (100 mg) (2-azahypoxanthine) | F-1 |  | F (12/01) | [63907-29-9] | \$487 |
| 1162400 | Dactinomycin ( 50 mg ) | I |  |  | [50-76-0] | \$427 |
| 1162501 | Danazol ( 200 mg ) | H |  | G (10/00) | [17230-88-5] | \$156 |
| 1164008 | Dapsone (125 mg) | G-3 |  | G-2 (08/99) | [80-08-0] | \$124 |
| 1164700 | Daunorubicin Hydrochloride (200 mg) | LOB307 |  | $\begin{aligned} & \text { K (11/03) } \\ & \text { J (08/00) } \end{aligned}$ | [23541-50-6] | \$479 |
| 1165000 | Decamethonium Bromide ( 250 mg ) | F |  |  | [541-22-0] | \$156 |
| 1166003 | Deferoxamine Mesylate ( 500 mg ) | I |  |  | [138-14-7] | \$156 |
| 1166309 | Dehydroacetic Acid (200 mg) | F |  |  | [520-45-6] | \$156 |
| 1166400 | Dehydrocarteolol Hydrochloride ( 100 mg ) | F |  |  | n/f | \$487 |
| 1166502 | Dehydrocholic Acid ( 200 mg ) | F-1 |  | F (03/04) | [81-23-2] | \$156 |
| 1169001 | Demecarium Bromide ( 250 mg ) | F |  |  | [56-94-0] | \$156 |
| 1170000 | Demeclocycline Hydrochloride (200 mg) | H1C036 |  | $\begin{aligned} & \hline \text { H (08/04)G-1 } \\ & (08 / 01) \\ & \hline \end{aligned}$ | [64-73-3] | \$156 |
| 1171003 | Denatonium Benzoate ( 200 mg ) | IOB129 |  | H (09/02) | [86398-53-0] | \$156 |
| 1171706 | Desacetyl Diltiazem Hydrochloride ( 50 mg ) | 1 |  | H (08/00) | [23515-45-9] | \$487 |
| 1171900 | Desflurane ( 0.5 mL ) | F0C187 |  |  | [57041-67-5] | \$156 |
| 1171910 | Desflurane Related Compound A ( 0.1 mL ) (bis-(1,2,2,2-tetrafluoroethyl) ether) | F0C031 |  |  | n/f | \$487 |
| 1172006 | Desipramine Hydrochloride ( 125 mg ) | H-1 |  | H (10/99) | [58-28-6] | \$124 |
| 1173009 | Deslanoside ( 100 mg ) | H-1 |  |  | [17598-65-1] | \$156 |
| 1173235 | Desogestrel ( 50 mg ) | G0C390 | 2 | F0B282 (11/04) | [54024-22-5] | \$156 |
| 1173246 | Desogestrel Related Compound A (15 mg) (13-Ethyl-11-methylene-18, 19-dinor-5alpha, 17alpha-preg-3-en-20-yl-17-ol, desogestrel delta-3 isomer) | F0B279 |  |  | n/f | \$487 |
| 1173257 | Desogestrel Related Compound B (15 mg) (3-Hydroxy-desogestrel) | FOB284 |  |  | n/f | \$487 |
| 1173268 | Desogestrel Related Compound C ( 25 mg ) (3-Keto-desogestrel) | FOB281 |  |  | [54048-10-1] | \$487 |
| 1173508 | Desoximetasone ( 200 mg ) | H0B036 |  | G (01/04) | [382-67-2] | \$156 |

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| 1174001 | Desoxycorticosterone Acetate (200 mg) | J0C014 |  | $\begin{aligned} & \text { I (01/04) } \\ & \mathrm{H}(05 / 00) \end{aligned}$ | [56-47-3] | \$156 |
| 1175004 | Desoxycorticosterone Pivalate ( 125 mg ) | H0C276 |  | G (01/04) | [808-48-0] | \$124 |
| 1176007 | Dexamethasone ( 125 mg ) | J |  |  | [50-02-2] | \$124 |
| 1176506 | Dexamethasone Acetate ( $200 \mathrm{mg} \mathrm{)}$ | G |  | F-1 (06/99) | [55812-90-3] | \$156 |
| 1177000 | Dexamethasone Phosphate (200 mg) | J1B070 |  | $\begin{array}{\|l\|} \hline J(08 / 03) \\ I(03 / 00) \\ \hline \end{array}$ | [312-93-6] | \$156 |
| 1178002 | Dexbrompheniramine Maleate (200 mg) | $J$ |  | 1 (03/03) | [2391-03-9] | \$156 |
| 1179005 | Dexchlorpheniramine Maleate ( 500 mg ) | G1A025 |  | G (12/02) | [2438-32-6] | \$156 |
| 1179504 | Dexpanthenol ( 500 mg ) | J0C293 |  | $\begin{aligned} & \text { I (08/04) } \\ & H(02 / 02) \end{aligned}$ | [81-13-0] | \$160 |
| 1179708 | Dextran 40 ( 50 mg ) | F0C247 |  |  | [9004-54-0] | \$156 |
| 1179741 | Dextran 70 ( 50 mg ) | F0C260 |  |  | [9004-54-0] | \$156 |
| 1179854 | Dextran 4 Calibration ( 100 mg ) | F0C002 |  |  | [9004-54-0] | \$156 |
| 1179865 | Dextran 10 Calibration ( 100 mg ) | F0C010 |  |  | [9004-54-0] | \$156 |
| 1179876 | Dextran 40 Calibration ( 100 mg ) | F0C011 |  |  | [9004-54-0] | \$156 |
| 1179720 | Dextran 40 System Suitability ( 200 mg ) | F0B181 |  |  | [9004-54-0] | \$156 |
| 1179887 | Dextran 70 Calibration ( 100 mg ) | F0C013 |  |  | [9004-54-0] | \$156 |
| 1179763 | Dextran 70 System Suitability ( 200 mg ) | F0B182 |  |  | [9004-54-0] | \$156 |
| 1179898 | Dextran 250 Calibration ( 100 mg ) | F0C039 |  |  | [9004-54-0] | \$156 |
| 1179800 | Dextran Vo Marker ( 100 mg ) | F0B242 |  |  | [9004-54-0] | \$156 |
| 1180004 | Dextroamphetamine Sulfate CII (500 mg) | H |  | $\begin{array}{\|l\|} \hline G(08 / 03) \\ \text { F-6 }(12 / 99) \\ \hline \end{array}$ | [51-63-8] | \$216 |
| 1180503 | Dextromethorphan (2 g) | H |  | G (06/00) | [125-71-3] | \$487 |
| 1181007 | Dextromethorphan Hydrobromide ( 500 mg ) | J0B167 |  | 1 (07/03) | [6700-34-1] | \$156 |
| 1181302 | Dextrose ( 500 mg ) | J-1 |  | $\begin{array}{\|l\|} \hline J(11 / 02) \\ I(08 / 99) \\ \hline \end{array}$ | [50-99-7] | \$124 |
| 1181506 | Diacetylated Monoglycerides (200 mg) | G |  |  | [68990-54-5] | \$156 |
| 1182000 | Diacetylfluorescein (200 mg) | H |  | G (01/02) | [596-09-8] | \$156 |
| 1183002 | Diacetylmorphine Hydrochloride CI (25 mg) (AS) (Heroin Hydrochloride) | $J$ |  | I-1 (10/99) | [1502-95-0] | \$207 |
| 1184005 | Diatrizoic Acid ( 100 mg ) | G |  |  | [50978-11-5] | \$156 |
| 1184027 | Diatrizoic Acid Related Compound A ( 50 mg ) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid) | I |  | H (02/00) | [1713-07-1] | \$487 |
| 1185008 | Diazepam CIV (100 mg) | 1 |  | H (12/01) | [439-14-5] | \$207 |
| 1185020 | Diazepam Related Compound A (25 mg) (2-Methyl-amino-5-chlorobenzophenone) | 1 |  | $\begin{aligned} & \mathrm{H}-1(11 / 02) \\ & \mathrm{H}(04 / 00) \\ & \hline \end{aligned}$ | [1022-13-5] | \$487 |
| 1023403 | Diazepam Related Compound B (25 mg) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril) | I1C102 | 2,8 | $\begin{array}{\|l\|l\|} \hline I(12 / 04) \\ H(04 / 01) \\ \hline \end{array}$ | [5220-02-0] | \$487 |
| 1186000 | Diazoxide (200 mg) | G1C017 |  | G (12/03) | [364-98-7] | \$156 |
| 1187003 | Dibucaine Hydrochloride (200 mg) | 1 |  | H-2 (01/03) | [61-12-1] | \$156 |
| 1187207 | Dichloralphenazone CIV (200 mg) | F0B010 |  |  | [480-30-8] | \$207 |
| 1188006 | Dichlorphenamide ( $200 \mathrm{mg} \mathrm{)}$ | G-1 |  |  | [120-97-8] | \$156 |
| 1188800 | Diclofenac Sodium (200 mg) | H0B150 |  | $\begin{aligned} & \text { G-1 (03/04) } \\ & \text { G (05/01) } \end{aligned}$ | [15307-79-6] | \$156 |
| 1188811 | Diclofenac Related Compound A (100 mg) (N-(2,6-dichlorophenyl)in-dolin-2-one) | H |  | G (05/02) | [15362-40-0] | \$490 |
| 1189009 | Dicloxacillin Sodium ( 500 mg ) | J0C182 |  | $\begin{aligned} & \text { IOB142 (09/04) } \\ & \text { H (05/03) } \end{aligned}$ | [13412-64-1] | \$156 |
| 1190008 | Dicumarol (200 mg) | G |  |  | [66-76-2] | \$156 |

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| 1191000 | Dicyclomine Hydrochloride ( 125 mg ) | H |  | G (03/99) | [67-92-5] | \$124 |
| 1192003 | Dienestrol ( 125 mg ) | 1 |  |  | [84-17-3] | \$124 |
| 1193006 | Diethylcarbamazine Citrate ( 200 mg ) | G-1 |  |  | [1642-54-2] | \$156 |
| 1193301 | Diethylene Glycol Monoethyl Ether ( $0.5 \mathrm{~mL} /$ ampule) | F0B095 |  |  | [111-90-0] | \$156 |
| 1193505 | Diethyl Phthalate ( 200 mg ) | G |  | F-1 (03/00) | [84-66-2] | \$156 |
| 1194009 | Diethylpropion Hydrochloride CIV (200 mg) | H |  |  | [134-80-5] | \$207 |
| 1195001 | Diethylstilbestrol (200 mg) | K5B291 |  | K-4 (05/04) | [56-53-1] | \$156 |
| 1197007 | Diethyltoluamide ( 3 g ) | H |  |  | [134-62-3] | \$124 |
| 1197302 | Diflorasone Diacetate (200 mg) | G |  | F-1 (03/00) | [33564-31-7] | \$156 |
| 1197506 | Diflunisal ( 200 mg ) | G |  |  | [22494-42-4] | \$156 |
| 1198000 | Digitalis (3 g) | F |  |  | [8031-42-3] | \$156 |
| 1199002 | Digitoxin (200 mg) | M |  |  | [71-63-6] | \$156 |
| 1200000 | Digoxin ( 250 mg ) | O0B096 |  | N-1 (04/03) | [20830-75-5] | \$156 |
| 1200600 | Dihydrocapsaicin (25 mg) | G0C071 |  | $\begin{aligned} & \hline \text { F-1 (12/03) } \\ & \text { F (01/00) } \\ & \hline \end{aligned}$ | [19408-84-5] | \$156 |
| 1200804 | Dihydrocodeine Bitartrate CII (200 mg) | H |  | G (03/01) | [5965-13-9] | \$207 |
| 1201002 | 17alpha-Dihydroequilin ( 50 mg ) | 10 C 277 |  | H (07/04) | [6639-99-2] | \$208 |
| 1202005 | Dihydroergotamine Mesylate ( 250 mg ) (List Chemical) | J0B085 |  | I (03/03) | [6190-39-2] | \$156 |
| 1203008 | Dihydrostreptomycin Sulfate ( 200 mg ) | $J$ |  |  | [5490-27-7] | \$156 |
| 1204000 | Dihydrotachysterol ( $30 \mathrm{mg} / \mathrm{ampule}$; 4 ampules) | I |  |  | [67-96-9] | \$156 |
| 1204102 | Dihydroxyacetone ( 250 mg ) | F |  |  | [96-26-4] | \$156 |
| 1204805 | Diloxanide Furoate ( $200 \mathrm{mg} \mathrm{)}$ | F0C026 |  |  | [3736-81-0] | \$156 |
| 1205003 | Diltiazem Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  |  | [33286-22-5] | \$156 |
| 1206006 | Dimenhydrinate (100 mg) | J0B055 |  | 1 (06/03) | [523-87-5] | \$156 |
| 1208001 | Dimethisoquin Hydrochloride (2 g) | G |  |  | [2773-92-4] | \$156 |
| 1210105 | N -(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8-germaspiro [4:5]de-cane-1,3-dione (AS) | F |  |  | [41992-23-8] | \$156 |
| 1211006 | Dimethyl Sulfoxide (3 g) | G0C198 |  | $\begin{aligned} & \hline \text { F-3 (07/04) } \\ & \text { F-2 (05/02) } \\ & \hline \end{aligned}$ | [67-68-5] | \$208 |
| 1213001 | Dinoprost Tromethamine ( 50 mg ) | F |  |  | [38562-01-5] | \$1,525 |
| 1213103 | Dinoprostone ( 50 mg ) | F0C030 |  |  | [363-24-6] | \$1,525 |
| 1214004 | Dioxybenzone ( 150 mg ) | F1B277 |  | F (10/03) | [131-53-3] | \$156 |
| 1216000 | Diphemanil Methylsulfate ( 500 mg ) | H |  |  | [62-97-5] | \$156 |
| 1217909 | Diphenhydramine Citrate ( 125 mg ) | H0B128 |  | G (04/03) | [88637-37-0] | \$124 |
| 1218005 | Diphenhydramine Hydrochloride (200 mg) | J0B013 |  | I (07/03) | [147-24-0] | \$156 |
| 1219008 | Diphenoxylate Hydrochloride CII (200 mg) | 1 |  | H (03/02) | [3810-80-8] | \$207 |
| 1220302 | Dipivefrin Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  | H (06/99) | [64019-93-8] | \$156 |
| 1220506 | Dipyridamole (200 mg) | H |  | G-1 (01/99) | [58-32-2] | \$156 |
| 1220700 | Dirithromycin (200 mg) | F |  |  | [62013-04-1] | \$156 |
| 1221000 | Disodium Guanylate ( 300 mg ) (FCC) | F-1 |  |  | [5550-12-9] | \$156 |
| 1222002 | Disodium Inosinate ( 500 mg ) (FCC) | F |  |  | [4691-65-0] | \$156 |
| 1222501 | Disopyramide Phosphate ( 200 mg ) | H-1 |  | H (03/02) | [22059-60-5] | \$156 |
| 1223005 | 2,4-Disulfamyl-5-trifluoromethylaniline ( 125 mg ) | G |  |  | [654-62-6] | \$487 |
| 1224008 | Disulfiram (200 mg) | F-3 |  | F-2 (07/02) | [97-77-8] | \$156 |
| 1224507 | Dobutamine Hydrochloride ( 600 mg ) | H-1 |  | H (01/00) | [49745-95-1] | \$156 |
| 1224700 | Docusate Calcium ( 500 mg ) | H0B044 |  | G-1 (07/02) | [128-49-4] | \$156 |
| 1224802 | Docusate Sodium ( 500 mg ) | $J$ |  | I-1 (05/02) | [577-11-7] | \$156 |
| 1224904 | Docusate Potassium ( 100 mg ) | F-1 |  | F (11/99) | [7491-09-0] | \$156 |
| 1224959 | Dolasetron Mesylate (200 mg) | F0C319 |  |  | [115956-13-3] | \$156 |

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| 1224960 | Dolasetron Mesylate Related Compound A ( 25 mg ) (Hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3(4H)-one hydrochloride) | F0C321 |  |  | n/f | \$487 |
| 1225204 | Dopamine Hydrochloride ( 200 mg ) | G |  | F-5 (05/02) | [62-31-7] | \$156 |
| 1225281 | Dorzolamide Hydrochloride ( 500 mg ) | FOC040 |  |  | [130693-82-2] | \$156 |
| 1225292 | Dorzolamide Hydrochloride Related Compound A (20 mg) ((4R,6R)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide, monohydrochloride) | F0C068 |  |  | n/f | \$487 |
| 1225000 | Doxapram Hydrochloride ( 200 mg ) | F4C053 |  | F-3 (07/04) | [7081-53-0] | \$156 |
| 1225419 | Doxazosin Mesylate (200 mg) | F0C079 |  |  | [77883-43-3] | \$156 |
| 1225500 | Doxepin Hydrochloride ( 500 mg ) | 1 |  |  | [1229-29-4] | \$156 |
| 1225703 | Doxorubicin Hydrochloride ( 50 mg ) | K |  | J (06/02) | [25316-40-9] | \$479 |
| 1226003 | Doxycycline Hyclate (200 mg) | 1 |  | H (01/00) | [24390-14-5] | \$156 |
| 1227006 | Doxylamine Succinate ( 300 mg ) | IOB266 |  | H (01/04) | [562-10-7] | \$156 |
| 1229001 | Droperidol ( 250 mg ) | H-1 |  | H (04/99) | [548-73-2] | \$156 |
| 1230000 | Dyclonine Hydrochloride (200 mg) | G |  |  | [536-43-6] | \$156 |
| 1231003 | Dydrogesterone (200 mg) | IOB114 |  | H (01/04) | [152-62-5] | \$156 |
| 1231502 | Dyphylline (200 mg) | G-2 |  | G-1 (11/02) | [479-18-5] | \$156 |
| 1231808 | Econazole Nitrate ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | [68797-31-9] | \$156 |
| 1232006 | Edetate Calcium Disodium (200 mg) | H0B272 | 2 | $\begin{aligned} & \text { G-3 }(11 / 04) \\ & \text { G-2 }(11 / 99) \\ & \hline \end{aligned}$ | [23411-34-9] | \$156 |
| 1233009 | Edetate Disodium (200 mg) | H |  | G-2 (04/02) | [6381-92-6] | \$156 |
| 1233508 | Edetic Acid ( 200 mg ) | F-1 |  |  | [60-00-4] | \$156 |
| 1234001 | Edrophonium Chloride ( 200 mg ) | H |  | G (08/99) | [116-38-1] | \$156 |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 |  |  | [84696-12-5] | \$520 |
| 1234806 | Emedastine Difumarate ( 100 mg ) | F0C059 |  |  | [87233-62-3] | \$156 |
| 1235004 | Emetine Hydrochloride ( 300 mg ) | H0B201 |  | G (05/03) | [316-42-7] | \$156 |
| 1235274 | Enalaprilat ( 300 mg ) | 1 |  | $\begin{aligned} & \mathrm{H}(03 / 01) \\ & \mathrm{G}(08 / 99) \end{aligned}$ | [84680-54-6] | \$124 |
| 1235300 | Enalapril Maleate (200 mg) | J |  | I (06/01) | [76095-16-4] | \$156 |
| 1235503 | Endotoxin (10,000 USP Endotoxin Units) | G2B274 |  | $\begin{aligned} & \text { G-1 (12/03) } \\ & \text { G (06/99) } \\ & \hline \end{aligned}$ | n/f | \$156 |
| 1235809 | Enflurane ( 1 mL ) | G-1 |  | G (02/01) | [13838-16-9] | \$156 |
| 1236007 | Ephedrine Sulfate (200 mg) (List Chemical) | H-2 |  | H-1 (11/02) | [134-72-5] | \$156 |
| 1236506 | 4-Epianhydrotetracycline Hydrochloride ( 50 mg ) | J0C041 |  | $\begin{array}{\|l\|} \hline \text { I-1 (12/03) } \\ \text { I (06/00) } \\ \hline \end{array}$ | [4465-65-0] | \$487 |
| 1236801 | Epilactose (200 mg) | G |  | F-1 (06/00) | [103302-12-1] | \$487 |
| 1237000 | Epinephrine Bitartrate (200 mg) | 0 |  |  | [51-42-3] | \$156 |
| 1237509 | Epitetracycline Hydrochloride ( 200 mg ) | F |  |  | [23313-80-6] | \$487 |
| 1238002 | Equilin ( 25 mg ) | 11B290 | 2 | $\begin{array}{\|l} \hline \text { I (11/04) } \\ \mathrm{H}-1(05 / 00) \\ \hline \end{array}$ | [474-86-2] | \$208 |
| 1239005 | Ergocalciferol (30 mg/ampule; 5 ampules) (Vitamin D2) | P0B275 |  | $\begin{array}{\|l} \hline \mathrm{O}(02 / 04) \\ \mathrm{N}(12 / 99) \\ \hline \end{array}$ | [50-14-6] | \$168 |
| 1239504 | Ergoloid Mesylates ( $300 \mathrm{mg} \mathrm{)}$ | 1 |  | H-1 (01/00) | [8067-24-1] | \$156 |
| 1240004 | Ergonovine Maleate (100 mg) (List Chemical) | N |  | M-1 (07/02) | [129-51-1] | \$156 |
| 1241007 | Ergosterol ( 50 mg ) | H |  |  | [57-87-4] | \$156 |
| 1241506 | Ergotamine Tartrate (150 mg) (List Chemical) | IOB174 |  | H (01/04) | [379-79-3] | \$156 |
| 1241550 | Ergotaminine ( 100 mg ) (List Chemical) | G0B177 |  | F-1 (06/04) | [639-81-6] | \$156 |
| 1242000 | Erythromycin (250 mg) | M |  | L (08/99) | [114-07-8] | \$156 |

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| 1242010 | Erythromycin B (150 mg) | G1C080 | 2 | $\begin{array}{\|l\|l} \hline G(11 / 04) \\ F-1(09 / 01) \\ F(05 / 01) \\ \hline \end{array}$ | [527-75-3] | \$156 |
| 1242021 | Erythromycin C (50 mg) | F-3 |  | $\begin{array}{\|l\|} \hline \text { F-2 (01/03) } \\ \text { F-1 (02/02) } \\ \text { F (02/99) } \\ \hline \end{array}$ | n/f | \$156 |
| 1242032 | Erythromycin Related Compound $\mathrm{N}(50 \mathrm{mg})$ (N-Demethylerythromycin A) | F2A023 |  | $\begin{aligned} & \text { F-1 (06/04) } \\ & F(09 / 99) \\ & \hline \end{aligned}$ | n/f | \$156 |
| 1243002 | Erythromycin Estolate (200 mg) | H |  | G (01/03) | [3521-62-8] | \$156 |
| 1245008 | Erythromycin Ethylsuccinate ( 200 mg ) | H |  | G-1 (06/01) | [1264-62-6] | \$156 |
| 1246000 | Erythromycin Gluceptate (200 mg) | H |  | G (07/03) | [23067-13-2] | \$156 |
| 1247003 | Erythromycin Lactobionate ( $200 \mathrm{mg} \mathrm{)}$ | H-1 |  | H (01/02) | [3847-29-8] | \$156 |
| 1248006 | Erythromycin Stearate ( 200 mg ) | H0B187 |  | G-1 (05/03) | [643-22-1] | \$156 |
| 1249009 | Erythrosine Sodium ( 100 mg ) | F |  |  | [49746-10-3] | \$156 |
| 1250008 | Estradiol ( 500 mg ) | K1B007 |  | K (04/03) | [50-28-2] | \$156 |
| 1251000 | Estradiol Benzoate ( 250 mg ) (AS) | G-1 |  |  | [50-50-0] | \$156 |
| 1252003 | Estradiol Cypionate ( 200 mg ) | G-1 |  | G (02/00) | [313-06-4] | \$156 |
| 1254009 | Estradiol Valerate ( 100 mg ) | L |  | K (05/02) | [979-32-8] | \$156 |
| 1254508 | Estriol ( 100 mg ) | J |  | I-1 (06/01) | [50-27-1] | \$156 |
| 1255001 | Estrone (200 mg) | K1B099 |  | $\begin{array}{\|l} \mathrm{K}(07 / 03) \\ \mathrm{J}-1(07 / 00) \\ \hline \end{array}$ | [53-16-7] | \$156 |
| 1255500 | Estropipate ( 500 mg ) | J0B262 |  | $\begin{array}{\|l\|l\|} \hline I(12 / 03) \\ H(09 / 01) \\ \hline \end{array}$ | [7280-37-7] | \$156 |
| 1256004 | Ethacrynic Acid (200 mg) | F |  |  | [58-54-8] | \$156 |
| 1257007 | Ethambutol Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G (08/02) | [1070-11-7] | \$156 |
| 1258305 | Ethchlorvynol CIV ( 0.7 ml ) | F0B011 |  |  | [113-18-8] | \$207 |
| 1260001 | Ethinyl Estradiol (150 mg) | P1B193 |  | $\begin{aligned} & \text { POB052 (01/04) } \\ & \text { P (03/03) } \\ & \text { O (08/99) } \\ & \hline \end{aligned}$ | [57-63-6] | \$156 |
| 1260012 | Ethinyl Estradiol Related Compound A (20 mg) (6-Keto-ethinyl estradiol) | F0B252 |  |  | n/f | \$487 |
| 1261004 | Ethionamide ( $200 \mathrm{mg} \mathrm{)}$ | H0B148 |  | G (03/03) | [536-33-4] | \$156 |
| 1262801 | Ethopabate ( 125 mg ) | F |  |  | [59-06-3] | \$156 |
| 1262823 | Ethopabate Related Compound A ( 25 mg ) (Methyl-4-acetamido-2hydroxybenzoate) | F |  |  | n/f | \$487 |
| 1263000 | Ethopropazine Hydrochloride ( 300 mg ) | G |  |  | [1094-08-2] | \$156 |
| 1264002 | Ethosuximide ( 125 mg ) | H |  | $\begin{array}{ll} \text { G-2 } & (11 / 01) \\ \text { G-1 } & (05 / 99) \\ \hline \end{array}$ | [77-67-8] | \$124 |
| 1264501 | Ethotoin (200 mg) | F |  |  | [86-35-1] | \$156 |
| 1265005 | Ethoxzolamide (200 mg) | F |  |  | [452-35-7] | \$156 |
| 1265504 | Ethylcellulose ( 1 g ) | H-1 |  | H (06/99) | [9004-57-3] | \$156 |
| 1266008 | Ethyl Maltol (1 g) (FCC) | H |  |  | [4940-11-8] | \$156 |
| 1266507 | Ethylnorepinephrine Hydrochloride ( 200 mg ) | F |  |  | [3198-07-0] | \$156 |
| 1267000 | Ethylparaben (200 mg) | 10 A016 |  | H (01/04) | [120-47-8] | \$156 |
| 1267500 | Ethyl Vanillin (200 mg) | F2B134 |  | F-1 (04/04) | [121-32-4] | \$156 |
| 1268003 | Ethynodiol Diacetate (200 mg) | I0A033 |  | $\begin{aligned} & \mathrm{H}-1(01 / 03) \\ & \mathrm{H}(04 / 01) \end{aligned}$ | [297-76-7] | \$156 |
| 1268502 | Etidronate Disodium (200 mg) | G |  | F-2 (02/03) | [7414-83-7] | \$156 |
| 1268604 | Etidronic Acid Monohydrate (1 g) | G |  | F-1 (05/99) | [2809-21-4] | \$156 |
| 1268706 | Etodolac ( 400 mg ) | G |  | F (10/01) | [41340-25-4] | \$156 |

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| 1268728 | Etodolac Related Compound A (25 mg) ((+/-)-8-ethyl-1-methyl-1,3,4,9tetrahydropyrano [3,4-b]-indole-1-acetic acid) | F-1 |  | F (05/02) | [109518-50-5] | \$208 |
| 1268808 | Etoposide ( 300 mg ) | H0C315 | 2 | G (11/04) | [33419-42-0] | \$124 |
| 1268852 | Etoposide Resolution Mixture ( 30 mg ) | F0B209 |  |  | [33419-42-0] | \$208 |
| 1269006 | Evans Blue ( 200 mg ) DISCONTINUED |  |  | G (04/04) | [314-13-6] | \$156 |
| 1269200 | Famotidine ( 125 mg ) | H-1 |  | $\begin{aligned} & \hline \text { H }(11 / 02) \\ & \text { G }(03 / 99) \\ & \hline \end{aligned}$ | [76824-35-6] | \$124 |
| 1269389 | Felodipine (200 mg) | F-1 |  | F (09/02) | [72509-76-3] | \$156 |
| 1269390 | Felodipine Related Compound A (100 mg) (ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate) | F0B207 |  |  | [96302-71-7] | \$487 |
| 1269403 | Fenbendazole ( 100 mg ) | F |  |  | [43210-67-9] | \$487 |
| 1269458 | Fenoldopam Mesylate (200 mg) | F0C125 |  |  | [67227-57-0] | \$156 |
| 1269469 | Fenoldopam Related Compound A ( 20 mg ) (1-Methyl-3-benzazapine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate) | F0C124 |  |  | n/f | \$487 |
| 1269470 | Fenoldopam Related Compound B (20 mg) (1H-3-Benzazapine-7,8diol, 2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate) | F0C126 |  |  | n/f | \$487 |
| 1269505 | Fenoprofen Calcium ( 500 mg ) | G-1 |  |  | [53746-45-5] | \$156 |
| 1269550 | Fenoprofen Sodium ( 500 mg ) | G |  | F-1 (05/02) | [66424-46-2] | \$156 |
| 1270005 | Fentanyl Citrate CII (100 mg) | K0C264 | 2 | $\begin{array}{\|l\|} \hline \text { J2B227 (11/04) } \\ \mathrm{J}-1(09 / 03) \\ \mathrm{J}(05 / 02) \\ \mathrm{I}(06 / 00) \\ \hline \end{array}$ | [990-73-8] | \$207 |
| 1270402 | Finasteride ( 200 mg ) | F |  |  | [98319-26-7] | \$156 |
| 1270800 | Flecainide Acetate (200 mg) | F-1 |  | F (06/03) | [54143-56-5] | \$156 |
| 1270821 | Flecainide Related Compound A ( 75 mg ) (3-[2,5-bis(2,2,2-trifluor-oethoxy)phenyl]-1,5,6,7,8,8a-hexahydroimidazo-[1,5a]pyridine Hydrochloride) | F |  |  | n/f | \$487 |
| 1271008 | Floxuridine ( 250 mg ) | F-2 |  | F-1 (08/01) | [50-91-9] | \$156 |
| 1272000 | Flucytosine ( 200 mg ) | F |  |  | [2022-85-7] | \$156 |
| 1272204 | Fludarabine Phosphate ( 300 mg ) | F0C374 | 1 |  | [75607-67-9] | \$156 |
| 1273003 | Fludrocortisone Acetate ( $250 \mathrm{mg} \mathrm{)}$ | H |  | G (08/01) | [514-36-3] | \$156 |
| 1273808 | Flumazenil ( 200 mg ) | F0C305 |  |  | [78755-81-4] | \$780 |
| 1274006 | Flumethasone Pivalate ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  | H (01/02) | [2002-29-1] | \$156 |
| 1274505 | Flunisolide ( 200 mg ) | 1 |  | H (01/01) | [77326-96-6] | \$156 |
| 1274607 | Flunixin Meglumine ( 300 mg ) | G |  | $\begin{array}{\|l\|} \hline \text { F-1 (04/02) } \\ \text { F (09/99) } \\ \hline \end{array}$ | [42461-84-7] | \$156 |
| 1275009 | Fluocinolone Acetonide ( 100 mg ) | J |  | I (11/99) | [67-73-2] | \$156 |
| 1276001 | Fluocinonide ( 100 mg ) | 1 |  |  | [356-12-7] | \$156 |
| 1277004 | Fluorescein (200 mg) | G0B171 |  | F-1 (02/03) | [2321-07-5] | \$156 |
| 1277208 | Fluoride Dentifrice: Sodium Fluoride-Calcium Pyrophosphate (high beta-phase) ( 180 g ) DISCONTINUED |  |  | F (01/04) | n/f | \$487 |
| 1277252 | Fluoride Dentifrice: Sodium Fluoride/Silica (4.5 oz) | J0C294 |  | $\begin{array}{\|l\|} \hline \text { I (08/04) } \\ \text { H }(04 / 99) \\ \hline \end{array}$ | n/f | \$458 |
| 1277274 | Fluoride Dentifrice: Sodium Fluoride/Sodium Bicarbonate Powder (4 oz) | F |  |  | n/f | \$487 |
| 1277300 | Fluoride Dentifrice: Sodium Monofluorophosphate-Calcium Carbonate (4.6 oz) | G |  |  | n/f | \$487 |
| 1277354 | Fluoride Dentifrice: Sodium Monofluorophosphate/Dicalcium Phosphate (4.6 oz) | G |  |  | n/f | \$487 |
| 1277401 | Fluoride Dentifrice: Sodium Monofluorophosphate (1000 ppm)/Silica ( 5.25 oz ) | G-1 |  | G (08/99) | n/f | \$487 |

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| 1277423 | Fluoride Dentifrice: Sodium Monofluorophosphate ( 1500 ppm )/Silica ( 5.25 oz ) | F-1 |  | F (07/99) | n/f | \$487 |
| 1277456 | Fluoride Dentifrice: Stannous Fluoride-Silica (4 oz) | H0B105 |  | G (11/02) | n/f | \$487 |
| 1278007 | Fluorometholone ( 200 mg ) | IOB184 |  | H-1 (11/02) | [426-13-1] | \$156 |
| 1278109 | Fluorometholone Acetate ( 200 mg ) | F |  |  | [3801-06-7] | \$156 |
| 1278302 | Fluoroquinolonic Acid ( 50 mg ) | G |  | F-1 (12/99) | [86393-33-1] | \$487 |
| 1279000 | Fluorouracil ( 250 mg ) | $\mathrm{H}-1$ |  | H (01/02) | [51-21-8] | \$156 |
| 1279804 | Fluoxetine Hydrochloride ( 200 mg ) | F-1 |  | F (11/99) | [59333-67-4] | \$156 |
| 1279815 | Fluoxetine Related Compound A ( 15 mg ) (N-methyl-3-phenyl-3-[(al-pha,alpha,alpha-(trifluoro-m-tolyl)oxy]propylamine Hydrochloride) | H0C131 |  | $\begin{aligned} & \text { G (06/04) } \\ & \text { F-1 (05/01) } \\ & \text { F (06/00) } \end{aligned}$ | n/f | \$487 |
| 1279826 | Fluoxetine Related Compound B ( 5 mL of a 0.01 N HCl solution, approx. $2 \mathrm{mg} / \mathrm{mL}$ ) (N-methyl-3-phenylpropylamine) | F3C085 |  | F-2 (06/04) <br> F-1 (09/02) <br> F (09/00) | [23580-89-4] | \$156 |
| 1279837 | Fluoxetine Related Compound C (15 mg) (N-Methyl-N-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-succinamic acid) | F0C352 |  |  | n/f | \$487 |
| 1280009 | Fluoxymesterone CIII ( 200 mg ) | G-2 |  | G-1 (04/00) | [76-43-7] | \$207 |
| 1280803 | Fluphenazine Decanoate Dihydrochloride ( 500 mg ) | G |  | F-1 (10/01) | n/f | \$159 |
| 1281001 | Fluphenazine Enanthate Dihydrochloride ( 125 mg ) | H |  | G (02/99) | [3105-68-8] | \$124 |
| 1282004 | Fluphenazine Hydrochloride ( 125 mg ) | H |  |  | [146-56-5] | \$124 |
| 1284000 | Flurandrenolide ( 100 mg ) | IOB245 |  | H (09/03) | [1524-88-5] | \$156 |
| 1285002 | Flurazepam Hydrochloride CIV ( 200 mg ) |  |  | I (09/03) | [1172-18-5] | \$207 |
| 1285308 | Flurazepam Related Compound C ( 50 mg ) (5-chloro-2-(2-diethylami-noethyl(amino)-2'-fluorobenzophenone Hydrochloride) | H-1 |  |  | n/f | \$487 |
| 1285603 | Flurazepam Related Compound F (50 mg) (7-chloro-5-(2-fluorophenyl)- <br> 1,3-dihydro-2H-1,4-benzodiazepin-2-one) | 10 C 092 |  | H (01/04) | [2886-65-9] | \$487 |
| 1285750 | Flurbiprofen (200 mg) | G |  |  | [5104-49-4] | \$156 |
| 1285760 | Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid) | H |  | G (03/01) | n/f | \$487 |
| 1285807 | Flurbiprofen Sodium (200 mg) | F |  |  | [56767-76-1] | \$156 |
| 1285851 | Flutamide (200 mg) | G |  | F-1 (06/00) | [13311-84-7] | \$156 |
| 1285862 | o-Flutamide ( 50 mg ) | F-1 |  | F (01/00) | n/f | \$156 |
| 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) | P |  | O (07/00) | [59-30-3] | \$156 |
| 1286027 | Folic Acid Related Compound A ( 50 mg ) (Calcium Formyltetrahydrofolate) | 10B176 |  | $\begin{aligned} & \hline \mathrm{H}-1(04 / 04) \\ & \mathrm{H}(01 / 00) \\ & \hline \end{aligned}$ | [1492-18-8] | \$156 |
| 1286060 | Formononetin ( 50 mg ) | F0C196 |  |  | [485-72-3] | \$520 |
| 1286209 | 4-Formylbenzenesulfonamide ( 50 mg ) | F |  |  | n/f | \$487 |
| 1286300 | 10-Formylfolic Acid (25 mg) | F2B226 |  | F-1 (01/04) | [134-05-4] | \$156 |
| 1286366 | Fosphenytoin Sodium ( 250 mg ) | F0C156 |  |  | [92134-98-0] | \$156 |
| 1286504 | Fructose ( 125 mg ) | I-2 |  | $\begin{aligned} & \hline \text { I-1 (11/02) } \\ & \text { I (08/99) } \\ & \hline \end{aligned}$ | [57-48-7] | \$124 |
| 1286708 | Fumaric Acid (200 mg) | G-1 |  | G (04/02) | [110-17-8] | \$156 |
| 1286800 | Furazolidone (200 mg) | G-2 |  | G-1 (01/01) | [67-45-8] | \$156 |
| 1287008 | Furosemide ( 125 mg ) | J1B131 |  | J (10/03) | [54-31-9] | \$124 |
| 1287020 | Furosemide Related Compound A ( 50 mg ) (2-Chloro-4-N-furfurylami-no-5-sulfamoylbenzoic Acid) | J |  | I (08/02) | n/f | \$487 |
| 1287030 | Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid) | 10 C 248 |  | $\begin{aligned} & \hline \text { H (08/04) } \\ & \text { G-3 }(03 / 01) \end{aligned}$ | [3086-91-7] | \$487 |
| 1287303 | Gabapentin ( 250 mg ) | F |  |  | [60142-96-3] | \$156 |
| 1287325 | Gabapentin Related Compound A (100 mg) (3,3-pentamethylene-5butyrolactam) | F |  |  | [64744-50-9] | \$487 |

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| 1287507 | Gadodiamide ( 500 mg ) | F |  |  | [131410-48-5] | \$156 |
| 1287518 | Gadodiamide Related Compound A ( 50 mg ) (gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide) | F |  |  | n/f | \$487 |
| 1287529 | Gadodiamide Related Compound B (50 mg) (gadolinium disodium diethylenetriamine pentaacetic acid) | F |  |  | n/f | \$487 |
| 1287609 | Gadopentetate Monomeglumine ( 500 mg ) | F |  |  | [92923-57-4] | \$156 |
| 1287631 | Gadoteridol ( 500 mg ) | F |  |  | [120066-54-8] | \$156 |
| 1287642 | Gadoteridol Related Compound A (50 mg) (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid) | F0A002 |  |  | [120041-08-9] | \$487 |
| 1287653 | Gadoteridol Related Compound B (50 mg) (1,4,7,10-Tetraazacyclodo-decane-1,4,7-triacetic acid, monogadolinium salt) | F0B198 |  |  | [112188-16-6] | \$487 |
| 1287664 | Gadoteridol Related Compound C (50 mg) (1,4,7,10-Tetraaza-11-oxo-bicyclo[8.2.2]tetradecane-4,7-diacetic acid) | F0B199 |  |  | [220182-19-4] | \$487 |
| 1287675 | Gadoversetamide ( 200 mg ) | F0C172 |  |  | [131069-91-5] | \$156 |
| 1287686 | Gadoversetamide Related Compound A (200 mg) (Hydrogen[8,11,14-tris(carboxymethyl)-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(4-)]gadolinium) | F0C173 |  |  | n/f | \$487 |
| 1287700 | Galactose (200 mg) | F-4 |  | F-3 (05/01) | [59-23-4] | \$487 |
| 1288000 | Gallamine Triethiodide ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [65-29-2] | \$156 |
| 1288306 | Ganciclovir ( 200 mg ) | F0C287 |  |  | [82410-32-0] | \$364 |
| 1288317 | Ganciclovir Related Compound A (15 mg) ((RS)-2-Amino-9-(2,3-dihy-droxy-propoxymethyl)-1,9-dihydro-purin-6-one) | F0C288 |  |  | n/f | \$624 |
| 1288500 | Gemfibrozil ( 200 mg ) | H |  |  | [25812-30-0] | \$156 |
| 1288510 | Gemfibrozil Related Compound A (20 mg) (2,2-dimethyl-5-[2,5-di-methyl-4-propene-1-yl)phenoxy]valeric acid) | F0C101 |  |  | n/f | \$487 |
| 1289003 | Gentamicin Sulfate (200 mg) | K |  | J-1 (04/00) | [1405-41-0] | \$156 |
| 1290002 | Gentian Violet ( 650 mg ) | F |  |  | [548-62-9] | \$156 |
| 1291005 | Gibberellic Acid (200 mg) (FCC) | G |  | F (04/01) | [77-06-5] | \$156 |
| 1291504 | Powdered Ginger ( 500 mg ) | F |  |  | n/f | \$156 |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | F0B289 |  |  | [50647-08-0] | \$520 |
| 1292008 | Gitoxin ( 50 mg ) | G |  | F-3 (07/00) | [4562-36-1] | \$487 |
| 1292507 | Glipizide ( 125 mg ) | G1C174 |  | G (07/04) | [29094-61-9] | \$124 |
| 1292609 | Glipizide Related Compound A (25 mg) (N-\{2-[(4-aminosulfonyl)pheny-I]ethyl\|-5-methyl-pyrazinecarboxamide) | G-1 |  | G (04/99) | n/f | \$487 |
| 1294003 | Glucagon ( $25 \mathrm{mg}, 0.95 \mathrm{U} / \mathrm{mg}$ ) | H |  |  | [16941-32-5] | \$156 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 |  |  | [66-84-2] | \$156 |
| 1294976 | Glutamic Acid ( $200 \mathrm{mg} \mathrm{)}$ | F0C069 |  |  | [56-86-0] | \$156 |
| 1294808 | Glutamine ( 100 mg ) | FOB244 |  |  | [56-85-9] | \$156 |
| 1294848 | gamma-Glutamyl-S-allyl-L-cysteine ( 25 mg ) | F |  |  | n/f | \$675 |
| 1295006 | Glutethimide CII ( 500 mg ) | F |  |  | [77-21-4] | \$207 |
| 1295505 | Glyburide ( $200 \mathrm{mg} \mathrm{)}$ | G |  | F-2 (11/02) | [10238-21-8] | \$156 |
| 1295607 | Glycerin (2 mL) | H0C073 |  | $\begin{aligned} & \text { G1A001 (04/04) } \\ & \text { G (12/02) } \\ & \text { F (04/99) } \\ & \hline \end{aligned}$ | [56-81-5] | \$156 |
| 1295709 | Glyceryl Behenate (200 mg) | F3B113 |  | F-2 (03/03) | [18641-57-1] | \$156 |
| 1295800 | Glycine (200 mg) | F-3 |  | F-2 (02/00) | [56-40-6] | \$156 |
| 1296009 | Glycopyrrolate ( 200 mg ) | H0B304 |  | G (05/04) | [596-51-0] | \$156 |
| 1295888 | Glycyrrhizic Acid ( 25 mg ) | F0C006 |  |  | [1405-86-3] | \$487 |
| 1297001 | Human Chorionic Gonadotropin (1 vial, 5,760 USP Units per package) | H |  | G (07/00) | [9002-61-3] | \$156 |
| 1298004 | Gramicidin (200 mg) | I |  | H-1 (07/02) | [1405-97-6] | \$156 |

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| 1299007 | Griseofulvin (200 mg) | 1 |  | H-1 (09/02) | [126-07-8] | \$156 |
| 1299200 | Griseofulvin Permeability Diameter (2 g) | J0C380 | 2 | $\begin{aligned} & \text { 10C138 (10/04) } \\ & \text { H (08/03) } \end{aligned}$ | [126-07-8] | \$156 |
| 1300004 | Guaiacol ( 1 g ) | K |  | $J$ (04/00) | [90-05-1] | \$156 |
| 1301007 | Guaifenesin (200 mg) | 1 |  | H (09/02) | [93-14-1] | \$156 |
| 1301404 | Guanabenz Acetate ( 200 mg ) | G |  | F-1 (06/00) | [23256-50-0] | \$156 |
| 1301608 | Guanadrel Sulfate (200 mg) | F-1 |  |  | [22195-34-2] | \$156 |
| 1301801 | Guanethidine Monosulfate ( 200 mg ) | F |  |  | [645-43-2] | \$156 |
| 1302000 | Guanethidine Sulfate ( 500 mg ) | G-1 |  |  | [60-02-6] | \$156 |
| 1302101 | Guanfacine Hydrochloride (125 mg) | G0B123 |  |  | [29110-48-3] | \$124 |
| 1302305 | Halazepam CIV (200 mg) (AS) | F1C224 | 2,3 | F (12/04) | [23092-17-3] | \$207 |
| 1302509 | Halcinonide ( 300 mg ) | F |  |  | [3093-35-4] | \$156 |
| 1303002 | Haloperidol ( 200 mg ) | 1 |  | H-1 (05/02) | [52-86-8] | \$156 |
| 1303013 | Haloperidol Related Compound A (15 mg) (4,4-Bis[(4-p-chlorophenyl)-4-hydroxy-piperidino]-butyrophenone) | K0C362 | 2,3 | J (12/04) | [67987-08-0] | \$487 |
| 1303308 | Haloprogin ( 200 mg ) | F |  |  | [777-11-7] | \$156 |
| 1303501 | Halothane ( 1 mL ) | F-1 |  |  | [151-67-7] | \$156 |
| 1304005 | Heparin Sodium ( $10 \times 1 \mathrm{~mL}$ ) | K-5 |  | $\begin{array}{ll} \hline \text { K-4 }(08 / 03) \\ \text { K-3 }(02 / 99) \\ \hline \end{array}$ | [9041-08-1] | \$156 |
| 1305008 | Hexachlorophene ( 500 mg ) | I |  | H-2 (01/01) | [70-30-4] | \$156 |
| 1307003 | Hexobarbital CIII ( 500 mg ) | F |  |  | [56-29-1] | \$207 |
| 1308006 | Hexylcaine Hydrochloride (1 g) | F-1 |  |  | [532-76-3] | \$156 |
| 1308200 | Hexylene Glycol (125 mg) | G |  | $\begin{aligned} & \hline \text { F-2 (04/02) } \\ & \text { F-1 (04/99) } \\ & \hline \end{aligned}$ | [107-41-5] | \$156 |
| 1308307 | Hexylresorcinol (200 mg) | F |  |  | [136-77-6] | \$156 |
| 1308505 | L-Histidine (200 mg) | G0A018 |  | $\begin{aligned} & \hline \text { F-2 (01/03) } \\ & \text { F-1 (04/00) } \\ & \hline \end{aligned}$ | [71-00-1] | \$156 |
| 1309009 | Histamine Dihydrochloride (250 mg) | M0C280 |  | L (07/04) | [56-92-8] | \$156 |
| 1310008 | Homatropine Hydrobromide ( $200 \mathrm{mg} \mathrm{)}$ | H-1 |  | H (08/02) | [51-56-9] | \$156 |
| 1311000 | Homatropine Methylbromide ( 250 mg ) | J |  | $\begin{aligned} & \mathrm{I}-1(06 / 01) \\ & \mathrm{H}-1(10 / 01) \\ & \hline \end{aligned}$ | [80-49-9] | \$156 |
| 1311408 | Homosalate ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | F0B102 |  |  | [118-56-9] | \$156 |
| 1312003 | Hyaluronidase ( 500 mg ) | H |  |  | [9001-54-1] | \$156 |
| 1313006 | Hydralazine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | K |  | J-1 (09/02) | [304-20-1] | \$156 |
| 1314009 | Hydrochlorothiazide ( 200 mg ) | 1 |  | H (05/02) | [58-93-5] | \$156 |
| 1315001 | Hydrocodone Bitartrate ClI (250 mg) | J0A026 |  | $\begin{array}{\|l} \hline \mathrm{I}-1(12 / 02) \\ \mathrm{I}(07 / 02) \\ \mathrm{H}-2(11 / 99) \\ \hline \end{array}$ | [34195-34-1] | \$207 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl) | F0C214 |  |  | [847-86-9] | \$513 |
| 1316004 | Hydrocortisone (200 mg) | M1C110 |  | $\begin{aligned} & \hline \text { M (10/04) } \\ & \text { L (09/00) } \end{aligned}$ | [50-23-7] | \$156 |
| 1317007 | Hydrocortisone Acetate (200 mg) | K |  | J (10/99) | [50-03-3] | \$156 |
| 1317302 | Hydrocortisone Butyrate (200 mg) | H |  |  | [13609-67-1] | \$156 |
| 1318000 | Hydrocortisone Cypionate ( 200 mg ) | F |  |  | [508-99-6] | \$156 |
| 1319002 | Hydrocortisone Hemisuccinate ( 200 mg ) | H |  | $\begin{aligned} & \text { G-3 }(03 / 02) \\ & \text { G-2 }(08 / 99) \\ & \hline \end{aligned}$ | [83784-20-7] | \$156 |
| 1320001 | Hydrocortisone Phosphate Triethylamine (200 mg) | F-1 |  |  | n/f | \$156 |
| 1321004 | Hydrocortisone Valerate (200 mg) | F-1 |  | F (07/02) | [57524-89-7] | \$156 |
| 1322007 | Hydroflumethiazide ( 200 mg ) | F-2 |  |  | [135-09-1] | \$156 |

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| 1323000 | Hydromorphone Hydrochloride CII (50 mg) | I |  | H-2 (03/01) | [71-68-1] | \$207 |
| 1324002 | Hydroquinone ( 500 mg ) | H0C249 |  | $\begin{aligned} & \text { G-1 (10/04) } \\ & \text { G }(11 / 01) \\ & \text { F-4 (02/99) } \\ & \hline \end{aligned}$ | [123-31-9] | \$156 |
| 1325005 | Hydroxyamphetamine Hydrobromide ( 200 mg ) | G |  | F (06/01) | [306-21-8] | \$156 |
| 1327000 | Hydroxychloroquine Sulfate ( 200 mg ) | J0B297 |  | I (05/04) | [747-36-4] | \$156 |
| 1329006 | Hydroxyprogesterone Caproate ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  | [630-56-8] | \$156 |
| 1329709 | Hydroxypropyl Betadex ( 200 mg ) | F0B295 |  |  | [128446-35-5] | \$156 |
| 1329800 | Hydroxypropyl Cellulose (200 mg) | F-1 |  |  | [9004-64-2] | \$156 |
| 1332000 | Hydroxyurea (200 mg) | H |  | G (01/00) | [127-07-1] | \$156 |
| 1333003 | Hydroxyzine Hydrochloride ( 500 mg ) | H |  |  | [2192-20-3] | \$156 |
| 1333058 | Hydroxyzine Related Compound A ( 25 mg ) (p-Chlorobenzhydrylpiperazine) | H |  |  | [303-26-4] | \$208 |
| 1334006 | Hydroxyzine Pamoate ( 500 mg ) | H0C016 |  | G-1 (07/03) | [10246-75-0] | \$156 |
| 1335009 | Hyoscyamine Sulfate ( 125 mg ) |  |  | $\begin{aligned} & \text { G2A007 (09/04) } \\ & \text { G-1 (08/02) } \\ & \text { G (10/99) } \end{aligned}$ | [6835-16-1] | \$124 |
| 1335202 | Hyperoside ( 50 mg ) | F |  |  | [482-36-0] | \$855 |
| 1330005 | Hypromellose (250 mg) (Hydroxypropyl Methylcellulose) | H0C387 | 2,8 | $\begin{aligned} & \text { G-1 (11/04) } \\ & \text { G (02/02) } \\ & \hline \end{aligned}$ | [9004-65-3] | \$156 |
| 1335304 | Hypromellose Phthalate (100 mg) | F-1 |  | F (12/00) | [9050-31-1] | \$156 |
| 1335508 | Ibuprofen ( 750 mg ) | $J$ |  | I (06/02) | [15687-27-1] | \$156 |
| 1335701 | Idarubicin Hydrochloride ( 50 mg ) | H0C061 |  | $\begin{aligned} & G(11 / 03) \\ & F(06 / 00) \\ & \hline \end{aligned}$ | [57852-57-0] | \$479 |
| 1336001 | Idoxuridine ( 250 mg ) | H1B230 |  | H (07/04) | [54-42-2] | \$156 |
| 1336205 | Ifosfamide ( 500 mg ) | G |  | $\begin{aligned} & \text { F-1 (11/00) } \\ & \text { F (02/99) } \\ & \hline \end{aligned}$ | [3778-73-2] | \$156 |
| 1336500 | Imidazole (200 mg) | G1B132 |  | G (01/04) | [288-32-4] | \$487 |
| 1336806 | Imidurea (200 mg) | H |  | G (10/99) | [39236-46-9] | \$156 |
| 1337004 | Iminodibenzyl (25 mg) | 10C253 |  | H (11/04) | [494-19-9] | \$487 |
| 1337809 | Imipenem Monohydrate ( 100 mg ) | G |  | F (01/01) | [74431-23-5] | \$156 |
| 1338007 | Imipramine Hydrochloride ( 200 mg ) | I |  | H (09/01) | [113-52-0] | \$156 |
| 1338801 | Indapamide ( 250 mg ) | H |  | $\mathrm{G}(07 / 02)$ | [26807-65-8] | \$156 |
| 1339000 | Indigotindisulfonate Sodium ( 500 mg ) | H1B153 |  | H (06/03) | [860-22-0] | \$156 |
| 1340009 | Indocyanine Green (200 mg) | IOB045 |  | H (09/01) | [3599-32-4] | \$156 |
| 1341001 | Indomethacin (200 mg) | JOB165 |  | $\begin{aligned} & \text { I (01/04) } \\ & \text { H (05/99) } \end{aligned}$ | [53-86-1] | \$156 |
| 1342004 | Insulin (100 mg) | H |  |  | [9004-10-8] | \$156 |
| 1342106 | Insulin Human (100 mg) | H1A031 |  | $\begin{aligned} & \mathrm{H}(11 / 02) \\ & \mathrm{G}(04 / 00) \\ & \hline \end{aligned}$ | [11061-68-0] | \$156 |
| 1342208 | Insulin (Beef) (100 mg) | F |  |  | [11070-73-8] | \$156 |
| 1342300 | Insulin (Pork) (100 mg) | F |  |  | [12584-58-6] | \$156 |
| 1342503 | locetamic Acid (200 mg) | F |  |  | [16034-77-8] | \$156 |
| 1343007 | lodipamide ( 200 mg ) |  |  | G (12/04) | [606-17-7] | \$156 |
| 1343517 | lodixanol (200 mg) | F0B240 |  |  | [92339-11-2] | \$156 |
| 1343540 | lodixanol Related Compound C (25 mg) (5-Acetyl[ 3 -[[3,5-bis[[2,3-dihydroxypropyl)amino]carbonyl]-2,4,6-triiodophenyl]amino]-2-hydroxy-propyl]amino]-N,N'-bis-(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B236 |  |  | n/f | \$487 |

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| 1343550 | lodixanol Related Compound D (50 mg) (5-[Acetyl(2-hydroxy-3-methyl-propyl)amino]-N,N'-bis(2,3-dihydroxypropyl)2,4,6-triodo-1,3-benzenedicarboxamide) | F0B231 |  |  | [89797-00-2] | \$487 |
| 1343561 | lodixanol Related Compound E (25 mg) (5-[[3-[[3-[[(2,3-Dihydoxypro-pyl)amino]carbonyl]-5-[[amino]carbonyl]-2,4,6-triiodophenyl](acetylimi-no)]-2-hydroxypropyl]-(acetylimino)]-N,N'-bis(2,3-dihydoxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B229 |  |  | n/f | \$487 |
| 1344305 | o-lodohippuric Acid (100 mg) | F |  |  | [147-58-0] | \$156 |
| 1344509 | lodoquinol ( 100 mg ) | H |  | G (07/02) | [83-73-8] | \$156 |
| 1344600 | lohexol ( 100 mg ) | F-1 |  | F (01/99) | [66108-95-0] | \$124 |
| 1344622 | Iohexol Related Compound A (100 mg) (5-(acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F-1 |  | F (10/01) | n/f | \$487 |
| 1344644 | Iohexol Related Compound B ( 50 mg ) ( 5 -amino-N,N'-bis(2,3-dihydrox-ypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F-1 |  | F (01/04) | [76801-93-9] | \$487 |
| 1344666 | lohexol Related Compound C (100 mg) (N,N'-bis(2,3-dihydroxypropyl)-5-nitro-1,3-benzenedicarboxamide) | F-1 |  | F (09/03) | n/f | \$156 |
| 1344702 | lopamidol (200 mg) | G |  |  | [60166-93-0] | \$156 |
| 1344724 | lopamidol Related Compound A (50 mg) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoiso-phthalamide) | G |  |  | [60166-98-5] | \$487 |
| 1344735 | lopamidol Related Compound B (100 mg) (5-Glycolamido-N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodoisophthalamide) | F |  |  | n/f | \$487 |
| 1344804 | lopromide ( 400 mg ) | F |  |  | [73334-07-3] | \$156 |
| 1344826 | lopromide Related Compound A ( 50 mg ) ( 5 -Amino-N,N'-bis(2,3-dihy-droxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide) | F |  |  | n/f | \$487 |
| 1344837 | lopromide Related Compound B ( 50 mg ) (5-(Acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide) | F |  |  | n/f | \$487 |
| 1345002 | lothalamic Acid (200 mg) | G |  |  | [2276-90-6] | \$156 |
| 1345104 | loversol ( 200 mg ) | F |  |  | [87771-40-2] | \$156 |
| 1345115 | Ioversol Related Compound A ( 50 mg ) (5-Amino-N,N'-bis(2,3-dihydrox-ypropyl)-2,4,6-triiodoisophthalamide) | F |  |  | [76801-93-9] | \$487 |
| 1345126 | loversol Related Compound B ( 50 mg ) (N,N'-bis(2,3-dihydroxypropyl)-5-[(N-(2-hydroxyethyl)-carbonyl)methoxy]-2,4,6-triiodoisophthalamide) | F |  |  | n/f | \$487 |
| 1345159 | Ioxaglic Acid (100 mg) | F |  |  | [59017-64-0] | \$156 |
| 1345206 | Ioxilan (400 mg) | F |  |  | [107793-72-6] | \$156 |
| 1345228 | Ioxilan Related Compound A (100 mg) (5-amino-2,4,6-triiodo-3 N-(2hydroxyethyl)carbamoyl benzoic acid) | F |  |  | [22871-58-5] | \$487 |
| 1346005 | Ipodate Calcium (200 mg) | F |  |  | [1151-11-7] | \$156 |
| 1347008 | Ipodate Sodium (200 mg) | F-1 |  |  | [1221-56-3] | \$156 |
| 1347755 | Isoamyl Methoxycinnamate ( $750 \mathrm{mg} / \mathrm{ampule}$ ) | F0B017 |  |  | [71617-10-2] | \$156 |
| 1348000 | Isocarboxazid ( 200 mg ) | F-1 |  |  | [59-63-2] | \$156 |
| 1348500 | Isoetharine Hydrochloride ( 250 mg ) | F-2 |  |  | [2576-92-3] | \$156 |
| 1348907 | Isoflupredone Acetate (200 mg) | F0C109 |  |  | [338-98-7] | \$156 |
| 1349003 | Isoflurane ( 1 mL ) | H1C199 | 2 | H (12/04) | [26675-46-7] | \$156 |
| 1349014 | Isoflurane Related Compound A ( 0.1 mL ) (1-Chloro-2,2,2-trifluoroethyl chlorodifluoromethyl ether) | F0C232 | 1 |  | n/f | \$487 |
| 1349025 | Isoflurane Related Compound B ( 0.1 mL ) (2,2,2-Trifluoroethyldifluoromethyl ether) | F0C233 | 1 |  | n/f | \$487 |
| 1349502 | L-Isoleucine ( 200 mg ) | F-2 |  | F-1 (09/02) | [73-32-5] | \$156 |
| 1349604 | Isomalathion ( 50 mg ) | F1B107 |  | F (01/03) | [3344-12-5] | \$487 |
| 1349659 | Isometheptene Mucate (200 mg) | F |  |  | [7492-31-1] | \$156 |
| 1349706 | Isoniazid (200 mg) | H |  |  | [54-85-3] | \$156 |
| 1350002 | Isopropamide lodide (200 mg) | F-2 |  |  | [71-81-8] | \$156 |

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| 1350400 | Isopropyl Myristate ( 500 mg ) | 1 |  |  | [110-27-0] | \$156 |
| 1350603 | Isopropyl Palmitate ( 500 mg ) | I |  | H (10/99) | [142-91-6] | \$156 |
| 1351005 | Isoproterenol Hydrochloride ( 125 mg ) | K |  |  | [51-30-9] | \$124 |
| 1352008 | Isosorbide (75\% solution, 1 g ) | 1 |  | H-2 (10/00) | [652-67-5] | \$156 |
| 1353000 | Diluted Isosorbide Dinitrate ( 500 mg of $25 \%$ mixture with mannitol) | I-1 |  | I (10/99) | [87-33-2] | \$156 |
| 1353500 | Isotretinoin ( 200 mg ) | 1 |  | H (10/00) | [4759-48-2] | \$156 |
| 1354003 | Isoxsuprine Hydrochloride (200 mg) | F-3 |  |  | [579-56-6] | \$156 |
| 1354207 | Isradipine (200 mg) | G0B054 |  | F (05/03) | [75695-93-1] | \$156 |
| 1354218 | Isradipine Related Compound A ( 25 mg ) (Isopropyl methyl 4-(4-benzofurazanyl)-2,6-dimethyl-3,5-pyridinedicarboxylate) | F |  |  | n/f | \$487 |
| 1354309 | Ivermectin (200 mg) | F0B196 |  |  | [70288-86-7] | \$156 |
| 1355006 | Kanamycin Sulfate (200 mg) | J |  | I (06/99) | [25389-94-0] | \$156 |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 |  |  | n/f | \$260 |
| 1355753 | Kawain (200 mg) | F0C160 |  |  | [500-64-1] | \$208 |
| 1356009 | Ketamine Hydrochloride CIII (250 mg) | G-2 |  | G-1 (07/00) | [1867-66-9] | \$207 |
| 1356020 | Ketamine Related Compound A (50 mg) (1-[(2-Chlorophenyl)(methylimino)methyl]cylcopentanol) | F0C118 |  |  | [6740-87-0] | \$487 |
| 1356508 | Ketoconazole ( 200 mg ) | G4B179 |  | $\begin{array}{\|l\|} \text { G-3 }(01 / 04) \\ \text { G-2 (06/01) } \\ \text { G-1 } \\ \hline \end{array}(1 / 99)$ | [65277-42-1] | \$156 |
| 1356632 | Ketoprofen (200 mg) | H0B216 |  | $\begin{aligned} & \text { G (07/04) } \\ & \text { F-2 (05/99) } \\ & \hline \end{aligned}$ | [22071-15-4] | \$156 |
| 1356643 | Ketoprofen Related Compound A ( 25 mg ) (alpha-Methyl-3-(4-methylbenzoyl) benzeneacetic acid) | G |  |  | [107257-20-5] | \$487 |
| 1356665 | Ketorolac Tromethamine (200 mg) | G |  | F-2 (04/99) | [74103-07-4] | \$156 |
| 1356654 | Labetalol Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G |  | $\begin{array}{\|l\|l} \hline \text { F-2 (01/02) } \\ \text { F-1 }(03 / 01) \\ \hline \end{array}$ | [32780-64-6] | \$156 |
| 1356676 | Anhydrous Lactose (100 mg) | G |  | F (06/01) | [63-42-3] | \$156 |
| 1356687 | Lactitol ( 500 mg ) | F0B005 |  |  | [81025-04-9] | \$156 |
| 1356701 | Lactose Monohydrate ( 500 mg ) | G-1 |  | G (08/02) | [5989-81-1] | \$156 |
| 1356803 | Lactulose (1 g) | H |  | G-1 (08/00) | [4618-18-2] | \$156 |
| 1356836 | Lamivudine (200 mg) | F0C361 |  |  | [134678-17-4] | \$156 |
| 1356880 | Lanolin (20 g) | F |  |  | [8006-54-0] | \$156 |
| 1356905 | Lanolin Alcohols (5 g) | F |  |  | [8027-33-6] | \$156 |
| 1356916 | Lansoprazole (200 mg) | FOB310 |  |  | [103577-45-3] | \$156 |
| 1356927 | Lansoprazole Related Compound A (25 mg) (2-[[[3-methyl-4-(2,2,2-triflouroethoxy)-2-pyridyl]methyl]sulfonyl]benzimidazole) | F0B311 |  |  | n/f | \$487 |
| 1356971 | Letrozole ( 200 mg ) | F0B170 |  |  | [112809-51-5] | \$156 |
| 1356982 | Letrozole Related Compound A ( 15 mg ) ( $4,4^{\prime}$-(1H-1,3,4-triazol-1ylmethylene)dibenzonitrile) | F0B168 |  |  | n/f | \$487 |
| 1357001 | L-Leucine (200 mg) | H0B237 |  | $\begin{aligned} & \text { G-1 (04/04) } \\ & \text { G (08/00) } \\ & \hline \end{aligned}$ | [61-90-5] | \$156 |
| 1358004 | Leucovorin Calcium (500 mg) | J2B219 |  | $\begin{array}{\|l\|l\|} \hline \mathrm{J}-1(07 / 04) \\ \mathrm{J}(05 / 02) \\ \hline \end{array}$ | [1492-18-8] | \$160 |
| 1359007 | Levallorphan Tartrate (200 mg) DISCONTINUED |  |  | $\begin{aligned} & \text { G-1 (09/04) } \\ & \text { G (11/02) } \\ & \hline \end{aligned}$ | [71-82-9] | \$156 |
| 1359302 | Levamisole Hydrochloride (125 mg) | F2C122 |  | F-1 (05/04) | [16595-80-5] | \$124 |
| 1359506 | Levmetamfetamine CII ( 75 mg ) | F |  |  | [33817-09-3] | \$207 |
| 1359801 | Levobunolol Hydrochloride (200 mg) | G |  |  | [27912-14-7] | \$156 |
| 1359903 | Levocarnitine ( 400 mg ) | G0B197 |  | $\begin{aligned} & \text { F-2 (06/03) } \\ & \text { F-1 (12/00) } \\ & \hline \end{aligned}$ | [541-15-1] | \$156 |

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| 1359925 | Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride) | F-1 |  | F (08/01) | [6538-82-5] | \$208 |
| 1361009 | Levodopa ( 200 mg ) | 1 |  | H (09/00) | [59-92-7] | \$156 |
| 1361010 | Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydroxyphenyl)alanine) | K |  | $\begin{array}{\|l\|l\|} \hline J(01 / 03) \\ I(06 / 00) \\ \hline \end{array}$ | [27244-64-0] | \$487 |
| 1420006 | Levodopa Related Compound B (50 mg) (3-Methoxytyrosine) | 10 C 300 |  | H (07/04) |  | \$487 |
| 1362001 | Levo-alpha-acetylmethadol Hydrochloride CII ( 25 mg ) (AS) DISCONTINUED |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (08/03) } \\ \hline \text { F (07/01) } \\ \hline \end{array}$ | [43033-72-3] | \$207 |
| 1362500 | Levonordefrin ( 200 mg ) | F-1 |  |  | [829-74-3] | \$156 |
| 1363004 | Levopropoxyphene Napsylate ( 300 mg ) | G |  |  | [55557-30-7] | \$156 |
| 1364007 | Levorphanol Tartrate CII (500 mg) | H |  | G (03/01) | [5985-38-6] | \$207 |
| 1365000 | Levothyroxine ( 500 mg ) | K |  | $J(10 / 00)$ | [51-48-9] | \$156 |
| 1366002 | Lidocaine ( 250 mg ) | L |  |  | [137-58-6] | \$156 |
| 1367005 | Lincomycin Hydrochloride ( 200 mg ) | H2B130 |  | H-1 (01/04) | [7179-49-9] | \$156 |
| 1367504 | Lindane ( 200 mg ) | F-2 |  |  | [58-89-9] | \$156 |
| 1368008 | Liothyronine (250 mg) | L1C262 |  | $\begin{aligned} & \text { L (08/04) } \\ & \text { K (08/01) } \end{aligned}$ | [6893-02-3] | \$156 |
| 1368609 | Lisinopril (300 mg) | I |  | $\begin{array}{\|l\|} \hline H(09 / 01) \\ G(10 / 99) \\ \hline \end{array}$ | [83915-83-7] | \$156 |
| 1369000 | Lithium Carbonate (300 mg) | G0B031 |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 (01/03) } \\ \text { F-1 } & (01 / 01) \end{array}$ | [554-13-2] | \$156 |
| 1370000 | Loperamide Hydrochloride (200 mg) | H0C2O2 |  | $\begin{aligned} & \text { G-2 (09/04) } \\ & \text { G-1 }(02 / 03) \\ & \hline \end{aligned}$ | [34552-83-5] | \$156 |
| 1370203 | Loracarbef ( 200 mg ) | F |  |  | [121961-22-6] | \$156 |
| 1370225 | Loracarbef L-Isomer ( 25 mg ) | F |  |  | n/f | \$156 |
| 1370270 | Loratadine (200 mg) | F0C414 | 1 |  | [79794-75-5] | \$260 |
| 1370305 | Lorazepam CIV (200 mg) | 10 C 048 |  | H0B023 (06/04) | [846-49-1] | \$207 |
| 1370327 | Lorazepam Related Compound A ( 25 mg ) (7-Chloro-5-(o-chlorophe-nyl)-1,3-dihydro-3-acetoxy-2H-1,4-benzodiazepin-2-one) | G |  | F-1 (06/01) | [2848-96-6] | \$487 |
| 1370338 | Lorazepam Related Compound B ( 25 mg ) (2-Amino-2',5-dichlorobenzophenone) | G |  | F-2 (01/04) | [2958-36-3] | \$487 |
| 1370349 | Lorazepam Related Compound C ( 25 mg ) (6-Chloro-4-(o-chlorophe-nyl)-2-quinazolinecarboxaldehyde) | H |  | $\begin{aligned} & \hline \mathrm{G}(01 / 03) \\ & \mathrm{F}-3(01 / 02) \end{aligned}$ | n/f | \$487 |
| 1370350 | Lorazepam Related Compound D ( 25 mg ) (6-Chloro-4-(o-chlorophe-nyl)-2-quinazolinecarboxylic Acid) | G0A014 |  | F-2 (01/04) | [54643-79-7] | \$487 |
| 1370360 | Lorazepam Related Compound E ( 25 mg ) (6-Chloro-4-(o-chlorophe-nyl)-2-quinazoline Methanol) | G |  | $\begin{aligned} & \hline \text { F-3 (07/02) } \\ & \text { F-2 (04/99) } \\ & \hline \end{aligned}$ | n/f | \$487 |
| 1370600 | Lovastatin (125 mg) | H2C012 |  | $\begin{array}{\|l} \hline \text { H1B067 (01/04) } \\ \text { H (08/03) } \\ \hline \end{array}$ | [75330-75-5] | \$124 |
| 1370611 | Lovastatin Related Compound A (20 mg) (Butanoic acid, 2-methyl-,1,2,3,4,4a,7,8,8a-octahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[alpha(R*), 3alpha,7beta,8beta( $\left.2 \mathrm{~S}^{*}, 4 \mathrm{~S}^{*}\right)$, 8alpha beta]]-) | G0C326 |  | F0B235 (09/04) | n/f | \$487 |
| 1370702 | Loxapine Succinate ( 125 mg ) | G0B026 |  | $\begin{aligned} & \text { F-2 (06/03) } \\ & \text { F-1 (07/01) } \\ & \hline \text { F (03/99) } \\ & \hline \end{aligned}$ | [27833-64-3] | \$124 |
| 1370906 | Lynestrenol (20 mg) | F0B314 |  |  | [52-76-6] | \$203 |
| 1371002 | Lysergic Acid Diethylamide Tartrate CI (10 mg) (AS) (LSD) | 1 |  |  | [50-37-3] | \$207 |
| 1371501 | L-Lysine Acetate ( 200 mg ) | F1C027 | 2 | F (11/04) | [57282-49-2] | \$156 |
| 1372005 | L-Lysine Hydrochloride ( 200 mg ) | H |  | G (07/00) | [657-27-2] | \$156 |
| 1373008 | Mafenide Acetate (200 mg) | F |  |  | [13009-99-9] | \$156 |

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| 1374000 | Magaldrate ( 200 mg ) | F-1 |  |  | [74978-16-8] | \$156 |
| 1374306 | Magnesium Salicylate (200 mg) | F2B081 |  | F-1 (01/04) | [18917-95-8] | \$156 |
| 1374408 | Malathion ( 500 mg ) | F-1 |  | F (08/01) | [121-75-5] | \$156 |
| 1374500 | Maleic Acid ( 300 mg ) | G |  | F-2 (12/00) | [110-16-7] | \$487 |
| 1374601 | Malic Acid (200 mg) | G0B158 |  | F-1 (04/03) | [617-48-1] | \$156 |
| 1374907 | Maltitol (200 mg) | G |  | F-1 (12/99) | [585-88-6] | \$156 |
| 1375003 | Maltol (4 g) (FCC) | G |  | F-1 (12/99) | [118-71-8] | \$156 |
| 1375058 | Mandelic Acid ( 500 mg ) | F |  |  | [90-64-2] | \$156 |
| 1375105 | Mannitol ( 200 mg ) | IOB212 |  | H (03/04) | [69-65-8] | \$156 |
| 1375207 | Maprotiline Hydrochloride ( 200 mg ) | H |  | G (07/02) | [10347-81-6] | \$156 |
| 1375309 | Mazindol CIV ( 350 mg ) | H |  | G (02/03) | [22232-71-9] | \$207 |
| 1375502 | Mebendazole (200 mg) | G1C195 | 2 | G (11/04) | [31431-39-7] | \$156 |
| 1375706 | Mebrofenin ( 100 mg ) | F |  |  | [78266-06-5] | \$156 |
| 1376006 | Mecamylamine Hydrochloride ( 200 mg ) | F-2 |  |  | [826-39-1] | \$156 |
| 1376505 | Mechlorethamine Hydrochloride ( 100 mg ) | F-1 |  | F (09/00) | [55-86-7] | \$156 |
| 1377009 | Meclizine Hydrochloride ( 500 mg ) | $\mathrm{I}-1$ |  |  | [31884-77-2] | \$156 |
| 1377508 | Meclocycline Sulfosalicylate ( 300 mg ) | G |  |  | [73816-42-9] | \$156 |
| 1377803 | Meclofenamate Sodium ( 500 mg ) | H |  |  | [6385-02-0] | \$156 |
| 1378001 | Medroxyprogesterone Acetate ( 200 mg ) | H-2 |  | H-1 (04/03) | [71-58-9] | \$156 |
| 1379004 | Medrysone ( 500 mg ) | F |  |  | [2668-66-8] | \$156 |
| 1379605 | Mefenamic Acid (200 mg) | G0C025 |  | $\begin{array}{\|l\|l\|} \hline \text { F3A032 (08/04) } \\ \text { F-2 (01/03) } \\ \hline \end{array}$ | [61-68-7] | \$156 |
| 1379106 | Megestrol Acetate ( 500 mg ) | 1 |  | H (05/00) | [595-33-5] | \$156 |
| 1379300 | Melphalan Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | [3223-07-2] | \$156 |
| 1381006 | Menadione (200 mg) (Vitamin K3) | H-3 |  | H-2 (02/00) | [58-27-5] | \$156 |
| 1381709 | Menthol ( 250 mg ) | IOB049 |  | H (04/03) | [2216-51-5] | \$156 |
| 1381742 | Menthyl Anthranilate ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | F0B103 |  |  | [134-09-8] | \$156 |
| 1382009 | Mepenzolate Bromide (200 mg) | F |  |  | [76-90-4] | \$156 |
| 1383001 | Meperidine Hydrochloride CII (200 mg) | I |  | H-1 (12/99) | [50-13-5] | \$207 |
| 1384004 | Mephentermine Sulfate ( 250 mg ) | F-1 |  |  | [1212-72-2] | \$156 |
| 1385007 | Mephenytoin (250 mg) | G |  |  | [50-12-4] | \$156 |
| 1386000 | Mephobarbital CIV (250 mg) | G |  | F (01/01) | [115-38-8] | \$207 |
| 1387002 | Mepivacaine Hydrochloride ( 200 mg ) | H |  | G-4 (02/99) | [1722-62-9] | \$156 |
| 1388005 | Meprednisone ( 200 mg ) | G |  |  | [1247-42-3] | \$156 |
| 1389008 | Meprobamate CIV (200 mg) | G-1 |  | G (03/02) | [57-53-4] | \$207 |
| 1390007 | Meprylcaine Hydrochloride (200 mg) | F |  |  | [956-03-6] | \$156 |
| 1391000 | 3-Mercapto-2-methylpropanoic Acid 1,2-Diphenylethylamine Salt ( 75 mg ) | G |  |  | n/f | \$487 |
| 1392002 | Mercaptopurine ( 500 mg ) | 12C263 |  | $\begin{array}{\|l\|l\|} \hline \text { I-1 (10/04) } \\ \text { I (07/02) } \\ H(12 / 99) \\ \hline \end{array}$ | [6112-76-1] | \$156 |
| 1392454 | Meropenem ( 300 mg ) | F0C201 |  |  | [119478-56-7] | \$182 |
| 1392705 | Mesalamine (200 mg) | G1B001 |  | $\begin{array}{\|l} \hline \text { G (01/03) } \\ \mathrm{F}-1(03 / 00) \\ \hline \end{array}$ | [89-57-6] | \$156 |
| 1393005 | Mesoridazine Besylate ( 250 mg ) | J0C117 | 2 | I-1 (12/04) | [32672-69-8] | \$156 |
| 1394008 | Mestranol ( 200 mg ) | K0C065 |  | $\begin{array}{\|l\|} \hline J \text { (07/04) } \\ \text { I-1 (09/99) } \\ \hline \end{array}$ | [72-33-3] | \$156 |
| 1395500 | Metaproterenol Sulfate ( 200 mg ) | F-3 |  |  | [5874-97-5] | \$156 |
| 1396003 | Metaraminol Bitartrate (200 mg) | F-3 |  |  | [33402-03-8] | \$156 |

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| 1396309 | Metformin Hydrochloride (200 mg) | F0C209 |  |  | [1115-70-4] | \$182 |
| 1396310 | Metformin Related Compound A (50 mg) (1-Cyanoguanidine) | F0C210 |  |  | [461-58-5] | \$487 |
| 1396400 | Methacrylic Acid Copolymer Type A (200 mg) | G0B140 |  | F-2 (04/03) | n/f | \$156 |
| 1396502 | Methacrylic Acid Copolymer Type B (200 mg) | G0B141 |  | F-2 (04/03) | n/f | \$156 |
| 1396604 | Methacrylic Acid Copolymer Type C (100 mg) | G1B088 |  | G (08/03) | n/f | \$124 |
| 1397006 | Methacycline Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G (04/01) | [3963-95-9] | \$156 |
| 1398009 | Methadone Hydrochloride CII (200 mg) | IOB163 |  | H-1 (08/03) | [1095-90-5] | \$207 |
| 1399001 | Methamphetamine Hydrochloride CII (125 mg) | 1 |  |  | [51-57-0] | \$207 |
| 1401001 | Methantheline Bromide ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [53-46-3] | \$156 |
| 1402004 | Methapyrilene Fumarate (200 mg) | F-1 |  |  | [33032-12-1] | \$156 |
| 1404000 | Methaqualone Cl ( 500 mg ) | F-1 |  |  | [72-44-6] | \$207 |
| 1405002 | Metharbital CIII (200 mg) | F-2 |  | F-1 (07/99) | [50-11-3] | \$207 |
| 1406005 | Methazolamide ( 500 mg ) | H0B239 |  | G-1 (05/04) | [554-57-4] | \$156 |
| 1407008 | Methdilazine (200 mg) | F-1 |  |  | [1982-37-2] | \$156 |
| 1408000 | Methdilazine Hydrochloride ( 200 mg ) | G |  |  | [1229-35-2] | \$156 |
| 1409003 | Methenamine ( 500 mg ) | H0C047 |  | G (05/04) | [100-97-0] | \$156 |
| 1409502 | Methenamine Hippurate (200 mg) | F |  |  | [5714-73-8] | \$156 |
| 1409604 | Methenamine Mandelate ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  | F-1 (11/00) | [587-23-5] | \$156 |
| 1410002 | Methicillin Sodium ( 500 mg ) |  |  | $\begin{array}{\|l\|l\|} \hline \text { I1B186 (11/04) } \\ \text { I (03/03) } \\ H \text { ( } 03 / 00) \\ \hline \end{array}$ | [7246-14-2] | \$156 |
| 1411005 | Methimazole (200 mg) | G |  | F (02/01) | [60-56-0] | \$156 |
| 1411504 | L-Methionine ( 200 mg ) | G |  | F-2 (11/99) | [63-68-3] | \$156 |
| 1412008 | Methocarbamol (200 mg) | H2B029 |  | H-1 (03/04) | [532-03-6] | \$156 |
| 1413000 | Methohexital CIV ( 500 mg ) | F-2 |  |  | [18652-93-2] | \$207 |
| 1414003 | Methotrexate ( 500 mg ) | 1 |  |  | [59-05-2] | \$156 |
| 1415006 | Methotrimeprazine ( 125 mg ) | F-2 |  | F-1 (05/99) | [60-99-1] | \$124 |
| 1416009 | Methoxamine Hydrochloride ( 200 mg ) | F |  |  | [61-16-5] | \$156 |
| 1417001 | Methoxsalen ( 500 mg ) | H |  |  | [298-81-7] | \$156 |
| 1418004 | Methoxyflurane ( 1 mL ) | G |  |  | [76-38-0] | \$156 |
| 1419007 | Methoxyphenamine Hydrochloride ( 250 mg ) | F |  |  | [5588-10-3] | \$156 |
| 1421009 | Methscopolamine Bromide ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | [155-41-9] | \$156 |
| 1422001 | Methsuximide ( 500 mg ) | F-2 |  | F-1 (08/99) | [77-41-8] | \$156 |
| 1424007 | Methyclothiazide ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | [135-07-9] | \$156 |
| 1424018 | Methyclothiazide Related Compound A (100 mg) (4-amino-6-chloro-N-3-methyl-m-benzenedisulfonamide) | G |  | F-2 (12/00) | n/f | \$487 |
| 1424222 | Methyl Benzylidene Camphor (200 mg) | FOB118 |  |  | [36861-47-9] | \$156 |
| 1424233 | Methyl Caprate ( 300 mg ) | F |  |  | [110-42-9] | \$156 |
| 1424244 | Methyl Caproate ( 300 mg ) | F |  |  | [106-70-7] | \$156 |
| 1424255 | Methyl Caprylate ( 300 mg ) | F |  |  | [111-11-5] | \$156 |
| 1424506 | Methylcellulose (1 g) (AS) | G0B222 |  | F-2 (05/03) | [9004-67-5] | \$156 |
| 1425000 | 4-Methyl-2,5-dimethoxyamphetamine Hydrochloride CI (25 mg) (AS) (STP) | F |  |  | [15589-00-1] | \$207 |
| 1426002 | Methyldopa ( 500 mg ) | 1 |  |  | [41372-08-1] | \$156 |
| 1427005 | Methyldopate Hydrochloride ( 200 mg ) | G-2 |  |  | [2508-79-4] | \$156 |
| 1428008 | Methylene Blue ( 250 mg ) | G |  |  | [7220-79-3] | \$156 |
| 1429000 | Methylenedioxy-3,4-amphetamine Hydrochloride $\mathbf{C l}(25 \mathrm{mg})$ (AS) (MDA) | F-1 |  |  | [6292-91-7] | \$207 |
| 1430000 | Methylergonovine Maleate ( 50 mg ) (List Chemical) | J |  | I (05/02) | [57432-61-8] | \$156 |
| 1430305 | Methyl Laurate ( 500 mg ) | F |  |  | [111-82-0] | \$156 |

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| 1430327 | Methyl Linoleate ( $5 \times 50 \mathrm{mg}$ ) | F |  |  | [112-63-0] | \$156 |
| 1430349 | Methyl Linolenate ( $5 \times 50 \mathrm{mg}$ ) | F |  |  | [301-00-8] | \$156 |
| 1430509 | $3-\mathrm{O}-\mathrm{Methylmethyldopa} \mathrm{( } 50 \mathrm{mg}$ ) | G-1 |  |  | n/f | \$487 |
| 1431002 | Methyl 5-methyl-3-isoxazolecarboxylate ( 25 mg ) | F-1 |  | F (01/01) | n/f | \$487 |
| 1431501 | Methyl Myristate ( 300 mg ) | F |  |  | [124-10-7] | \$156 |
| 1431556 | Methyl Oleate ( 500 mg ) | G0C148 |  | F (04/04) | [112-62-9] | \$156 |
| 1431603 | Methyl Palmitate ( 300 mg ) | F |  |  | [112-39-0] | \$156 |
| 1431625 | Methyl Palmitoleate ( 300 mg ) | F |  |  | n/f | \$156 |
| 1432005 | Methylparaben ( 125 mg ) | J-1 |  | J (03/03)) | [99-76-3] | \$124 |
| 1433008 | Methylphenidate Hydrochloride CII (125 mg) | I |  | H (05/01) | [298-59-9] | \$165 |
| 1434000 | Methylphenidate Hydrochloride Erythro Isomer CII ( 25 mg ) | J0B294 |  | $\begin{aligned} & \text { IOAOO6 (09/03) } \\ & \text { H-1 (01/03) } \\ & \text { H (06/01) } \\ & \hline \end{aligned}$ | [298-59-9] | \$560 |
| 1434022 | Methylphenidate Related Compound A (50 mg) (alpha-Phenyl-2piperidineacetic Acid Hydrochloride) | G |  | F-2 (10/99) | n/f | \$487 |
| 1435003 | Methylprednisolone ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  | [83-43-2] | \$156 |
| 1436006 | Methylprednisolone Acetate ( 200 mg ) | G-2 |  | G-1 (02/00) | [53-36-1] | \$156 |
| 1437009 | Methylprednisolone Hemisuccinate ( 200 mg ) | IOC146 |  | H (07/04) | [2921-57-5] | \$156 |
| 1437508 | Methyl Stearate ( 300 mg ) | F |  |  | [112-61-8] | \$156 |
| 1438001 | Methyltestosterone CIII ( $200 \mathrm{mg} \mathrm{)}$ | $J$ |  | I (11/01) | [58-18-4] | \$207 |
| 1440003 | Methysergide Maleate ( 200 mg ) | H |  |  | [129-49-7] | \$156 |
| 1440808 | Metoclopramide Hydrochloride ( 500 mg ) | G |  | F-2 (06/99) | [54143-57-6] | \$156 |
| 1441006 | Metocurine lodide ( $300 \mathrm{mg} \mathrm{)}$ | G |  |  | [7601-55-0] | \$156 |
| 1441200 | Metolazone ( 200 mg ) | G0B246 |  | F-1 (05/03) | [17560-51-9] | \$156 |
| 1441287 | Metoprolol Fumarate (200 mg) | F |  |  | [119637-66-0] | \$156 |
| 1441232 | Metoprolol Related Compound A (20 mg) ((+/-)1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol) | F0C343 |  |  | n/f | \$520 |
| 1441243 | Metoprolol Related Compound B (50 mg) ((+/-)1-chloro-2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]-propane) | F0C377 | 1 |  | n/f | \$520 |
| 1441254 | Metoprolol Related Compound C $(20 \mathrm{mg})((+/-) 4-[2-H y d r o x y-3-(1-$ methylethyl)aminopropoxy]benzaldehyde) | F0C344 |  |  | n/f | \$520 |
| 1441265 | Metoprolol Related Compound D (50 mg) ((+/-)N,N-bis-[2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl](1-methylethyl)amine) | F0C378 | 1 |  | n/f | \$520 |
| 1441301 | Metoprolol Tartrate (200 mg) | H1B059 |  | $\begin{aligned} & \hline \text { H (01/04) } \\ & \text { G-1 (11/99) } \\ & \hline \end{aligned}$ | [56392-17-7] | \$156 |
| 1441505 | Metrizamide ( 500 mg ) | F |  |  | [31112-62-6] | \$156 |
| 1442009 | Metronidazole ( 100 mg ) | 1 |  |  | [443-48-1] | \$156 |
| 1443001 | Metyrapone ( 200 mg ) | H |  | G (06/01) | [54-36-4] | \$156 |
| 1443205 | Metyrosine ( 200 mg ) | F |  |  | [672-87-7] | \$156 |
| 1443250 | Mexiletine Hydrochloride (200 mg) | F-2 |  | F-1 (09/02) | [5370-01-4] | \$156 |
| 1443307 | Mezlocillin Sodium ( 350 mg ) | G |  |  | [59798-30-0] | \$156 |
| 1443409 | Miconazole ( 200 mg ) | G-1 |  | G (07/02) | [22916-47-8] | \$156 |
| 1443500 | Miconazole Nitrate (200 mg) | 1 |  | H (06/99) | [22832-87-7] | \$156 |
| 1443850 | Powdered Milk Thistle Extract (250 mg) | F0B321 |  |  | [84604-20-6] | \$260 |
| 1443908 | Milrinone ( 500 mg ) | F0C050 |  |  | [78415-72-2] | \$260 |
| 1443919 | Milrinone Related Compound A ( 50 mg ) (1,6-Dihydro-2-methyl-6-oxo(3,4'-bipyridine)-5-carboxamide) | F0C051 |  |  | [80047-24-1] | \$487 |
| 1444004 | Minocycline Hydrochloride ( 200 mg ) | 10C178 |  | $\begin{aligned} & \mathrm{H}-3(04 / 04) \\ & \mathrm{H}-2(07 / 02) \\ & \hline \end{aligned}$ | [13614-98-7] | \$156 |

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| 1444208 | Minoxidil (125 mg) | H1C168 |  | $\begin{aligned} & \text { H (03/04) } \\ & \text { G (05/99) } \end{aligned}$ | [38304-91-5] | \$124 |
| 1444707 | Mitomycin ( 50 mg ) | K |  | $J$ (07/01) | [50-07-7] | \$479 |
| 1445007 | Mitotane ( 500 mg ) | GOC044 |  | F (07/04) | [53-19-0] | \$156 |
| 1445200 | Mitoxantrone Hydrochloride ( 400 mg ) | H |  | G (03/01) | [70476-82-3] | \$498 |
| 1445222 | Mitoxantrone Related Compound A Hydrochloride ( 30 mg ) ( 8 -amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione Hydrochloride) |  |  | $\begin{aligned} & \text { F-1 (07/04) } \\ & \text { F (03/01) } \end{aligned}$ | n/f | \$208 |
| 1445459 | Molindone Hydrochloride ( 500 mg ) | F |  |  | [15622-65-8] | \$156 |
| 1445470 | Mometasone Furoate (200 mg) | G0B073 |  | $\begin{array}{\|l} \hline \text { F-1 (04/03) } \\ \text { F (02/01) } \\ \hline \end{array}$ | [83919-23-7] | \$156 |
| 1445481 | Monensin Sodium (200 mg) | F0B293 |  |  | [22373-78-0] | \$156 |
| 1445506 | Monobenzone (200 mg) | F |  |  | [103-16-2] | \$156 |
| 1445801 | Mono- and Di-acetylated Monoglycerides (200 mg) | F |  |  | [68990-54-5] | \$156 |
| 1446000 | Monoglycerides (125 mg) | H |  |  | [68990-53-4] | \$124 |
| 1446804 | Monostearyl Maleate ( $100 \mathrm{mg} \mathrm{)}$ | G |  | F-2 (04/00) | [2424-62-6] | \$487 |
| 1446950 | Moricizine Hydrochloride ( 100 mg ) | F |  |  | [29560-58-5] | \$156 |
| 1447002 | Morphine Monohydrate CII (50 mg) (AS) | G |  |  | [6009-81-0] | \$207 |
| 1448005 | Morphine Sulfate CII (500 mg) | LOB056 |  | $\begin{aligned} & \hline \mathrm{K}(06 / 03) \\ & \mathrm{J}-1(07 / 00) \\ & \hline \end{aligned}$ | [6211-15-0] | \$332 |
| 1448504 | Moxalactam Disodium ( 500 mg ) | F-1 |  |  | [64953-12-4] | \$156 |
| 1448901 | Mupirocin ( 50 mg ) | F-1 |  | F (03/02) | [12650-69-0] | \$156 |
| 1448923 | Mupirocin Lithium ( 100 mg ) | G |  | F (02/01) | [73346-79-9] | \$156 |
| 1449008 | Myristyl Alcohol (1 g) | G |  | F (02/02) | [112-72-1] | \$156 |
| 1449518 | Nabumetone ( 200 mg ) | F0C072 |  |  | [42924-53-8] | \$156 |
| 1449700 | Nadolol (200 mg) | F-3 |  | F-2 (04/02) | [42200-33-9] | \$156 |
| 1450007 | Nafcillin Sodium (200 mg) | H |  |  | [7177-50-6] | \$156 |
| 1450404 | Naftifine Hydrochloride ( 200 mg ) | F |  |  | [65473-14-5] | \$156 |
| 1451000 | Nalidixic Acid (200 mg) | G |  |  | [389-08-2] | \$156 |
| 1452002 | Nalorphine Hydrochloride CIII (250 mg) | 1 |  |  | [57-29-4] | \$207 |
| 1453005 | Naloxone (125 mg) | LOB124 |  | $\begin{array}{\|l\|l\|} \hline \text { K-1 (12/02) } \\ \text { K (07/01) } \\ \hline \end{array}$ | [465-65-6] | \$124 |
| 1453504 | Naltrexone (200 mg) | H0C150 |  | $\begin{aligned} & \text { G1B039 (03/04) } \\ & \text { G (02/03) } \\ & \hline \end{aligned}$ | [16590-41-3] | \$156 |
| 1453526 | Naltrexone Related Compound A CII (30 mg) (N-(3-butenyl)-noroxymorphone Hydrochloride) | F |  |  | n/f | \$207 |
| 1454008 | Nandrolone CIII ( 50 mg ) | F-3 |  |  | [434-22-0] | \$560 |
| 1455000 | Nandrolone Decanoate CIII (250 mg) | 1 |  |  | [360-70-3] | \$207 |
| 1456003 | Nandrolone Phenpropionate CIII (250 mg) | H |  |  | [62-90-8] | \$207 |
| 1457006 | Naphazoline Hydrochloride (200 mg) | K |  |  | [550-99-2] | \$156 |
| 1457301 | Naproxen (200 mg) | I-1 |  | $\begin{array}{\|l\|l\|} \hline \text { I (03/03) } \\ \text { H-1 (01/01) } \\ \hline \end{array}$ | [22204-53-1] | \$156 |
| 1457403 | Naproxen Sodium (200 mg) | 1 |  |  | [26159-34-2] | \$156 |
| 1457505 | Natamycin (200 mg) | 1 |  | H (11/99) | [7681-93-8] | \$156 |
| 1458009 | Neomycin Sulfate ( 200 mg ) | L-2 |  | $\begin{array}{\|l\|l} \hline \text { L-1 (09/01) } \\ \text { L (02/99) } \\ \hline \end{array}$ | [1405-10-3] | \$156 |
| 1459001 | Neostigmine Bromide (200 mg) | G |  |  | [114-80-7] | \$156 |
| 1460000 | Neostigmine Methylsulfate ( 200 mg ) | 1 |  | H (07/00) | [51-60-5] | \$156 |
| 1460500 | Netilmicin Sulfate ( 500 mg ) | H |  | G (05/02) | [56391-57-2] | \$156 |
| 1461003 | Niacin (200 mg) | H-1 |  |  | [59-67-6] | \$156 |
| 1462006 | Niacinamide (500 mg) (Vitamin B3) | M-1 |  | M (02/01) | [98-92-0] | \$156 |

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| 1463304 | Nicotine Bitartrate Dihydrate ( 500 mg ) | G |  | F (05/99) | [6019-06-3] | \$156 |
| 1463508 | Nifedipine ( 125 mg ) | J0B243 |  | I-1 (04/04) | [21829-25-4] | \$124 |
| 1463600 | Nifedipine Nitrophenylpyridine Analog ( 25 mg ) | K |  | J (04/01) | n/f | \$487 |
| 1463701 | Nifedipine Nitrosophenylpyridine Analog ( 25 mg ) | K |  | $J$ (07/02) | n/f | \$487 |
| 1464001 | Nitrofurantoin ( 500 mg ) | J |  | I-1 (11/02) | [67-20-9] | \$156 |
| 1465004 | Nitrofurazone ( 200 mg ) | H-1 |  | H (09/01) | [59-87-0] | \$156 |
| 1465503 | Nitrofurfural Diacetate ( 100 mg ) |  |  | F-1 (12/04) | [92-55-7] | \$487 |
| 1466007 | Nitrofurazone Related Compound A ( 500 mg ) (5-Nitro-2-furfuraldazine) | H0B100 |  | G (07/03) | n/f | \$487 |
| 1466506 | Diluted Nitroglycerin ( 5 ampules, approx. 200 mg of a $0.948 \%$ solution in propylene glycol each) | G |  |  | [55-63-0] | \$156 |
| 1467804 | Nizatidine (200 mg) | G |  | F-1 (06/00) | [76963-41-2] | \$156 |
| 1467950 | Nonoxynol 9 ( 0.5 mL ) | H-1 |  | H (03/02) | [26027-38-3] | \$156 |
| 1468002 | Nonoxynol 10 (200 mg) | F |  |  | [26027-38-3] | \$156 |
| 1468400 | Nordazepam CIV (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-ben-zodiazepin-2-one) | H1B035 |  | $\begin{aligned} & \text { H (03/03) } \\ & \text { G (03/00) } \end{aligned}$ | [1088-11-5] | \$560 |
| 1468501 | Norepinephrine Bitartrate (125 mg) | H |  |  | [69815-49-2] | \$124 |
| 1469005 | Norethindrone ( 200 mg ) | J1B065 |  | $\begin{array}{\|l} \hline J-1(05 / 03) \\ \mathrm{J}(07 / 02) \\ \mathrm{l}-1(03 / 01) \\ \hline \end{array}$ | [68-22-4] | \$156 |
| 1470004 | Norethindrone Acetate (100 mg) | J0B072 |  | $\begin{array}{\|l} \hline \text { I (04/03) } \\ \text { H (06/99) } \\ \hline \end{array}$ | [51-98-9] | \$156 |
| 1471007 | Norethynodrel (200 mg) | G |  |  | [68-23-5] | \$156 |
| 1471506 | Norfloxacin (200 mg) | H |  | G (04/01) | [70458-96-7] | \$156 |
| 1471914 | Norgestimate ( 200 mg ) | F0C086 |  |  | [35189-28-7] | \$156 |
| 1472000 | Norgestrel (125 mg) | J0C269 |  | $\begin{array}{\|l\|} \hline \text { I (07/04) } \\ \text { H }(05 / 99) \\ \hline \end{array}$ | [6533-00-2] | \$124 |
| 1473002 | Noroxymorphone Hydrochloride CII (50 mg) | H1C177 |  | H (11/04) | n/f | \$560 |
| 1474005 | Nortriptyline Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  | H (04/00) | [894-71-3] | \$156 |
| 1474504 | Noscapine ( 500 mg ) | G |  |  | [128-62-1] | \$156 |
| 1475008 | Novobiocin ( 200 mg ) | G-2 |  |  | [303-81-1] | \$156 |
| 1476000 | Nylidrin Hydrochloride ( 200 mg ) | F-2 |  |  | [849-55-8] | \$156 |
| 1477003 | Nystatin (200 mg) | N1B004 |  | N (01/03) | [1400-61-9] | \$156 |
| 1477900 | Octinoxate ( 500 mg ) (Octyl Methoxycinnamate) | G0C024 |  | FOB032 (12/03) | [5466-77-3] | \$156 |
| 1477411 | Octocrylene ( 500 mg ) | G0C211 |  | FOB104 (05/04) | [6197-30-4] | \$156 |
| 1477502 | Octoxynol 9 (200 mg) | G |  | F-2 (07/00) | [9002-93-1] | \$156 |
| 1477808 | Octyldodecanol (200 mg) | G |  | F-1 (07/99) | [5333-42-6] | \$156 |
| 1477943 | Octyl Salicylate (400 mg) | F0B091 |  |  | [118-60-5] | \$156 |
| 1478108 | Ofloxacin (200 mg) | F-2 |  | F-1 (08/02) | [82419-36-1] | \$156 |
| 1478505 | Omeprazole (200 mg) | H1B211 |  | $\begin{array}{\|l\|l} \hline \text { H (05/04) } \\ \text { G-1 (04/02) } \\ \text { G (09/01) } \\ \hline \end{array}$ | [73590-58-6] | \$156 |
| 1478582 | Ondansetron Hydrochloride ( 300 mg ) | F0C222 |  |  | [103639-04-9] | \$208 |
| 1478593 | Ondansetron Related Compound A ( 50 mg ) (3[(Dimethylamino)-methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride) | FOC191 |  |  | [119812-29-2] | \$487 |
| 1478618 | Ondansetron Related Compound C (50 mg) (1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4-one) | F0C251 |  |  | [27397-31-1] | \$487 |
| 1478629 | Ondansetron Related Compound D (50 mg) (1,2,3,9-Tetrahydro-9-methyl-3-methylene-4H-carbazol-4-one) | F0C226 |  |  | n/f | \$487 |
| 1479009 | Orphenadrine Citrate (200 mg) | G |  | F-4 (05/02) | [4682-36-4] | \$156 |
| 1481000 | Oxacillin Sodium (200 mg) | J |  | I (03/02) | [7240-38-2] | \$156 |

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| 1481500 | Oxamniquine (200 mg) | F |  |  | [21738-42-1] | \$156 |
| 1481703 | Oxamniquine Related Compound A (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolinemethyl methanesulfonate) | F |  |  | n/f | \$487 |
| 1481805 | Oxamniquine Related Compound B ( 25 mg ) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-5-nitro-6-quinolinemethanol) | F |  |  | n/f | \$487 |
| 1482003 | Oxandrolone CIII (50 mg) | G0B220 |  | F-4 (07/03) | [53-39-4] | \$207 |
| 1482207 | Oxaprozin (200 mg) | F0C115 |  |  | [21256-18-8] | \$156 |
| 1483006 | Oxazepam CIV (200 mg) | G-1 |  | G (12/00) | [604-75-1] | \$207 |
| 1483301 | Oxfendazole (200 mg) | F0C128 |  |  | [53716-50-0] | \$156 |
| 1483505 | Oxprenolol Hydrochloride ( 200 mg ) | H |  |  | [6452-73-9] | \$156 |
| 1484009 | Oxtriphylline ( 500 mg ) | G |  |  | [4499-40-5] | \$156 |
| 1485001 | Oxybenzone ( 150 mg ) | H0B263 |  | $\begin{array}{\|l\|} \hline \text { G (11/03) } \\ \text { F-2 }(12 / 99) \\ \hline \end{array}$ | [131-57-7] | \$156 |
| 1485103 | Oxybutynin Chloride (200 mg) | G-1 |  | G (11/02) | [1508-65-2] | \$156 |
| 1485114 | Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid) | G |  | F-2 (01/00) | [4335-77-7] | \$487 |
| 1485191 | Oxycodone CII (200 mg) | IOB046 |  | $\begin{aligned} & \hline \text { H }(01 / 03) \\ & \text { G-1 (01/01) } \\ & \hline \end{aligned}$ | [76-42-6] | \$207 |
| 1486004 | Oxymetazoline Hydrochloride (200 mg) | 1 |  |  | [2315-02-8] | \$156 |
| 1487007 | Oxymetholone CIII (200 mg) | G1B247 |  | G (10/03) | [434-07-1] | \$207 |
| 1488000 | Oxymorphone CII ( 500 mg ) | H0B214 |  | G (03/03) | [76-41-5] | \$207 |
| 1489002 | Oxyphenbutazone (1 g) | H |  |  | [7081-38-1] | \$156 |
| 1490103 | Oxyquinoline Sulfate (200 mg) | F-1 |  | F (07/02) | [134-31-6] | \$156 |
| 1491004 | Oxytetracycline (200 mg) | I-1 |  |  | [6153-64-6] | \$156 |
| 1491300 | Oxytocin (5 vials, 46 USP units per vial) | F |  |  | [50-56-6] | \$156 |
| 1491332 | Paclitaxel ( 200 mg ) | F0C180 |  |  | [33069-62-4] | \$1,508 |
| 1491343 | Paclitaxel Related Compound A (20 mg) (Cephalomannine) | F0C179 |  |  | [71610-00-9] | \$754 |
| 1491354 | Paclitaxel Related Compound B (20 mg) (10-Deacetyl-7-epipaclitaxel) | F0C181 |  |  | nf | \$754 |
| 1491503 | Padimate O ( 300 mg ) | H0B154 |  | G (04/03) | [21245-02-3] | \$156 |
| 1492007 | Palmitic Acid ( 500 mg ) | I |  |  | [57-10-3] | \$156 |
| 1493000 | Pamoic Acid (250 mg) | G-4 |  | G-3 (01/03) | [130-85-8] | \$156 |
| 1494057 | Pancreatin Amylase and Protease (2 g) | 1 |  | H (10/00) | [8049-47-6] | \$156 |
| 1494079 | Pancreatin Lipase (2 g) | 1 |  | H-1 (03/01) | [8049-47-6] | \$156 |
| 1494501 | Panthenol, Racemic (200 mg) | G |  | F-1 (02/00) | [16485-10-2] | \$156 |
| 1494807 | Pantolactone ( 500 mg ) | F |  |  | [599-04-2] | \$487 |
| 1495005 | Papain (1 g) | H |  | G (12/01) | [9001-73-4] | \$156 |
| 1496008 | Papaverine Hydrochloride (200 mg) | H |  |  | [61-25-6] | \$156 |
| 1497000 | Paramethadione ( 500 mg ) | G |  |  | [115-67-3] | \$156 |
| 1498003 | Paramethasone Acetate (200 mg) | G |  | F-1 (05/01) | [1597-82-6] | \$156 |
| 1498706 | Parbendazole ( 200 mg ) | F |  |  | [14255-87-9] | \$156 |
| 1499006 | Pargyline Hydrochloride (200 mg) | F-1 |  |  | [306-07-0] | \$156 |
| 1500003 | Paromomycin Sulfate ( 125 mg ) | G |  | F-3 (01/01) | [1263-89-4] | \$156 |
| 1500218 | Paroxetine Hydrochloride ( 500 mg ) |  |  | FOB288 (09/04) | [110429-35-1] | \$156 |
| 1500229 | Paroxetine Related Compound A ( 20 mg ) (trans-4-(p-methoxyphenyl)-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine Hydrochloride) | F0B172 |  |  | n/f | \$487 |
| 1500230 | Paroxetine Related Compound B ( 20 mg ) (trans-4-phenyl-3-[( $(3,4-$ methylenedioxy)phenoxy]methylpiperidine acetate) | F0B189 |  |  | n/f | \$487 |
| 1500240 | Paroxetine Related Compound C ( 25 mg ) ((+)-trans-Paroxetine hydrochloride) | F0B192 |  |  | [130855-30-0] | \$487 |

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| 1500251 | Paroxetine Related Compound D (15 mg) ((-)-cis-Paroxetine hydrochloride) | F0C228 |  |  | n/f | \$487 |
| 1500400 | Parthenolide ( 25 mg ) | F |  |  | [20554-84-1] | \$156 |
| 1500502 | Particle Count Set (2 blanks and 2 suspensions) | 1 |  | H (09/02) | n/f | \$487 |
| 1500808 | Penbutolol Sulfate (200 mg) | F |  |  | [38363-32-5] | \$156 |
| 1501006 | Penicillamine (200 mg) | H1B164 |  | H (01/04) | [52-67-5] | \$156 |
| 1501108 | Penicillamine Disulfide ( 100 mg ) | H |  | G (07/00) | [20902-45-8] | \$487 |
| 1502009 | Penicillin G Benzathine ( $200 \mathrm{mg} \mathrm{)}$ | J |  |  | [41372-02-5] | \$156 |
| 1502508 | Penicillin G Potassium ( 200 mg ) | 1 |  | H (02/99) | [113-98-4] | \$156 |
| 1502552 | Penicillin G Procaine (200 mg) | G0C271 |  | $\begin{array}{\|l} \text { F-1 (08/04) } \\ \text { F (03/99) } \\ \hline \end{array}$ | [6130-64-9] | \$156 |
| 1502701 | Penicillin G Sodium (200 mg) | L-3 |  | L-2 (09/01) | [69-57-8] | \$156 |
| 1504489 | Penicillin V ( 200 mg ) | F |  |  | [87-08-1] | \$156 |
| 1504503 | Penicillin V Potassium ( 200 mg ) | H0C213 |  | $\begin{aligned} & \text { G-1 (06/04) } \\ & \text { G (06/00) } \\ & \hline \end{aligned}$ | [132-98-9] | \$156 |
| 1505007 | Pentazocine CIV (500 mg) | H |  | G-1 (11/00) | [359-83-1] | \$207 |
| 1505506 | Pentetic Acid (100 mg) | F-1 |  | F (09/01) | [67-43-6] | \$156 |
| 1507002 | Pentobarbital CII (200 mg) | H3C144 |  | $\begin{array}{ll} \hline \mathrm{H}-2(07 / 04) \\ \mathrm{H}-1(08 / 02) \\ \hline \end{array}$ | [76-74-4] | \$207 |
| 1508901 | Pentoxifylline (200 mg) | F0B202 |  |  | [6493-05-6] | \$156 |
| 1510007 | Pepsin (5 g) | F-2 |  |  | [9001-75-6] | \$156 |
| 1510801 | Perflubron ( 0.5 mL ) | G0C103 |  | F (04/04) | [423-55-2] | \$156 |
| 1510845 | Pergolide Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | F1C225 |  | F (07/04) | [66104-23-2] | \$194 |
| 1510867 | Pergolide Sulfoxide ( 50 mg ) | F0B014 |  |  | [72822-01-6] | \$194 |
| 1511000 | Perphenazine ( 200 mg ) | JOB249 |  | I (10/03) | [58-39-9] | \$156 |
| 1511203 | Perphenazine Sulfoxide ( $100 \mathrm{mg} \mathrm{)}$ | G-1 |  | G (07/02) | [10078-25-8] | \$487 |
| 1512002 | Phenacemide ( 250 mg ) | F |  |  | [63-98-9] | \$156 |
| 1513005 | Phenacetin ( 500 mg ) | H-1 |  | H (09/00) | [62-44-2] | \$156 |
| 1514008 | Phenacetin Melting Point Standard (500 mg) (Approximately 135 degrees) | H3A009 |  | $\begin{aligned} & \hline \text { H-2 (02/03) } \\ & \text { H-1 }(06 / 01) \\ & \hline \end{aligned}$ | [62-44-2] | \$92 |
| 1515000 | Phenazopyridine Hydrochloride ( 200 mg ) |  |  | G-4 (12/04) | [136-40-3] | \$156 |
| 1516003 | Phencyclidine Hydrochloride CII ( 25 mg ) (AS) | G1B025 |  | G (12/02) | [956-90-1] | \$207 |
| 1516502 | Phendimetrazine Tartrate CIII ( $350 \mathrm{mg} \mathrm{)}$ | G |  | F (01/01) | [50-58-8] | \$207 |
| 1517006 | Phenelzine Sulfate ( 200 mg ) | G |  | F-1 (04/02) | [156-51-4] | \$156 |
| 1517301 | D-Phenethicillin Potassium (200 mg) | F |  |  | n/f | \$487 |
| 1517607 | L-Phenethicillin Potassium ( 200 mg ) | F |  |  | n/f | \$156 |
| 1520000 | Phenformin Hydrochloride (200 mg) | G |  |  | [834-28-6] | \$156 |
| 1522006 | Phenindione ( 250 mg ) | F |  |  | [83-12-5] | \$156 |
| 1522301 | Pheniramine Maleate ( 100 mg ) | F1C342 |  | F (08/04) | [132-20-7] | \$156 |
| 1523009 | Phenmetrazine Hydrochloride CII (200 mg) | F-2 |  |  | [1707-14-8] | \$207 |
| 1524001 | Phenobarbital CIV (200 mg) | J |  |  | [50-06-6] | \$207 |
| 1524908 | Phenolphthalein ( $250 \mathrm{mg} \mathrm{)}$ | F-3 |  |  | [77-09-8] | \$156 |
| 1525004 | Phenolsulfonphthalein ( 100 mg ) | F-2 |  |  | [143-74-8] | \$156 |
| 1526007 | Phenoxybenzamine Hydrochloride ( $250 \mathrm{mg} \mathrm{)}$ | G |  |  | [63-92-3] | \$156 |
| 1527000 | Phenprocoumon (200 mg) DISCONTINUED |  |  | F-1 (02/04) | [435-97-2] | \$156 |
| 1528002 | Phensuximide ( 500 mg ) | G |  | F-1 (03/01) | [86-34-0] | \$156 |
| 1528501 | Phentermine Hydrochloride CIV (200 mg) | H0B309 |  | G (08/03) | [1197-21-3] | \$207 |
| 1529005 | Phentolamine Hydrochloride ( 300 mg ) | F |  |  | [73-05-2] | \$156 |
| 1530004 | Phentolamine Mesylate (200 mg) | 1 |  |  | [65-28-1] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1530503 | L-Phenylalanine (200 mg) | H |  | G (02/02) | [63-91-2] | \$156 |
| 1530809 | Phenylbenzimidazole Sulfonic Acid (200 mg) | F |  |  | [27503-81-7] | \$156 |
| 1531007 | Phenylbutazone ( 250 mg ) | J0A008 |  | I-1 (02/03) | [50-33-9] | \$156 |
| 1533002 | Phenylephrine Hydrochloride (125 mg) | K |  | J (02/99) | [61-76-7] | \$124 |
| 1533308 | 5 -Phenylhydantoin ( 100 mg ) | F |  |  | [89-24-7] | \$487 |
| 1533851 | Phenylpropanediol ( 100 mg ) | F |  |  | n/f | \$487 |
| 1533909 | Phenylpropanolamine Bitartrate ( 100 mg ) (List Chemical) | F |  |  | [67244-90-0] | \$156 |
| 1534005 | Phenylpropanolamine Hydrochloride (250 mg) (List Chemical) | J |  | 1 (02/02) | [154-41-6] | \$156 |
| 1535008 | Phenytoin (200 mg) | I2B233 |  | $\begin{array}{\|l\|} \hline \text { I-1 (03/04) } \\ \text { I (04/01) } \\ \hline \end{array}$ | [57-41-0] | \$156 |
| 1535507 | Phenytoin Sodium (200 mg) | H |  | G (05/99) | [630-93-3] | \$156 |
| 1535019 | Phenytoin Related Compound A (50 mg) (2,2-Diphenylglycine) | F0C155 |  |  | [3060-50-2] | \$487 |
| 1535020 | Phenytoin Related Compound B ( 50 mg ) (alpha-((aminocarbony) ami-no)-alpha-phenyl benzeneacetic acid) | F0C157 |  |  | [6802-95-5] | \$487 |
| 1535700 | Phosphated Riboflavin ( 100 mg ) | G1B286 |  | G (07/04) | [6184-17-4] | \$124 |
| 1537003 | Physostigmine Salicylate ( 200 mg ) | H-1 |  | H (06/00) | [57-64-7] | \$156 |
| 1538006 | Phytonadione (500 mg) (Vitamin K1) | N0B303 |  | $\begin{array}{\|l\|} \hline \text { M-1 (07/04) } \\ M(09 / 01) \\ \hline \end{array}$ | [84-80-0] | \$156 |
| 1538505 | Pilocarpine ( 300 mg ) | F |  |  | [92-13-7] | \$156 |
| 1538902 | Pilocarpine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  | [54-71-7] | \$156 |
| 1539009 | Pilocarpine Nitrate (200 mg) | 1 |  |  | [148-72-1] | \$156 |
| 1539508 | Pimozide ( 200 mg ) | G |  |  | [2062-78-4] | \$156 |
| 1539701 | Pindolol ( 200 mg ) | IOB210 | 2 | H-1 (12/04) | [13523-86-9] | \$156 |
| 1541000 | Piperacetazine ( 250 mg ) | F |  |  | [3819-00-9] | \$156 |
| 1541500 | Piperacillin ( 500 mg ) | H |  |  | [66258-76-2] | \$156 |
| 1541703 | Piperazine Adipate (200 mg) | F |  |  | [142-88-1] | \$156 |
| 1541805 | Piperazine Citrate ( 200 mg ) | F |  |  | [144-29-6] | \$156 |
| 1541907 | Piperazine Dihydrochloride (200 mg) | F |  |  | [142-64-3] | \$156 |
| 1542003 | Piperazine Phosphate ( 200 mg ) | F |  |  | [14538-56-8] | \$156 |
| 1543006 | Piperidolate Hydrochloride (200 mg) | F |  |  | [129-77-1] | \$156 |
| 1544508 | Piroxicam (200 mg) | H |  | G (01/99) | [36322-90-4] | \$156 |
| 1545205 | Plicamycin ( 50 mg ) | H |  | G (04/00) | [18378-89-7] | \$479 |
| 1545409 | Polacrilex Resin (100 mg) | F |  |  | n/f | \$156 |
| 1545500 | Polacrilin Potassium (200 mg) | F-2 |  | F-1 (09/00) | $\mathrm{n} / \mathrm{f}$ | \$156 |
| 1546106 | Poloxalene ( 500 mg ) | F0C009 |  |  | [9003-11-6] | \$156 |
| 1546300 | Polydimethylsiloxane ( 500 mg ) | H0C020 |  | $\begin{aligned} & \text { G-5 (05/04) } \\ & \text { G-4 (06/01) } \end{aligned}$ | [9016-00-6] | \$156 |
| 1546707 | Polyethylene, High Density (3 strips) | G |  | F-1 (04/01) | [9002-88-4] | \$156 |
| 1546809 | Polyethylene, Low Density (3 strips) | G1B166 |  | $\begin{aligned} & \mathrm{G}(06 / 04) \\ & \mathrm{F}-2(12 / 99) \\ & \hline \end{aligned}$ | [9002-88-4] | \$156 |
| 1546853 | Polyethylene Oxide ( 100 mg ) | F-1 |  |  | [25322-68-3] | \$156 |
| 1546900 | Polyethylene Terephthalate (PET) (3 Strips) | F |  |  | [25038-59-9] | \$156 |
| 1546922 | Polyethylene Terephthalate G (PETG) (3 Strips) | F |  |  | [25640-14-6] | \$156 |
| 1547007 | Polymyxin B Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | K |  | J-1 (09/99) | [1405-20-5] | \$156 |
| 1547404 | Polyoxyl 50 Stearate ( 200 mg ) | F |  |  | [9004-99-3] | \$156 |
| 1547903 | Polyoxyl 40 Stearate ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  | F-1 (05/00) | [9004-99-3] | \$156 |
| 1548000 | Polythiazide ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [346-18-9] | \$156 |
| 1550001 | Potassium Gluconate (200 mg) | H0C064 |  | G (06/04) | [299-27-4] | \$156 |
| 1551004 | Potassium Guaiacolsulfonate ( 500 mg ) | J0B292 |  | $\begin{array}{\|l} \hline \text { I-1 (07/03) } \\ \text { I (11/00) } \\ \hline \end{array}$ | [78247-49-1] | \$156 |

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| 1551150 | Potassium Sucrose Octasulfate (300 mg) | IOB283 |  | H0B119 (04/04) <br> G-1 (04/03) <br> G (02/01) | [76578-81-9] | \$156 |
| 1551300 | Potassium Trichloroammineplatinate ( 20 mg ) |  |  | H0B149 (12/04) <br> G-1 (01/03) <br> G (07/99) | [13820-91-2] | \$487 |
| 1551503 | Povidone (100 mg) | F-1 |  | F (11/01) | [9003-39-8] | \$156 |
| 1553000 | Pralidoxime Chloride (200 mg) | G-2 |  | $\begin{aligned} & \text { G-1 (03/01) } \\ & \text { G (08/99) } \end{aligned}$ | [51-15-0] | \$156 |
| 1554002 | Pramoxine Hydrochloride ( 500 mg ) | 1 |  | H (11/02) | [637-58-1] | \$156 |
| 1554501 | Prazepam CIV (500 mg) | G0C066 |  | F-1 (11/02) | [2955-38-6] | \$207 |
| 1554603 | Praziquantel ( 200 mg ) | G |  | $\begin{array}{\|l\|l\|} \hline \text { F-3 }(07 / 02) \\ \text { F-2 }(09 / 00) \\ \hline \end{array}$ | [55268-74-1] | \$156 |
| 1554658 | Praziquantel Related Compound A (50 mg) (2-benzoyl-1,2,3,6,7,11b-hexahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one) | F-1 |  |  | n/f | \$487 |
| 1554669 | Praziquantel Related Compound B ( 50 mg ) (2-(cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one) | F-2 |  | F-1 (06/00) | n/f | \$487 |
| 1554670 | Praziquantel Related Compound C ( 50 mg ) (2-(N-formylhexahydrohip-puroyl-1,2,3,4-tetrahydroisoquinolin-1-one) | F-2 |  | F-1 (06/00) | n/f | \$487 |
| 1554705 | Prazosin Hydrochloride ( 500 mg ) | G-1 |  | G (02/01) | [19237-84-4] | \$156 |
| 1555005 | Prednisolone (200 mg) | M |  | L-1 (04/02) | [50-24-8] | \$156 |
| 1556008 | Prednisolone Acetate (200 mg) | $J$ |  | I-1 (02/02) | [52-21-1] | \$156 |
| 1556507 | Prednisolone Hemisuccinate ( 125 mg ) | H-1 |  | H (02/99) | [2920-86-7] | \$124 |
| 1558003 | Prednisolone Tebutate ( 200 mg ) | F |  |  | [7681-14-3] | \$156 |
| 1559006 | Prednisone ( 250 mg ) | L1B251 | 2 | $\begin{array}{\|l\|} \hline \text { L (11/04) } \\ \text { K-1 (01/02) } \\ \text { K (02/00) } \\ \hline \end{array}$ | [53-03-2] | \$156 |
| 1559505 | Prednisone Tablets (Dissolution Calibrator, Disintegrating) (30 tablets) | O0C056 |  | $\begin{array}{\|l\|l} \hline N(06 / 04) \\ M(09 / 02) \\ L(11 / 00) \\ \hline \end{array}$ | [53-03-2] | \$180 |
| 1561008 | Prilocaine Hydrochloride (200 mg) | F3B215 |  | F-2 (03/04) | [1786-81-8] | \$156 |
| 1561507 | Primaquine Phosphate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [63-45-6] | \$156 |
| 1562000 | Primidone (200 mg) | G |  | F-6 (04/99) | [125-33-7] | \$156 |
| 1563003 | Probenecid (200 mg) | IOA011 |  | H-1 (03/03) | [57-66-9] | \$156 |
| 1563309 | Probucol ( 200 mg ) | G |  | F-1 (01/02) | [23288-49-5] | \$156 |
| 1563320 | Probucol Related Compound A (25 mg) (2,2',6,6'-tetra-tert-butyldiphenoquinone) | F-2 | 2 | F-1 (12/04) | n/f | \$487 |
| 1563331 | Probucol Related Compound B (25 mg) (4,4'-dithio-bis(2,6-di-tertbutylphenol)) | F-2 |  | F-1 (08/03) | n/f | \$487 |
| 1563342 | Probucol Related Compound C ( 25 mg ) (4-[(3,5-di-tert-butyl-2-hydro-xyphenylthio)isopropylidenethio]-2,6-di-tert-butylphenol) | F-2 |  | F-1 (05/00) | n/f | \$487 |
| 1563502 | Procainamide Hydrochloride ( 200 mg ) | H1B117 |  | H (04/03) | [614-39-1] | \$156 |
| 1564006 | Procaine Hydrochloride (200 mg) | H |  |  | [51-05-8] | \$156 |
| 1565009 | Procarbazine Hydrochloride ( 200 mg ) | F |  |  | [366-70-1] | \$156 |
| 1566001 | Prochlorperazine Maleate ( 200 mg ) | H-1 |  |  | [84-02-6] | \$156 |
| 1567004 | Procyclidine Hydrochloride (200 mg) | G |  |  | [1508-76-5] | \$156 |
| 1568007 | Progesterone (200 mg) | H6C088 | 2 | $\begin{aligned} & \mathrm{H}-5(11 / 04) \\ & \mathrm{H}-4(07 / 02) \end{aligned}$ | [57-83-0] | \$124 |
| 1568506 | L-Proline ( 200 mg ) | F-2 |  | F-1 (01/02) | [147-85-3] | \$156 |
| 1569000 | Promazine Hydrochloride ( 200 mg ) | H0B261 |  | G (10/03) | [53-60-1] | \$156 |
| 1570009 | Promethazine Hydrochloride ( 500 mg ) | K |  | J-1 (10/00) | [58-33-3] | \$156 |

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| 1570304 | Propafenone Hydrochloride (200 mg) | G1C184 | 2 | $\begin{array}{\|l\|} \hline \text { G (12/04) } \\ \text { F-1 }(01 / 01) \\ \hline \end{array}$ | [34183-22-7] | \$156 |
| 1570508 | Propantheline Bromide ( 200 mg ) | IOA019 |  | H (11/02) | [50-34-0] | \$156 |
| 1329505 | Propantheline Bromide Related Compound A (50 mg) (9-Hydroxypropantheline bromide) | G0B258 |  | F-1 (12/03) | n/f | \$487 |
| 1571001 | Proparacaine Hydrochloride ( 200 mg ) | G |  |  | [5875-06-9] | \$156 |
| 1573007 | Propoxycaine Hydrochloride ( 200 mg ) | F |  |  | [550-83-4] | \$156 |
| 1574000 | Propoxyphene Hydrochloride CII (1 g) | L0C285 |  | K (09/04) | [1639-60-7] | \$207 |
| 1575002 | Propoxyphene Napsylate CII (1 g) | H |  |  | [26570-10-5] | \$207 |
| 1575206 | Propoxyphene Related Compound A ( 50 mg ) (alpha-d-4-dimethylami-no-1,2-diphenyl-3-methyl-2-butanol Hydrochloride) | G-5 |  |  | n/f | \$487 |
| 1576005 | Propranolol Hydrochloride ( 200 mg ) | H-1 |  | H (09/01) | [318-98-9] | \$156 |
| 1576504 | Propylene Carbonate (200 mg) | F |  |  | [108-32-7] | \$156 |
| 1576708 | Propylene Glycol (1 mL) | 10C022 |  | $\begin{aligned} & \mathrm{H}(03 / 04) \\ & \mathrm{G}(02 / 99) \end{aligned}$ | [57-55-6] | \$156 |
| 1576720 | Propylene Glycol Diacetate ( 250 mg ) | F |  |  | [623-84-7] | \$156 |
| 1576800 | Propyl Gallate ( 200 mg ) | G-1 |  | G (01/03) | [121-79-9] | \$156 |
| 1577008 | Propylparaben (200 mg) | 1 |  | H (02/00) | [94-13-3] | \$156 |
| 1578000 | Propylthiouracil (200 mg) | G |  | F-1 (01/00) | [51-52-5] | \$156 |
| 1578500 | Prostaglandin A1 (25 mg) | H0B108 |  | G (04/03) | [14152-28-4] | \$529 |
| 1580002 | Protriptyline Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [1225-55-4] | \$156 |
| 1581005 | Pseudoephedrine Hydrochloride (125 mg) (List Chemical) | J1B203 |  | $\begin{array}{\|l\|} \hline J(01 / 04) \\ I(05 / 02) \\ \hline \end{array}$ | [345-78-8] | \$124 |
| 1581504 | Pseudoephedrine Sulfate (200 mg) (List Chemical) | G1C135 |  | $\begin{array}{\|l\|} \hline \text { G (06/04) } \\ \text { F-2 (05/02) } \\ \hline \end{array}$ | [7460-12-0] | \$156 |
| 1584003 | Pyrantel Pamoate (1 g) | 1 |  | H-1 (04/00) | [22204-24-6] | \$156 |
| 1585006 | Pyrazinamide ( 200 mg ) | G |  | F-2 (02/00) | [98-96-4] | \$156 |
| 1586009 | Pyridostigmine Bromide ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  | [101-26-8] | \$156 |
| 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) | P |  | O-1 (04/00) | [58-56-0] | \$156 |
| 1588004 | Pyrilamine Maleate ( 200 mg ) | IOB276 |  | H (12/03) | [59-33-6] | \$156 |
| 1589007 | Pyrimethamine (200 mg) | H |  | G (07/02) | [58-14-0] | \$156 |
| 1592001 | Pyrvinium Pamoate ( 500 mg ) | G |  |  | [3546-41-6] | \$156 |
| 1592205 | Quazepam CIV (200 mg) | F |  |  | [36735-22-5] | \$207 |
| 1592227 | Quazepam Related Compound A (30 mg) (7-Chloro-1-(2,2,2-trifluor-oethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one) | F |  |  | n/f | \$487 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 |  |  | [6151-25-3] | \$156 |
| 1593004 | Quinacrine Hydrochloride (200 mg) | F-1 |  |  | [6151-30-0] | \$156 |
| 1593412 | Quinapril Related Compound A ( 50 mg ) (Ethyl[3S-[2(R*),3a,11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-phenylethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate) | F0C114 |  |  | [103733-49-9] | \$487 |
| 1593423 | Quinapril Related Compound B ( 50 mg ) (3-Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahy-dro-,[3S-[2[R* $\left.\left.\left.\left.\left.\mathrm{R}^{*}\right)\right], 3 \mathrm{R}^{*}\right]\right]-\right)$ | F0C116 |  |  | [85441-60-7] | \$487 |
| 1594007 | Quinethazone ( 1.5 g ) | G |  |  | [73-49-4] | \$156 |
| 1594506 | Quinic Acid ( 200 mg ) | F |  |  | [77-95-2] | \$156 |
| 1595000 | Quinidine Gluconate ( 200 mg ) | H1A028 |  | H (04/03) | [7054-25-3] | \$156 |
| 1595509 | Quinidine Sulfate ( 500 mg ) | H-1 |  | H (12/99) | [6591-63-5] | \$156 |
| 1596807 | Quinine Hydrochloride Dihydrate (1 g) | F0C108 |  |  | [6119-47-7] | \$156 |
| 1597005 | Quinine Sulfate (200 mg) | H |  |  | [6119-70-6] | \$156 |
| 1597504 | Quininone ( 50 mg ) | H0B034 |  | G-1 (03/04) | [84-31-1] | \$487 |
| 1598008 | 3-Quinuclidinyl Benzilate ( 25 mg ) | H |  | G (11/01) | [6581-06-2] | \$515 |

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| 1598303 | Ramipril ( 200 mg ) | F0C099 |  |  | [87333-19-5] | \$156 |
| 1598314 | Ramipril Related Compound A (20 mg) ((2S,3aS,6aS)-1-[(S)2-[(S)1-(methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclo-penta[b]pyrrole-2-carboxylic acid) | F0C100 |  |  | [91224-69-0] | \$487 |
| 1598405 | Ranitidine Hydrochloride (200 mg) | H0B268 |  | G (01/04) | [66357-59-3] | \$156 |
| 1598507 | Ranitidine Related Compound A (50 mg) (5-[[(2-aminoethyl)thio]-methyl]-N,N-dimethyl-2-furanmethanamine hemifumarate) | H1B137 |  | $\begin{array}{\|l} \hline \mathrm{H}(01 / 04) \\ \mathrm{G}(01 / 01) \\ \hline \end{array}$ | [91224-69-0] | \$487 |
| 1598609 | Ranitidine Related Compound B ( 50 mg ) ( $\mathrm{N}, \mathrm{N}$ '-bis[2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thiojethyl]-2-nitro-1,1-ethenediamine) | G |  | F-4 (04/02) | [72126-78-4] | \$487 |
| 1598700 | Ranitidine Related Compound C ( 50 mg ) ( $\mathrm{N}-[2-[[[5-[(d i m e t h y l a m i n o)-$ methyl]-2-furanyl]methyl]sulfinyl]ethyl]-N-methyl-2-nitro-1,1-ethenediamine) | 11B136 |  | $\begin{aligned} & \mathrm{I}(01 / 04) \\ & \mathrm{H}(05 / 01) \end{aligned}$ | [73851-70-4] | \$487 |
| 1599000 | Rauwolfia Serpentina (15 g) | G |  |  | [8063-17-0] | \$156 |
| 1599500 | Powdered Red Clover Extract ( 500 mg ) | F0C188 |  |  | n/f | \$260 |
| 1600813 | Repaglinide ( 200 mg ) | F0B265 |  |  | [135062-02-1] | \$156 |
| 1600824 | Repaglinide Related Compound A (50 mg) ((S)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butylamine, N -acetyl-L-glutamate salt) | F0B267 |  |  | n/f | \$487 |
| 1600835 | Repaglinide Related Compound B ( 50 mg ) (3-Ethoxy-4-ethoxycarbo-nyl-phenylacetic acid) | F0B269 |  |  | [99469-99-5] | \$487 |
| 1600846 | Repaglinide Related Compound C (25 mg) ((S)-2-Ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl] benzoic acid) | F0B271 |  |  | [107362-12-9] | \$487 |
| 1601000 | Reserpine ( 200 mg ) | O0C106 |  | N (06/03) | [50-55-5] | \$156 |
| 1602003 | Resorcinol ( 200 mg ) | H-1 |  | H (04/01) | [108-46-3] | \$156 |
| 1602706 | Ribavirin ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G (08/01) | [36791-04-5] | \$289 |
| 1603006 | Riboflavin (500 mg) (Vitamin B2) | N0C021 |  | $\begin{aligned} & \text { M-1 (09/04) } \\ & \text { M (11/00) } \end{aligned}$ | [83-88-5] | \$156 |
| 1603800 | Rifabutin ( 50 mg ) | G0B040 |  | F (11/02) | [72559-06-9] | \$156 |
| 1604009 | Rifampin ( 300 mg ) | $J$ |  | I (09/00) | [13292-46-1] | \$156 |
| 1604202 | Rifampin Quinone ( 50 mg ) | H |  | G (12/01) | [13983-13-6] | \$156 |
| 1604508 | Rimantadine Hydrochloride ( 300 mg ) | F0C266 |  |  | [1501-84-4] | \$156 |
| 1604600 | Rimexolone ( 100 mg ) | F |  |  | [49697-38-3] | \$156 |
| 1604701 | Ritodrine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G-1 |  |  | [23239-51-2] | \$156 |
| 1606208 | Roxarsone ( 200 mg ) | F |  |  | [121-19-7] | \$156 |
| 1606503 | Rutin ( 100 mg ) | F |  |  | [153-18-4] | \$156 |
| 1607007 | Saccharin (200 mg) | G-3 |  | G-2 (12/01) | [81-07-2] | \$156 |
| 1608000 | Salicylamide (200 mg) | F-4 |  | F-3 (05/03) | [65-45-2] | \$156 |
| 1609002 | Salicylic Acid (125 mg) | J2B147 |  | $\begin{array}{\|l} \hline \mathrm{J}-1(10 / 03) \\ \mathrm{J}(10 / 02) \\ \mathrm{I}(07 / 99) \\ \hline \end{array}$ | [69-72-7] | \$124 |
| 1609501 | Salicylic Acid Tablets (Dissolution Calibrator, Non-disintegrating) (33 tablets) | 0 |  | N (02/02) | [69-72-7] | \$156 |
| 1609807 | Salsalate ( 125 mg ) | G |  |  | [552-94-3] | \$124 |
| 1609829 | Saquinavir Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | F0B008 |  |  | [149845-06-7] | \$156 |
| 1609831 | Saquinavir Related Compound A ( 25 mg ) ( N -tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-D-asparaginyl]a-mino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide) | F0B009 |  |  | n/f | \$487 |
| 1610001 | Scopolamine Hydrobromide ( 250 mg ) | J0B051 |  | I-1 (01/03) | [6533-68-2] | \$156 |
| 1610090 | Scopoletin (20 mg) | F0C329 |  |  | [92-61-5] | \$156 |
| 1611004 | Secobarbital CII (200 mg) | H |  |  | [76-73-3] | \$207 |
| 1611900 | Selegiline Hydrochloride (200 mg) | G |  |  | [14611-52-0] | \$156 |
| 1611955 | Selenomethionine (100 mg) | F0B006 |  |  | [1464-42-2] | \$156 |

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| 1612007 | Sennosides ( 250 mg ) | H1B223 |  | H (04/04) | $\begin{aligned} & {[81-27-6] \quad(A)} \\ & {[128-57-4] \text { (B) }} \end{aligned}$ | \$156 |
| 1612506 | L-Serine ( 200 mg ) | G |  | F-3 (11/00) | [56-45-1] | \$156 |
| 1612540 | Sevoflurane (1 mL) | F0C219 |  |  | [28523-86-6] | \$156 |
| 1612550 | Sevoflurane Related Compound A ( 0.2 mL ) (1,1,3,3,3-Pentafluoroisopropenyl fluoromethyl ether) | F0C261 |  |  | [58109-34-5] | \$487 |
| 1612608 | Silver Sulfadiazine (200 mg) | 1 |  | H (04/01) | [22199-08-2] | \$156 |
| 1612630 | Silybin ( 50 mg ) | F |  |  | [22888-70-6] | \$156 |
| 1612641 | Silydianin ( 20 mg ) | F |  |  | [29782-68-1] | \$156 |
| 1612652 | Simethicone ( 50 g ) | G |  | F (07/00) | [8050-81-5] | \$156 |
| 1612700 | Simvastatin (200 mg) | H1B093 |  | $\begin{array}{\|l\|} \hline \text { H (07/03) } \\ \text { G (02/02) } \\ \text { F-1 (05/99) } \\ \hline \end{array}$ | [79902-63-9] | \$156 |
| 1612801 | Sisomicin Sulfate (500 mg) | 10C238 |  | $\begin{array}{\|l} \hline H(04 / 04) \\ G(10 / 00) \\ \hline \end{array}$ | [53179-09-2] | \$156 |
| 1613509 | Sodium Ascorbate (200 mg) | G-1 |  |  | [134-03-2] | \$156 |
| 1613600 | Sodium Butyrate ( 25 mg ) | F |  |  | [156-54-7] | \$156 |
| 1614002 | Sodium Fluoride ( 1 g ) | H-1 |  | H (05/01) | [7681-49-4] | \$156 |
| 1614308 | Sodium Lactate (200 mg) | H |  | G (06/00) | [867-56-1] | \$156 |
| 1614501 | Sodium Nitroprusside ( 500 mg ) | H |  | G (11/99) | [13755-38-9] | \$156 |
| 1614603 | Sodium Propionate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  | F (03/02) | [6700-17-0] | \$156 |
| 1614669 | Sodium Starch Glycolate ( 400 mg ) | F0C087 |  |  | [9063-38-1] | \$156 |
| 1614705 | Sodium Stearyl Fumarate ( 200 mg ) | G |  | F-2 (05/01) | [4070-80-8] | \$156 |
| 1616008 | 1,4-Sorbitan (200 mg) | 10A003 |  | $\begin{aligned} & \hline \text { H }(04 / 03) \\ & \mathrm{G}(02 / 00) \\ & \hline \end{aligned}$ | [27299-12-3] | \$156 |
| 1617000 | Sorbitol (125 mg) | H1B139 |  | H (01/04) | [50-70-4] | \$124 |
| 1617408 | Sotalol Hydrochloride ( 300 mg ) | FOC234 |  |  | [959-24-0] | \$182 |
| 1617419 | Sotalol Related Compound A ( 50 mg ) (N-[4-[[(1-Methylethyl)amino]acetyl] $]$ phenyl] $\mathrm{methanesulfonamide} \mathrm{monohydrochloride)}$ | F0C235 |  |  | n/f | \$487 |
| 1617420 | Sotalol Related Compound B ( 50 mg ) ( N -(4-Formylphenyl)methanesulfonamide) | F0C236 |  |  | n/f | \$487 |
| 1617430 | Sotalol Related Compound C ( 50 mg ) (N-[4-[2-[(1-Methylethyl)amino]ethyl]phenyl]methanesulfonamide hydrochloride) | F0C237 |  |  | n/f | \$487 |
| 1618003 | Spectinomycin Hydrochloride ( 200 mg ) | F-2 |  |  | [22189-32-8] | \$156 |
| 1619006 | Spironolactone ( 125 mg ) | J-1 |  |  | [52-01-7] | \$124 |
| 1619505 | Squalane ( 500 mg ) | G-1 |  |  | [111-01-3] | \$156 |
| 1620005 | Stanozolol CIII ( 200 mg ) | F-3 |  | F-2 (02/01) | [10418-03-8] | \$207 |
| 1621008 | Stearic Acid ( 500 mg ) | J |  | I (10/01) | [57-11-4] | \$156 |
| 1621507 | Stearoyl Polyoxyglycerides (100 mg) | F0C286 |  |  | n/f | \$156 |
| 1622000 | Stearyl Alcohol (125 mg) | H2B217 | 2 | $\begin{aligned} & \text { H-1 (12/04) } \\ & \text { H (09/99) } \\ & \hline \end{aligned}$ | [112-92-5] | \$124 |
| 1623003 | Streptomycin Sulfate (200 mg) | J0B195 |  | I (04/03) | [3810-74-0] | \$156 |
| 1623502 | Succinylcholine Chloride ( 500 mg ) | H |  |  | [71-27-2] | \$156 |
| 1623604 | Succinylmonocholine Chloride ( 150 mg ) | G |  | F-1 (02/01) | n/f | \$487 |
| 1623626 | Sucralose ( 400 mg ) | G0B028 |  | F (04/03) | [56038-13-2] | \$156 |
| 1623637 | Sucrose (100 mg) | H1C223 | 2 | $\begin{array}{\|l\|l\|} \hline \text { HOB002 (11/04) } \\ \text { G-1 (03/03) } \\ \text { G (05/99) } \\ \hline \end{array}$ | [57-50-1] | \$156 |
| 1623648 | Sufentanil Citrate CII (25 mg) | H0B208 |  | $\begin{array}{\|l} \hline \text { G (05/03) } \\ \text { F-1 (04/02) } \\ \text { F (09/99) } \\ \hline \end{array}$ | [60561-17-3] | \$207 |

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| 1623670 | Sulbactam ( 250 mg ) | G |  | F-1 (05/00) | [68373-14-8] | \$156 |
| 1623681 | Sulconazole Nitrate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  | F (05/02) | [61318-91-0] | \$156 |
| 1623706 | Sulfabenzamide ( 200 mg ) | G |  |  | [127-71-9] | \$156 |
| 1623808 | Sulfacetamide ( 300 mg ) | G-1 |  |  | [144-80-9] | \$156 |
| 1624006 | Sulfacetamide Sodium (500 mg) | 11B318 |  | $\begin{array}{\|l\|} \hline I(09 / 04) \\ H(08 / 01) \\ \hline \end{array}$ | [6209-17-2] | \$156 |
| 1624505 | Sulfachlorpyridazine (200 mg) | F |  |  | [80-32-0] | \$156 |
| 1625009 | Sulfadiazine ( 200 mg ) | J |  | $1(03 / 04)$ | [68-35-9] | \$156 |
| 1626001 | Sulfadimethoxine (200 mg) | F4C298 | 2 | $\begin{aligned} & \text { F-3 }(11 / 04) \\ & \text { F-2 (03/99) } \\ & \hline \end{aligned}$ | [122-11-2] | \$156 |
| 1626500 | Sulfadoxine (200 mg) | F-2 |  | F-1 (07/02) | [2447-57-6] | \$156 |
| 1628007 | Sulfamerazine ( 500 mg ) | H1C171 | 2,3 | H (12/04) | [127-79-7] | \$156 |
| 1629000 | Sulfamethazine (1 g) | G-3 |  |  | [57-68-1] | \$156 |
| 1630009 | Sulfamethizole (200 mg) | F-3 |  | F-2 (01/03) | [144-82-1] | \$156 |
| 1631001 | Sulfamethoxazole ( 200 mg ) | I-1 |  | I (04/02) | [723-46-6] | \$156 |
| 1631500 | Sulfamethoxazole N4-glucoside ( 25 mg ) | H |  | G (11/01) | n/f | \$487 |
| 1632004 | Sulfanilamide (5 g) | O0B047 |  | N (01/04) | [63-74-1] | \$156 |
| 1633007 | Sulfanilamide Melting Point Standard ( 500 mg ) (Approximately 165 degrees) | K0B133 |  | $\begin{array}{\|l} \hline \mathrm{J}-1(03 / 04) \\ \mathrm{J}(09 / 99) \\ \hline \end{array}$ | [63-74-1] | \$75 |
| 1633506 | Sulfanilic Acid (200 mg) | G |  | F-2 (09/00) | [121-57-3] | \$487 |
| 1634000 | Sulfapyridine (200 mg) | IOB298 |  | H (07/04) | [144-83-2] | \$156 |
| 1635002 | Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees) | J |  | I (07/00) | [144-83-2] | \$92 |
| 1635206 | Sulfaquinoxaline ( 200 mg ) | F0A005 |  |  | [59-40-5] | \$156 |
| 1636005 | Sulfasalazine ( 125 mg ) | G-2 |  | G-1 (06/99) | [599-79-1] | \$124 |
| 1636504 | Sulfathiazole ( 350 mg ) | H |  | G (08/00) | [72-14-0] | \$156 |
| 1637008 | Sulfinpyrazone ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | [57-96-5] | \$156 |
| 1638000 | Sulfisoxazole (200 mg) | $J$ |  | I-1 (06/99) | [127-69-5] | \$156 |
| 1639003 | Sulfisoxazole Acetyl ( 200 mg ) | H-1 |  |  | [80-74-0] | \$156 |
| 1640002 | Sulfisoxazole Diolamine ( 500 mg ) | F |  |  | [4299-60-9] | \$156 |
| 1642008 | Sulindac ( 200 mg ) | H |  | G-1 (12/01) | [38194-50-2] | \$156 |
| 1642154 | Sumatriptan ( 50 mg ) | F0C220 |  |  | [103628-46-2] | \$208 |
| 1642201 | Sumatriptan Succinate ( 200 mg ) | F0C231 |  |  | [103628-48-4] | \$208 |
| 1642212 | Sumatriptan Succinate Related Compound A (15 mg) ([3-[2-(dimethy-lamino)ethyl]-2-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-1H-in-dol-5-yl]-N-methylmethansulfonamide, succinate salt) | F0C221 |  |  | n/f | \$624 |
| 1642223 | Sumatriptan Succinate Related Compound C ( 50 mg ) ([3-[2-(dimethy-lamino)ethyl]-1-(hydroxymethyl)-1H-indol-5-yl]-N-methylmethanesulfonamide succinate salt) | F0C230 |  |  | n/f | \$624 |
| 1642507 | Suprofen ( 200 mg ) | F |  |  | [40828-46-4] | \$156 |
| 1642700 | Tacrine Hydrochloride ( 500 mg ) | FOC119 |  |  | [1684-40-8] | \$156 |
| 1643000 | Talbutal CIII (250 mg) | F |  |  | [115-44-6] | \$207 |
| 1643306 | Tamoxifen Citrate (200 mg) | H |  | $\begin{aligned} & \text { G-2 (09/01) } \\ & \text { G-1 }(05 / 00) \\ & \hline \end{aligned}$ | [54965-24-1] | \$156 |
| 1643361 | Taurine ( 100 mg ) | FOC104 |  |  | [107-35-7] | \$156 |
| 1643408 | Temazepam CIV (200 mg) | H0C205 |  | $\begin{aligned} & \hline G(06 / 04) \\ & F(12 / 99) \\ & \hline \end{aligned}$ | [846-50-4] | \$207 |
| 1643452 | Terazosin Hydrochloride (200 mg) | F0C244 |  |  | [70024-40-7] | \$156 |
| 1643463 | Terazosin Related Compound A (50 mg) (1-(4-Amino-6,7-dimethoxy-2quinazolinyl)piperazine dihydrochloride) | F0C245 |  |  | n/f | \$487 |

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| 1643474 | Terazosin Related Compound B (50 mg) (1-(4-hydroxy-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]piperazine) | F0C218 |  |  | n/f | \$487 |
| 1643485 | Terazosin Related Compound C (25 mg) (1,4-bis(4-amino-6,7-di-methoxy-2-quinazolinyl)piperazine dihydrochloride) | F0C257 |  |  | n/f | \$487 |
| 1643500 | Terbutaline Sulfate ( 125 mg ) | H |  | G (04/99) | [23031-32-5] | \$124 |
| 1643703 | Terconazole (200 mg) | G-2 |  | $\begin{aligned} & \hline \text { G-1(04/01) } \\ & \text { G (03/99) } \\ & \hline \end{aligned}$ | [67915-31-5] | \$156 |
| 1643805 | Terfenadine (200 mg) | H |  | G (12/99) | [50679-08-8] | \$156 |
| 1643907 | Terfenadine Related Compound A (100 mg) (1-[4-(1,1-dimethylethyl)-phenyl]-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-butanone) | G |  |  | n/f | \$487 |
| 1643929 | Terfenadine Related Compound B ( 50 mg ) (Terfenadine-N-oxide) | F |  |  | n/f | \$487 |
| 1644003 | Terpin Hydrate ( 750 mg ) | G |  |  | [2451-01-6] | \$156 |
| 1645006 | Testolactone CIII ( 125 mg ) | F-1 |  |  | [968-93-4] | \$165 |
| 1646009 | Testosterone CIII (125 mg) | 11B253 |  | 1 (08/04) | [58-22-0] | \$165 |
| 1647001 | Testosterone Cypionate CIII ( $200 \mathrm{mg} \mathrm{)}$ | G-1 |  | G (08/01) | [58-20-8] | \$207 |
| 1648004 | Testosterone Enanthate CIII ( 200 mg ) | J |  |  | [315-37-7] | \$207 |
| 1649007 | Testosterone Propionate CIII ( 200 mg ) | L1C005 |  | $\begin{array}{\|l\|} \hline \text { L (08/04) } \\ \text { K-1 }(11 / 01) \\ \hline \end{array}$ | [57-85-2] | \$207 |
| 1650006 | Tetracaine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | J |  |  | [136-47-0] | \$156 |
| 1651009 | Tetracycline Hydrochloride ( 200 mg ) | K |  |  | [64-75-5] | \$156 |
| 1652001 | Tetrahydrozoline Hydrochloride ( 200 mg ) | G1A015 |  | G (03/03) | [522-48-5] | \$156 |
| 1652500 | Thalidomide ( 200 mg ) | F0C107 |  |  | [50-35-1] | \$182 |
| 1653004 | Theophylline (200 mg) | J0B180 |  | I (01/04) | [58-55-9] | \$156 |
| 1653106 | Theophylline Extended-Release Beads (Drug Release Calibrator, Multiple Unit) (20 g) |  |  | F-1 (11/04) | [58-55-9] | \$156 |
| 1655000 | Thiabendazole (100 mg) | G0A027 |  | $\begin{array}{\|l} \hline \text { F-1 (04/03) } \\ \text { F (04/01) } \\ \hline \end{array}$ | [148-79-8] | \$156 |
| 1656002 | Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride) | 0 |  | $\begin{array}{\|l\|} \hline \mathrm{N}(11 / 02) \\ \mathrm{M}-1(04 / 99) \\ \hline \end{array}$ | [67-03-8] | \$156 |
| 1656308 | Thiamylal CIII ( 200 mg ) | F |  |  | [77-27-0] | \$207 |
| 1657005 | Thiethylperazine Malate ( $200 \mathrm{mg} \mathrm{)}$ | G |  | F-1 (09/00) | [52239-63-1] | \$156 |
| 1658008 | Thiethylperazine Maleate ( 200 mg ) | F-1 |  |  | [1179-69-7] | \$156 |
| 1659000 | Thimerosal ( 500 mg ) | H1B205 |  | $\begin{aligned} & \mathrm{H}(09 / 04) \\ & \mathrm{G}(12 / 99) \end{aligned}$ | [54-64-8] | \$156 |
| 1660000 | Thioguanine (200 mg) | F-1 |  |  | [154-42-7] | \$156 |
| 1661002 | Thiopental CIII ( 250 mg ) | 1 |  |  | [76-75-5] | \$207 |
| 1662504 | Thioridazine ( 200 mg ) | H |  |  | [50-52-2] | \$156 |
| 1663008 | Thioridazine Hydrochloride ( 200 mg ) | H |  |  | [130-61-0] | \$156 |
| 1663700 | Thiostrepton ( 200 mg ) | F1B022 |  | F (11/02) | [1393-48-2] | \$156 |
| 1664000 | Thiotepa ( 500 mg ) | 1 |  | H (01/99) | [52-24-4] | \$156 |
| 1665003 | Thiothixene ( 250 mg ) | G |  |  | [3313-26-6] | \$156 |
| 1666006 | (E)-Thiothixene (100 mg) | H |  | G-1 (05/00) | [3313-27-7] | \$487 |
| 1667100 | Thonzonium Bromide ( 200 mg ) | F |  |  | [553-08-2] | \$156 |
| 1667202 | L-Threonine ( 200 mg ) | G |  | F-3 (12/00) | [72-19-5] | \$156 |
| 1667279 | Thromboplastin, Human Recombinant (set) (1 vial Thromboplastin and 1 vial Diluent) DISCONTINUED |  |  | F (10/04) | [9002-05-5] | \$156 |
| 1667290 | Tiamulin Fumarate ( $250 \mathrm{mg} \mathrm{)}$ | F0C327 |  |  | [55297-96-6] | \$156 |
| 1667337 | Tiamulin Related Compound A (50 mg) (Tosyl pleuromutilin) | F0C328 |  |  | n/f | \$494 |
| 1667304 | Ticarcillin Monosodium Monohydrate ( 200 mg ) | H |  | G-1 (03/99) | [74682-62-5] | \$156 |
| 1667359 | Tiletamine Hydrochloride ( 200 mg ) | F0C019 |  |  | [14176-50-2] | \$156 |
| 1667406 | Timolol Maleate (200 mg) | G-1 |  |  | [26921-17-5] | \$156 |

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| 1667520 | Tinidazole (200 mg) | F0C093 |  |  | [19387-91-8] | \$156 |
| 1667530 | Tinidazole Related Compound A (100 mg) (2-methyl-5-nitroimidazole) | F0C091 |  |  | [696-23-1] | \$487 |
| 1667439 | Tioconazole ( 200 mg ) | H |  | G (04/02) | [65899-73-2] | \$156 |
| 1667450 | Tioconazole Related Compound A (25 mg) (1-[2,4-Dichloro-beta-[(3-thenyl)-oxy]phenethyl]jimidazole Hydrochloride) | G |  |  | n/f | \$487 |
| 1667461 | Tioconazole Related Compound B (25 mg) (1-[2,4-Dichloro-beta-[(2,5-dichloro-3-thenyl)oxy]phenethyl]imidazole Hydrochloride) | G |  |  | n/f | \$487 |
| 1667472 | Tioconazole Related Compound C ( 25 mg ) (1-[2,4-Dichloro-beta-[(5-bromo-2-chloro-3-thenyl)-oxy]-phenethyl]imidazole Hydrochloride) | G |  |  | n/f | \$487 |
| 1667508 | Tobramycin (250 mg) | K0B248 |  | $J(08 / 03)$ | [32986-56-4] | \$156 |
| 1667552 | Tocainide Hydrochloride ( 125 mg ) | F-1 |  | F (04/99) | [35891-93-1] | \$124 |
| 1667600 | Alpha Tocopherol (250 mg) (Vitamin E Alcohol) | M |  | L-1 (01/00) | [10191-41-0] | \$156 |
| 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) | K |  | J (06/99) | [7695-91-2] | \$156 |
| 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) | F-5 |  | F-4 (01/02) | [4345-03-3] | \$156 |
| 1668001 | Tolazamide (200 mg) | G-2 |  | G-1 (06/00) | [1156-19-0] | \$156 |
| 1669004 | Tolazoline Hydrochloride ( 300 mg ) | F |  |  | [59-97-2] | \$156 |
| 1670003 | Tolbutamide ( 200 mg ) | 1 |  | H (06/00) | [64-77-7] | \$156 |
| 1670502 | Tolmetin Sodium ( 500 mg ) | IOB064 |  | H (09/03) | [64490-92-2] | \$156 |
| 1671006 | Tolnaftate (200 mg) | I |  |  | [2398-96-1] | \$156 |
| 1672009 | Toluenesulfonamides, ortho and para (200 mg of each supplied in a set) | F-4 |  | F-3 (11/99) | $\begin{aligned} & {[88-19-7](\mathrm{o})} \\ & {[70-55-3] \text { (p) }} \end{aligned}$ | \$487 |
| 1672304 | Torsemide ( 200 mg ) | F0B090 |  |  | [56211-40-6] | \$156 |
| 1672315 | Torsemide Related Compound A (75 mg) (4-[(3-methylphenyl)amino]-3-pyridinesulfonamide) | F0B071 |  |  | n/f | \$487 |
| 1672326 | Torsemide Related Compound B (75 mg) (N-[(n-butylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide) | F0B083 |  |  | n/f | \$487 |
| 1672337 | Torsemide Related Compound C (75 mg) (N-[(ethylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide) | F0B078 |  |  | n/f | \$487 |
| 1672803 | Transplatin ( 25 mg ) | H0B287 |  | G (03/04) | [14913-33-8] | \$487 |
| 1673500 | Trazodone Hydrochloride ( 200 mg ) | F-2 |  |  | [25332-39-2] | \$156 |
| 1674004 | Tretinoin ( $30 \mathrm{mg} / \mathrm{ampule;} 5$ ampules) | I2B185 |  | $\begin{array}{\|l} \hline \text { I-1 (01/04) } \\ \text { I (01/02) } \\ H(06 / 01) \\ \hline \end{array}$ | [302-79-4] | \$156 |
| 1675007 | Triacetin (1 g) | G-1 |  | G (06/01) | [102-76-1] | \$156 |
| 1676000 | Triamcinolone ( 250 mg ) | H-1 |  |  | [124-94-7] | \$156 |
| 1677002 | Triamcinolone Acetonide ( 500 mg ) | K |  | J (03/99) | [76-25-5] | \$156 |
| 1678005 | Triamcinolone Diacetate ( 200 mg ) | G |  |  | [67-78-7] | \$156 |
| 1679008 | Triamcinolone Hexacetonide ( 125 mg ) | G |  |  | [5611-51-8] | \$124 |
| 1680007 | Triamterene ( 200 mg ) | 1 |  |  | [396-01-0] | \$156 |
| 1680506 | Triazolam CIV (200 mg) | H0B041 |  | G-1 (03/03) | [28911-01-5] | \$207 |
| 1680608 | Tributyl Citrate ( 500 mg ) | F |  |  | [77-94-1] | \$156 |
| 1680801 | Trichlorfon ( 200 mg ) | F |  |  | [52-68-6] | \$156 |
| 1681000 | Trichlormethiazide ( 200 mg ) | H |  |  | [133-67-5] | \$156 |
| 1682206 | Triclosan (200 mg) | FOB135 |  |  | [3380-34-5] | \$156 |
| 1683005 | Tridihexethyl Chloride ( 200 mg ) | F-1 |  |  | [4310-35-4] | \$156 |
| 1683504 | Trientine Hydrochloride (125 mg) | F2B257 |  | $\begin{array}{\|l\|l\|} \hline \text { F-1 (09/03) } \\ \text { F (08/96) } \\ \hline \end{array}$ | [38260-01-4] | \$124 |
| 1683606 | Triethyl Citrate ( 500 mg ) | F-1 |  | F (03/02) | [77-93-0] | \$156 |
| 1685000 | Trifluoperazine Hydrochloride ( 200 mg ) | H0A010 |  | G (03/03) | [440-17-5] | \$156 |
| 1685500 | 2-[ N -(2,2,2-Trifluoro-ethyl)amino-5]-chlorobenzophenone ( 25 mg ) | F |  |  | n/f | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1686003 | Triflupromazine Hydrochloride (200 mg) | F-2 |  | F-1 (03/04) | [1098-60-8] | \$156 |
| 1686309 | Trifluridine (200 mg) | F |  |  | [70-00-8] | \$156 |
| 1686310 | Trifluridine Related Compound A (20 mg) (5-Carboxy-2'-deoxyuridine) | F |  |  | [14599-46-3] | \$487 |
| 1687006 | Trihexyphenidyl Hydrochloride (200 mg) | $J$ |  | 1 (07/01) | [52-49-3] | \$156 |
| 1689001 | Trimeprazine Tarrrate (200 mg) | F-3 |  | F-2 (08/01) | [4330-99-8] | \$156 |
| 1690000 | Trimethadione (200 mg) | G |  |  | [127-48-0] | \$156 |
| 1692006 | Trimethobenzamide Hydrochloride ( 500 mg ) | H-2 |  | H-1 (06/02) | [554-92-7] | \$156 |
| 1692505 | Trimethoprim ( 300 mg ) | J0B228 |  | 1 (01/04) | [738-70-5] | \$156 |
| 1693009 | Trioxsalen (200 mg) | H0C278 |  | G (04/04) | [3902-71-4] | \$156 |
| 1694001 | Tripelennamine Citrate ( 200 mg ) | G |  | F (02/03) | [6138-56-3] | \$156 |
| 1695004 | Tripelennamine Hydrochloride (200 mg) | $J$ |  |  | [154-69-8] | \$156 |
| 1696007 | Triprolidine Hydrochloride ( 500 mg ) | 1 |  | H-1 (02/02) | [6138-79-0] | \$156 |
| 1696109 | Triprolidine Hydrochloride Z-Isomer (100 mg) | G |  | F-1 (02/02) | n/f | \$487 |
| 1696200 | Trisalicylic Acid (100 mg) | G |  | F-1 (10/99) | n/f | \$487 |
| 1697000 | Troleandomycin (250 mg) | F-1 |  |  | [2751-09-9] | \$156 |
| 1698002 | Tromethamine (125 mg) | G |  | F-3 (07/99) | [77-86-1] | \$124 |
| 1699005 | Tropicamide ( 125 mg ) | G-1 |  | G (02/99) | [1508-75-4] | \$124 |
| 1700002 | Trypsin Crystallized ( 300 mg ) | H |  | G (12/99) | [9002-07-7] | \$156 |
| 1700501 | L-Tryptophan (200 mg) | G-1 |  | G (09/00) | [73-22-3] | \$156 |
| 1702008 | Tubocurarine Chloride ( 250 mg ) | K-1 |  |  | [6989-98-6] | \$156 |
| 1703805 | Tylosin (250 mg) | F0C008 |  |  | [1401-69-0] | \$156 |
| 1704003 | Tyloxapol (600 mg) | H |  | G (02/00) | [25301-02-4] | \$156 |
| 1704502 | Tyropanoate Sodium ( 500 mg ) | F |  |  | [7246-21-1] | \$156 |
| 1705006 | L-Tyrosine ( 500 mg ) | $J$ |  |  | [60-18-4] | \$156 |
| 1705301 | Ubidecarenone (200 mg) | F0B191 |  |  | [303-98-0] | \$156 |
| 1705312 | Ubidecarenone for System Suitability ( 25 mg ) | FOB194 |  |  | [303-98-0] | \$156 |
| 1705505 | Undecylenic Acid (200 mg) | G2C018 |  | $\begin{aligned} & \text { G-1 (11/04) } \\ & \text { G (01/02) } \\ & \hline \end{aligned}$ | [112-38-9] | \$156 |
| 1705800 | Uracil Arabinoside ( 50 mg ) | G |  | F-1 (06/99) | [3083-77-0] | \$156 |
| 1706009 | Uracil Mustard ( 500 mg ) | F |  |  | [66-75-1] | \$156 |
| 1706701 | Urea C 13 (100 mg) | F0C078 |  |  | [57-13-6] | \$182 |
| 1707806 | Ursodiol ( 125 mg ) | G |  | $\begin{aligned} & \hline \text { F-1 (11/01) } \\ & \text { F (09/99) } \\ & \hline \end{aligned}$ | [128-13-2] | \$124 |
| 1707908 | Valerenic Acid (25 mg) | G0B146 |  | F (01/04) | [3569-10-6] | \$696 |
| 1708503 | L-Valine ( 200 mg ) | F-2 |  | F-1 (05/02) | [72-18-4] | \$156 |
| 1708707 | Valproic Acid (500 mg) | J1B127 |  | $\begin{aligned} & \mathrm{J}(01 / 04) \\ & \mathrm{I}-1(11 / 00) \\ & \hline \end{aligned}$ | [99-66-1] | \$156 |
| 1708729 | Valproic Acid Related Compound A ( 0.25 mL ) (diallylacetic acid) | F1B156 |  | F (01/03) | [99-67-2] | \$208 |
| 1708773 | Valsartan Related Compound A (20 mg) ((R)-N-Valeryl-N-([2'-(1-H-tetrazole)-5-yl)-biphenyl-4-yl]-methyl)-valine) | F0C215 |  |  | n/f | \$624 |
| 1708795 | Valsartan Related Compound C (10 mg) ((S)-N-Valeryl-N-([2'-(1-H-tetrazole)-5-yl)-biphenyl-4-yl]-methyl)-valine benzyl ester) | F0C208 |  |  | n/f | \$624 |
| 1709007 | Vancomycin Hydrochloride (4 vials, each vial contains $100,500 \mathrm{mcg}$ of vancomycin activity) | L |  | K (08/01) | [1404-93-9] | \$156 |
| 1710006 | Vanillin (200 mg) | 1 |  | H (04/99) | [121-33-5] | \$156 |
| 1711009 | Vanillin Melting Point Standard (1 g) (Approximately 82 degrees) | J |  | $\begin{aligned} & \text { I-1 (03/03) } \\ & \text { I (11/00) } \\ & \hline \end{aligned}$ | [121-33-5] | \$92 |
| 1711155 | Vecuronium Bromide (60 mg) | F0C367 | 1 |  | [50700-72-6] | \$156 |
| 1711166 | Vecuronium Bromide Related Compound A ( 25 mg ) (3alpha, 17beta-diacetyl-oxy-2beta, 16beta-bispiperidinyl-5alpha-androstan) | F0B178 |  |  | n/f | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1711202 | Verapamil Hydrochloride (200 mg) | G |  | F-4 (06/00) | [152-11-4] | \$156 |
| 1711304 | Verapamil Related Compound A (50 mg) (3,4-Dimethoxy-alpha-[3-(methylamino)propyl]-alpha-(1-methylethyl)-benzeneacetonitrile monoHydrochloride) | H |  | G (01/01) | n/f | \$487 |
| 1711406 | Verapamil Related Compound B ( 50 mg ) (alpha-[2-[[2-(3,4-dimethox-yphenyl)-ethyl]methylamino]ethyl]-3,4-dimethoxy-alpha-(1-methylethyl)benzeneacetonitrile monoHydrochloride) | G |  |  | [1794-55-4] | \$487 |
| 1711461 | Verteporfin ( 200 mg ) | F0C166 |  |  | [129497-78-5] | \$156 |
| 1711472 | Verteporfin Related Compound A (50 mg) ((+/-)18-Ethenyl-4,4a-dihy-dro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23H,25H-ben-zo[b]prophine-9,13-dipropanoic acid) | F0C167 |  |  | n/f | \$487 |
| 1711508 | Vidarabine ( 200 mg ) | G-1 |  |  | [24356-66-9] | \$156 |
| 1713004 | Vinblastine Sulfate ( 50 mg ) | M0B308 | 2,3 | $\begin{aligned} & \hline \text { L (12/04) } \\ & \text { K (05/99) } \end{aligned}$ | [143-67-9] | \$354 |
| 1714007 | Vincristine Sulfate ( $50 \mathrm{mg} / \mathrm{ampule}$ ) | O0B062 |  | $\begin{aligned} & \hline N(01 / 03) \\ & M(04 / 99) \end{aligned}$ | [2068-78-2] | \$479 |
| 1714506 | Vinorelbine Tartrate (200 mg) | F0C243 |  |  | [125317-39-7] | \$156 |
| 1714528 | Vinorelbine Related Compound A ( 25 mg ) (4-O-Deacetylvinorelbine tartrate) | F0C242 |  |  | n/f | \$487 |
| 1715000 | Viomycin Sulfate ( 200 mg ) | F |  |  | [37883-00-4] | \$156 |
| 1716002 | Vitamin A (10 ampules containing vitamin A acetate in cottonseed/ peanut oil) | VoC258 |  | U (04/04) | [127-47-9] | \$156 |
| 1717504 | Vitamin D Assay System Suitability (1.5 g) | F |  |  | [67-97-0] | \$156 |
| 1717708 | Vitexin ( 30 mg ) | F0C142 |  |  | [3681-93-4] | \$520 |
| 1719000 | Warfarin (200 mg) | 10B305 |  | $\begin{array}{\|l\|l\|} \hline \mathrm{H}-2(08 / 04) \\ \mathrm{H}-1(11 / 01) \\ \hline \end{array}$ | [81-81-2] | \$156 |
| 1719102 | Warfarin Related Compound A (50 mg) (3-(o-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one) | G1B111 |  | G (01/04) | [37209-23-7] | \$156 |
| 1720000 | Xanthanoic Acid (100 mg) | G-1 |  | G (12/00) | [82-07-5] | \$487 |
| 1720203 | Xanthone ( 100 mg ) | F-1 |  |  | [90-47-1] | \$487 |
| 1720407 | Xylazine ( 200 mg ) | F |  |  | [7361-61-7] | \$156 |
| 1720429 | Xylazine Hydrochloride ( 200 mg ) | F |  |  | [23076-35-9] | \$156 |
| 1720600 | Xylitol ( 1 g ) | G0B037 |  |  | [87-99-0] | \$156 |
| 1721002 | Xylometazoline Hydrochloride ( 125 mg ) | IOB101 |  | H-1 (05/03) | [1218-35-5] | \$124 |
| 1722005 | Xylose (1 g) | F |  |  | [58-86-6] | \$156 |
| 1724000 | Yohimbine Hydrochloride ( 200 mg ) | F |  |  | [65-19-0] | \$156 |
| 1724306 | Zalcitabine ( 200 mg ) | F |  |  | [7481-89-2] | \$156 |
| 1724317 | Zalcitabine Related Compound A (50 mg) (2',3'-Didehydro-2', $3^{\prime}$ 'dideoxycytidine) | F0B234 |  |  | [7481-88-1] | \$487 |
| 1724500 | Zidovudine ( 400 mg ) | G |  | F (09/01) | [30516-87-1] | \$156 |
| 1724521 | Zidovudine Related Compound B ( 25 mg ) (3'-chloro-3'-deoxythymidine) | G0B116 |  | $\begin{array}{\|l\|} \hline \text { F-1 (03/03) } \\ \hline \mathrm{F}(06 / 01) \\ \hline \end{array}$ | [25526-94-7] | \$487 |
| 1724532 | Zidovudine Related Compound C (100 mg) (thymine) | F-1 |  | F (09/01) | [65-71-4] | \$487 |
| 1724656 | Zileuton ( 150 mg ) | F0C062 |  |  | [111406-87-2] | \$156 |
| 1724667 | Zileuton Related Compound A ( 50 mg ) ( N -(1-Benzo[b]thien-2-ylethyl) urea) | F0B316 |  |  | n/f | \$487 |
| 1724678 | Zileuton Related Compound B (50 mg) (2-(Benzo[b]thien-2-oyl)benzo[b]thiophene) | F0B313 |  |  | n/f | \$487 |
| 1724689 | Zileuton Related Compound C (50 mg) (1-Benzo[b]thien-2-ylethanone) | F0B299 |  |  | n/f | \$487 |
| 1724805 | Zolazepam Hydrochloride ( 500 mg ) | G0C023 |  | $\begin{aligned} & \mathrm{F}-1(03 / 04) \\ & \mathrm{F}(05 / 02) \\ & \hline \end{aligned}$ | [33754-49-3] | \$156 |

## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. No. | New Description |
| :---: | :---: | :---: | :---: |
| 00200-6 | 5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid ( 50 mg ) (Limit Test) | 1184027 | Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid) |
| 02200-3 | 3-Amino-4-carboxamidopyrazole Hemisulfate ( 50 mg ) (Limit Test) | 1013024 | Allopurinol Related Compound A ( 50 mg ) (3-Amino-4-carboxamidopyrazole Hemisulfate) |
| 02250-2 | 4-Amino-6-chloro-1,3-benzenedisulfonamide ( 100 mg ) (Lim- it Test) | 1057507 | Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide) |
| 1023403 | 3-Amino-6-chloro-1-methyl-4-phenylcarbostyril (25 mg) | 1023403 | Diazepam Related Compound B ( 25 mg ) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril) |
| 02380-0 | 2-Amino-2'-chloro-5-nitrobenzophenone ( 25 mg ) (Limit Test) | 1140338 | Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5-nitrobenzophenone) |
| 02420-2 | 4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide ( 100 mg ) (Limit Test) | 1424018 | Methyclothiazide Related Compound A (100 mg) (4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide) |
| 02240-6 | 2-Amino-4-chlorophenol (50 mg) (Limit Test) | 1130527 | Chlorzoxazone Related Compound A (25 mg) ( 2-Amino-4chlorophenol) |
| 02460-0 | 3-Amino-4-(2-chloro-phenyl)-6-nitrocarbostyril (25 mg) (Limit Test) | 1140327 | Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril) |
| 02490-5 | 2-Amino-2',5-dichlorobenzophenone (25 mg) (Limit Test) | 1370338 | Lorazepam Related Compound B (25 mg) (2-Amino-2',5dichlorobenzophenone) |
| 02610-6 | 3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid ( 25 mg ) (Limit Test) Test) | 1078325 | Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid) |
| 02620-8 | alpha-Aminopropiophenone Hydrochloride ( 50 mg ) (Limit Test) | 1096804 | Cathinone Hydrochloride CI (50 mg) (alpha-Aminopropiophenone Hydrochloride) |
| 06300-0 | 5-Benzyl-3,6-dioxo-2-piperazineacetic Acid ( 250 mg ) (Limit Test) | 1043728 | Aspartame Related Compound A (75 mg) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid) |
| 07350-3 | 2-(4-Biphenylyl)propionic Acid (100 mg) (Limit Test) | 1285760 | Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid) |
| 07480-1 | N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide ( 50 mg ) (Limit Test) | 1344724 | lopamidol Related Compound A ( 50 mg ) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide) |
| 07500-4 | 4,4'-Bis[4-(p-chlorophenyl)-4-hydroxypiperidino]-butyrophenone ( 25 mg ) (Limit Test) | 1303013 | Haloperidol Related Compound A ( 25 mg ) ( $4,4-\operatorname{Bis}[4-\mathrm{p}-$ chlorophenyl)-4-hydroxypiperidino]-butyrophenone |
| 08650-5 | Calcium Formyltetrahydrofolate ( 50 mg ) (AS) (For Qualitiative Use Only) | 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) |
| 11230-0 | p-Chlorobenzhydrylpiperazine ( 25 mg ) | 1333058 | Hydroxyzine Related Compound A ( 25 mg ) (p-Chlorobenzhydrylpiperazine) |
| 11310-9 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxaldehyde ( 25 mg ) (Limit Test) | 1370349 | Lorazepam Related Compound C (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde) |
| 11320-0 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxylic Acid ( 25 mg ) (Limit Test) | 1370350 | Lorazepam Related Compound D ( 25 mg ) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid) |
| 11330-2 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazoline Methanol ( 25 mg ) (Limit Test) | 1370360 | Lorazepam Related Compound E (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol) |
| 11400-0 | 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one ( 50 mg ) (Limit Test) | 1468400 | Nordazepam CIV ( 50 mg ) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) |
| 11500-2 | 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one $4-\mathrm{oxide}$ ( 25 mg ) (Limit Test) | 1110020 | Chlordiazepoxide Related Compound A ( 25 mg ) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide) |
| 11510-4 | 2-Chloro-4-N-furfuryl-amino-5-sulfamolybenzoic acid ( 50 mg ) (Limit Test) | 1287020 | Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid) |
| 11550-1 | 2-Chloro-3,5-dimethyl-phenol (50 mg) (Limit Test) | 1122722 | Chloroxylenol Related Compound A (50 mg) (2-Chloro-3,5-dimethyl-phenol) |
| 11650-4 | (o-Chlorophenyl)diphenyl-methanol (25 mg) (Limit Test) | 1141024 | Clotrimazole Related Compound A ( 25 mg ) ((o-Chlorophe-nyl)diphenyl-methanol ) |
| 11670-8 | 4-(4-Chlorophenyl)-2-pyrrolidinone (75 mg) (Limit Test) | 1048222 | Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone) |

## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. <br> No. | New Description |
| :---: | :---: | :---: | :---: |
| 11900-3 | 4-Chloro-5-sulfamoylanthranilic Acid (100 mg) (Limit Test) | 1287030 | Furosemide Related Compound B (100 mg) (4-Chloro-5sulfamoylanthranilic Acid) |
| 1119309 | 4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid $(100 \mathrm{mg})$ | 1119309 | Chlorthalidone Related Compound A ( 25 mg ) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid) |
| 15870-8 | Cyclosporine U (25 mg) DISCONTINUED | 1158650 | Cyclosporine Resolution Mixture ( 25 mg ) (Replaces Cat. No. 15870-8 Cyclosporine U ( 25 mg )) |
| 21000-3 | alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride ( 125 mg ) (Limit Test) | 1575206 | Propoxyphene Related Compound A ( 50 mg ) (alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride) |
| 1268820 | Etoposide Related Compound A ( 25 mg ) (4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-alpha-D-glucopyranoside) DISCONTINUED | 1268852 | Etoposide Resolution Mixture ( 30 mg ) |
| 32720-4 | 3-Hydroxy-1-methylquinuclidinium Bromide ( 250 mg ) (Limit Test) | 1135021 | Clidinium Bromide Related Compound A ( 250 mg ) (3-Hydroxy -1-methylquinuclindinium Bromide) |
| 1329505 | 9-Hydroxypropantheline Bromide (50 mg) | 1329505 | Propantheline Bromide Related Compound A ( 50 mg ) (9Hydroxypropantheline bromide) |
| 1330005 | Hydroxypropyl Methylcellulose ( 250 mg ) | 1330005 | Hypromellose (250 mg) (Hydroxypropyl Methylcellulose) |
| 33010-7 | Hydroxypropyl Methylcellulose Phthalate ( 100 mg ) | 1335304 | Hypromellose Phthalate (100 mg) |
|  | Melting Point Standard - Acetanilide ( 500 mg ; approximately 114 degrees) | 1004001 | Acetanilide Melting Point Standard ( 500 mg ) (Approximately 114 degrees) |
|  | Melting Point Standard - Caffeine (1 g; approximately 236 degrees) | 1086006 | Caffeine Melting Point Standard (1 g) (Approximately 236 degrees) |
|  | Melting Point Standard - Phenacetin ( 500 mg ; approximately 135 degrees) | 1514008 | Phenacetin Melting Point Standard ( 500 mg ) (Approximately 135 degrees) |
|  | Melting Point Standard - Sulfanilamide ( 1 g ; approximately 165 degrees) | 1633007 | Sulfanilamide Melting Point Standard ( 500 mg ) (Approximately 165 degrees) |
|  | Melting Point Standard - Sulfapyridine (2 g; approximately 191 degrees) | 1635002 | Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees) |
|  | Melting Point Standard - Vanillin (1 g; approximately 82 degrees) | 1711009 | Vanillin Melting Point Standard (1 g) (Approximately 82 degrees) |
| 1420006 | 3-Methoxytyrosine ( 50 mg ) | 1420006 | Levodopa Related Compound B (50 mg) (3-Methoxytyrosine) |
| 42420-0 | 2-Methylamino-5-chlorobenzophenone (25 mg) (Limit Test) | 1185020 | Diazepam Related Compound A ( 25 mg ) (2-Methylamino-5chlorobenzophenone) |
| 42430-2 | 3-O-Methylcarbidopa ( 50 mg ) | 1095517 | Carbidopa Related Compound A ( 50 mg ) (3-O-Methylcarbidopa) |
| 46600-7 | 5-Nitro-2-furfuraldazine ( 500 mg ) | 1466007 | Nitrofurazone Related Compound A (500mg) (5-Nitro-2furfuraldazine) |
| 46660-8 | 3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid (25 mg) (Limit Test) | 1078336 | Bumetanide Related Compound B ( 25 mg ) (3-Nitro-4-phe-noxy-5-sulfamoylbenzoic Acid) |
| 1477900 | Octyl Methoxycinnamate ( 500 mg ) | 1477900 | Octinoxate ( 500 mg ) (Octyl Methoxycinnamate) |
| 49400-2 | Pancreatin (2 g) | $\begin{aligned} & 1494057 \\ & \text { and/or } \\ & 1494079 \\ & \hline \end{aligned}$ | Pancreatin Amylase and Protease ( 2 g ) and/or Pancreatin Lipase (2 g) |
| 53180-1 | Phenylcyclohexylglycolic Acid (100 mg) (Limit Test) | 1485114 | Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid) |
| 53350-1 | alpha-Phenyl-2-piperidineacetic Acid Hydrochloride ( 50 mg ) (Limit Test) | 1434022 | Methylphenidate Related Compound A (50 mg) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride) |
| 54500-1 | Plastic, Negative Control | 1546707 | Polyethylene, High Density (3 strips) |
| 61500-5 | Sodium Taurocholate (20 g) | 1071304 | Bile Salts (10 g) (Sodium Taurocholate) |
| 68800-9 | 3-(3,4,6-Trihydroxyphenyl)-alanine (50 mg) (Limit Test) | 1361010 | Levodopa Related Compound A ( 50 mg ) (3-(3,4,6-Trihydrox-yphenyl)-alanine) |
|  | Vitamin B1 Hydrochloride | 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) |
|  | Vitamin B2 | 1603006 | Riboflavin ( 500 mg ) (Vitamin B2) |
|  | Vitamin B3 | 1462006 | Niacinamide (500 mg) (Vitamin B3) |

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## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. No. | New Description |
| :---: | :---: | :---: | :---: |
|  | Vitamin B5 | 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) |
|  | Vitamin B6 | 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) |
|  | Vitamin B12 | 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) |
|  | Vitamim Bc | 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) |
|  | Vitamin C | 1043003 | Ascorbic Acid (1 g) (Vitamin C) |
|  | Vitamin D2 | 1239005 | Ergocalciferol ( $150 \mathrm{mg} ; 30 \mathrm{mg} / \mathrm{ampule} ; 5$ ampules) (Vitamin D2) |
|  | Vitamin D3 | 1131009 | Cholecalciferol (30 mg/ampul; 5 ampuls) (Vitamin D3) |
|  | Vitamin E Alcohol | 1667600 | Alpha Tocopherol (250 mg) (Vitamin E Alcohol) |
|  | Vitamin E Acetate | 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) |
|  | Vitamin E Acid Succinate | 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) |
|  | Vitamin K1 | 1538006 | Phytonadione ( 500 mg ) (Vitamin K1) |
|  | Vitamin K3 | 1381006 | Menadione ( 200 mg ) (Vitamin K3) |
|  | Vitamin M | 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) |

## Dietary Supplement Reference Standards Available from USP

| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| AMINO ACIDS |  |  |  |
| 1012509 | L-Alanine (200 mg) | F-2 | \$156 |
| 1021000 | Aminocaproic Acid (200 mg) | F-4 | \$156 |
| 1042500 | L-Arginine (200 mg) | G-1 | \$156 |
| 1042601 | Arginine Hydrochloride ( 125 mg ) | G0B060 | \$124 |
| 1161509 | L-Cysteine Hydrochloride ( 200 mg ) | H | \$156 |
| 1294976 | Glutamic Acid ( $200 \mathrm{mg} \mathrm{)}$ | F0C069 | \$156 |
| 1294808 | Glutamine ( 100 mg ) | FOB244 | \$156 |
| 1295800 | Glycine ( 200 mg ) | F-3 | \$156 |
| 1308505 | L-Histidine ( 200 mg ) | G0A018 | \$156 |
| 1349502 | L-Isoleucine (200 mg) | F-2 | \$156 |
| 1357001 | L-Leucine (200 mg) | H0B237 | \$156 |
| 1359903 | Levocarnitine ( 400 mg ) | G0B197 | \$156 |
| 1359925 | Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride) | F-1 | \$208 |
| 1371501 | L-Lysine Acetate ( $200 \mathrm{mg} \mathrm{)}$ | F1C027 | \$156 |
| 1372005 | L-Lysine Hydrochloride (200 mg) | H | \$156 |
| 1411504 | L-Methionine ( 200 mg ) | G | \$156 |
| 1530503 | L-Phenylalanine (200 mg) | H | \$156 |
| 1568506 | L-Proline (200 mg) | F-2 | \$156 |
| 1612506 | L-Serine ( 200 mg ) | G | \$156 |
| 1667202 | L-Threonine ( 200 mg ) | G | \$156 |
| 1700501 | L-Tryptophan (200 mg) | G-1 | \$156 |
| 1705006 | L-Tyrosine ( 500 mg ) | J | \$156 |
| 1708503 | L-Valine ( 200 mg ) | F-2 | \$156 |
| BOTANICALS |  |  |  |
| CAPSAICIN/CAPSICUM |  |  |  |
| 1091108 | Capsaicin (100 mg) | G-1 | \$156 |
| 1200600 | Dihydrocapsaicin (25 mg) | G0C071 | \$156 |
| CHAMOMILE |  |  |  |
| 1040708 | Apigenin-7-Glucoside ( 30 mg ) | F | \$487 |
| CRANBERRY LIQUID |  |  |  |
| 1134368 | Citric Acid (200 mg) | F1B092 | \$156 |
| 1181302 | Dextrose ( 500 mg ) | J-1 | \$124 |
| 1286504 | Fructose (125 mg) | I-2 | \$124 |
| 1374601 | Malic Acid (200 mg) | G0B158 | \$156 |
| 1594506 | Quinic Acid (200 mg) | F | \$156 |
| 1617000 | Sorbitol ( 125 mg ) | H1B139 | \$124 |
| 1623637 | Sucrose ( 100 mg ) | H1C223 | \$156 |
| ELEUTHERO |  |  |  |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | \$520 |
| FEVERFEW |  |  |  |
| 1500400 | Parthenolide ( 25 mg ) | F | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| GARLIC |  |  |  |
| 1012145 | Agigenin (25 mg) | F | \$156 |
| 1012950 | Alliin (25 mg) | F | \$1,525 |
| 1115556 | beta-Chlorogenin (20 mg) | F | \$156 |

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## Dietary Supplement Reference Standards Available from USP

| Cat. No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1294848 | gamma-Glutamyl-S-allyl-L-cysteine ( 25 mg ) | F | \$675 |
| 1411504 | L-Methionine (200 mg) | G | \$156 |
| GARLIC FLUID EXTRACT |  |  |  |
| 1013057 | S-Allyl-L-Cysteine (25 mg) | F | \$487 |
| GINGER |  |  |  |
| 1091108 | Capsaicin (100 mg) | G-1 | \$156 |
| 1291504 | Powdered Ginger ( 500 mg ) | F | \$156 |
| GINKGO |  |  |  |
| 1592409 | Quercetin (500 mg) | F0B015 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| AMERICAN GINSENG |  |  |  |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | FOB289 | \$520 |
| ASIAN GINSENG |  |  |  |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | FOB289 | \$520 |
| HAWTHORN LEAF WITH FLOWER |  |  |  |
| 1335202 | Hyperoside ( 50 mg ) | F | \$855 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 | \$156 |
| 1717708 | Vitexin ( 30 mg ) | FOC142 | \$520 |
| KAVA |  |  |  |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 | \$260 |
| KAWAIN |  |  |  |
| 1355753 | Kawain (200 mg) | F0C160 | \$208 |
| LICORICE |  |  |  |
| 1295888 | Glycyrrhizic Acid (25 mg) | F0C006 | \$487 |
| MILK THISTLE |  |  |  |
| 1443850 | Powdered Milk Thistle Extract (250 mg) | F0B321 | \$260 |
| 1612630 | Silybin ( 50 mg ) | F | \$156 |
| 1612641 | Silydianin ( 20 mg ) | F | \$156 |
| RED CLOVER |  |  |  |
| 1286060 | Formononetin ( 50 mg ) | F0C196 | \$520 |
| 1599500 | Powdered Red Clover Extract (500 mg) | FOC188 | \$260 |
| SAW PALMETTO |  |  |  |
| 1424233 | Methyl Caprate ( 300 mg ) | F | \$156 |
| 1424244 | Methyl Caproate ( 300 mg ) | F | \$156 |
| 1424255 | Methyl Caprylate ( 300 mg ) | F | \$156 |
| 1430305 | Methyl Laurate ( 500 mg ) | F | \$156 |
| 1430327 | Methyl Linoleate ( $5 \times 50 \mathrm{mg}$ ) | F | \$156 |
| 1430349 | Methyl Linolenate ( $5 \times 50 \mathrm{mg}$ ) | F | \$156 |
| 1431501 | Methyl Myristate ( 300 mg ) | F | \$156 |
| 1431556 | Methyl Oleate ( 500 mg ) | G0C148 | \$156 |
| 1431603 | Methyl Palmitate ( 300 mg ) | F | \$156 |
| 1431625 | Methyl Palmitoleate ( $300 \mathrm{mg} \mathrm{)}$ | F | \$156 |
| 1437508 | Methyl Stearate ( 300 mg ) | F | \$156 |
| ST. JOHN S WORT |  |  |  |
| 1335202 | Hyperoside ( 50 mg ) | F | \$855 |
| 1485001 | Oxybenzone ( 150 mg ) | H0B263 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| VALERIAN |  |  |  |
| 1707908 | Valerenic Acid (25 mg) | G0B146 | \$696 |

## Dietary Supplement Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| MISCELLANEOUS DIETARY SUPPLEMENTS |  |  |  |
| 1133570 | Chondroitin Sulfate Sodium ( 300 mg ) | FOB256 | \$156 |
| 1133638 | Chromium Picolinate ( 100 mg ) | F | \$156 |
| 1150353 | Creatinine ( 100 mg ) | F | \$156 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 | \$156 |
| 1611955 | Selenomethionine ( 100 mg ) | F0B006 | \$156 |
| VITAMINS-MINERALS |  |  |  |
| 1043003 | Ascorbic Acid (1 g) (Vitamin C) | Q0B012 | \$156 |
| 1071508 | Biotin ( 200 mg ) | H1B019 | \$156 |
| 1086356 | Calcium Ascorbate (200 mg) | F-1 | \$156 |
| 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) | N-1 | \$156 |
| 1131009 | Cholecalciferol ( $30 \mathrm{mg} / \mathrm{ampule}$; 5 ampules) (Vitamin D3) | M0B157 | \$159 |
| 1131803 | Delta-4,6-cholestadienol ( 30 mg ) | F | \$156 |
| 1152009 | Cyanocobalamin (1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) | N | \$156 |
| 1179504 | Dexpanthenol ( 500 mg ) | J0C293 | \$160 |
| 1239005 | Ergocalciferol ( $30 \mathrm{mg} / \mathrm{ampule;} 5$ ampules) (Vitamin D2) | P0B275 | \$168 |
| 1241007 | Ergosterol ( 50 mg ) | H | \$156 |
| 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) | P | \$156 |
| 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) | IOB176 | \$156 |
| 1381006 | Menadione (200 mg) (Vitamin K3) | H-3 | \$156 |
| 1461003 | Niacin (200 mg) | H-1 | \$156 |
| 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) | M-1 | \$156 |
| 1494501 | Panthenol, Racemic ( $200 \mathrm{mg} \mathrm{)}$ | G | \$156 |
| 1494807 | Pantolactone ( 500 mg ) | F | \$487 |
| 1538006 | Phytonadione ( 500 mg ) (Vitamin K1) | N0B303 | \$156 |
| 1550001 | Potassium Gluconate ( $200 \mathrm{mg} \mathrm{)}$ | H0C064 | \$156 |
| 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) | P | \$156 |
| 1603006 | Riboflavin ( 500 mg ) (Vitamin B2) | NOC021 | \$156 |
| 1613509 | Sodium Ascorbate (200 mg) | G-1 | \$156 |
| 1614002 | Sodium Fluoride (1 g) | H-1 | \$156 |
| 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) | 0 | \$156 |
| 1667600 | Alpha Tocopherol ( 250 mg ) (Vitamin E Alcohol) | M | \$156 |
| 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) | K | \$156 |
| 1667803 | Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate) | F-5 | \$156 |
| 1716002 | Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil) | V0C258 | \$156 |
| 1717504 | Vitamin D Assay System Suitability (1.5 g) | F | \$156 |

## Controlled Substances Reference Standards Available from USP

| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1012906 | Alfentanil Hydrochloride CII (500 mg) | F0B016 | \$207 |
| 1014005 | Alphaprodine Hydrochloride CII ( $250 \mathrm{mg} \mathrm{)}$ | F | \$207 |
| 1015008 | Alprazolam CIV (200 mg) | H | \$207 |
| 1030001 | Amobarbital CII (200 mg) | F-2 | \$207 |
| 1036008 | Anileridine Hydrochloride CII ( $250 \mathrm{mg} \mathrm{)}$ | F | \$207 |
| 1042000 | Aprobarbital CIII ( 200 mg ) (AS) | F-1 | \$207 |
| 1059003 | Benzphetamine Hydrochloride CIII (200 mg) (AS) | F-1 | \$207 |
| 1078700 | Buprenorphine Hydrochloride CIII ( 50 mg ) | F-1 | \$207 |
| 1079000 | Butabarbital CIII (200 mg) | H0C007 | \$207 |
| 1081002 | Butalbital CIII ( 200 mg ) | H0C054 | \$207 |
| 1082504 | Butorphanol Tartrate CIV (500 mg) | $J$ | \$207 |
| 1089004 | Cannabidiol Cl ( 25 mg ) (AS) | F-2 | \$207 |
| 1090003 | Cannabinol CI (25 mg) (AS) |  | \$207 |
| 1096804 | Cathinone Hydrochloride CI (50 mg) (alpha-Aminopropiophenone Hydrochloride) | 1 | \$560 |
| 1109000 | Chlordiazepoxide CIV (200 mg) | IOB063 | \$207 |
| 1110009 | Chlordiazepoxide Hydrochloride CIV (200 mg) | G-4 | \$207 |
| 1140305 | Clonazepam CIV (200 mg) | G1B175 | \$207 |
| 1140509 | Clorazepate Dipotassium CIV (125 mg) | G0B027 | \$207 |
| 1143008 | Cocaine Hydrochloride CII (250 mg) | IOB074 | \$207 |
| 1143802 | Codeine N-Oxide Cl (50 mg) | G0A034 | \$207 |
| 1144000 | Codeine Phosphate CII (100 mg) | J0C200 | \$207 |
| 1145003 | Codeine Sulfate CII ( 250 mg ) | H-2 | \$207 |
| 1180004 | Dextroamphetamine Sulfate CII (500 mg) | H | \$216 |
| 1183002 | Diacetylmorphine Hydrochloride (Heroin Hydrochloride) CI (25 mg) (AS) | J | \$207 |
| 1185008 | Diazepam CIV (100 mg) | 1 | \$207 |
| 1187207 | Dichloralphenazone CIV (200 mg) | F0B010 | \$207 |
| 1194009 | Diethylpropion Hydrochloride CIV (200 mg) | H | \$207 |
| 1200804 | Dihydrocodeine Bitartrate CII ( $200 \mathrm{mg} \mathrm{)}$ | H | \$207 |
| 1219008 | Diphenoxylate Hydrochloride CII (200 mg) | I | \$207 |
| 1258305 | Ethchlorvynol CIV ( 0.7 ml ) | F0B011 | \$207 |
| 1270005 | Fentanyl Citrate CII (100 mg) | K0C264 | \$207 |
| 1280009 | Fluoxymesterone CIII (200 mg) | G-2 | \$207 |
| 1285002 | Flurazepam Hydrochloride CIV ( 200 mg ) |  | \$207 |
| 1295006 | Glutethimide CII ( 500 mg ) | F | \$207 |
| 1302305 | Halazepam CIV (200 mg) (AS) | F1C224 | \$207 |
| 1307003 | Hexobarbital CIII ( 500 mg ) | F | \$207 |
| 1315001 | Hydrocodone Bitartrate CII (250 mg) | JOA026 | \$207 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl) | F0C214 | \$513 |
| 1323000 | Hydromorphone Hydrochloride CII (50 mg) | 1 | \$207 |
| 1356009 | Ketamine Hydrochloride CIII ( 250 mg ) | G-2 | \$207 |
| 1359506 | Levmetamfetamine CII (75 mg) | F | \$207 |
| 1364007 | Levorphanol Tartrate CII ( 500 mg ) | H | \$207 |
| 1370305 | Lorazepam CIV (200 mg) | 10C048 | \$207 |
| 1371002 | Lysergic Acid Diethylamide Tartrate (LSD) Cl (10 mg) (AS) | 1 | \$207 |
| 1375309 | Mazindol CIV ( $350 \mathrm{mg} \mathrm{)}$ | H | \$207 |
| 1383001 | Meperidine Hydrochloride CII (200 mg) | 1 | \$207 |
| 1386000 | Mephobarbital CIV (250 mg) | G | \$207 |
| 1389008 | Meprobamate CIV (200 mg) | G-1 | \$207 |

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## Controlled Substances Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1398009 | Methadone Hydrochloride CII (200 mg) | IOB163 | \$207 |
| 1399001 | Methamphetamine Hydrochloride CII (125 mg) | 1 | \$207 |
| 1404000 | Methaqualone Cl ( 500 mg ) | F-1 | \$207 |
| 1405002 | Metharbital CIII (200 mg) | F-2 | \$207 |
| 1413000 | Methohexital CIV ( 500 mg ) | F-2 | \$207 |
| 1425000 | 4-Methyl-2,5-dimethoxyamphetamine Hydrochloride (STP) CI (25 mg) (AS) | F | \$207 |
| 1429000 | Methylenedioxy-3,4-amphetamine Hydrochloride (MDA) CI (25 mg) (AS) | F-1 | \$207 |
| 1433008 | Methylphenidate Hydrochloride CII (125 mg) | 1 | \$165 |
| 1434000 | Methylphenidate Hydrochloride Erythro Isomer CII ( 25 mg ) | J0B294 | \$560 |
| 1438001 | Methyltestosterone CIII (200 mg) | J | \$207 |
| 1447002 | Morphine Monohydrate CII (50 mg) (AS) | G | \$207 |
| 1448005 | Morphine Sulfate CII (500 mg) | LOB056 | \$332 |
| 1452002 | Nalorphine Hydrochloride CIII (250 mg) | 1 | \$207 |
| 1453526 | Naltrexone Related Compound A CII ( 30 mg ) ( N -(3-butenyl)-noroxymorphone hydrochloride) | F | \$207 |
| 1454008 | Nandrolone CIII ( 50 mg ) | F-3 | \$560 |
| 1455000 | Nandrolone Decanoate CIII (250 mg) | I | \$207 |
| 1456003 | Nandrolone Phenpropionate CIII (250 mg) | H | \$207 |
| 1468400 | Nordazepam CIV (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) | H1B035 | \$560 |
| 1473002 | Noroxymorphone Hydrochloride CII (50 mg) | H1C177 | \$560 |
| 1482003 | Oxandrolone CIII ( 50 mg ) | G0B220 | \$207 |
| 1483006 | Oxazepam CIV (200 mg) | G-1 | \$207 |
| 1485191 | Oxycodone CII (200 mg) | IOB046 | \$207 |
| 1487007 | Oxymetholone CIII (200 mg) | G1B247 | \$207 |
| 1488000 | Oxymorphone CII ( 500 mg ) | H0B214 | \$207 |
| 1505007 | Pentazocine CIV ( 500 mg ) | H | \$207 |
| 1507002 | Pentobarbital CII (200 mg) | H3C144 | \$207 |
| 1516003 | Phencyclidine Hydrochloride CII (25 mg) (AS) | G1B025 | \$207 |
| 1516502 | Phendimetrazine Tartrate CIII ( 350 mg ) | G | \$207 |
| 1523009 | Phenmetrazine Hydrochloride CII (200 mg) | F-2 | \$207 |
| 1524001 | Phenobarbital CIV (200 mg) | J | \$207 |
| 1528501 | Phentermine Hydrochloride CIV (200 mg) | H0B309 | \$207 |
| 1554501 | Prazepam CIV (500 mg) | G0C066 | \$207 |
| 1574000 | Propoxyphene Hydrochloride CII (1 g) | L0C285 | \$207 |
| 1575002 | Propoxyphene Napsylate CII (1 g) | H | \$207 |
| 1592205 | Quazepam CIV (200 mg) | F | \$207 |
| 1611004 | Secobarbital CII (200 mg) | H | \$207 |
| 1620005 | Stanozolol CIII (200 mg) | F-3 | \$207 |
| 1623648 | Sufentanil Citrate CII ( 25 mg ) | H0B208 | \$207 |
| 1643000 | Talbutal CIII (250 mg) | F | \$207 |
| 1643408 | Temazepam CIV (200 mg) | H0C205 | \$207 |
| 1645006 | Testolactone CIII (125 mg) | F-1 | \$165 |
| 1646009 | Testosterone CIII (125 mg) | 11B253 | \$165 |
| 1647001 | Testosterone Cypionate CIII ( $200 \mathrm{mg} \mathrm{)}$ | G-1 | \$207 |
| 1648004 | Testosterone Enanthate CIII ( 200 mg ) | J | \$207 |
| 1649007 | Testosterone Propionate CIII (200 mg) | L1C005 | \$207 |
| 1656308 | Thiamylal CIII ( 200 mg ) | F | \$207 |
| 1661002 | Thiopental CIII (250 mg) | 1 | \$207 |
| 1680506 | Triazolam CIV (200 mg) | H0B041 | \$207 |

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## THE JOURNAL OF STANDARDS DEVELOPMENT AND OFFICIAL COMPENDIA REVISION

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Pharmacopeial Forum is covered in Current Contents/Life Sciences and in the Science Citation Index (SCI), in International Pharmaceutical Abstracts, and in Current Awareness in Biological Sciences.

The United States Pharmacopeial Convention comprises representatives from colleges and national and state organizations of medicine and pharmacy. It publishes the U.S. Pharmacopeia and National Formulary, the legally recognized compendia of standards for drugs and products of other health care technologies. The USP and NF include assays and tests for the determination of strength, quality, and purity and requirements for packaging and labeling.

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## Moving?

Our subscribers' records and publication labels are computergenerated. Please send your new address, and your latest label, or an exact copy of it, to: USPC, PF Customer Service Dept., 12601 Twinbrook Parkway, Rockville, MD 20852. Fax: (301) 816-8148.

## STANDARDS DEVELOPMENT

This section presents an overview of the public review and comment process, conducted through Pharmacopeial Forum $(P F)$, for the development of official pharmaceutical standards.

USP publishes Pharmacopeial Forum ( $P F$ ) bimonthly as the working vehicle of the USP Council of Experts. PF provides interested parties an opportunity to review and comment as the Council of Experts develops or revises standards for the United States Pharmacopeia and the National Formulary (USP-NF).
$P F$ includes the following:

1. Potential revisions-entirely new standards, revision ideas, and drafts not yet targeted for official adoption (Pharmacopeial Previews)
2. Proposed revisions-new or revised standards targeted for official adoption (In-Process Revision)
3. Adopted revisions-new or revised standards that become official and binding before the publication of the next $U S P-$ NF or Supplement (Interim Revision Announcement)

USP welcomes comments and data on potential, proposed, or official standards. ${ }^{*}$ Comments, along with USP's responses, will be published either in PF Briefings, the Commentary section of $P F$, the Commentary section of Supplements to USP-NF, or the Commentary section of $U S P-N F$.

[^90]The chart below shows the public review and comment process and its relationship to standards development.

# Public Review and Comment Process for Standards Development 



Questions on the process should be addressed to John W. Gasper, M.A., J.D., Director, Office of the Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: jg@usp.org).

## HOW TO USE PF

This section provides descriptions of the various parts of $P F$. It also includes Committee Designations and the Staff Directory.

The contents of the different sections of $P F$ are briefly described below. Readers will get an idea of how each section is relevant to their job functions. They may contact USP scientific staff liaisons or staff members of the Executive Secretariat (listed in the Staff Directory) if they have any questions. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a Request for Revision is available on the USP website (www.usp.org/standards/revisionguideline/).

# Proposed and Adopted Revisions 

| Section | Content | How Readers Can Respond |
| :---: | :---: | :---: |
| Pharmacopeial <br> Previews <br> Early ideas for revisions | -Briefing: Scientific rationale for potential inclusion or change. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -Potential revisions not yet targeted for official adoption that require a longer public review and comment process because of issues such as: <br> - the controversial nature of an item; <br> - the application of new technologies that require further study; and <br> - articles produced by multiple sources. | Review drafts and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview. |
| In-Process Revision Revisions targeted for adoption | -Briefing: Scientific rationale for proposed changes. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -New and revised standards that have been approved for publication by the appropriate USP Committee when it is considering whether to advance standards to official status (see Standards Development). New or revised text is marked with symbols ( ${ }^{\square}$ or ) to specify the tentative earliest date on which the revision would be officially adopted. | Review material and send comments promptly to USP staff liaison (see the Staff Directory). Guidelines on how to comment are found at the end of the Policies and Announcements section. |
| Harmonization <br> Items the Pharmacopeial Discussion Group (PDG) is trying to harmonize internationally | - Briefing: Scientific rationale for the potential inclusion or change or for the proposed change. The designated stage of harmonization. The stage determines whether an item appears under Pharmacopeial Previews or under In-Process Revision, both separate sections of Harmonization. <br> -For In-Process Revision, new or revised text is marked with symbols (■) to specify the tentative, earliest date on which the revision would be officially adopted. | Review material and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview or In-Process Revision. |
| Interim Revision <br> Announcement <br> Adopted standards | Standards that have been adopted and will become officially binding on the specified date. Effective date is specified in the section's introductory page or within parentheses following a particular item. New or revised text is set off by the symbols ${ }^{\circ}$. | Review to see if affected by any of the changes. Note effective date when standards become official and ensure compliance. |

## Other Sections

## Committee Designations

Names of the committees (composed of volunteer scientific experts) that USP staff work with on the development of standards.

## Staff Directory

Names of all USP scientific staff liaisons with contact information.

## Policies and Announcements

- General scientific and policy issues affecting $U S P-N F$ standards and processes
- Update on standards-related issues being considered by USP
- Summaries of meetings of the Council of Experts
- Guidelines on how to comment
- Publication and comment schedules


## Stimuli to the Revision Process

- Articles on standards development issues authored by the USP Council of Experts, USP staff, or other interested parties
- Discussions of issues on which USP desires public input prior to further development


## Nomenclature

- Latest adopted United States Adopted Names (USAN) and International Nonproprietary Names (INN) for drugs
- Revisions to existing names as a supplement to the USP Dictionary of USAN and International Drug Names
- Suggested, proposed, and recommended USAN and INN
- Information on how nonproprietary drug names are devised
- Articles relevant to compendial nomenclature issues


## Index

Cumulative directory for the content of all issues of $P F$ beginning with $P F$ 30(1).

## Reference Standards Catalog

List of official USP Reference Standards specified in $U S P-N F$, along with availability and ordering information.

## Chromatographic Reagents Used in USP-NF and Pharmacopeial Forum

Update of chromatographic reagents based on the proposals published in this issue of $P F$.

## EXPERT COMMITTEE DESIGNATIONS*

The names of the Committees and their abbreviations are as follows:

| AER | Aerosols |
| :---: | :---: |
| AMB | Analytical Microbiology |
| BBP | Blood and Blood Products |
| BNA | Bioavailability and Nutrient Absorption |
| BNT | Biotechnology and Natural Therapeutics and Diagnostics |
| BPC | Biopharmaceutics |
| BST | Biostatistics |
| CRX | Compounding Pharmacy |
| DSB | Dietary Supplements-Botanicals |
| DSI | Dietary Supplements-Information |
| DSN | Dietary Supplements-Non-Botanicals |
| EMC | Excipient Monograph Content ${ }^{\dagger}$ |
| ESC | Excipients-Substances and Characterization ${ }^{\dagger}$ |
| ETM | Excipients-Test Methods |
| GCT | Gene Therapy, Cell Therapy, and Tissue Engineering |
| GTB | General Toxicity and Biocompatibility |
| NL | Nomenclature and Labeling |
| PA1 | Pharmaceutical Analysis 1 |
| PA2 | Pharmaceutical Analysis 2 |
| PA3 | Pharmaceutical Analysis 3 |
| PA4 | Pharmaceutical Analysis 4 |
| PA5 | Pharmaceutical Analysis 5 |
| PA6 | Pharmaceutical Analysis 6 |
| PA7 | Pharmaceutical Analysis 7-Antibiotics |
| PDF | Pharmaceutical Dosage Forms |
| PPC | Parenteral Products-Compounding and Preparation |
| PPI | Parenteral Products-Industrial |
| PSD | Packaging, Storage, and Distribution |
| PW | Pharmaceutical Waters |
| RMI | Radiopharmaceuticals and Medical Imaging |
| SMU | Safe Medication Use |
| VET | Veterinary Drugs |
| VVI | Vaccines, Virology, and Immunology |

[^91]
## STAFF DIRECTORY

This is an updated directory that reflects assignment changes based on the reorganization of USP. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Committee is not identified. The Fax number is (301) 816-8373.

| STAFF | E-MAIL | PHONE | ASSIGNMENT |
| :--- | :--- | :--- | :--- |
| Clydewyn M. Anthony, <br> Senior Scientific Associate | cma@usp.org | $(301) 816-8139$ | Pharmaceutical Analysis 1 <br> (PA1) |
| Frank P. Barletta, Consultant <br> Charles H. Barnstein, Consultant | fpb@usp.org <br> ehbarnstein@ <br> email.msn.com | $(301) 816-8328$ | Pharmaceutical Waters (PW) |
| Daniel K. Bempong, <br> Scientist | dkb@usp.org | $(301) 774-9457$ | Nomenclature and Labeling <br> (NL) |
| Lokesh Bhattacharyya, Director, <br> Non-Complex Actives and <br> Excipients | Ib@usp.org | $(301) 816-8143$ | Excipient Monograph <br> Content (EMC) |
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STAFF DIRECTORY (continued)
\(\left.\left.$$
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\text { Scientist and Latin American } \\
\text { Liaison }\end{array} & \text { gig@usp.org } & (301) 816-8343 & \begin{array}{c}\text { Dietary Supplements-Botani- } \\
\text { cals (DSB); Dietary } \\
\text { Supplements- Bioavail- }\end{array}
$$ <br>

ability and Nutrient\end{array}\right] $$
\begin{array}{c}\text { Absorption (BNA) }\end{array}
$$\right]\)| Pharmaceutical Analysis 4 |
| :---: |
| (PA4) |

STAFF DIRECTORY (continued)

| STAFF | E-MAIL | PHONE | ASSIGNMENT |
| :--- | :--- | :--- | :--- |
| Eric B. Sheinin, Vice President, <br> Information and Standards <br> Development | es@usp.org | $(301) 816-8103$ |  |
| Radhakrishna S. Tirumalai, <br> Scientist | rst@usp.org | $(301) 816-8339$ | Blood \& Blood Products <br> (BBP); General Toxicity and |
| Andrzej Wilk, Senior Scientific <br> Associate | aw@usp.org | Biocompatibility (GTB) | Pharmaceutical Analysis 5 |

## POLICIES AND ANNOUNCEMENTS

In this section, readers may find statements about general scientific and policy issues that may have an impact on $U S P-N F$ standards and processes, announcements about issues being considered by USP, and summaries of Council of Experts meetings. This section also includes publication and comment schedules.

USP TO HOLD FIRST ANNUAL SCIENTIFIC MEETING. MEETING FOCUSES ON PRODUCT AND PROCESS STANDARDS. The United States Pharmacopeia (USP) is pleased to announce that it will hold its first USP Annual Scientific Meeting at the Sheraton Woodbridge Place in Iselin, N.J. from Sept. 27 to 29, 2004. The new USP Annual Scientific Meeting, which replaces the organization's open conference format, will allow stakeholders the opportunity to learn about and discuss science topics that are the foundation of USP's standardssetting activities.
"We are creating one annual meeting to allow USP to address multiple topics and to allow more people to participate in USP's standards-setting activities," said Roger L. Williams, M.D., USP executive vice president and chief executive officer. "This one-stop approach allows stakeholders the opportunity to meet with USP at one time and in one convenient location."

Preliminary USP Annual Scientific Meeting topics to be presented are the following:

- Biologics and Biotechnology Products
- Chromatography
- Dissolution
- Excipients and Pharmaceutical Waters
- Making the $U S P-N F$ Work for You
- Microbiology
- Process Analytical Technology
- Specifications

In addition, USP will offer its Pharmacopeial Education courses on Analytical Method Validation, Basic Statistics and their Practical Applications to USP, Dissolution, Microbiology, and USP 100 and 101. These courses and the USP Annual Scientific Meeting session tracks will be approved for continuing pharmaceutical education units (CEUs). Attendees of the USP Annual Scientific Meeting also can learn about other USP initiatives and how to become involved in USP's processes through the various USP volunteer bodies.

The USP Annual Scientific Meeting is designed for $U S P-$ $N F$ and USP Reference Standards customers and other USP stakeholders including pharmaceutical scientists focusing on chemistry, microbiology, biologics and biotechnology, Process Analytical Technology, excipients, dissolution, and chromatography.

For further information about the USP Annual Scientific Meeting, please visit www.usp.org/conferences, or call 301-816-8226.

USAN COUNCIL SECRETARIAT REVISES USAN FEE-FOR-SERVICE CHARGES. A revised schedule of fee-for-service charges has been placed in effect as of January 1, 2004. The increased fees appear on the USAN submission forms that are provided under Appendix XI of the 2004 edition of the USP Dictionary of USAN and International Drug Names. This announcement will be important to inform users of the USP Dictionary who are not yet using the revised 2004 edition of the changes.

For further information please contact:

United States Adopted Names (USAN) Program<br>American Medical Association<br>515 North State Street<br>Chicago, IL 60610<br>Phone: 312-464-4046<br>Fax: 312-464-4028<br>Web site: http://www.ama-assn.org/go/usan

PLASMA SPECTROCHEMISTRY. There are currently no monographs in the $U S P-N F$ that use inductively-coupled plasma as an analytical technique. Considering that use of this technique could have a great impact on the future of pharmaceutical testing for inorganic elements, in Pharmacopeial Forum 28(6) [Nov.-Dec. 2002], USP published a proposed new general chapter Inductively Coupled Plasma $\langle 730\rangle$, for public review and comment. Several comments were received, which led to the formation of a working group that was charged with identifying issues and redrafting the chapter. USP's working group on Plasma Spectrochemistry then organized a Roundtable Discussion session at the 2004 Winter Conference on Plasma Spectrochemistry (Jan. 210,2004, Ft. Lauderdale, Florida) in order to get additional public input before publishing a revised proposal. Titled $\langle 730\rangle$ Plasma Spectrochemistry, this proposed new general chapter is presented in this issue of Pharmacopeial Forum for public review and comment. For further information contact Kahkashan Zaidi, Ph.D. at 301-816-8269 or via email at kxz@usp.org.

NOTICE OF REVISION PERTAINING TO THE PACKAGING AND STORAGE STATEMENTS FOR EXCIPIENT ARTICLES. Changes in the Packaging and storage sections of the following excipient monographs will appear in this Pharmacopeial Forum, 30(3) [MayJune 2004].

This will apply to the following new excipient monographs, which became official in USP27-NF22: Ammonium Sulfate, Candelilla Wax, Cetrimonium Bromide, Hydrogenated Cottonseed Oil, Tribasic Sodium Phosphate, Glyceryl Distearate, Glyceryl Monolinoleate, and Glyceryl Monooleate.

It will also apply to the following new and revised excipient monographs, which became official in the First Supplement to USP27-NF22: Dibutyl Phthalate, Diethylene Glycol Stearates, Ethylene Glycol Stearates, Hydrogenated Soybean Oil, Hymetellose, Low-Substituted Carboxymethylcellulose Sodium, Medium-Chain Triglycerides, Polyisobutylene, Sodium Cetostearyl Sulfate, Sorbitol, Sorbitol Solution, Maltitol Solution, and Noncrystallizing Sorbitol Solution.

As well, it will apply to the following official excipient monographs for which revision proposals are currently presented in Pharmacopeial Forum: Pregelatinized Starch and Tapioca Starch.

Lastly, the Committee wishes to apply this principle to proposed new excipient monographs for which revision proposals are currently presented in Pharmacopeial Forum: Copovidone, Modified Starch, Pregelatinized Modified Starch, Maltose, Anhydrized Liquid Sorbitol, Phenolsulfonphthalein, and Hypromellose Acetate Succinate.

For more information, please contact Catherine Sheehan at 301-816-8262 or cxs@usp.org.

USP GUIDELINE FOR SUBMITTING REQUESTS FOR REVISION TO THE USP-NF. We are pleased to announce the availability of the USP Guideline for Submitting Requests for Revision to the USP-NF. This document was developed in conjunction with the USP Council of Experts and its Expert Committees, USP Staff, and the Drug Substance, Complex Actives, and Excipients

Project Teams of the Prescription/Nonprescription Stakeholders Forum. This document includes information to aid submission of new monographs and revisions to existing monographs for Non-Complex Active Substances and Products, Biological and Biotech Substances and Products, Excipients, and Vaccines. It incorporates many of the concepts and suggestions included in the ICH Q3A, Q3B, Q3C, Q6A, and Q6B guidelines. These include the definition of a specification and incorporate much of the terminology of Q3A for the control of impurities. The guideline clearly defines the information needed for the USP's Council of Experts and its Expert Committees to evaluate a request for revision. The document is approximately 75 pages in length with about 25 pages of addenda and is available in PDF format from the USP website at www.usp.org. Hard copies will be provided upon request.

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education series has been developed to enhance the knowledge, skills, and expertise of pharmaceutical industry personnel.

The following list indicates tentatively scheduled course dates. For further information, contact Laura A. McCurry, Manager, Pharmacopeial Education, lam@usp.org, 301-816-8285; Diana Lenahan, Program Associate, dpl@usp.org, 301-816-8530; or visit the website at www.usp.org/ education to register. Call 301-816-8530 to get information on customized courses offered at USP or at your site.

Calendar of Pharmacopeial Education Courses, 2004

| Date | Name of course | Location |
| :--- | :--- | :--- |
| May 19 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| May 20 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| June 10 | Fundamentals of Microbiological Testing | USP Headquarters, Rockville, MD |
| July 19 and 20 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| August 10 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| August 11 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| August 12 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| October 14 | Fundamentals of Microbiological Testing | USP Headquarters, Rockville, MD |
| October 18 and 19 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| November 11 | Analytical Method Validation | USP Headquarters, Rockville, MD |

Calendar of Pharmacopeial Education Courses, 2004 (continued)

| Date | Name of course | Location |
| :--- | :--- | :--- |
| November 11 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| November 12 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| November 12 | Fundamentals of Dissolution (Lecture) | USP Headquarters, Rockville, MD |
| December 2 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| December 8 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| December 9 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |

VISIT THE USP WEB SITE AT 〈http://www.usp.org . Various resources related to Pharmacopeial standards are presented, including highlights from $P F$.

## USP-NF AVAILABLE IN THREE ELECTRONIC

FORMATS. The trusted reference for official pharmaceutical standards is available in three convenient electronic formats-CD, intranet, and online. The CD is ideal for single users who prefer to have $U S P-N F$ on their hard drives. The intranet format allows Web browser-based access to multiple users within a company, through their own intranet server. The online format can be accessed by individual registered users through the World Wide Web. All three electronic formats provide fast and easy access to official $U S P-N F$ content. More information can be obtained by visiting www.usp.org/products or by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

## CHROMATOGRAPHIC REAGENTS NOW AVAILABLE.

 Chromatographic Reagents lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic test methods that has been published in Pharmacopeial Forum (PF) since 1980. Chromatographic Reagents also helps to track which column reagents were used to validate methods that have become official and are included in $U S P-N F$. The branded column reagents list is updated bimonthly through Pharmacopeial Forum. Chromatographic Reagents can be ordered by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.INTERNATIONAL CORRESPONDENCE. Individuals who wish to correspond with the European and Japanese Pharmacopoeias concerning monographs in the Official Inquiry and Consensus stages of international
harmonization should address their comments to the coordinating pharmacopeia for a given article. The addresses for the European and Japanese Pharmacopoeias are as follows:

Technical Secretariat of the
European Pharmacopoeia Commission
B.P. 907

F 67029 Strasbourg Cedex 1
France

NAKASHIMA Nobumasa
Evaluation and Licensing Division
Pharmaceutical and Medical Safety Bureau
Ministry of Health, Labour and Welfare, Japan
Tel. +81-3-3595-2431, Fax. +81-3-3597-9535
E-mail: nakashima-nobumasa@mhlw.go.jp

HOW TO SUBMIT COMMENTS. The USP welcomes and encourages interested parties to submit comments and data regarding potential, proposed, or adopted (official) standards. Submissions concerning a particular item that has appeared in a $P F$ should be submitted to the appropriate USP scientific staff liaison identified at the end of the Briefing accompanying each item. To submit comments and data to a liaison, use the e-mail address and telephone numbers listed in the Staff Directory included in every $P F$.

Please note that $U S P-N F$ is being published in an annual edition with one main book and two Supplements a year. In addition, the following schedule will repeat every year so that users will know what to expect and become familiar with the deadlines.

The publication and comment schedule for USP 27-NF 22 is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2003 | November 2003 | January 2004 |
| Supplement One | October 15, 2003 | February 2004 | April 2004 |
| Supplement Two | February 17, 2004 | June 2004 | August 2004 |

The publication and comment schedule for USP $28-N F 23$ is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2004 | November 2004 | January 2005 |
| Supplement One | October 15, 2004 | February 2005 | April 2005 |
| Supplement Two | February 17, 2005 | June 2005 | August 2005 |

In the future, USP anticipates including the comment submission deadline in each briefing of every revision proposal when it is published for public review and comment.

For general inquiries or in cases where a particular liaison is not identified, use the general USP telephone number 301-881-0666 or FAX number 301-816-8373.

All official revisions are published in Supplements to $U S P-N F$ (twice yearly). Between Supplements, official revisions are published in $P F$ in the Interim Revision Announcement; these revisions are also incorporated in the upcoming Supplement. The electronic version of $U S P-N F$ is updated as each Supplement becomes available and, therefore, contains all official text up to and including the contents of the latest Supplement.

## Publication Schedules

| Publication | Publication Date | Official Date |
| :---: | :---: | :---: |
| $1{ }^{\text {st }}$ Supplement | Feb. 2004 | Apr. 1, 2004 |
| PF 30(2) [Mar.-Apr. 2004] | Mar. 2004 | Not Applicable |
| $2^{\text {nd }} I R A$ [published in $P F 30(2)$ ] | Mar. 2004 | Apr. 1, 2004 |
| PF 30(3) [May-June 2004] | May 2004 | Not Applicable |
| $3{ }^{\text {rd }}$ IRA [published in PF 30(3)] | May 2004 | June 1, 2004 |
| $2^{\text {nd }}$ Supplement | June 2004* | Aug. 2, 2004 ${ }^{*}$ |
| PF 30(4) [July-Aug. 2004] | July 2004* | Not Applicable |
| $4^{\text {th }}$ IRA [published in $P F$ 30(4)] | July 2004* | Aug. 2, 2004* |
| PF 30(5) [Sept.-Oct. 2004] | Sept. 2004* | Not Applicable |
| $5{ }^{\text {th }}$ IRA [published in $P F 30(5)$ ] | Sept. 2004* | Oct. 1, 2004 ${ }^{*}$ |
| PF 30(6) [Nov.-Dec. 2004] | Nov. 2004 ${ }^{*}$ | Not Applicable |
| $6^{\text {th }}$ IRA [published in PF 30(6)] | Nov. 2004* | Dec. 1, 2004* |

* Tentative


## INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

- The list of new USP Reference Standards that have become available
- The list of assays or tests that are adopted but held in abeyance pending availability of required USP Reference Standards
- New adopted (official) revisions to the $U S P-N F$ that become effective before the effective date of the next Supplement or that were not ready for adoption by the closing date for the upcoming Supplement. (The effective date for these revisions is stated on the next page.)

Readers should review this section to determine if they are affected by any of the changes.
Symbols-Interim revisions are shown with new text (if any) enclosed in circles, ${ }^{\bullet}$ new text $\mathbf{D}_{\mathbf{0}}$. Text enclosed in squares, ${ }^{\bullet}$ new text $_{\square}$, has already been adopted in a Supplement. Where the symbols appear together with no enclosed text, such as ${ }^{\bullet}$ • or ${ }^{\bullet}$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the $I R A$ or Supplement in which the revision first appeared. For example, $\bullet_{2}$ indicates that the revision was officially adopted in the Second Interim Revision Announcement, and $\quad \mathbf{m S O}_{2 S}$ (USP27) indicates that the revision was officially adopted in the Second Supplement to USP 27.

Errata-At the end of the Interim Revision Announcement section is a list of errata and corrections to USP 27-NF 22. The page number indicates where the item is found in $U S P-N F$. If necessary, this list will be updated with every issue of $P F$. This information will also be cumulative in the next available Supplement, and will appear in its corrected form in the next annual edition of $U S P-N F$. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.
THIRD INTERIM REVISION ANNOUNCEMENT ..... 783
MONOGRAPHS (USP) ..... 785
Mitoxantrone Hydrochloride ..... 785
Mitoxantrone Injection ..... 785
GENERAL CHAPTERS ..... 785
<11〉 USP Reference Standards ..... 785
Errata List for USP 27-NF 22 ..... 787

# THIRD INTERIM REVISION ANNOUNCEMENT 

By authority of the United States Pharmacopeial Convention, Inc.<br>Prepared by the Council of Experts and published by the Board of Trustees<br>Larry L. Braden, Chair<br>USP Board of Trustees<br>Roger L. Williams, Executive Vice President and Chairman, USP Council of Experts

John W. Gasper, Director, Executive Secretariat

Official June 1, 2004.
Released May 1, 2004.

[^92]
## New USP Reference Standards

The following USP Reference Standards, which were indicated in past Supplements to USP-NF as being not yet available, have since become available. Thus, the official date of each USP 27 or NF 22 standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list.

USP Benazepril Hydrochloride RS (July 1, 2004)
USP Benazepril Related Compound A RS (May 1, 2004)
USP Benazepril Related Compound B RS (May 1, 2004)
USP Positive Bioreaction RS (November 1, 2004)
USP Cefpiramide RS (September 1, 2004)
USP Powdered Chaste Tree Extract RS (November 1, 2004)
USP Chlorhexidine RS (July 1, 2004)
USP Chlorhexidine Acetate RS (July 1, 2004)
USP Chlorhexidine Related Compounds RS (November 1, 2004)
USP Chlorogenic Acid RS (November 1, 2004)
USP Clonazepam Related Compound C RS (July 1, 2004)
USP Clonidine RS (September 1, 2004)
USP Clonidine Related Compound A RS (September 1, 2004)
USP Clonidine Related Compound B RS (November 1, 2004)
USP Cyclandelate RS (September 1, 2004)
USP Desflurane RS (May 1, 2004)
USP Dextran 40 RS (May 1, 2004)
USP Dextran 70 RS (May 1, 2004)
USP Dolasetron Mesylate RS (July 1, 2004)
USP Dolasetron Mesylate Related Compound A RS (July 1, 2004)
USP Powdered Echinacea purpurea Extract RS (November 1, 2004)

USP Powdered Eleuthero Extract RS (July 1, 2004)
USP Fludarabine RS (September 1, 2004)
USP Flumazenil RS (May 1, 2004)
USP Fluoxetine Related Compound C RS (July 1, 2004)
USP Ganciclovir RS (May 1, 2004)
USP Ganciclovir Related Compound A RS (July 1, 2004)
USP Glucosamine Hydrochloride RS (July 1, 2004)
USP $2 E, 4 E$-Hexadienoic Acid Isobutlamide RS (November 1, 2004)

USP Isoflurane Related Compound A RS (September 1, 2004)
USP Isoflurane Related Compound B RS (September 1, 2004)
USP Lamivudine RS (July 1, 2004)
USP Lamivudine Resolution Mixture A RS (November 1, 2004)
USP Loratadine RS (September 1, 2004)
USP Medroxyprogesterone Acetate Related Compound A RS (November 1, 2004)
USP Methylphenidate Hydrochloride Erythro Isomer Solution CII RS (November 1, 2004)
USP Metoprolol Related Compound A RS (July 1, 2004)
USP Metoprolol Related Compound B RS (September 1, 2004)
USP Metoprolol Related Compound C RS (September 1, 2004)
USP Metoprolol Related Compound D RS (September 1, 2004)
USP Metoprolol Succinate RS (November 1, 2004)
USP Mitoxantrone System Suitability Mixture RS (November 1, 2004)

USP Naratriptan Hydrochloride RS (November 1, 2004)
USP Paroxetine Related Compound D RS (May 1, 2004)
USP Phenytoin Related Compound B RS (July 1, 2004)
USP Powdered Red Clover Extract RS (May 1, 2004)
USP Residual Solvent Class 1—Benzene RS (November 1, 2004)

USP Residual Solvent Class 1-1,2 Dichloroethane RS (November 1, 2004)
USP Residual Solvent Class 1-1,2 Dichloroethene RS (November 1, 2004)
USP Residual Solvent Class 1-Carbon Tetrachloride RS (November 1, 2004)
USP Residual Solvent Class 1-1,1,1-Trichloroethane RS (November 1, 2004)
USP Residual Solvent Mixture-Class 1 RS (November 1, 2004)
USP Rimantidine Hydrochloride RS (July 1, 2004)
USP Scopoletin RS (July 1, 2004)
USP Sevoflurane RS (May 1, 2004)
USP Sevoflurane Related Compound A RS (May 1, 2004)
USP Sotalol Hydrochloride RS (July 1, 2004)
USP Sotalol Related Compound A RS (May 1, 2004)
USP Sotalol Related Compound B RS (May 1, 2004)
USP Sotalol Related Compound C RS (May 1, 2004)
USP Stearoyl Polyoxylglycerides RS (May 1, 2004)
USP Tiamulin Fumarate RS (July 1, 2004)
USP Tiamulin Related Compound A RS (July 1, 2004)
USP Valsartan RS (November 1, 2004)
USP Vecuronium Bromide RS (September 1, 2004)
USP Vinorelbine Tartrate RS (May 1, 2004)

The official dates of any USP 27 or NF 22 standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards.

## USP Alteplase RS

USP Amiloxate RS
USP Cinoxate RS
USP Decoquinate RS
USP Diethylstilbestrol Diphosphate RS
USP Enalapril Related Compound B RS
USP Enzacamene RS
USP Fludeoxyglucose RS
USP Ginseng Extract RS
USP Gonadorelin Hydrochloride RS
USP Hypericin RS
USP Lactase RS
USP Menotropins RS
USP Methyldopa-Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Ondansetron Related Compound B RS
USP Potassium Perchlorate RS
USP Pyrethrum Extract RS
USP Sargramostim RS
USP Sulisobenzone RS
USP $\Delta^{8}$-tetrahydrocannabinol RS
USP $\Delta^{9}$-tetrahydrocannabinol RS
USP Thiacetarsamide RS
USP Tilmicosin RS
USP Tinidazole Related Compound B RS
USP Trenbolone RS
USP Trenbolone Acetate RS
USP Powdered Valerian RS
USP Vasopressin RS

## MONOGRAPHS (USP)

## Mitoxantrone Hydrochloride

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Mitoxantrone Hydrochloride RS. ${ }^{\bullet}$ USP Mitoxantrone System Suitability Mixture $R S$. ${ }^{\circ}$

## Change to read:

Assay-
Sodium 1-heptanesulfonate solution-Dissolve 22.0 g of sodium 1-heptanesulfonate in about 150 mL of water, pass through a suitable filter having a $0.5-\mu \mathrm{m}$ or finer porosity, and transfer the filtrate to a $250-\mathrm{mL}$ volumetric flask. Wash the filter with about 50 mL of water, adding the filtrate to the $250-\mathrm{mL}$ volumetric flask. Add 32.0 mL of glacial acetic acid to the volumetric flask, dilute with water to volume, and mix.

Mobile phase-Prepare a suitable degassed mixture of water, acetonitrile, and Sodium 1-heptanesulfonate solution (750:250:25). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution- Prepare a solution of USP Mitoxantrone System Suitability Mixture RS in a suitable volume of Mo bile phase to obtain a solution containing about 0.2 mg of 8 -amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10anthracenedione hydrochloride (mitoxantrone related compound A) and 0.1 mg of mitoxantrone hydrochloride per $\mathrm{mL} . \bullet 3$

Standard preparation-Transfer about 20 mg of USP Mitoxantrone Hydrochloride RS, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, add 40 mL of Mobile phase, and dissolve by sonicating for about 5 minutes. Cool to room temperature, dilute with Mobile phase to volume, and mix.

Assay preparation-Transfer about 20 mg of Mitoxantrone Hydrochloride, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, add 40 mL of Mobile phase, and dissolve by sonicating for about 5 minutes. Cool to room temperature, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a 254 -nm detector and a 3.9$\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L11. The flow rate is about 3 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for mitoxantrone and 1.0 for mitoxantrone related compound A ; the resolution, $R$, between mitoxantrone and mitoxantrone related compound A is not less than 3.0 ; and the tailing factor for the mitoxantrone peak is not more than 2.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, for mitoxantrone is not less than 3.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. NOTE-After use, wash the column with a mixture of acetonitrile and water (50:50), and store in this mixture. Calculate the quantity, in mg , of $\mathrm{C}_{22} \mathrm{H}_{28} \mathrm{~N}_{4} \mathrm{O}_{6} \cdot 2 \mathrm{HCl}$ in the portion of Mitoxantrone Hydrochloride taken by the formula:

$$
50 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of anhydrous mitoxantrone hydrochloride in the Standard preparation, as determined from the content of USP Mitoxantrone Hydrochloride RS corrected for the water content determined by a titrimetric water determination; and $r_{U}$ and $r_{S}$ are the mitoxantrone peak areas ob-
tained from the Assay preparation and the Standard preparation, respectively.

## Mitoxantrone Injection

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Mitoxantrone Hydrochloride RS. ${ }^{\bullet}$ USP Mitoxantrone System Suitability Mixture $R S$. $\bullet_{3}$

## GENERAL CHAPTERS

## General Tests and Assays

## General Requirements for Tests and Assays

## 〈11〉 USP REFERENCE STANDARDS

## Change to read:

USP Positive Bioreaction RS-© Exercise care in handling. Prepare samples as directed in the respective USP General Test Chapters. $\bullet 3$

## Change to read:

USP Cefpodoxime Proxetil RS-Do not dry; determine the water content titrimetrically on a separate portion prior to use. Keep container tightly closed. ${ }^{\bullet}$ Protect from light. Store in a refrigerator. $\bullet 3$

## Change to read:

USP Chlorhexidine Related Compounds RS-- Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator. $\bullet 3$

## Change to read:

USP Powdered Echinacea angustifolia Extract RS- Do not dry. Keep container tightly closed. Protect from light. $\bullet_{3}$

## Change to read:

USP Powdered Echinacea purpurea Extract RS- ${ }^{\bullet}$ Do not dry. Keep container tightly closed. Protect from light. ${ }^{3}$

## Change to read:

USP Fluoxetine Related Compound B RS [ $N$-methyl-3-phenylpropylamine] $\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{~N} \triangleleft 149.24\right)$ - This is a solution containing approximately 2 mg of fluoxetine related compound B in diluted hydrochloric acid (approximately 0.01 N ). Store in a refrigerator. After opening the ampul, store it in a tightly closed container. ${ }^{\circ}$

## Change to read:

USP Flurazepam Hydrochloride RS-- Do not dry. ${ }_{\bullet 3}$ Keep container tightly closed. Protect from light. Store in a desiccator.

## Change to read:

USP 2E,4E-Hexadienoic Acid Isobutylamide RS- ${ }^{\bullet}$ Do not dry. Keep container tightly closed. Store in a refrigerator. Protect from light. $\bullet 3$

## Change to read:

USP Hydroxyzine Hydrochloride RS-_Caution-the dried material is hygroscopic.] Dry portion in vacuum at $75^{\circ}$ for 3 hours before using. Keep container tightly closed. ${ }^{\bullet}$ Store in a refrigerator. ${ }^{\circ}$

## Change to read:

USP Imipenem Monohydrate RS-Do not dry before using. Keep container tightly closed. ${ }^{\bullet}$ Store in a freezer. ${ }^{\circ}$

## Change to read:

USP Lamivudine Resolution Mixture A RS-Do not dry. Keep container tightly closed. Protect from light. ${ }^{\bullet}$ Store in a freezer. $\bullet 3$

## Change to read:

USP Medroxyprogesterone Acetate RS-- Do not dry.es Keep container tightly closed. Protect from light.

## Change to read:

USP Metoprolol Succinate RS-- Do not dry. Keep container tightly closed. Protect from light. $\bullet 3$

## Change to read:

USP Mitoxantrone ${ }^{\boldsymbol{\bullet}}$ System Suitability Mixture ${ }_{\mathbf{0} 3}$ RS [9, 10-anthracenedione, 8-amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)a-mino]ethyl]amino]-, hydrochloride] $\left(\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{5} \cdot \mathrm{HCl} \diamond\right.$ 393.83)—Do not dry. Keep container tightly closed.

## Change to read:

${ }^{\mathbf{4}}$ USP Naratriptan Hydrochloride RS-Do not dry. ${ }_{\text {USSP27 }}{ }^{\bullet}$ Keep container tightly closed. Protect from light. Store in a freezer. $\bullet 3$

## Change to read:

USP Norethindrone RS- ${ }^{\bullet}$ Do not dry. ${ }^{3}$ Keep container tightly closed.

## Change to read:

USP Propantheline Bromide Related Compound A RS ${ }^{\bullet}$ [9-hydroxypropantheline bromide ${ }_{\bullet 3}\left(\mathrm{C}_{23} \mathrm{H}_{30} \mathrm{BrNO}_{4} \diamond 464.39\right)$-Do not dry. Keep container tightly closed. Avoid contact. Store in a desiccator. Protect from light. Store under inert atmosphere.

## Change to read:

USP Sulfadoxine RS-- ${ }^{\circ}$ Do not dry.es Keep container tightly closed. Protect from light.

## Change to read:

USP Triacetin RS-Do not dry before using. ${ }^{\bullet}$ After opening ampul, store in a tightly closed container. $\bullet 3$ Avoid contact with metal.

## Change to read:

USP Triclosan RS ${ }^{\bullet}$-Do not dry. Keep container tightly closed. Protect from light.es

## Change to read:

USP L-Tyrosine RS-- Do not dry. $\bullet_{3}$ Keep container tightly closed.

Following is a list of errata and corrections to $U S P 27-N F 22$. The page number indicates where the item is found in USP 27-NF 22. If necessary, this list will be updated with every issue of $P F$. This information will also be available as a cumulative table in the next available Supplement and will appear in its corrected form in the next annual edition of $U S P-N F$. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff are available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

| Page | Title | Section | Description |
| :---: | :---: | :---: | :---: |
| 58 | Alclometasone Dipropionate Ointment | Assay | Line 11 under Procedure: Change "obtained from the and the Standard preparation, respectively." to: obtained from the Assay preparation and the Standard preparation, respectively. |
| 302 | Calcium Carbonate, Magnesia, and Simethicone Tablets | Assay for calcium carbonate and magnesium hydroxide | Line 10 under Procedure for magnesium hydroxide: Change " $(58.34 / 24.305)(1000 C / 3 V)\left(A_{U} / A_{S}\right)$," to: $(58.34 / 24.305)(1000 C / 3 V)(A / W)\left(A_{U} / A_{S}\right)$, |
| 364 | Cefonicid Sodium | Assay | Lines 3-5 under Assay preparation: Delete "Transfer 10.0 mL of the resulting solution to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix." as approved in Supplement 4 to USP 24. |
|  |  |  | Line 7 under Procedure: Change " $2000(C / M)\left(r_{U} / r_{S}\right)$," to: $200(C / M)\left(r_{U} / r_{S}\right)$, |
| 738 | Erythromycin Ethylsuccinate Tablets | Dissolution | FOR TABLETS LABELED AS CHEWABLE, line 1 under Medium: Change " 0.01 M acetate buffer" to: 0.1 M acetate buffer |
| 1553 | Procainamide Hydrochloride | Assay | Line 10 under Chromatographic system: Change "as directed under r" to: as directed for Procedure: the relative standard deviation for |
| 2334 | 〈781〉 Optical Rotation | First equation | Change |

$$
[\alpha] \frac{t}{\lambda}=\frac{100 a}{l c}
$$

to:

$$
[\alpha]_{\lambda}^{t}=\frac{100 a}{l c},
$$

| 2510 | $\langle 1086\rangle$ Impurities in Official <br> Articles | Introduction the last paragraph: Change "There is consistency be- <br> tween compendial standards and Good Manufacturing <br> Practice for Finished Pharmaceuticals $\langle 1077\rangle$, and it <br> is presumed" to: It is presumed |
| :--- | :--- | :--- |
| 2847 | Powdered Cellulose | Line 3 under Identification C: Change "Identification <br> test $C$ " to: Identification test $B$ |

## IN-PROCESS REVISION

This section contains proposals for adoption as official USP or $N F$ standards (either proposed new standards or proposed revisions of current $U S P$ or $N F$ standards). These may be any of the following: (1) items that previously appeared under Pharmacopeial Previews and are now formally proposed as revisions; (2) proposed revisions placed directly under In-Process Revision; or (3) modifications of revisions previously proposed under In-Process Revision. Readers should review material in this section and provide comments to the staff liaison (use the Staff Directory to find the contact information). Information on how to comment is found in the Policies and Announcements section. It is important to send comments promptly so that the Committee members can consider readers' input as they are deciding whether to advance standards to official status.

Briefings Each Proposal is preceded by a Briefing in the following format:

## BRIEFING

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being proposed, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see How to Use $P F$ ), the name of the scientific staff liaison who handled the particular issue, and the USP tracking correspondence number, as shown in the example below:
(PA5: K. Russo) RTS-55678-1
Symbols Proposed revisions are shown with language proposed for deletion or replacement crossed off. New text (if any) follows, and is enclosed in symbols and set off from the current official text by a paragraph break and by larger type, as shown in the examples below:

- new text.
if slated for an Interim Revision Announcement to USP 27-NF 22 (IRA);
$\Delta_{\text {new text }}{ }_{\mathbf{U S P 2 8}}$
if slated for USP 28-NF 23; and
- $_{\text {new text }}$
if slated for a Supplement to $U S P-N F$. The same symbols not set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as ${ }^{\bullet}$. or ${ }^{\bullet}$ or ${ }_{\Delta}$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular IRA or Supplement or indicates the USP or NF as the publication where the revision will appear if approved. For example, $\bullet_{2}$ indicates that the revision is proposed for the Second Interim Revision Announcement, and $\mathbf{N 2 S}_{\text {(USP 27) }}$ indicates that the proposed revision is slated for the Second Supplement to USP 27, and $\Delta_{\Delta S P 28}$ and $\Delta_{\Delta F 23}$ indicate that the revisions are proposed for USP 28 and NF 23, respectively.

Official Title Changes Where the specification "Monograph title change" is found, it indicates that the official title stated after that specification will be substituted for the former title in the appropriate places throughout that monograph once this revision becomes official.
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Preservation, Packaging, Storage, and Labeling ( $1^{\text {st }}$ Supp to USP 28) ..... 798
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Acyclovir (1st Supp to USP 28) ..... 802
Alendronic Acid Tablets [new] (Proposal for $4^{\text {th }}$ IRA) ..... 804
Amphetamine Sulfate ( ${ }^{\text {st }}$ Supp to USP 28) ..... 807
Atracurium Besylate Injection ( $1^{\text {st }}$ Supp to USP 28) ..... 808
Benzocaine (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 809
Bupropion Hydrochloride Extended-Release Tablets ( $1^{\text {st }}$ Supp to USP 28) ..... 810
Carbidopa ( $1^{\text {st }}$ Supp to USP 28) ..... 811
Methionine C 11 Injection (Proposal for $4^{\text {th }}$ IRA) ..... 811
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Indinavir Sulfate [new] (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 862
Indomethacin Topical Gel [new] (1st Supp to USP 28) ..... 866
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## Briefing

General Notices and Requirements, $U S P 27$ page 1, page 3034 of the First Supplement, and page 424 of PF 30(2) [Mar.Apr. 2004]. It is proposed to revise the section, Tests and Assays, to clarify the default conditions for reporting assay and other test results. It is also proposed to insert a statement in the section for Preservation, Packaging, Storage, and Labeling on the basis of discussions at a recent Open Conference on Packaging, Storage, and Distribution that was held October 12-15, 2003. Of particular interest to the participants were those monographs relating to excipients and active pharmaceutical ingredients (APIs). It was noted that most excipients are temperature stable, and, therefore, do not need storage restrictions, especially during shipping and distribution. This statement is intended to provide guidance to those preparing monographs for submission to USP so that there is consistency in the methods used when formulating the packaging and storage standards.
(PA6: K. Zaidi; PSD: C. Okeke) RTS-40982-1; 41095-1

## Change to read:

## SIGNIFICANT FIGURES AND TOLERANCES

Where limits are expressed numerically herein, the upper and lower limits of a range include the two values themselves and all intermediate values, but no values outside the limits. The limits expressed in monograph definitions and tests, regardless of whether the values are expressed as percentages or as absolute numbers, are considered significant to the last digit shown.

Equivalence Statements in Titrimetric Procedures-The directions for titrimetric procedures conclude with a statement of the weight of the analyte that is equivalent to each mL of the standardized titrant. In such an equivalence statement, it is to be understood that the number of significant figures in the concentration of the titrant corresponds to the number of significant figures in the weight of the analyte. Blank corrections are to be made for all titrimetric assays where appropriate (see Titrimetry $\langle 541\rangle$ ).

Tolerances-The limits specified in the monographs for Pharmacopeial articles are established with a view to the use of these articles as drugs, nutritional or dietary supplements, or devices, except where it is indicated otherwise. The use of the molecular formula for the active ingredient(s) named in defining the required strength of a Pharmacopeial article is intended to designate the chemical entity or entities, as given in the complete chemical name of the article, having absolute ( 100 percent) purity.

A dosage form shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label. The tolerances and limits stated in the definitions in the monographs for Pharmacopeial articles allow for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions.

Where the minimum amount of a substance present in a nutritional or dietary supplement is required to be higher than the lower tolerance limit allowed for in the monograph because of applicable legal requirements, then the upper tolerance limit contained in the monograph shall be increased by a corresponding amount.

The specified tolerances are based upon such attributes of quality as might be expected to characterize an article produced from suitable raw materials under recognized principles of good manufacturing practice.

The existence of compendial limits or tolerances does not constitute a basis for a claim that an official substance that more nearly approaches 100 percent purity "exceeds" the Pharmacopeial quality. Similarly, the fact that an article has been prepared to closer tolerances than those specified in the monograph does not constitute a basis for a claim that the article "exceeds" the Pharmacopeial requirements.
Interpretation of Requirements-Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated limits to determine whether there is conformance with compendial assay or test requirements. The observed or calculated values usually will contain more significant figures than there are in the stated limit, and absereater tated
$\square_{\text {a reportable }}^{\mathbf{m}_{2 S}}{ }_{(U S P 27)}$
result is to be rounded off to the number of places that is in agreement with the limit expression by the following procedure. ENOTE-Limits, which are fixed numbers, are not rounded off.]
-Intermediate calculations (e.g., slope for linearity in Validation of Compendial Methods $\langle 1225\rangle$ ) may be rounded for reporting purposes, but the original value (not rounded) should be used for any additional required calculations. Rounding off should not be done until the final calculations for the reportable value have been completed. [NOTE-Limits, which are fixed numbers, are not rounded off.]

A reportable value is often a summary value for several individual determinations. It is the end result of a completed measurement method, as documented. It is the value compared with the acceptance criterion. In most cases, the reportable value is used as documentation for internal or external
users.■2S (USP27)
When rounding off is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5 , it is eliminated and the preceding digit is unchanged. If this digit is greater than 5 , it is eliminated and the preceding digit is increased by one. If this digit equals 5 , the 5 is eliminated and the preceding digit is increased by one.

| Illustration of Rounding Numerical Values <br> for Comparison with Requirements |  |  |  |
| :---: | :---: | :---: | :---: |
| Compendial | Unrounded | Rounded |  |
| Requirement | Value | Result | Conforms |
| Assay limit $\geq 98.0 \%$ | $97.96 \%$ | $98.0 \%$ | Yes |
|  | $97.92 \%$ | $97.9 \%$ | No |
|  | $97.95 \%$ | $98.0 \%$ | Yes |
| Assay limit $\leq 101.5 \%$ | $101.55 \%$ | $101.6 \%$ | No |
|  | $101.46 \%$ | $101.5 \%$ | Yes |
|  | $101.45 \%$ | $101.5 \%$ | Yes |


| Illustration of Rounding Numerical Values <br> for Comparison with Requirements |  |  |  |
| :---: | :---: | :---: | :---: |
| Compendial | Unrounded | Rounded |  |
| Requirement | Value | Result | Conforms |
| Limit test $\leq 0.02 \%$ | $0.025 \%$ | $0.03 \%$ | No |
|  | $0.015 \%$ | $0.02 \%$ | Yes |
|  | $0.027 \%$ | $0.03 \%$ | No |
| Limit test $\leq 3 \mathrm{ppm}$ | $0.00035 \%$ | $0.0004 \%$ | No |
|  | $0.00025 \%$ | $0.0003 \%$ | Yes |
|  | $0.00028 \%$ | $0.0003 \%$ | Yes |

## Change to read：

## GENERAL CHAPTERS

Each general chapter is assigned a number that appears in brack－ ets adjacent to the chapter name（e．g．，$\langle 621\rangle$ Chromatography）． General chapters that include general requirements for tests and as－ says are numbered from $\langle\lambda\rangle$ to－$\langle\boldsymbol{\theta} 99\rangle$ ，chapters that are informat tonal are numbered from－$\langle 1000$ ）to $\langle 1999$ ，and chapters pertaining to nutrition supplements are numbered above $\langle 2000$ ）：
－Articles recognized in this compendia must comply with the official standards and tests and assays in the General No－ tices，relevant monographs，and General Chapters numbered below 1000．General Chapters numbered above 1000 are considered to be interpretive and are intended to provide in－ formation on，give definition to，or describe a particular sub－ ject．They contain no official standards，tests，assays，or other mandatory requirements applicable to any pharmaco－ peial article unless specifically referenced in a monograph or elsewhere in the Pharmacopeia．${ }^{\text {2S }}$（USP27）

The use of the general chapter numbers is encouraged for the identification and rapid access to general tests and information．It is especially helpful where monograph section headings and chap－ ter names are not the same（e．g．，Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ in a monograph refers to method $\langle 197 \mathrm{U}\rangle$ under general tests chapter〈197〉 Spectrophotometric Identification Tests；Specific rotation $\langle 781 \mathrm{~S}\rangle$ in a monograph refers to method $\langle 781 \mathrm{~S}\rangle$ under general tests chapter $\langle 781\rangle$ Optical Rotation；and Calcium $\langle 191\rangle$ in a mono－ graph refers to the tests for Calcium under general tests chapter〈191〉 Identification Tests－General）．

## Change to read：

## TESTS AND ASSAYS

Apparatus－A specification for a definite size or type of con－ tainer or apparatus in a test or assay is given solely as a recommen－ dation．Where volumetric flasks or other exact measuring， weighing，or sorting devices are specified，this or other equipment of at least equivalent accuracy shall be employed．（See also Ther－
mometers $\langle 21\rangle$ ，Volumetric Apparatus $\langle 31\rangle$ ，and Weights and Bal－ ances $\langle 41\rangle$ ．）Where low－actinic or light－resistant containers are specified，clear containers that have been rendered opaque by ap－ plication of a suitable coating or wrapping may be used．

Where an instrument for physical measurement，such as a spec－ trophotometer，is specified in a test or assay by its distinctive name， another instrument of equivalent or greater sensitivity and accuracy may be used．In order to obtain solutions having concentrations that are adaptable to the working range of the instrument being used，solutions of proportionately higher or lower concentrations may be prepared according to the solvents and proportions thereof that are specified for the procedure．

Where a particular brand or source of a material，instrument，or piece of equipment，or the name and address of a manufacturer or distributor，is mentioned（ordinarily in a footnote），this identifica－ tion is furnished solely for informational purposes as a matter of convenience，without implication of approval，endorsement，or cer－ tification．Items capable of equal or better performance may be used if these characteristics have been validated．

Where the use of a centrifuge is indicated，unless otherwise spe－ cified，the directions are predicated upon the use of apparatus hav－ ing an effective radius of about 20 cm （ 8 inches）and driven at a speed sufficient to clarify the supernatant layer within 15 minutes．

Unless otherwise specified，for chromatographic tubes and col－ umns the diameter specified refers to internal diameter（ID）；for other types of tubes and tubing the diameter specified refers to out－ side diameter（OD）．

Steam Bath－Where the use of a steam bath is directed，exposure to actively flowing steam or to another form of regulated heat，cor－ responding in temperature to that of flowing steam，may be used．

Water Bath－Where the use of a water bath is directed without qualification with respect to temperature，a bath of vigorously boil－ ing water is intended．

Foreign Substances and Impurities－Tests for the presence of foreign substances and impurities are provided to limit such sub－ stances to amounts that are unobjectionable under conditions in which the article is customarily employed（see also Impurities in Official Articles $\langle 1086\rangle$ ）．

While one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity，strength，quality， and purity，it is manifestly impossible to include in each mono－ graph a test for every impurity，contaminant，or adulterant that might be present，including microbial contamination．These may arise from a change in the source of material or from a change in the processing，or may be introduced from extraneous sources． Tests suitable for detecting such occurrences，the presence of which is inconsistent with applicable good manufacturing practice or good pharmaceutical practice，should be employed in addition to the tests provided in the individual monograph．

Other Impurities－Official substances may be obtained from more than one process，and thus may contain impurities not con－ sidered during preparation of monograph assays or tests．Wherever a monograph includes a chromatographic assay or purity test based on chromatography，other than a test for erganic velatile impuri ties，
$\square_{\text {residual solvents }}{ }_{\text {n2S }}$（USP27）
and that monograph does not detect such an impurity，solvents ex－ cepted，the impurity shall have its amount and identity，where both are known，stated under the heading Other Impurity（ies）by the la－ beling（certificate of analysis）of the official substance．

The presence of any unlabeled impurity in an official substance is a variance from the standard if the content is $0.1 \%$ or greater． Tests suitable for detection and quantitating unlabeled impurities， when present as the result of process change or other identifiable， consistent occurrence，shall be submitted to the USP for inclusion in the individual monograph．Otherwise，the impurity shall be identified，preferably by name，and the amount listed under the heading Other Impurity（ies）in the labeling（certificate of analysis） of the official substance．The sum of all Other Impurities combined
with the monograph-detected impurities does not exceed $2.0 \%$ (see Ordinary Impurities $\langle 466\rangle$ ), unless otherwise stated in the monograph.

Categories of drug substances excluded from Other Impurities requirements are fermentation products and semi-synthetics derived therefrom, radiopharmaceuticals, biologics, biotechnologyderived products, peptides, herbals, and crude products of animal or plant origin. Any substance known to be toxic must not be listed under Other Impurities.

■Residual Solvents-The requirements are stated in Or ganic Volatile Impurities $\langle 467\rangle$ together with information in Impurities in Official Articles $\langle 1086\rangle$. Thus all drug substances, excipients, and products are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. The requirements have been aligned with the ICH guideline on this topic. If solvents are used during production, they are of suitable quality. In addition, the toxicity and residual level of each solvent are taken into consideration, and the solvents are limited according to the principles defined and the requirements specified in Organic Volatile Impurities $\langle 467\rangle$, using the general methods presented therein or other suitable methods. $\quad$ 2S (USP27)

Procedures-Assay and test procedures are provided for determining compliance with the Pharmacopeial standards of identity, strength, quality, and purity.

In performing the assay or test procedures in this Pharmacopeia, it is expected that safe laboratory practices will be followed. This includes the utilization of precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures utilized. Prior to undertaking any assay or procedure described in this Pharmacopeia, the individual should be aware of the hazards associated with the chemicals and the procedures and means of protecting against them. This Pharmacopeia is not designed to describe such hazards or protective measures.

Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing process validation studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards.

Automated procedures employing the same basic chemistry as those assay and test procedures given in the monograph are recognized as being equivalent in their suitability for determining compliance. Conversely, where an automated procedure is given in the monograph, manual procedures employing the same basic chemistry are recognized as being equivalent in their suitability for determining compliance. Compliance may be determined also by the use of alternative methods, chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or com-
puterized data reduction or in other special circumstances. Such alternative or automated procedures or methods shall be validated. However, Pharmacopeial standards and procedures are interrelated; therefore, where a difference appears or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

In the performance of assay or test procedures, not fewer than the specified number of dosage units should be taken for analysis. Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards may be taken, provided the measurement is made with at least equivalent accuracy and provided that any subsequent steps, such as dilutions, are adjusted accordingly to yield concentrations equivalent to those specified and are made in such manner as to provide at least equivalent accuracy. To minimize environmental impact or contact with hazardous materials, apparatus and chemicals specified in Pharmacopeial procedures also may be proportionally changed.

Where it is directed in an assay or a test that a certain quantity of substance or a counted number of dosage units is to be examined, the specified quantity or number is a minimal figure (the singlet determination) chosen only for convenience of analytical manipulation; it is not intended to restrict the total quantity of substance or number of units that may be subjected to the assay or test or that should be tested in accordance with good manufacturing practices.

Where it is directed in the assay of Tablets to "weigh and finely powder not fewer than" a given number, usually 20, of the Tablets, it is intended that a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered tablets taken for assay is representative of the whole Tablets and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Tablet by multiplying this result by the average Tablet weight and dividing by the weight of the portion taken for the assay.

Similarly, where it is directed in the assay of Capsules to remove, as completely as possible, the contents of not fewer than a given number, usually 20, of the Capsules, it is intended that a counted number of Capsules should be carefully opened and the contents quantitatively removed, combined, mixed, and weighed accurately. The portion of mixed Capsules contents taken for the assay is representative of the contents of the Capsules and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Capsule by multiplying this result by the average weight of Capsule content and dividing by the weight of the portion taken for the assay.

Where the definition in a monograph states the tolerances as being "calculated on the dried (or anhydrous or ignited) basis," the directions for drying or igniting the sample prior to assaying are generally omitted from the Assay procedure. Assay and test procedures may be performed on the undried or unignited substance and the results calculated on the dried, anhydrous, or ignited basis, provided a test for Loss on drying, or Water, or Loss on ignition, respectively, is given in the monograph.
-Results are calculated on an "as-is" basis unless otherwise

## specified in the monograph. 1S (USP28) $_{1 S}$

Where the presence of moisture or other volatile material may interfere with the procedure, previous drying of the substance is specified in the individual monograph and is obligatory.

Throughout a monograph that includes a test for Loss on drying or Water, the expression "previously dried" without qualification signifies that the substance is to be dried as directed under Loss on drying or Water (gravimetric determination).

Unless otherwise directed in the test or assay in the individual monograph or in a general chapter, USP Reference Standards are to be dried before use, or used without prior drying, specifically in accordance with the instructions given in the chapter USP Reference Standards $\langle 11\rangle$, and on the label of the Reference Standard. Where the label instructions differ in detail from those in the chapter, the label text is determinative.

In stating the appropriate quantities to be taken for assays and tests, the use of the word "about" indicates a quantity within $10 \%$ of the specified weight or volume. However, the weight or volume taken is accurately determined and the calculated result is based upon the exact amount taken. The same tolerance applies to specified dimensions.

Where the use of a pipet is directed for measuring a specimen or an aliquot in conducting a test or an assay, the pipet conforms to the standards set forth under Volumetric Apparatus $\langle 31\rangle$, and is to be used in such manner that the error does not exceed the limit stated for a pipet of its size. Where a pipet is specified, a suitable buret, conforming to the standards set forth under Volumetric Apparatus $\langle 31\rangle$, may be substituted. Where a "to contain" pipet is specified, a suitable volumetric flask may be substituted.

Expressions such as " 25.0 mL " and " 25.0 mg ," used with respect to volumetric or gravimetric measurements, indicate that the quantity is to be "accurately measured" or "accurately weighed" within the limits stated under Volumetric Apparatus $\langle 31\rangle$ or under Weights and Balances $\langle 41\rangle$.

The term "transfer" is used generally to specify a quantitative manipulation.

The term "concomitantly," used in such expressions as "concomitantly determine" or "concomitantly measured," in directions for assays and tests, is intended to denote that the determinations or measurements are to be performed in immediate succession. See also Use of Reference Standards under Spectrophotometry and Light-Scattering $\langle 851\rangle$.

Blank Determination-Where it is directed that "any necessary correction" be made by a blank determination, the determination is to be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test, but with the substance itself omitted.

Desiccator-The expression "in a desiccator" specifies the use of a tightly closed container of suitable size and design that maintains an atmosphere of low moisture content by means of silica gel or other suitable desiccant.

A "vacuum desiccator" is one that maintains the low-moisture atmosphere at a reduced pressure of not more than 20 mm of mercury or at the pressure designated in the individual monograph.

Dilution-Where it is directed that a solution be diluted "quantitatively and stepwise," an accurately measured portion is to be diluted by adding water or other solvent, in the proportion indicated, in one or more steps. The choice of apparatus to be used should take into account the relatively larger errors generally associated with using small-volume volumetric apparatus (see Volumetric Apparatus $\langle 31\rangle$ ).

Drying to Constant Weight-The specification "dried to constant weight" means that the drying shall be continued until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional hour of drying.

Filtration-Where it is directed to "filter," without further qualification, the intent is that the liquid be filtered through suitable filter paper or equivalent device until the filtrate is clear.

Identification Tests-The Pharmacopeial tests headed Identification are provided as an aid in verifying the identity of articles as they are purported to be, such as those taken from labeled containers. Such tests, however specific, are not necessarily sufficient to establish proof of identity; but failure of an article taken from a labeled container to meet the requirements of a prescribed identification test indicates that the article may be mislabeled. Other tests and specifications in the monograph often contribute to establishing or confirming the identity of the article under examination.

Ignition to Constant Weight-The specification "ignite to constant weight" means that the ignition shall be continued, at $800 \pm 25^{\circ}$ unless otherwise indicated, until two consecutive
weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional 15-minute ignition period.

Indicators-Where the use of a test solution ("TS") as an indicator is specified in a test or an assay, approximately 0.2 mL , or 3 drops, of the solution shall be added, unless otherwise directed.

Logarithms-Logarithms used in the assays are to the base 10.
Microbial Strains-Where a microbial strain is cited and identified by its ATCC catalog number, the specified strain shall be used directly or, if subcultured, shall be used not more than five passages removed from the original strain.

Negligible-This term indicates a quantity not exceeding 0.50 mg .

Odor-Terms such as "odorless," "practically odorless," "a faint characteristic odor," or variations thereof, apply to examination, after exposure to the air for 15 minutes, of either a freshly opened package of the article (for packages containing not more than 25 g ) or (for larger packages) of a portion of about 25 g of the article that has been removed from its package to an open evaporating dish of about $100-\mathrm{mL}$ capacity. An odor designation is descriptive only and is not to be regarded as a standard of purity for a particular lot of an article.

Pressure Measurements-The term " mm of mercury" used with respect to measurements of blood pressure, pressure within an apparatus, or atmospheric pressure refers to the use of a suitable manometer or barometer calibrated in terms of the pressure exerted by a column of mercury of the stated height.

Solutions-Unless otherwise specified in the individual monograph, all solutions called for in tests and assays are prepared with Purified Water.

An expression such as "( 1 in 10 )" means that 1 part by volume of a liquid is to be diluted with, or 1 part by weight of a solid is to be dissolved in, sufficient of the diluent or solvent to make the volume of the finished solution 10 parts by volume.

An expression such as " $20: 5: 2$ )" means that the respective numbers of parts, by volume, of the designated liquids are to be mixed, unless otherwise indicated.

The notation "VS" after a specified volumetric solution indicates that such solution is standardized in accordance with directions given in the individual monograph or under Volumetric Solutions in the section Reagents, Indicators, and Solutions, and is thus differentiated from solutions of approximate normality or molarity.

Where a standardized solution of a specific concentration is called for in a test or an assay, a solution of other normality or molarity may be used, provided allowance is made for the difference in concentration and provided the error of measurement is not increased thereby.

Specific Gravity-Unless otherwise stated, the specific gravity basis is $25^{\circ} / 25^{\circ}$, i.e., the ratio of the weight of a substance in air at $25^{\circ}$ to the weight of an equal volume of water at the same temperature.

Temperatures-Unless otherwise specified, all temperatures in this Pharmacopeia are expressed in centigrade (Celsius) degrees, and all measurements are made at $25^{\circ}$. Where moderate heat is specified, any temperature not higher than $45^{\circ}\left(113^{\circ} \mathrm{F}\right)$ is indicated. See Storage Temperature under Preservation, Packaging, Storage, and Labeling for other definitions.

Time Limit-In the conduct of tests and assays, 5 minutes shall be allowed for the reaction to take place unless otherwise specified.

Vacuum-The term "in vacuum", denotes exposure to a pressure of less than 20 mm of mercury unless otherwise indicated.

Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used.

Water-Where water is called for in tests and assays, Purified Water is to be used unless otherwise specified. For special kinds of water such as "carbon dioxide-free water," see the introduction to the section Reagents, Indicators, and Solutions. For High-purity Water see Containers $\langle 661\rangle$.

Water and Loss on Drying - Where the water of hydration or adsorbed water of a Pharmacopeial article is determined by the titrimetric method, the test is generally given under the heading Water. Monograph limits expressed as a percentage are figured on a weight/weight basis unless otherwise specified. Where the determination is made by drying under specified conditions, the test is generally given under the heading Loss on drying. However, Loss on drying is most often given as the heading where the loss in weight is known to represent residual volatile constituents including organic solvents as well as water.

Test Results, Statistics, and Standards-Interpretation of results from official tests and assays requires an understanding of the nature and style of compendial standards, in addition to an understanding of the scientific and mathematical aspects of laboratory analysis and quality assurance for analytical laboratories.

Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs. Compendial standards define what is an acceptable article and give test procedures that demonstrate that the article is in compliance. These standards apply at any time in the life of the article from production to consumption. The manufacturer's release specifications, and compliance with good manufacturing practices generally, are developed and followed to assure that the article will indeed comply with compendial standards until its expiration date, when stored as directed. Thus, when tested from the viewpoint of commercial or regulatory compliance, any specimen tested as directed in the monograph for that article shall comply.

Tests and assays in this Pharmacopeia prescribe operation on a single specimen, that is, the singlet determination, which is the minimum sample on which the attributes of a compendial article should be measured. Some tests, such as those for Dissolution and Uniformity of dosage units, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen. These procedures should not be confused with statistical sampling plans. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations are neither specified nor proscribed by the compendia; such decisions are dependent on the objectives of the testing. Commercial or regulatory compliance testing, or manufacturer's release testing, may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies. Treatments of data handling are available from organizations such as ISO, IUPAC, and AOAC.
-Where the Content Uniformity determinations have been made using the same procedure specified in the Assay, the average of all of the individual Content Uniformity determinations may be used as the Assay value. 1 1s (USP27)

Description-Information on the "description" pertaining to an article, which is relatively general in nature, is provided in the reference table Description and Relative Solubility of USP and NF Articles in this Pharmacopeia for those who use, prepare, and dispense drugs and/or related articles, solely to indicate properties of an article complying with monograph standards. The properties are not in themselves standards or tests for purity even though they may indirectly assist in the preliminary evaluation of an article.

Solubility-The statements concerning solubilities given in the reference table Description and Relative Solubility of USP and NF Articles for Pharmacopeial articles are not standards or tests for purity but are provided primarily as information for those who use, prepare, and dispense drugs and/or related articles. Only where a quantitative solubility test is given, and is designated as such, is it a test for purity.

The approximate solubilities of Pharmacopeial substances are indicated by the descriptive terms in the accompanying table. Soluble Pharmacopeial articles, when brought into solution, may show traces of physical impurities, such as minute fragments of filter paper, fibers, and other particulate matter, unless limited or excluded by definite tests or other specifications in the individual monographs.

|  | Parts of Solvent <br> Required for <br> 1 Part of Solute |
| :--- | :--- |
| Descriptive <br> Term | Less than 1 <br> Very soluble |
| Freely soluble 1 to 10 |  |
| Soluble | From 10 to 30 |
| Sparingly soluble | From 30 to 100 |
| Slightly soluble <br> Very slightly soluble <br> Practically insoluble, <br> or Insoluble | From 100 to 1000 |

Interchangeable Methods-Certain general chapters contain a statement that the text in question is harmonized with the corresponding text of the European Pharmacopoeia and/or the Japanese Pharmacopoeia and that these texts are interchangeable. Therefore, if a substance or preparation is found to comply with a requirement using an interchangeable method from one of these pharmacopeias, it should comply with the requirements of the United States Pharmacopeia. However, where a difference appears, or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

## Change to read:

## PRESERVATION, PACKAGING, STORAGE, AND LABELING

Containers-The container is that which holds the article and is or may be in direct contact with the article. The immediate contain$e r$ is that which is in direct contact with the article at all times. The closure is a part of the container.

Prior to its being filled, the container should be clean. Special precautions and cleaning procedures may be necessary to ensure that each container is clean and that extraneous matter is not introduced into or onto the article.

The container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements.

The Pharmacopeial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph.

Tamper-Evident Packaging - The container or individual carton of a sterile article intended for ophthalmic or otic use, except where extemporaneously compounded for immediate dispensing on prescription, shall be so sealed that the contents cannot be used without obvious destruction of the seal.

Articles intended for sale without prescription are also required to comply with the tamper-evident packaging and labeling requirements of the FDA where applicable.
Preferably, the immediate container and/or the outer container or protective packaging utilized by a manufacturer or distributor for all dosage forms that are not specifically exempt is designed so as to show evidence of any tampering with the contents.

Light-Resistant Container (see Light Transmission under Containers $\langle 661\rangle$ )-A light-resistant container protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. Alternatively, a clear and colorless or a translucent container
may be made light-resistant by means of an opaque covering, in which case the label of the container bears a statement that the opaque covering is needed until the contents are to be used or administered. Where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended.

Where an article is required to be packaged in a light-resistant container, and if the container is made light-resistant by means of an opaque covering, a single-use, unit-dose container or mnemonic pack for dispensing may not be removed from the outer opaque covering prior to dispensing.

Well-Closed Container-A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Tight Container-A tight container protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight re-closure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article.

A gas cylinder is a metallic container designed to hold a gas under pressure. As a safety measure, for carbon dioxide, cyclopropane, helium, nitrous oxide, and oxygen, the Pin-index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

NOTE-Where packaging and storage in a tight container or a well-closed container is specified in the individual monograph, the container utilized for an article when dispensed on prescription meets the requirements under Containers-Permeation $\langle 671\rangle$.

Hermetic Container-A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Single-Unit Container-A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

Single-Dose Container (see also Containers for Injections under Injections $\langle 1\rangle$ )-A single-dose container is a single-unit container for articles intended for parenteral administration only. A singledose container is labeled as such. Examples of single-dose containers include pre-filled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

Unit-Dose Container-A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container.

Unit-of-Use Container-A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. A unit-of-use container is labeled as such.

Multiple-Unit Container-A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

Multiple-Dose Container (see also Containers for Injections under Injections $\langle 1\rangle$ )-A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only.

Storage Temperature and Humidity-Specific directions are stated in some monographs with respect to the temperatures and humidity at which Pharmacopeial articles shall be stored and distributed (including the shipment of articles to the consumer) when
stability data indicate that storage and distribution at a lower or a higher temperature and a higher humidity produce undesirable results. Such directions apply except where the label on an article states a different storage temperature on the basis of stability studies of that particular formulation. Where no specific storage directions or limitations are provided in the individual monograph, but the label of an article states a storage temperature that is based on stability studies of that particular formulation, such labeled storage directions apply (see also Stability under Pharmaceutical Dosage Forms $\langle 1151\rangle$ ). The conditions are defined by the following terms.

Freezer-A place in which the temperature is maintained thermostatically between $-25^{\circ}$ and $-10^{\circ}\left(-13^{\circ}\right.$ and $\left.14^{\circ} \mathrm{F}\right)$.

Cold-Any temperature not exceeding $8^{\circ}\left(46^{\circ} \mathrm{F}\right)$. A refrigerator is a cold place in which the temperature is maintained thermostatically between $2^{\circ}$ and $8^{\circ}\left(36^{\circ}\right.$ and $\left.46^{\circ} \mathrm{F}\right)$.

Cool-Any temperature between $8^{\circ}$ and $15^{\circ}\left(46^{\circ}\right.$ and $\left.59^{\circ} \mathrm{F}\right)$. An article for which storage in a cool place is directed may, alternatively, be stored and distributed in a refrigerator, unless otherwise specified by the individual monograph.

Room Temperature-The temperature prevailing in a working area.

Controlled Room Temperature-A temperature maintained thermostatically that encompasses the usual and customary working environment of $20^{\circ}$ to $25^{\circ}\left(68^{\circ}\right.$ to $77^{\circ} \mathrm{F}$ ); that results in a mean kinetic temperature calculated to be not more than $25^{\circ}$; and that allows for excursions between $15^{\circ}$ and $30^{\circ}\left(59^{\circ}\right.$ and $86^{\circ} \mathrm{F}$ ) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to $40^{\circ}$ are permitted as long as they do not exceed 24 hours. Spikes above $40^{\circ}$ may be permitted if the manufacturer so instructs. Articles may be labeled for storage at "controlled room temperature" or at "up to $25^{\circ}$ ", or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations. (See also Stability under Pharmaceutical Dosage Forms $\langle 1151\rangle$.)

An article for which storage at Controlled room temperature is directed may, alternatively, be stored and distributed in a cool place, unless otherwise specified in the individual monograph or on the label.

Warm-Any temperature between $30^{\circ}$ and $40^{\circ}\left(86^{\circ}\right.$ and $\left.104^{\circ} \mathrm{F}\right)$. Excessive Heat-Any temperature above $40^{\circ}\left(104{ }^{\circ} \mathrm{F}\right)$.
Protection from Freezing-Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

Dry Place-The term "dry place" denotes a place that does not exceed $40 \%$ average relative humidity at Controlled Room Temperature or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place or may be based on reported climatic conditions. Determination is based on not less than 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to $45 \%$ relative humidity provided that the average value is $40 \%$ relative humidity.

Storage in a container validated to protect the article from moisture vapor, including storage in bulk, is considered a dry place.
${ }^{\boldsymbol{4}}$ Storage under Nonspecific Conditions-Where no specific directions or limitations are provided in the packaging and storage section of individual monographs or in the article's labeling, the conditions of storage shall include storage at controlled room temperature, protection from moisture, and, where necessary, protection from light. Articles shall be protected from moisture, freezing,
and excessive heat, and, where necessary, from light during shipping and distribution. Active pharmaceutical ingredients are exempt from this requirement. $\triangle U S P P^{27}$

■Repackaging Instructions-Except where a drug product is packaged in a container intended to be dispensed directly to the patient, such as a unit-of-use or unit-dose container, the labeling shall contain directions specifying the types of containers suitable for repackaging the drug product so as to maintain its identity, strength, quality, and purity. Such directions shall be sufficient to allow a repackager or dispenser to select an adequate container and shall include a description of the composition of the container(s), e.g., glass, polyethylene, polyvinyl chloride, and any moisture vapor transmission rate characteristics required. The labeling shall also indicate whether or not the container is to afford light protection, and shall include any storage or shipping temperature restrictions to which the drug as repackaged shall be limited (see 21 CFR 201.100).n.ms (USP27)

Labeling-The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

A shipping container containing a single article, unless such container is also essentially the immediate container or the outside of the consumer package, is labeled with a minimum of product identification (except for controlled articles), lot number, expiration date, and conditions for storage and distribution.

Articles in this Pharmacopeia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the Pharmacopeial requirements set forth for the articles.

Amount of Ingredient per Dosage Unit-The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

Pharmacopeial articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each such unit; except that, in the case of unit-dose oral solutions or suspensions, whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon addition of a designated volume of a specific diluent, the label shall express the quantity of each active ingredient or recognized nutrient delivered under the conditions prescribed in Deliverable Volume $\langle 698\rangle$. Pharmacopeial drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient (see Percentage Measurements), except that oral liquids or solids intended to be constituted to yield oral liquids may, alternatively, be labeled in terms of each $5-\mathrm{mL}$ portion of the liquid or resulting liquid. Unless
otherwise indicated in a monograph or chapter, such declarations of strength or quantity shall be stated only in metric units (see also Units of Potency in these General Notices).

Use of Leading and Terminal Zeros-In order to help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg$]$ ). The quantity of active ingredient when expressed as a decimal number smaller than one shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg ]).

Labeling of Salts of Drugs-It is an established principle that Pharmacopeial articles shall have only one official name. For purposes of saving space on labels, and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners as synonymous with the written forms, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids; but these symbols are not used where the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not to be written).

Labeling Vitamin-Containing Products-The vitamin content of an official drug product shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.
${ }^{\boldsymbol{\Delta}}$ Labeling Botanical-Containing Products-The label of
an herb or other botanical intended for use as a dietary sup-

plement bears the statement, "If you are pregnant or nursing a baby, seek the advice of a health professional before using this product." |  |
| :--- |
| USP28 |

Labeling Parenteral and Topical Preparations-The label of a preparation intended for parenteral or topical use states the names of all added substances (see Added Substances in these General Notices and Requirements, and see Labeling under Injections $\langle 1\rangle)$, and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

Labeling Electrolytes-The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

Labeling Alcohol-The content of alcohol in a liquid preparation shall be stated on the label as a percentage ( $\mathrm{v} / \mathrm{v}$ ) of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Special Capsules and Tablets-The label of any form of Capsule or Tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it is to be used.
Expiration Date and Beyond-Use Date-The label of an official drug product, nutritional or dietary supplement product shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., "EXP 6/89," "Exp. June 89," or "Expires 6/89"). [NOTE-For additional information and
guidance, refer to the Nonprescription Drug Manufacturers Association's Voluntary Codes and Guidelines of the OTC Medicines Industry.]

The monographs for some preparations state how the expiration date that shall appear on the label is to be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the article, with the following exception: the label need not show an expiration date in the case of a drug product or nutritional supplement packaged in a container that is intended for sale without prescription and the labeling of which states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions.

Where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article may be expected to meet the requirements of the Pharmacopeial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. Where an expiration date is stated only in terms of the month and the year, it is a representation that the intended expiration date is the last day of the stated month. The beyond-use date is the date after which an article must not be used. The dispenser shall place on the label of the prescription container a suitable beyond-use date to limit the patient's use of the article based on any information supplied by the manufacturer and the General Notices and Requirements of this Pharmacopeia. The be-yond-use date placed on the label shall not be later than the expiration date on the manufacturer's container.

For articles requiring constitution prior to use, a suitable be-yond-use date for the constituted product shall be identified in the labeling.

For all other dosage forms, in determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; any unusual storage conditions to which the article may be exposed; and the expected length of time of the course of therapy. The dispenser shall, on taking into account the foregoing, place on the label of a multi-ple-unit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, or in the absence of stability data to the contrary, such beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) one year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be one year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturer's container, whichever is earlier, unless stability data or the manufacturer's labeling indicates otherwise.

The dispenser must maintain the facility where the dosage forms are packaged and stored, at a temperature such that the mean kinetic temperature is not greater than $25^{\circ}$. The plastic material used in packaging the dosage forms must afford better protection than polyvinyl chloride, which does not provide adequate protection against moisture permeation. Records must be kept of the temperature of the facility where the dosage forms are stored, and of the plastic materials used in packaging.

Pharmaceutical Compounding-The label on the container or package of an official compounded preparation shall bear a be-yond-use date. The beyond-use date is the date after which a compounded preparation is not to be used. Because compounded
preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

The monograph for an official compounded preparation typically includes a beyond-use requirement that states the time period following the date of compounding during which the preparation, properly stored, is to be used. In the absence of stability information that is applicable to a specific drug and preparation, recommendations for maximum beyond-use dates have been devised for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated (see Stability Criteria and Beyond-Use Dating under Stability of Compounded Preparations in the general tests chapter ${ }^{\boldsymbol{\Delta}}$ Pharmaceutical Compounding-Nonsterile Preparations $\begin{array}{l}\text { USPP27 }\end{array}$ (795 $\rangle$ ).
-Guidelines for Packaging and Storage Statements in

## USP-NF Monographs

In order to provide users of the $U S P-N F$ with proper guidance on how to package and store compendial articles, every monograph in the $U S P-N F$ is required to have a packaging and storage specification.

For those instances where, for some reason, storage information is not yet found in the Packaging and storage specification of a monograph, the section Storage Under NonSpecific Conditions is included in the General Notices as interim guidance. The Storage Under Nonspecific Conditions statement is not meant to substitute for the inclusion of proper, specific storage information in the Packaging and storage statement of any monograph.

For the packaging portion of the statement, the choice of containers is given in the General Notices and includes Light-Resistant Container, Well-Closed Container, Tight Container, Hermetic Container, Single-Unit Container, Sin-gle-Dose Container, Unit-Dose Container, and Unit-of-Use Container. For most preparations, the choice is determined by the container in which it is to be dispensed (e.g., tight, well-closed, hermetic, unit-of-use, etc). For active pharmaceutical ingredients (APIs), the choice would appear to be tight, well-closed, or, where needed, a light-resistant container. For excipients, given their typical nature as large-volume commodity items, with containers ranging from drums to tank cars, a well-closed container is an appropriate de-
fault. Therefore, in the absence of data indicating a need for a more protective class of container, the phrase "Preserve in well-closed containers" should be used as a default for excipients.

For the storage portion of the statement, the choice of storage temperatures presented in the General Notices includes Freezer, Cold, Cool, Room Temperature, Controlled Room Temperature, Warm, Excessive Heat, and Protection from Freezing. The definition of a dry place is provided if protection from humidity is important.

For most preparations, the choice is determined by the experimentally determined stability of the preparation and may include any of the previously stated storage conditions as determined by the manufacturer. For APIs that are expected to be retested before incorporation into a preparation, a more general and nonrestrictive condition may be desired. In this case, the specification "room temperature" (the temperature prevailing in a working area) should suffice. The use of the permissive room temperature condition reflects the stability of an article over a wide temperature range. For excipients, the phrase "No storage requirements specified" in the Packaging and storage statement of the monograph would be appropriate.

Because most APIs in the $U S P-N F$ have associated Reference Standards, special efforts should be considered to ensure that the Reference Standards' storage conditions correspond to the conditions indicated in the $U S P-N F$ monographs.

The Packaging, Storage, and Distribution Expert Committee may review questionable Packaging and storage statements on a case-by-case basis. In cases where the Packaging and storage statements are incomplete, the monographs would move forward to publication while the Packaging and storage statements are temporarily deferred. 1 (USP28)

## Briefing

Acyclovir, USP 27 page 890, page 3039 of the First Supplement, and page 431 of $P F 30$ (2) [Mar.-Apr. 2004]. Based on available stability data and information, it is proposed to revise the Packaging and storage section; and the revision previously proposed in PF 30(2) is hereby cancelled. Minor editorial changes are also made to clarify the text.
(PA7b: B. Davani; PSD: C. Okeke) RTS-41101-1

## Change to read:

Packaging and storage-Preserve in tight containers. © Store ween $15^{\circ}$ and $25^{\circ}$.

■Store at room temperature.■1S (USP28)
Protect from light and moisture. 1 (USP27)

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. $\quad$ 2S (USP27)

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Acyclovir RS.

- USP Endotoxin RS. $\boldsymbol{\bullet}^{\text {2S (USP2T) }}$


## Add the following:

-Other requirements-Where the label states that Acyclovir is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Acyclovir for Injection. Where the label states that Acyclovir must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Acy-
clovir for Injection.■2S (USP27)

## Change to read:

## Assay and limit for guanine-

Mobile phase-Prepare a filtered and degassed solution of glacial acetic acid in water (1 in 1000). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

- System suitability preparation 1—Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having known concentrations of about 0.1 mg of each per mL .

System suitability preparation 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about $0.7 \mu \mathrm{~g}$ per $\mathrm{mL} . \bullet 4$

Guanine standard preparation-Transfer about 8.75 mg of guanine, accurately weighed, to a $500-\mathrm{mL}$ volumetric flask. Dissolve in 50 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix.
${ }^{\bullet}$ Transfer 2.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix to obtain a solution having a known concentration of about $0.7 \mu \mathrm{~g}$ per $\mathrm{mL} . \bullet 4$

Standard preparation-Dissolve about 25 mg of USP Acyclovir RS, accurately weighed, in 5 mL of 0.1 N sodium hydroxide in a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution and 2.0 mL of the Guanine stant and preparation
$\bullet$
to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix to obtain a solution having knownemeentrations of about 0.1 mg of USP Acyelovir PS per mL and $0.7 \mu \mathrm{~g}$ of granine per mL .
-a known concentration of about 0.1 mg of USP Acyclovir

## RS per mL. $\bullet 4$

Assay preparation-Dissolve about 100 mg of Acyclovir, accurately weighed, in 20 mL of 0.1 N sodium hydroxide in a $200-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a 4.2$\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph Stand preparation,
-System suitability preparation 1,@4
and record the peak responses as directed for Procedure: the resolution, $R$, between acyclovir and guanine is not less than 2.0; the tailing factor for the analyte peak is not more than 2 ; and the relative standard deviation for replicate injections
${ }^{\bullet}$ for the acyclovir peak ${ }_{\bullet 4}$
is not more than $2.0 \%$.
${ }^{\bullet}$ Chromatograph System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$. $\bullet$

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation,

- Guanine standard preparation, $\bullet 4$
and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in $\mu \mathrm{g}$, of guanine in the portion of Acyclovir taken by the formula:

$$
1000 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of guanine in the Stand preparation
${ }^{\bullet}$ Guanine standard preparation; $\bullet 4$
and $r_{U}$ and $r_{S}$ are the peak responses due to guanine in the Assay preparation and the stan,
${ }^{\bullet}$ Guanine standard preparation, $\bullet_{4}$
respectively: not more than $0.7 \%$ of guanine is found. Calculate the quantity, in mg , of $\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}$ in the portion of Acyclovir taken by the formula:

$$
1000 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses due to acyclovir in the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Alendronic Acid Tablets, page 440 of $P F 30(2)$ [Mar.-Apr. 2004]. Consistent with established policy of using the same terminology in the monograph title as appears in the strength expression for a dosage form, Alendronic Acid Tablets has been proposed to be the title for this new monograph.

A monograph on this proposed new $U S P$ dosage form first appeared in a Pharmacopeial Preview in PF 24(1) [Jan.-Feb. 1998] and, subsequently, under In-Process Revision in PF 25(5)[Sept.Oct. 1999], PF 26(2) [Mar.-Apr. 2000], and PF 28(1) [Jan.-Feb. 2002] under the name Alendronate Sodium Tablets. Revisions proposed by the Expert Committee on Nomenclature and Labeling in PF 28(3)[May-June 2002] included changing the title of this new monograph to Alendronic Acid Tablets. The briefing to that revision proposal stated "A previous USP Nomenclature Committee adopted a policy to name the active moiety in the title if the strength is expressed in terms of the active moiety, and name the derivative in the title if the strength is expressed in terms of the derivative. The nomenclature thus proposed for this monograph is changed from naming the drug ingredient as the salt to naming the active moiety to be consistent with policy."

USP received an objection to the "active moiety" terminology used in the briefing, the correspondent indicating that "the free acid is not the active moiety of this drug," and "evidence established that alendronic acid is never present at the site of action." Further to this, the correspondent added that "The ultimate site of action is in the bone and specifically in the osteoclast cell. When alendronate sodium is administered to a patient, it will be present in the osteoclast as alendronate and not alendronic acid because the intracellular pH is 7.0 approximately. The intracellular pH is well above the pKa of Alendronic acid." Removal of the term "active moiety" from the briefing section of the In-Process Revision monograph therefore was requested.

Concerning the proposal to change the title, the correspondent further stated "It is, however, our understanding that the USP policy on nomenclature is to utilize the name of the molecule on which dosing is based, according to the FDA approved labeling, in the title of the monograph. In this case, the labeling refers to 5,10 , 35,40 , and 70 mg doses based on the free acid form of Alendronate (i.e., Alendronic acid). Therefore, to be consistent with policy, Alendronic acid should be used in the title of the monograph. This policy is not intended to establish or define the pharmacologically active substance (i.e., active moiety)."

The Expert Committee on Nomenclature and Labeling found the correspondent's comments persuasive and determined that, although "active moiety" terminology appearing in the informational briefing statements was inappropriate and, inasmuch as there was no objection to the proposed title change, Alendronic Acid Tablets was approved as the title for the proposed new monograph. However, in subsequent actions taken by the Expert Committee on Nomenclature and Labeling, the title of the existing 15-year-old policy was changed from "Active Moiety Policy" to "Salt Nomenclature Policy." The policy, without substantive change other than its title, is stated as the following:

Salt Nomenclature Policy. The term used in the title of the monograph on a dosage form formulated with a salt of an acid or base shall be the same as that used in expressing the strength of the article. Where the strength is expressed in terms of the salt, the same salt name is used in the monograph title. Where the strength is expressed in terms of the free acid or base, the same acid or base name is used in the monograph title.

Alendronic Acid Tablets is proposed to be the title of the monograph on this dosage form, which is proposed to be included in USP 28-NF 23, but with an official date of July 1, 2006, which is 18 months later than the official date of USP $28-N F 23$. Use of the revised name would be permitted as of January 1, 2005,
the official date of USP 28-NF 23, but use of the name Alendronic Acid Tablets would not become mandatory until July 1, 2006. The 18-month extension is intended to allow for product label changes to be made and for health practitioners and consumers to become familiar with the terminology.
(NL: C. Barnstein) RTS-41136-1

## Add the following:

## AAlendronate Sodium- Tablets Alendronic Acid Tablets

-(Title for this new monograph—to become official July 1, 2006)

## » Alendronate Sodium Tablets entain Alendronic <br> Acid Tablets contain an amount of Alendronate Sodium, equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled <br> amount of alendronatesodium $\left(\mathrm{C}_{4} \mathrm{H}_{4_{2}} \mathrm{NNa}_{7} \mathrm{P}_{2} \cdots 3 \mathrm{H}_{2} \mathrm{O}\right)$. alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right)$.

Packaging and storage-Preserve in tight containers.
Store at between $15^{\circ}$ and $30^{\circ}$.
Labeling-The labeling indicates weekly dosing where appropriate.

USP Reference standards $\langle 11\rangle$ —USP Alendronate Sodium RS.

Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Dissolution $\langle 711\rangle$ -
Medium: water; 900 mL .
Apparatus 2: 50 rpm .

## Time: 15 minutes.

Determine the amount of $\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}$ dissolved by employing the following method.

Buffer solution and Mobile phase-Prepare as directed in the Assay.
0.05\% 9-Fluorenylmethyl chloroformate solutionTransfer 100 mg of 9-fluorenylmethyl chloroformate to a $200-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix. This solution must be freshly prepared.

Borate buffer-Dissolve 6.2 g of boric acid in approximately 950 mL of water, adjust with 1 N sodium hydroxide to a pH of 9.0 , and dilute with water to 1 L .

Diluent-Transfer 176.4 g of sodium citrate dihydrate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Dissolution Medium to volume, and mix.

Standard stock solution-Dissolve an accurately weighed quantity of USP Alendronate Sodium RS in Dissolution Medium, and dilute quantitatively and stepwise, with the same solvent to obtain a solution having a known concentration corresponding to the concentration that would be obtained by dissolving 1 Tablet in 900 mL of the same Medium. Calculate the concentration, $C$, in mg per mL , of anhydrous alendronate sodium in this solution.
Standard solution-Transfer 5.0 mL of the Standard stock solution to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube containing 1.0 mL of Diluent and 5.0 mL of Borate buffer, and mix for about 3 minutes. Add 4.0 mL of $0.05 \%$ 9-Fluorenylmethyl chloroformate solution, and agitate for about 30 seconds. Allow the solution to stand at room temperature for 25 minutes. Add 25 mL of methylene chloride, and agitate for about 40 seconds. Centrifuge the mixture for 5 minutes. Use a portion of the clear upper aqueous layer.

Reagent blank-Using 5 mL of water, proceed as directed for Standard solution, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."

Test solution-After 15 minutes, withdraw a portion of the solution under test, and centrifuge immediately. Using 5.0 mL of the clear supernatant, proceed as directed for Standard solution, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."

Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solution, the Test solution, and the Reagent blank into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right)$ dissolved by the formula:

$$
827.1 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is defined under the Standard stock solution; and $r_{U}$ and $r_{s}$ are the peak areas obtained from the Test solution and the Standard solution, respectively. [NOTE-827.1 is the molecular weight conversion factor $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right.$ ) $\mathrm{C}_{4} \mathrm{H}_{12} \mathrm{NNaO}_{7} \mathrm{P}_{2}$ ) multiplied by the volume of the Medium ( 900 mL ).]

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right)$ is dissolved in 15 minutes. Tablets labeled for weekly dosing: not less than $75 \%(Q)$ of the labeled amount of alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right)$ is dissolved in 15 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Assay- <br> Mobile phase Prepare a 7.2 mM solution of nitric acid im <br> HPLC grade water.

System suitability solution-Prepare a solution of USP
Alendrenate Sodium RS and sodium biphesphate in HPLC grade water containing 0.2 mg per mL and 0.1 mg per mL , respectively.

Standerd preparation-Prepare a solution-of USP Alen dronate Sodium-RS in HPLC grade water having a known eoneentration of about 0.52 mg of alendronate sodium trihy drate per mL.

Assay preparation Weigh and finely powder not fewer
than 20-Tablets. Transfer an aceurately weighed pertion of the powder, equivalent to about 100 mg of alemerenic acid, to a $250-\mathrm{mL}$ volumetric flack, discolve in HPLC grade water, senieate for 30 mintutes, and shake for 10 mintutes. Bilute with HPLC grade water to velume, and mix. Pass a pertion of this selution through a filter having a 0.45 mm-ar finer porosity, and use the flltrate.

Chromatographic system (see Chromatography $\langle 624\rangle$ )
The liquid chromatograph is equipped with a 240 -nm detecfor and a $4.1 \mathrm{~mm} \times 25 \mathrm{em}$ columm that contains packing L53. L\#\# (see-Chromatography $\langle 624\rangle$ ). The flow rate-is about 1.6 mL per minute. Chrematograph the-System sutability solution, and record the peak responses as-directed for Procedure: the resolution, $R$, between alendronate and phesphate is not less than 2.0; the tailing factor is net mere than 1.5 ; and the relative standard deviation for replieate in jections is net mere than $2.0 \%$.

Procedure Separately inject equal-volumes (about 100 HL) of the Standard preparation and the Assay preparation into the ehrematograph, record the chrematograms, and measure the respenses for the major peaks. Caleulate the
quantity, in mg, of alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{43} \mathrm{NO}_{7} \mathrm{P}_{2}\right)$ in the por tion of Tablets taken by the formula:

$$
250(249.10 / 325.12) C\left(r_{4}+r_{5}\right)
$$

in which 249.10 and 325.12 are the melecular weights of alendronic acid and alendronate sodium tribydrate, respeetively; $C$ is the eencentration, in mg per $m \mathrm{~mL}$, of alendrenate sodium tribydrate-in the Standard preparation; andrırandrs are the peak respenses obtained from the Assay preparation and the Standard preparation, respectively.

Diluent-Transfer 29.4 g of sodium citrate dihydrate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix.
Buffer solution-Transfer 14.7 g of sodium citrate dihydrate and 7.05 g of anhydrous dibasic sodium phosphate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in about 900 mL of water, adjust with phosphoric acid to a pH of 8.0 , dilute with water to volume, and mix.
$0.1 \%$ 9-Fluorenylmethyl chloroformate solution-Transfer 250 mg of 9 -fluorenylmethyl chloroformate to a 250 mL volumetric flask, dilute with acetonitrile to volume, and mix. Prepare this solution fresh just prior to use.
Borate solution-Transfer 38.1 g of sodium borate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution, acetonitrile, and methanol (75:20:5). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard stock preparation-Prepare a solution of USP Alendronate Sodium RS in diluent containing 0.03 mg of anhydrous alendronate sodium per mL .

Standard preparation-Transfer 5.0 mL of the Standard stock preparation to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube containing 5 mL of Borate solution, and mix for
about 3 minutes. Add 4 mL of $0.1 \%$ 9-Fluorenylmethyl chloroformate solution, and agitate for about 30 seconds. Allow the solution to stand at room temperature for $25 \mathrm{~min}-$ utes. Add 25 mL of methylene chloride, and agitate for about 40 seconds. Centrifuge the mixture for 10 minutes. Use the clear upper aqueous layer.

Assay stock preparation-Transfer not fewer than 10 Tablets to a $1000-\mathrm{mL}$ volumetric flask. Add 500 mL of Diluent, shake by mechanical means for 30 minutes, and sonicate for 5 minutes. Dilute with Diluent to volume, mix, and centrifuge a portion of this solution. Quantitatively dilute a portion of the clear supernatant to a concentration in a range of 0.02 to 0.03 mg per mL .

Assay preparation-Using 5.0 mL of the Assay stock preparation, proceed as directed for Standard preparation, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."

Reagent blank-Using 5 mL of Diluent, proceed as directed for Standard preparation, beginning with "to a $50-\mathrm{mL}$ polypropylene screw-cap centrifuge tube."

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a $266-\mathrm{nm}$ detector and a $4.1-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L21. The column is maintained at a constant temperature of about $35^{\circ}$. The flow rate is about 1 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard preparation, Assay preparation, and the Reagent blank into the chromatograph, record the chromatograms, and measure the responses for the major peaks.

Calculate the quantity, in mg , of alendronic acid $\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2}\right)$ in the portion of Tablets taken by the formula:

$$
0.919 D C\left(r_{U} / r_{s}\right),
$$

in which $D$ is the dilution factor for the Assay stock preparation; $C$ is the concentration, in mg per mL , of anhydrous USP Alendronate Sodium RS in the Standard stock preparation; and $r_{U}$ and $r_{S}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively. [NOTE-0.919 is the molecular weight conversion factor $\left.\left(\mathrm{C}_{4} \mathrm{H}_{13} \mathrm{NO}_{7} \mathrm{P}_{2} / \mathrm{C}_{4} \mathrm{H}_{12} \mathrm{NNaO}_{7} \mathrm{P}_{2}\right).\right]_{\mathbf{\Delta} U S P 28}$

## Briefing

Amphetamine Sulfate, USP 27 page 143 and page 443 of $P F$ 30(2) [Mar.-Apr. 2004]; Dextroamphetamine Sulfate, USP 27 page 576 and page 476 of PF 30(2) [Mar.-Apr. 2004]. A revision is proposed to increase the drying time of the benzoyl derivative formed in Identification test $A$, to assure that the sample is dry, and the melting range obtained is accurate.
(PA3: S. Salado) RTS-39348-2

## Change to read:

## Identification-

A: Dissolve about 100 mg in 5 mL of water, add 5 mL of 1 N sodium hydroxide, cool to about $10^{\circ}$, add 1 mL of a mixture of 1 volume of benzoyl chloride and 2 volumes of absolute ether, insert the stopper, and shake for 3 minutes. Filter the precipitate, wash with about 10 mL of cold water, and recrystallize from diluted alcohol: the crystals of the benzoyl derivative of amphetamine so obtained, after drying at $80^{\circ}$ for 2 homs,
-3 hours, 1 1S (USP28)
melt between $131^{\circ}$ and $135^{\circ}$, the procedure for Class $I$ being used (see Melting Range or Temperature $\langle 741\rangle$ ).
B: A solution (1 in 10) responds to the tests for Sulfate $\langle 191\rangle$.

## Change to read:

Chromatographic purity-
Diluent-Dilute 3.12 mL of phosphoric acid with water to 1000 mL .

Buffer solution-Dissolve 2.16 g of sodium 1-octanesulfonate in 1000 mL of water, and add 1.0 mL of $0.1 \%$ triethylamine solution (N).
triethylamine. $\triangle$ USP28
Mix, and adjust with phosphoric acid to a pH of 2.5 .
Mobile phase-Prepare a filtered and degassed mixture of Buffer solution, acetonitrile, and methanol (144:37:19). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Standard stock solution-Dissolve an accurately weighed quantity of USP Dextroamphetamine Sulfate RS in Diluent to obtain a solution having a known concentration of about 0.3 mg per mL .

Standard solution-Dilute an accurately measured volume of Standard stock solution in Diluent to obtain a solution having a known concentration of about 0.003 mg per mL .

Test solution-Transfer about 30 mg of Amphetamine Sulfate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in 50 mL of Diluent, sonicate for 5 minutes, dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a 4.6$\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard stock solution, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$. Chromatograph the Test solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the amphetamine peak and any adjacent peak, if any, is not less than 1.5.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Amphetamine Sulfate taken by the formula:

$$
10,000(C / W)\left(r_{i} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Dextroamphetamine Sulfate RS in the Standard solution; $W$ is the weight, in mg , of Amphetamine Sulfate taken to prepare the Test solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the peak response for amphetamine obtained from the Standard solution: not more than $0.1 \%$ of any individual impurity is found; and not more than $0.5 \%$ of total impurities is found.

## Change to read:

## Related compounds-

Buffer solution, Solution A, Solution B, Mobile phase, and Standard preparation-Proceed as directed in the Assay under Atracurium Besylate.

System suitability solution-Heat a portion of the Standard preparation at $90^{\circ}$ for 30 minutes, and chill immediately to about $5^{\circ}$.

Diluted standard preparation-Dilute a portion of the Standard preparation quantitatively, and stepwise if necessary, with Solution $A$ to obtain a solution having a known concentration of about 0.02 mg per mL .

Test preparation-Use the Assay preparation.
Chromatographic system-Prepare as directed for Chromatographic system in the Assay. Chromatograph the System suitability solution and the Diluted standard preparation, record the chromatograms, and measure the responses for the degradation products by comparing the peak responses of the System suitability solution to those of the Diluted standard preparation as directed for Procedure: the retention times relative to the atracurium besylate cis-cisisomer are about 0.22 for the acidic compound, 0.29 for laudanosine, 0.44 and 0.50 for the trans- and cis-isomers, respectively, of the hydroxy compound, and about 1.28 and 1.33 for the trans- and cis-isomers, respectively, of the monoacrylate.
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Diluted standard preparation and the Test preparation into the chromatograph, record the chromatograms, and measure the peak responses, except the peak due to benzenesulfonic acid occurring at a retention time of about 0.08 relative to the atracurium besylate cis-cis-isomer. Calculate the percentage of each impurity in the portion of Test preparation taken by the formula:

$$
100(C / \mathrm{M})\left(r_{i} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Atracurium Besylate RS in the Diluted standard preparation; $M$ is the concentration of atracurium besylate, in mg per mL , in the Test preparation; $r_{i}$ is the peak response for each impurity obtained from the Test preparation; and $r_{s}$ is the sum of the responses of all the peaks obtained from the Diluted standard preparation: not more than $6.0 \%$ of the acidic compound, not more than $6.0 \%$ of the combined cis- and trans-isomers of the hydroxy compound, not more than $3.0 \%$ of laudanosine, and not more than $3.0 \%$ of the combined cis- and trans-isomers of the monoacrylate, them $0.5 \%$ of other known impurities
-and not more than $2.0 \%$ of other known synthetic impur-
ities ${ }_{\text {1S (USP28) }}$
is found; not more than $0.1 \%$ of any other impurity is found; and not more than $15.0 \%$ of total impurities is found.
© (Postponed Indefinitely) $\Delta$ USP27
■ $\quad$ 1S (USP28)

## Change to read:

## Assay-

Buffer solution, Solution A, Solution B, Mobile phase, and Standard preparation - Proceed as directed in the Assay under Atracurium Besylate.

Assay preparation-Transfer an accurately measured volume of Injection, equivalent to about 50 mg of atracurium besylate, to a $50-\mathrm{mL}$ volumetric flask, dilute with Solution $A$ to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a 4.6$\mathrm{mm} \times 25-\mathrm{cm}$ column that contains base-deactivated packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 80 | 20 | equilibration |
| $0-5$ | 80 | 20 | isocratic |
| $5-15$ | $80 \rightarrow 40$ | $20 \rightarrow 60$ | linear gradient |
| $15-25$ | 40 | 60 | isocratic |
| $25-30$ | $40 \rightarrow 0$ | $60 \rightarrow 100$ | linear gradient |

Chromatograph replicate injections of the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.8 for the atracurium besylate trans-trans-isomer, 0.9 for the cis-trans-isomer, and 1.0 for the cis-cisisomer; the resolution, $R$, between the atracurium besylate trans-trans-isomer and the cis-trans-isomer and between the atracurium besylate cis-trans-isomer and the cis-cis-isomer is not less than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the three atracurium besylate isomer peaks. Calculate the quantity, in mg, of atracurium besylate $\left(\mathrm{C}_{65} \mathrm{H}_{82} \mathrm{~N}_{2} \mathrm{O}_{18} \mathrm{~S}_{2}\right)$ in each mL of the Injection taken by the formula:

$$
50(C N) 10 C\left(r_{\llcorner }+r_{n}\right)
$$

$$
{ }^{\mathbf{\Delta}} 50(C / V)\left(r_{U} / r_{S}\right), \mathbf{\Delta U S P 2 8}
$$

in which $C$ is the concentration, in mg per mL , of USP Atracurium Besylate RS in the Standard preparation; $V$ is the volume, in mL , of Injection taken for the Assay preparation; and $r_{U}$ and $r_{S}$ are the sums of the peak responses of the atracurium besylate trans-trans, trans-cis, and cis-cis-isomers obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Benzocaine, USP 27 page 217. It is proposed to revise the Assay with a newer method by replacing the current titration with a reverse phase HPLC procedure. It is proposed to change the upper assay limits in the Definition from 101.0 percent to 102.0 percent, based on the precision requirement of the proposed HPLC Assay procedure. The HPLC method was validated using a YMC phenyl brand of L11 column; benzocaine elutes at approximately 9 minutes.
(PA1: KAR) RTS-40722-1

## Change to read:

» Benzocaine, dried over phosphorus pentoxide for 3 hours, contains not less than 98.0 percent and not more than 101.0

- 102.0 $\mathbf{n}_{1 S}$ (USP28) percent of $\mathrm{C}_{9} \mathrm{H}_{11} \mathrm{NO}_{2}$.


## Change to read:

Assay- Pissolve about 300 mg of Benzoeaine, previously dried and aceurately weighed, in a mixture of 100 mL of water and 15 mL of hydrechloric acid. Cool the solution in an ice bath to about $10^{\circ}$, and titrate with 0.1 M sodium nitrite VS until a blue color is produced immediately when the titrated solution-is applied on stareh iodide paper. When the titration is complete, the endpeint is reproducible after the mixture has been allowed to stand for 5 mintutes. Perform a blank determination, and make any necessary eorrection. Each mL of 0.1 M sodium nitrite is equivalent to 16.52 mg of $\mathrm{C}_{9} \mathrm{H}_{4} \mathrm{NO}_{2}$.
-Aqueous solution-To 980 mL of water, add 20 mL of acetic acid and 1 mL of triethylamine, and mix well. The pH should be between 2.95 and 3.0 , adjust as needed.
Mobile phase-Prepare a filtered and degassed mixture of Aqueous solution and methanol ( $60: 40$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Benzocaine RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.024 mg per mL .

Assay preparation-Transfer about 24 mg of Benzocaine, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix. Dilute 10 mL of this solution with Mobile phase to 100 mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $285-\mathrm{nm}$ detector and a $2.0-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L11. The flow rate is about 0.2 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor of the benzocaine peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0\%.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the benzocaine peaks. Calculate the quantity, in mg, of $\mathrm{C}_{9} \mathrm{H}_{11} \mathrm{NO}_{2}$ in the portion of Benzocaine taken by the formula:

$$
1000 C\left(r_{U} / r_{s}\right),
$$

in which $C$ is the concentrations, in mg per mL, of USP Benzocaine RS in the Standard preparation; $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and Standard preparation, respectively; and the factor of 1000 is for the dilution factor for the Assay preparation. $\quad$ 1S (USP28)

## Briefing

Bupropion Hydrochloride Extended-Release Tablets, USP 27 page 280 and page 3047 of the First Supplement. It is proposed to add two Drug release tests to this monograph because the FDA recently approved two generic versions of this product. In the absence of any adverse comment, it is proposed to implement this revision via the Fifth Interim Revision Announcement pertaining to $U S P$ 27-NF 22, with an official date of October 1, 2004.
(BPC: M. Marques) RTS—39935-1; 40495-3

## Add the following:

${ }^{\bullet}$ Labeling-When more than one Drug release test is given, the labeling states the Drug release test used only if Test 1 is not used.es

## Change to read:

Drug release $\langle 724\rangle$ -
${ }^{\bullet}$ TEST $1-\bullet 5$
Medium: ${ }^{\bullet}$ water; 900 mL .

Apparatus 2: 50 rpm .
Times: 1, 4, and 8 hours.
Procedure- Determine the amount of $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{ClNO} \cdot \mathrm{HCl}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 298 nm , using a $1.0-\mathrm{cm}$ cell, on filtered portions of the solution under test, suitably diluted with Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same Medium.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{ClNO} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Ac ceptance Table $1\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $25 \%$ and $45 \%$ |
| 4 | between $60 \%$ and $85 \%$ |
| 8 | not less than $80 \%$ |

- TEST 2-If the product complies with this test, the labeling indicates that it meets USP Drug release Test 2.
Medium: $\quad 0.1 \mathrm{~N}$ hydrochloric acid, $\mathrm{pH} 1.5 ; 900 \mathrm{~mL}$.
Apparatus 1: 50 rpm .
Times: $1,2,4$, and 6 hours.
Determine the percentages of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{ClNO} \cdot \mathrm{HCl}$ dissolved by employing the following method.

Buffer solution-Dissolve 3.45 g of sodium phosphate monobasic monohydrate in 996 mL of water, add 4.0 mL of triethylamine, and mix. Adjust with phosphoric acid to a pH of $2.80 \pm 0.05$.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and methanol ( $65: 35$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard solution-Dissolve an accurately weighed quantity of USP Bupropion Hydrochloride RS in Medium, and dilute quantitatively, and stepwise if necessary, with Medium to obtain a solution having a known concentration similar to the one expected in the Test solution.
Test solution-Use portions of the solution under test, and pass through a $0.45-\mu \mathrm{m}$ nylon filter.
Chromatographic system (see Chromatography $\langle 621\rangle$ — The liquid chromatograph is equipped with a 298 -nm detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromato-
graph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of bupropion hydrochloride dissolved at each time point.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{ClNO} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Acceptance Table $1\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $25 \%$ and $50 \%$ |
| 2 | between $40 \%$ and $65 \%$ |
| 4 | between $65 \%$ and $90 \%$ |
| 6 | not less than $80 \%$ |

TEST 3-If the product complies with this test, the labeling indicates that it meets USP Drug release Test 3.

Medium, Apparatus, and Procedure-Proceed as directed for Test 1 , except using the wavelength of about 250 nm .

$$
\text { Times: } 1,2,4 \text {, and } 6 \text { hours. }
$$

Tolerances: The percentages of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{ClNO} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Acceptance Table $1\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $30 \%$ and $55 \%$ |
| 2 | between $50 \%$ and $75 \%$ |
| 4 | between $70 \%$ and $90 \%$ |
| 6 | not less than $80 \%$ |

## Briefing

Carbidopa, USP 27 page 327. To improve laboratory efficiency, it is proposed to revise Identification test $B$ by replacing the existing UV absorption test with an HPLC test, which uses data obtained in the Assay.
(PA3: S. Salado) RTS-40892-1

## Change to read:

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$.
B: Ultaviolet Abserption $\langle 197 \mathrm{U}\rangle$ -
Solution: -40 ne per mL.
Hedinm: hydrechloric acid in methand ( 4 in 100). Absorptiv ities at 282 nm , caleulated on the dried basis, do net differ by more than $3.0 \%$.
-B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay. ${ }^{15}$ (USP28)

## Briefing

Methionine C 11 Injection, USP 27 page 332 and page 468 of PF 30(2) [Mar.-Apr. 2004]. The proposal to revise the Definition to allow alternative labeling chemistry is now republished as a proposal to implement the revision via the Fourth Interim Revision Announcement pertaining to USP 27-NF 22, with an official date of August 4, 2004.
(RMI: A. Wilk) RTS-40885-1

## Delete the following:



## Change to read:

» Methionine C 11 Injection is a sterile isotonic solution, suitable for intravenous administration of $\pm[1-$ ${ }^{4}$ C] methionine,
${ }^{\bullet} \mathrm{L}\left[{ }^{11} \mathrm{C}\right]$ methionine, ${ }^{\circ}$
in which a portion of the molecules are labeled with radioactive ${ }^{11} \mathrm{C}$. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ${ }^{11} \mathrm{C}$ expressed in MBq (or in mCi ) at the time indicated in the labeling. It may contain preservatives and stabilizers.

## Briefing

Carboxymethylcellulose Sodium Suspension, page 8088 of PF 25(3) [May-June 1999]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded with modifications to In-Process Revision.
(CRX: C. Okeke) RTS-41007-1

## Add the following:

## ■Carboxymethylcellulose Sodium Suspension

» Carboxymethylcellulose Sodium Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled content of Carboxymethylcellulose Sodium in 100 mL of Sus-
pension. Prepare Carboxymethylcellulose Sodium Suspension of the designated percentage strength as follows (see Phatmacy Compothding Pr- (H64〉 Pharmaceutical Compounding—Nonsterile Preparations $\langle 795\rangle$ ):

Carboxymethylcellulose Sodium
(medium viscosity, between 400
and 1500 cps )
for $0.25 \%$ Suspension . . . . . . . 250 mg
for $0.5 \%$ Suspension . . . . . . . . $\quad 500 \mathrm{mg}$
for $1.0 \%$ Suspension . . . . . . . . $\quad 1.0 \mathrm{~g}$
Methylparaben. . . . . . . . . . . . . . . 120 mg
Purified Water, a sufficient quantity
to make. . . . . . . . . . . . . . . . . . $\quad 100 \mathrm{~mL}$
Dissolve the Methylparaben in 50 mL of Purified Water maintained at a temperature of $70^{\circ}$ to $80^{\circ}$. Slowly add the Carboxymethylcellulose Sodium to the hot solution while continuously stirring. Add sufficient refrigerated Purified Water (temperature $15^{\circ}$ or lower) to obtain 100 mL of suspension, and mix to produce the Suspension.

Packaging and storage-Preserve in tight, light-resistant containers. Store at room temperature or in a refrigerator.

Labeling-Label it to state, as part of the official title, the content of Carboxymethylcellulose Sodium expressed as a percentage. Label it also to indicate the viscosity, in centipoises, of the Carboxymethylcellulose Sodium taken for the Suspension. The label states that Carboxymethylcellulose Sodium Suspension is to be well shaken.

Beyond-use date-Fourteen days after the day on which it was compounded.

## Compliance assay-[To come.] $]_{\text {1S (USP28) }}$

## Briefing

Ciclopirox Olamine, USP 27 page 448 and page 3049 of the First Supplement. It is proposed to make a minor editorial revision to clarify the Procedure in the test for Related compounds.
(PA7b: B. Davani) RTS-40899-1

## Change to read:

${ }^{4}$ Related compounds-[NOTE-Carry out the operations avoiding exposure to actinic light. All materials that are in direct contact with Ciclopirox Olamine (i.e, column materials, reagents, solvents, etc.) should contain only very low amounts of extractable metal cations.]

Mobile phase-Prepare a filtered and degassed mixture of an edetate disodium solution ( 0.96 in 1000), acetonitrile, and glacial acetic acid (770:230:0.1). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Rinsing solution-Prepare a mixture of water, acetonitrile, glacial acetic acid, and acetylacetone (500:500:1:1).

Standard stock solution-Dissolve 15 mg of USP Ciclopirox Related Compound A RS and 15 mg of USP Ciclopirox Related Compound B RS, accurately weighed, in 1 mL of acetonitrile and 7 mL of Mobile phase. Dilute the solution thus obtained to 10.0 mL with Mobile phase to obtain a solution having a known concentration of 1.5 mg of each USP Reference Standard per mL.

Standard solution A-Dilute 1.0 mL of Standard stock solution to 200.0 mL with a mixture of Mobile phase and acetonitrile $(9: 1)$. Standard solution B-Dilute 2.0 mL of Standard solution A to 10.0 mL with a mixture of Mobile phase and acetonitrile $(9: 1)$.

Test solution-Dissolve 40 mg of Ciclopirox Olamine, accurately weighed, in a mixture of 2 mL of acetonitrile, $20 \mu \mathrm{~L}$ of glacial acetic acid, and 15 mL of Mobile phase. If necessary, use an ultrasonic bath to dissolve. Dilute with Mobile phase to 20.0 mL , and mix.

Resolution solution-Mix 5 mL of Standard stock solution with 5 mL of the Test solution.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a detector capable of recording at both 220 nm and 298 nm and a $4.0-\mathrm{mm} \times 8-\mathrm{cm}$ column that contains packing L10. [NOTE-Ciclopirox related compound A has an intense absorbance at 220 nm and 6-cyclohexyl-4-methyl$2(1 H)$-pyridone, ciclopirox related compound B , and ciclopirox have intense absorbances at 298 nm .] The flow rate is about 0.7 mL per minute. Chromatograph the Resolution solution at 298 nm , and record the peak responses as directed for Procedure: the resolution between the ciclopirox related compound B peak and
ciclopirox peak is not less than 2.0. Chromatograph the Standard solution $B$ at 298 nm , and record the peak responses as directed for Procedure: the chromatogram obtained shows at 298 nm a peak corresponding to ciclopirox related compound B with a signal-to-noise ratio of not less than 3. Chromatograph the Test solution at 298 nm , and record the peak responses as directed for Procedure: the tailing factor for the ciclopirox peak is less than 2.0 .

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of Standard solution A, Standard solution B, and the Test solution into the chromatograph, and record the chromatograms. [NOTE-In order to ensure desorption of disruptive metal ions, every new column must be rinsed with the Rinsing solution over a period of not less than 15 hours and then with the Mobile phase for not less than 5 hours with a flow rate of 0.2 mL per minute. The chromatographic run time is not less than 2.5 times the retention time of the ciclopirox peak.] The relative retention times are about 0.5 for ciclopirox related compound A, 0.9 for 6-cyclohexyl-4-methyl-2 $(1 H)$-pyridone, 1.0 for ciclopirox, and 1.3 for ciclopirox related compound B. The peak response at 220 nm of the ciclopirox related compound A peak in the chromatogram obtained from the Test solution is not more than the peak response at 220 nm of the corresponding peak in the chromatogram obtained from Standard solution $A$ ( $0.5 \%$ with reference to ciclopirox). The sum of responses at 298 nm of the
$\boldsymbol{m i m p u r i t y}_{\mathbf{m}_{1 S}}{ }_{\text {(USP28) }}$
peaks in the chromatogram obtained from the Test solution is not more than the peak response at 298 nm of the ciclopirox related compound B peak in the chromatogram obtained from Standard solution $A(0.5 \%$ with reference to ciclopirox). At 298 nm disregard any peak due to the solvent and any peak with a response less than the response of the ciclopirox related compound B peak in the chromatogram obtained from Standard solution B at $298 \mathrm{~nm}(0.1 \%$ with reference to ciclopirox). $\mathbf{\Delta U S P 2 7}$

## Briefing

Ciprofloxacin Injection, USP 27 page 456 and page 473 of $P F$ 30(2) [Mar.-Apr. 2004]. It is proposed to make a minor editorial revision to clarify the Procedure in the test for Limit of ciprofloxacin ethylenediamine analog.
(PA7b: B. Davani) RTS-40898-1

## Change to read:

» Ciprofloxacin Injection is a sterile solution of Ciprofloxacin
$\Delta^{\text {or Ciprofloxacin Hydrochloride }}{ }_{\Delta U S P 28}$
in Sterile Water for Injection, in 5 percent Dextrose Injection, or in 0.9 percent Sodium Chloride Injection prepared with the aid of Lactic Acid. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ciprofloxacin $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{FN}_{3} \mathrm{O}_{3}\right)$.

## Change to read:

Limit of ciprofloxacin ethylenediamine analog-
Mobile phase and Chromatographic system-Proceed as directed in the Assay under Ciprofloxacin.

Standard preparation, Resolution solution, and Assay prepara-tion-Proceed as directed in the Assay for ciprofloxacin.

Procedure-Proceed as directed for Procedure in the Assay for ciprofloxacin. Calculate the percentage of ciprofloxacin ethylenediamine analog from the chromatogram obtained from the Assay preparation in the Assay for ciprofloxacin by the formula:

$$
100\left[0.7 r_{A} /\left(0.7 r_{A}+r_{C}\right)\right]
$$

in which 0.7 is the respense
$\mathbf{■}_{\text {correction }}^{1 \mathrm{IS} \text { (USP28) }}$
factor for ciprofloxacin ethylenediamine analog; relative to that of eiprofloxacin

## -1S (USP28)

and $r_{A}$ and $r_{C}$ are the responses of the ciprofloxacin ethylenediamine analog peak and the ciprofloxacin peak, respectively. It contains not more than $0.5 \%$ of ciprofloxacin ethylenediamine analog.

## Briefing

Clonidine Transdermal System, page 84 of $P F 30(1)$ [Jan.Feb. 2004]. The USP Clonidine RS is corrected. Editorial style changes have also been made.
(PA5: A. Wilk) RTS-40494-1

## Add the following:

## Clonidine Transdermal System

» Clonidine Transdermal System contains not less than 80.0 percent and not more than 120.0 percent

Of the labeled amount of clonidine $\left(\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}\right) .2 .0 \mathrm{mg}$ and not more than 3.0 mg of elonidine, if labeled to deliver 0.1 mg of clonidine per day for one week; not less than 4.0 mg and not more than 6.0 mg of clonidine, if labeled to-deliver 0.2 mg of clonidine per day for one week; and not less than 6.0 mg and not more than 9.0 mg of clenidine, if labeled to deliver 0.3 mg - $f$ elonidine per day for one week. 80.0 percent and not more than 120.0 percent of the labeled amount of clonidine $\left(\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}\right)$.

Packaging and storage-Preserve in sealed, single-dose containers at a temperature not exceeding $30^{\circ}$.

Labeling-The label states the total amount of clonidine in the Transdermal System and the release rate, in mg per day, for the duration of the application of one system.

USP Reference standards $\langle 11\rangle$ —USP Clonidine Hydroehloride RS. USP Clonidine Related Compound B RS.

NOTE-Throughout the following procedures, avoid the use of tetrahydrofuran stabilized with butylated hydroxytoluene (BHT). In the presence of peroxides, BHT may react with clonidine, producing impurity peaks.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
pH 9.2, 2 M Tris buffer—Dissolve 121.14 g of tris-(hydroxymethyl)aminomethane in 500 mL of water. Adjust with dilute hydrochloric acid to a pH of 9.2.

Test specimen-Carefully peel the release liner from each Transdermal System, and place a number of Transdermal Systems, equivalent to about 25 mg of clonidine, into a $50-\mathrm{mL}$ screw-capped centrifuge tube. Add 5 mL of chloroform, and using a vortex mixer, mix for 5 minutes. Let stand for 30 minutes, and mix intermittently using a vortex mixer.

Transfer the chloroform solution to another $50-\mathrm{mL}$ centrifuge tube, and wash the residue with an additional 3 mL of chloroform, combining the extracts. Add 2 mL of 0.5 N hydrochloric acid to the extract, mix on a vortex mixer for 1 minute, and centrifuge at about 1000 rpm for 4 minutes. Remove and discard the bottom chloroform layer. Extract the aqueous layer with 4 mL of chloroform. Centrifuge at about 1000 rpm for an additional 5 minutes and again discard the bottom chloroform layer. Add 5 mL of $\mathrm{pH} 9.2,2$ M Tris buffer and 3 mL of methylene chloride. Mix on a vortex mixer for 1 minute. Centrifuge at about 1000 rpm for 4 minutes. Transfer the bottom methylene chloride layer into a $100-\mathrm{mL}$ beaker, and dry the methylene chloride with anhydrous sodium sulfate (about $1 / 4$ liquid height). Decant, and evaporate to dryness with a stream of nitrogen. Dry at $105^{\circ}$ for 30 min utes, and allow to cool in a desiccator.

## Spectal range: 3500 to $3600 \mathrm{~cm}^{-1}$.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Uniformity of dosage units $\langle 905\rangle$ : meets the requirements.

## Drug release $\langle 724\rangle$ -

Medium: $\quad 0.001 \mathrm{M}$ phosphoric acid; 80 mL for systems containing 5 mg or less of clonidine; 160 mL 200 mL for systems containing more than 5 mg of clonidine.

Times: $8,24,96$, and 168 hours.
Apparatus 7-Proceed as directed in the chapter, [Sizef sample holder using the transdermal system holder-angled disk (see Figure 7a). To prevent overhang, choose the appropriate size of the holder, 1.42 or 1.98 inches, based on the size of the system. Use $100-\mathrm{mL}$ beakers for Medium volumes of $80-\mathrm{mL}$ and $300-\mathrm{mL}$ beakers for Medium volumes of 200 mL . Gently press the Transdermal

System to a dry, smooth, square piece of cellulose membrane ${ }^{*}$, or equivalent, with the adhesive side against the membrane. Attach the membrane system to a suitable inert sample holder with a Viton O-ring, or equivalent, such that the backing of the system is adjacent to, and centered on, the bottom of the sample holder. Trim the excess of cellulose membrane with scissors. Suspend each sample holder from the arm of a reciprocating shaker such that each system is continuously immersed in a beaker containing the specified volume of Medium. The filled beakers are weighed and preequilibrated to $32.0 \pm 0.3^{\circ}$ prior to immersing the test sample. Agitate the sample in an up-down motion at a frequency of 30 cycles per minute with an amplitude of $2.0 \pm 0.1 \mathrm{~cm}$. The Medium must be added daily to the beakers during each interval to maintain sample immersion. At the end of each time interval, transfer the test sample to a fresh beaker containing the appropriate volume of Medium, weighed and pre-equilibrated to $32.0 \pm 0.3^{\circ}$.

Determine the amount of $\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}$ released by employing the following method.
Solvent Dissolve 2.04 g of menebasic petassitum phesphate and 2.88 g of 1 pentanesulfonic acid sodium 1 penta fesulfonate in 300 mL of water. Adjust with phospherie

```
acid to a pH of 3.5.
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Mobile phase -Prepare a filtered and degassed mixture of Solvent and methanol(26:14). Make adjustments if neeessary (see System Suitability under Chromatography $\langle 621\rangle$ ). Use a filtered and degassed $0.1 \%$ solution of triethylamine in a mixture of water and methanol ( $70: 30$ ), and adjust with phosphoric acid to a pH of $6.0 \pm 0.2$. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

[^93]Fest solution At each of the test times, withdraw a 10 mL aliquet of the solution from each container.

Standetrd solution Prepare a solution of USP Clonidine
Hydrochloride RS in 0.001 M phosphoric acid having a known concentration of clonidine similar to that of the Test

## soltition.

System suitability solution-Prepare a solution of USP Clonidine Hydrochloride RS in 0.001 M phosphoric acid having a known concentration of about $10 \mu \mathrm{~g}$ per mL .

Standard solutions-Prepare a minimum of four standard solutions of USP Clonidine Hydrechloride RS in 0.001 M phosphoric acid having known concentrations of clonidine similar to those of the Test solutions.

Test solutions-At the end of each release interval, allow the beakers to cool to room temperature, and make up for evaporative Medium losses by adding Medium to obtain the original weight. Mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210 \mathrm{~nm} 220-$ nm detector and a $4.0 \mathrm{~mm} \times 30 \mathrm{~cm} 4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the tailing factor is not more than $\geq 2.0$; the capacity factor is not less than 0.5 ; the column efficiency is not less than 2000 theoretical plates; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \pm 25 \mu \mathrm{~L}$ ) of filtered portions of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Construct a standard curve of concentration ( $\mu \mathrm{g}$ per mL ) of clonidine in the Standard solutions versus peak area
by linear regression analysis. The correlation coefficient is not less than 0.995 . Calculate the release rate of clonidine by the formula:

## CV/TA,

in which $C$ is the concentration, $\mu \mathrm{g}$ per mL , of clonidine in the sample obtained from the standard curve; $V$ is the volume, in mL , of the Medium; $T$ is the time, in hours; and $A$ is the area, in $\mathrm{cm}^{2}$, of the transdermal system.

## Tolerances - The amme of $\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}$ released,as a per-

 eentage of the labeled amemn of the dose absorbed in vive, as us per hour per $\mathrm{cm}^{2}$, at the time specified eonforms to Aceeplate Table 4.| Time (heurts) | Ameunt dissolved |
| :---: | :---: |
| 8 | between 28\% and 68\% |
| 96 | between 116\% and 288\% |
| 168 | been 170\% and 357\% |
| Time (hours) | Amount dissolved ( $\mathrm{\mu g} / \mathrm{h}-$ $\mathrm{em}^{2}+$ |
| 8 | between 7.5 and 16.0 |
| 24 | between 1.5 and 6.0 |
| 96 | between 1.5 and 4.6 |
| 168 | been 1.5 and 3.3 |

The ameunt of $\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}$ released, as a percentage of the tabeled amount of the dose absorbed in vive, as $\mu \mathrm{g}$ per hour per $\mathrm{cm}^{2}$, at the times specified conforms to Acceptance Table 4. The release rate of $\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}$ from the Transdermal System, expressed as $\mu \mathrm{g}$ per hour per $\mathrm{cm}^{2}$ at the times specified, conforms to Acceptance Table 4.

| Time <br> (hours) | Time for sampling <br> (hours) | Ameme dissolved Re- <br> lease rate $\left(\mu \mathrm{g} / \mathrm{h} / \mathrm{cm}^{2}\right)$ |
| :---: | :---: | :---: |
| $0-8$ | 8 | between 7.5 and 16.0 |
| $8-24$ | 24 | between 1.5 and 4.6 |
| $24-96$ | 96 | between 1.5 and 4.6 |
| $96-168$ | 168 | between 1.5 and 3.3 |

## Chromatographie purity -Related compounds-

Buffer solution Dissolve 2.0 of sodilum 1 pentanesut fenate, 13.61 g of menebasic petassitm phesphate, and 2 mL of triethylamine in about 1000 mL of water in a 2 liter velumetric flask, adjust with phespheric acid to a pH of $4.0 \pm 0.1$, dilute with water to volume, and mix.

Mebile phase Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $1: 1$ ), and, if necessaty, at just with phespheric acid to apHef $4.5 \pm 0.1$. Make adjust ments if necessary (see System Suitability under Chromatograplyy $\langle 624\rangle$ ).

Piltent 1. Dissolve 1 mL of triethylamine in about 800 mL of water in a 1 - liter volumetric flask, adjust with phesphoric acid to a pH of $10.0 \pm 0.1$, dilute with water to ve fame, and mix. Transfer this solution to a 2 - liter volumetrie flask, dilute with acetonitrile to volume, and mix.

Bithent 2 Dissolve 1 mL of triethylamine and 4.36 g of dibasic petassium phesphate in about 800 mL of water in a Hiter volumetrie flask, adjust with phesphorie acid to a pH of $10.0 \pm 0.1$, dillute with water to veltame, and mix. Transfer this selution to a 2 liter volumetric flask, dilute with acet enitrile to volume, and mix.

Standard solation Dissolve an aceurately weighed quantity of USP Clonidine Hydrechloride RS in Diltent 1 to obtain a solution having a known concentration of about $\theta .1 \mathrm{mg}$ per ml . Dilute an aceurately measured volume of this solution quantitatively with Diltuent 2 to obtain a solth
tion having a known concentration of about $16.2 \mu \mathrm{~g}$ of USP Clenidine-Hydrechloride-RS per mL (equivalent to about 14.0 ng of clenidine per mL ).

Fest solution-Carefully peel the release liner from each Transdermal System, and place a number of Transdermat Systems, equivalent to about 15 mg of clenidine, into a 150 mL polytef lined serew cap tabe. Add 30 mL of $n$ heptane, cap, and mix on a vortex mixer for 2 minutes. Allow to stand for about 3 hours, but every 30 mintutes during this period mix on a vortex mixer until the Transdermal Systems are delaminated. Add 0.3 mL of methanol and 45 mL of 0.01 N sulfuric acid, shake for at least 2 minutes, and centriftge. Retain the $n$ heptane layer, and transfer the aqueens stipernatant layer to a second $150-\mathrm{mL}$ polytef lined serew eap tube. Add 9 mL of ammonitum hydroxide to the aqueous stpernatant layer, and mix. Extract the $n$-heptane layer with an additional 45 mL of 0.01 N sulftric acid for at least 2 minutes, and combine this aqueous supernatant layer with the first aqueous layer in the $150-\mathrm{mL}$ polytef lined serew eap tube. [NOTE The total length of time of extraction with $\theta .01 \mathrm{~N}$ sulfuric acid-should not exceed 1 heur to avoid degradation of any related impurity that may be present.] Ex tract the aquerus layer by shaking vigerously for 2 mintutes with each of $30-\mathrm{mL}$ pertions of chloreform, collecting thechloreform extracts in a 150 -mL pelytef lined serew eap tube. Evaperate the chloreform extracts under nitrogen to dryness, and dissolve the residtue in 15.0 mL of Diltuent 2. Chromatographic system (see Chromatography $\langle 624\rangle$ ) The liquid chrematograph is equipped with a 210 - nm detec for and a $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}$ coltum that contains packing L10. The flow rate is about 1 mL per minte. Chromatograph the Statatad solttion, and record the peak responses as directed for Proedtre: the coltuma efficiency is not less
than- 4000 theoretieal plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate in jections is net mere than $2.0 \%$.

Procedure Separately inject equal volumes (about 20 HE) of the Statedted soltion and the Test solution into the ehromatograph, record the chromatograms, and meastre the peak responses. Calculate the pereentage of each impurity in the Transdermal Systems taken by the formula:-

$$
(230.10 / 266.56)(1.5 \mathrm{C} / \mathrm{NL})\left(+_{4}++_{s}\right),
$$

in whieh 230.10 and 266.56 are the molecular weights of elonidine and clonidine hydrechloride, respectively, $C$ is the concentration, in ehloride RS in the Standard solution; $N$ is the number of Transtermal Systems taken to prepare the Test solution; I is the labeled amount, in mg, of clonidine in each Transdermal System taken; $r_{t}$-is the peak respense for each impurity ebtained from the Test solution; and $x_{s}$ is the clonidine peak respense obtained frem the Standard solution: not more than $1.4 \%$ of total impurities is found. not mere that $1.4 \%$ of any impurity is feund, and not more than $2.4 \%$ of total impurities is found.

Mobile phase, Diluent, System suitability solution, and Chromatographic system-Proceed as directed in the Assay.

Standard solution-Dissolve an accurately weighed quantity of USP Clonidine Related Compound B RS in tetrahydrofuran, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 1 mg per mL . Prepare a minimum of four Standard solutions in Diluent that bracket the expected clonidine related compound B concentration in the sample. The standard concentrations should be within the range of 0.2 to $10.0 \mu \mathrm{~g}$ per mL . [NOTE-Standard solutions are stable for up to 2 days if stored at $4^{\circ}$.]

Test solution-Use the Assay preparation, prepared as directed in the Assay.
Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of at least three Standard solutions that will bracket the expected sample concentration range and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the clonidine related compound B. Calculate the peak response ratios of the analyte, and plot the results. Determine the linear regression equation of the standards by the mean-square method, and record the linear regression equation and the correlation coefficient; it should be not less than 0.995 . Determine the concentration of the clonidine related compound B. Calculate the amount, in $\mu \mathrm{g}$ per $\mathrm{cm}^{2}$, of the clonidine related compound B in the portion of the Transdermal System taken by the formula:

## CV/A,

in which $C$ is the concentration of clonidine related compound B , in $\mu \mathrm{g}$ per mL , obtained from the linear regression analysis; $V$ is the volume of the Test solution in mL ; and $A$ is the area of the sample system in $\mathrm{cm}^{2}$. Not more than $10.0 \mu \mathrm{~g}$ per $\mathrm{cm}^{2}$ of clonidine related compound $B$ is found.

## Assay-

Mobile phase Prepare a filtered and degassed mixtare of sodium 1-pentanesulfonate and methanol $(63: 36)$. Make adjustments if necessary (see System-Suitability under Chromatography $\langle 621$ ) .

Standard prepatation- Dissolve an aceurately weighed quantity of USP Clonidine Hydrochloride RS in 0.01N sut furic acid, and dilute quantitatively, and stepwise if necessary, with 0.01 N sulfuric acid to obtain a solution having a known concentration of about $46 \mu$ p per mL. 0.046 T per mL (equivalent to about $0.040 T$ of clonidine per mL ), $T$ being the total amount, in mg, of clonidine in each Transder-mal-System.

Assay preparation Carefully peel the release liner frem 1 Transdermal System, and cut the Transdermal System inte segments. Quantitatively transfer the-segments into an appropriate polytef lined serew cap centrifuge tube, add 10 mL of 0.01 N sulfuric acid sattrated with $n$ heptane, acet rately measured, cap, and heat to $60^{\circ}$ for 3 hours. Add 10 mL of $n$-heptane, cap, shake vigoreusly for 1 mintute, and heat to $60^{\circ}$ for about 16 hours. Allow the solution to-coel 6-roem temperature, add 15 mL of 0.01 N sulfuric acid sa ferated with $n$-heptane, cap, and mix in a vertex mixer for about 2 mintites. Allow to separate, and filter the aqueous layer. [NOTE If backing membrane has not delaminated, repeat with a new Transtermal System.] Use the aqueens layer as the Assay preparation.

Chromatographic system(see-Chrematography- $\langle 621\rangle$ )The liquid chromatograph is equipped with a 210 nm-detec tor, a $3.9-\mathrm{mm} \times 2 \mathrm{~cm}$ guard coltmm that contains packing L 2 , and a $3.9 \mathrm{~mm} \times 30 \mathrm{em}$ coltumm that contains packing E1. The flow rate is about 1.5 mL per minute. Chremate graph the Standard preparation, and record the peak respenses as directed forProcedtre: the tailing factor is net mere than 2.0 ; and the relative standard deviation for replieate injections is not more than $2.0 \%$.

Procedure Separately inject equal volumes (about 50 HL) of the Standtrd preparation and the Assay prepatation inte the-chremategraph, record the-chremategrams, and measure the respenses for the major peaks. Caleulate the quantity, in $\mu$ g, of clenidine $\left(\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}\right)$ in the Transtermat System taken by the formula:-

$$
21.58 C\left(r_{\llcorner }+r_{s}\right)
$$

$(230.10 / 266.56)(25 C)\left(r_{4}++_{s}\right)$,
in which 230.10 and 266.56 are the molecular weights of elonidine and clonidine hydrochloride, respectively; $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Clonidine Hydreehboride RS in the Standard preparation; and $t_{t}$ and $\Psi_{s}$ are the peak respenses-obtained from theAssay preparation and the Standard preparation,respectively.
Mobile phase-Dissolve 4 mL of triethylamine in 1.6 L of water, and adjust with phosphoric acid to a pH of 3.0. Add 2.4 L of acetonitrile, stir the solution for 30 minutes, filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Diluent-Prepare a mixture of tetrahydrofuran and methanol (1:1).

System suitability solution-Dissolve an accurately weighed quantity of USP Clonidine RS and USP Clonidine Related Compound B RS in Diluent to obtain a solution having known concentrations of about $250 \mu \mathrm{~g}$ per mL and $10 \mu \mathrm{~g}$ per mL , respectively.

Standard preparation-Dissolve a suitable amount, accurately weighed, of USP Clonidine Hydrehtride RS in tetrahydrofuran to obtain a solution having a known concentration of about 1 mg per mL . Prepare a minimum of four Standard preparations in Diluent that bracket the expected clonidine concentration in the sample. The standard concentrations should be within the range of 50 to $300 \mu \mathrm{~g}$ per mL. [NOTE-Standard preparations are stable for up to 2 days if stored at $4^{\circ}$.]

Assay preparation-Remove each Transdermal System from its package, discard the release liner from each system, and transfer into a $50-\mathrm{mL}$ centrifuge tube with a Teflon-lined screw cap. Add the appropriate volume of tetrahydrofuran indicated below. Vigorously mix on a vortex mixer until the systems are washed down and fully submerged in the tetrahydrofuran. Let the systems soak in tetrahydrofuran for about 5 minutes, and mix on a vortex mixer until the sys-
tems are completely delaminated. Allow the systems to remain submerged for an additional 60 minutes, and mix using a vortex mixer every 30 minutes. Add methanol in a volume equal to the volume of tetrahydrofuran, and mix vigorously on a vortex mixer. The solution turns milky. Centrifuge for ten minutes at 2000 rpm . Use the supernatant as the Assay preparation.

| For systems containing about 2.5 mg <br> of clonidine | 7.0 mL |
| :--- | :--- |
| For systems containing about 5.0 mg |  |
| of clonidine |  |$\quad 14.0 \mathrm{~mL}$

For systems containing about 7.5 mg
21.0 mL
of clonidine

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a detector capable of measuring at 210 nm and 242 nm , and a $4.6-\mathrm{mm} \times$ $15-\mathrm{cm}$ column that contains packing L10. The flow rate is about 1 mL per minute. The detector is programmed initially to 242 nm and 210 nm after the elution of the clonidine peak but prior to the elution of the clonidine related compound B. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention time is 1.0 for clonidine and 1.5 for clonidine related compound B ; the resolution, $R$, between clonidine and clonidine related compound $B$ is not less than 2.0 ; the capacity factor, $k^{\prime}$, is not less than 0.6 for clonidine; the tailing factor for both clonidine and clonidine related compound B is not more than 3.0 ; and the relative standard deviation of the clonidine peak area for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of at least three Standard preparations that will bracket the expected sample concentration range and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the clonidine. Calculate the peak response ratios of the analyte and plot the results. Determine the linear regression equation of the standards by the mean-square method, and record the linear regression equation and the correlation coefficient; it should be not less than 0.995 . Calculate the amount, in mg , of $\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{Cl}_{2} \mathrm{~N}_{3}$ in the Transdermal System taken by the formula:

$$
C V / 1000
$$

in which $C$ is the concentration of clonidine, in $\mu \mathrm{g}$ per mL , obtained from the linear regression analysis; and $V$ is the volume of the Assay preparation in mL per sample system.■1S (USP28)

## Briefing

Clopidogrel Tablets. Because there is no existing USP monograph for this dosage form, a new monograph is being proposed. The liquid chromatographic procedures in the test for Related compounds and in the Assay are based on analyses performed with a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ Ultron ES-OVM column that contains $5-\mu \mathrm{m}$ packing L\#\# (see Chromatography $\langle 621\rangle$ ). The typical retention time for clopidogrel is about 4.6 minutes.
(PA5: A. Wilk; BPC: M. Marques) RTS—36201-3; 40048-2

## Add the following:

## ■Clopidogrel Tablets

» Clopidogrel Tablets contain Clopidogrel Bisulfate equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of clopidogrel $\left(\mathrm{C}_{16} \mathrm{H}_{16} \mathrm{ClNO}_{2} \mathrm{~S}\right)$.

Packaging and storage-Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Clopidogrel Bisulfate RS. USP Clopidogrel Related Compound A RS. USP Clopidogrel Related Compound B RS. USP Clopidogrel Related Compound C RS.

## Identification-

A: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ -
Spectral range: 250 to 300 nm .
Solution: Use the test solution prepared as directed in the test for Uniformity of dosage units.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Dissolution $\langle 711\rangle$ -
Medium: $\quad \mathrm{pH} 2.0$ hydrochloric acid buffer (see Buffer solutions under Reagents, Indicators, and Solutions); 1000 mL .

Apparatus 2: 50 rpm .
Time: 30 minutes.
Standard solution-Dissolve an accurately weighed quantity of USP Clopidogrel RS in 20.0 mL of methanol, and dilute quantitatively, and stepwise if necessary, with Medium to obtain a solution having a known concentration corresponding to that of the solution under test.

Procedure-Determine the amount of $\mathrm{C}_{16} \mathrm{H}_{16} \mathrm{ClNO}_{2} \mathrm{~S}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 240 nm on filtered portions of the solution under test in comparison with the Standard solution.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{16} \mathrm{H}_{16} \mathrm{ClNO}_{2} \mathrm{~S}$ is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

Procedure for content uniformity-Using a suitable volumetric flask, place 1 Tablet in 50.0 mL of 0.1 N hydrochloric acid. Sonicate for 5 minutes, and cool. Quantitatively transfer 5.0 mL of this solution to the flask, and dilute with 0.1 N hydrochloric acid to 50.0 mL . Pass a portion of the solution through a suitable filter having a $0.45-\mu \mathrm{m}$ or finer porosity, discarding the first 5 mL . Determine the amount of clopidogrel by employing UV absorption at the wavelength of maximum absorbance at about 270 nm , in comparison with a Standard solution having a known concentration of USP Clopidogrel Bisulfate RS in 0.1 N hydrochloric acid.

## Related compounds-

Phosphate buffer and Mobile phase-Prepare as directed in the Assay under Clopidogrel Bisulfate.
System suitability solution-Dissolve accurately weighed quantities of USP Clopidogrel Bisulfate RS, USP Clopidogrel Related Compound A RS, USP Clopidogrel Related Compound B RS, and USP Clopidogrel Related Compound C RS in methanol. Dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having concentrations of about $1 \mu \mathrm{~g}$ per $\mathrm{mL}, 1 \mu \mathrm{~g}$ per $\mathrm{mL}, 2 \mu \mathrm{~g}$ per mL and $3 \mu \mathrm{~g}$ per mL , respectively.

Standard solution-Dissolve accurately weighed quantities of USP Clopidogrel Related Compound A RS and USP Clopidogrel Related Compound C RS in methanol. Di-
lute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having known concentrations of about $1 \mu \mathrm{~g}$ per mL and $5 \mu \mathrm{~g}$ per mL , respectively.

Test solution-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 75 mg of clopidogrel, to a $200-\mathrm{mL}$ volumetric flask, add 5 mL of methanol, dilute with Mobile phase to volume, and mix. Let it stand for 10 minutes, and mix. Pass a portion of this solution through a filter having a $0.45-\mu \mathrm{m}$ or finer porosity, and use the filtrate after discarding the first 5 mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L\#\#. The flow rate is about 1.0 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between clopidogrel and each of the two enantiomers of clopidogrel related compound $B$ is not less than 2.5. [NOTEThe relative retention times are about 0.5 for clopidogrel related compound A, 0.8 and 1.2 for the two enantiomers of clopidogrel related compound $\mathrm{B}, 1.0$ for clopidogrel, and 2.0 for clopidogrel related compound C]. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $15 \%$.

Procedure-Inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of related compounds in the portion of Tablets taken by the formula:

$$
20(C / W)\left(r_{U} / r_{s}\right),
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of the appropriate USP Reference Standard in the Standard solution; $W$ is the weight, in mg , of clopidogrel in the portion of Tablets used to prepare the Test solution based on the labeled quantity of clopidogrel per Tablet, Tablet weight, and the weight of the portion of Tablets used; and $r_{U}$ and $r_{S}$ are the peak responses of the corresponding related compounds obtained from the Test solution and the Standard solution, respectively: not more than $0.2 \%$ of clopidogrel related compound A is found, not more than $1.0 \%$ of clopidogrel related compound C is found, not more than $0.2 \%$ of any other single impurity (excluding clopidogrel related compound B) is found, and not more than $1.2 \%$ of total impurities (excluding clopidogrel related compound $B$ ) is found.

## Assay-

Phosphate buffer, Mobile phase, System suitability solution, Standard stock solution, Standard preparation, and Chromatographic system—Proceed as directed in the Assay under Clopidogrel Bisulfate.

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of clopidogrel bisulfate, to a $100-\mathrm{mL}$ volumetric flask, and add 50 mL of methanol. Sonicate for 5 minutes, and stir with a magnetic stirrer for 30 minutes. Dilute with methanol to volume, and mix. Transfer 5.0 mL of this solution to the flask, dilute with methanol to 50.0 mL , and mix. Pass a portion of this solution through a filter having a $0.45-\mu \mathrm{m}$ or finer porosity, and use the filtrate after discarding the first 5 mL .

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the analyte peaks. Calculate the
quantity, in mg, of clopidogrel $\left(\mathrm{C}_{16} \mathrm{H}_{16} \mathrm{ClNO}_{2} \mathrm{~S}\right)$ in the portion of Tablets taken by the formula:

$$
1000(321.82 / 419.90) C\left(r_{U} / r_{s}\right)
$$

in which 321.82 is the molecular weight of clopidogrel; 419.90 is the molecular weight of clopidogrel bisulfate; $C$ is the concentration, in mg per mL , of USP Clopidogrel $\mathrm{Bi}-$ sulfate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BriEfing

Desogestrel and Ethinyl Estradiol Tablets, page 1448 of PF 29(5) [Sept.-Oct. 2003]. It is proposed to add a second test to the Dissolution test because FDA has approved a new generic product that is bioequivalent to the Reference Listed Drug but, due to differences in the formulation, requires a new dissolution test.
(BPC: M. Marques) RTS-40002-3

## Add the following:

## ■Desogestrel and Ethinyl Estradiol Tablets

» Desogestrel and Ethinyl Estradiol Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}\right)$ and ethinyl estradiol $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}\right)$.

Packaging and storage-Preserve in well-closed containers.

Labeling-When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.

USP Reference standards $\langle 11\rangle-U S P$ Desogestrel $R S$. USP Desogestrel Related Competad B RS. USP Deseges trel Related Compend C RS. USP Ethinyl Estradiol RS. USP Ethinyl Estradiol Related Compennd A RS.

Thin-layer chromatographic identification test $\langle 201\rangle$ -
Adsorbent: oetadeeylsilanized ehromatographie siliea gel mixtare.

Test solution Transfer a quantity of finely ground Ta blets, equivalent to about 2.4 mg of desogestrel, to a stoppered $10-\mathrm{mL}$ centriftuge tube, add 4.8 mL of acetone, and shake vigereusly for 1 minute. Centrifuge for 5 minutes, and transfer 2.7 mL of the clear supernatant into a suitable eentainer, pretected frem light. Evaporate to dryness in a hood using nitrogen at room temperature, and dissolve the residue so obtained in 0.45 mL of methylene chloride. 0.25 mL of a mixture of hexanes, methanol, and isopropyl aleehol(90:15:5).

Standed solutions. Prepare-separate-selutions in methy lene chloride, a mixture of hexanes, methanol, and isopropyl alcohel (90: 15:5) to contain about 23 mg of USP Desegestrel RS per mL and $0.5-0.6 \mathrm{mg}$ of USP Ethinyl Estradiol RS per mL.

Application valume: $110 \mu \mathrm{~L}$.
Developing solvent system: a mixtare-of toltene-and ethyl acetate (80: 20).

Procedtre Proeed as directed in the chapter. Spray the plate with a solution of sulfuric acid in aleohel ( 1 in 50), and dry at $110^{\circ}$ for 5 to 10 mintutes. Visualize the spets under long wavelength UV light: ethinylestradiol and desogestrel exhibit $R_{x}$ values of about 0.30 and 0.58 , respectively.

Test solution-Transfer 25 Tablets to a suitable container, add 50 mL of water, and sonicate until the Tablets disintegrate (if necessary, remove any coating with water before sonication). Place the sample in a separatory funnel, add 25 mL of ether, and shake well to extract the actives. Using a glass pipet, transfer the ether layer to a clean beaker, and evaporate to about 10 mL .

Standard solution-Dissolve a quantity of USP Desogestrel RS and USP Ethinyl Estradiol RS in methanol to obtain a solution containing about 0.15 mg per mL and 0.03 mg per mL , respectively.
Application volume: $\quad 30 \mu \mathrm{~L}$.
Developing solvent system: a mixture of chloroform and alcohol ( $96: 4$ ).
Procedure-Proceed as directed in the chapter, and then air-dry. Spray the plate with a mixture of methanol and sulfuric acid (50:50), place in an oven at $105^{\circ}$ for about five minutes, and examine the plate: meets the requirements.

Dissolution $\langle 711\rangle$ -
TEST 1-
Medium: $\quad 0.05 \%$ soditm latryl sulfate dodecy soditm
sulfate sodium lauryl sulfate with an assay content of not less than $95 \%$; 500 mL .

Apparatus 2: 50 rpm .
Time: 30 minutes.
Determine the amounts of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}\right)$ and ethinyl estradiol $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}\right)$ dissolved by employing the following method.

Piltent, Soltion A, Soltion B, and Mobile phase Pro-
eeed as directed in the Assaty.
Standard solution Dissolve accurately weighed quantities of USP Desogestrel RS and USP Ethinyl Estradiol RS, and dilute quantitatively, and stepwise if necessary, with Pissolution Meditm to obtain a solution having knowneeneentrations equivalent to the expected concentrations of the
selution under test. [NOTE-A volume of acetonitrile Diltent net exceeding 6\% of the final total volume of the Standard solution may be used todissolveUSP Desogestrel RS, and a volume of a mixture of methanol and water $(90: 10)$ Diltent net exceeding $4 \%$ of the final total volume of the Standard seltition may be used to dissolveUSP Ethinyl EstradiolPS.]

Chromatographic system- Proceed as directed in the $A s$ say. Te-valuate the system-suitability requirements, use the

## Standard preparation prepared as direeted in the Assay.

Proedtre Separately inject equal volumes (about 200 HL) of the Standard solution and a filtered centrifuged por tion of the solution under test into the chromatograph, reeord the chromatograms, and measture the responses for the major peaks. Caleulate the quantities of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}\right)$ and ethinyl estradiol $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{z}\right)$ dissolved by eomparison with the correspending peak respenses obtained frem the Standard solation and the solution under test.

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 (50:50). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Desogestrel standard stock solution-Dissolve an accurately weighed quantity of USP Desogestrel RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.25 mg per mL .
Ethinyl estradiol standard stock solution-Dissolve an accurately weighed quantity of USP Ethinyl Estradiol RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.25 mg per mL .

Desogestrel diluted standard solution-Transfer 1.0 mL of Desogestrel standard stock solution to a $50-\mathrm{mL}$ volumetric flask. Dilute with Dissolution Medium to volume, and mix. This solution contains about 0.005 mg per mL of USP Desogestrel RS.
Ethinyl estradiol diluted standard solution-Transfer 1.0 mL of Ethinyl estradiol standard stock solution to a $50-\mathrm{mL}$ volumetric flask. Dilute with Dissolution Medium to volume, and mix. This solution contains about 0.005 mg per mL of USP Ethinyl Estradiol RS.

Standard solution-Dilute quantitative portions of Desogestrel diluted standard solution and Ethinyl estradiol diluted standard solution with Dissolution Medium to obtain a solution containing about $0.3 \mu \mathrm{~g}$ per mL and $0.06 \mu \mathrm{~g}$ per mL of USP Desogestrel RS and USP Ethinyl Estradiol RS, respectively.

Test solution-Centrifuge a portion of the dissolution sample, and use the clear supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector (for desogestrel analysis), a spectrofluorometric detector (for ethinyl estradiol analysis) with an excitation wavelength of 285 nm and an emission wavelength of 310 nm ; a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L11; and a $4.6-\mathrm{mm} \times 12.5-\mathrm{mm}$ guard column that also contains packing L11. The flow rate is about 2 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.2 for ethinyl estradiol and 1.0 for desogestrel, and the relative standard deviation is not more than $3.0 \%$.

Procedure-Separately inject equal volumes (about 200 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}$ and $\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}$ dissolved by the formula:

$$
(0.05 C)(100 / K)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Desogestrel RS or USP Ethinyl Estradiol RS in the Standard solution; $K$ is the labeled amount, in mg per Tablet, of $\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}$ or $\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}$; and $r_{U}$ and $r_{S}$ are the peak responses for desogestrel or ethinyl estradiol obtained from the Test solution and the Standard solution, respectively.
Tolerances-Not less than $80 \%(Q)$ of each of the labeled amounts of $\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}$ and $\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}$ is dissolved in 30 minutes.

TEST 2-If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium: $\quad 0.3 \%$ sodium lauryl sulfate; 500 mL .
Apparatus 2: 100 rpm.
Time: 30 minutes.
Determine the amounts of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}\right)$ and ethinyl estradiol $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}\right)$ dissolved by the chromatographic method used in Test 1.

Tolerances-Not less than $80 \%(Q)$ of each of the labeled amounts of $\left(\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}\right)$ and $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}\right)$ is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements for Content Uniformity with respect to desogestrel and to ethinyl estradiol.

Loss on drying $\langle 731\rangle$ —Powder zo-40 40 Tablets, and dry the portion at $105^{\circ}$ for 3 hours: it loses not more than $4.0 \%$ of its weight.

Water, Method Ic $\langle 921\rangle$ : net mere than 5.4\%, using 35 mg of ground Tablets heated at $170^{\circ}$. not more than $5.4 \%$ using a portion of the Tablet containing about 35 mg and a suitable evaporation technique that releases the water by heating the specimen in a stream of dry inert gas, this gas then being passed into the cell.

## Related compounds-

Piluent, Solution A, Solution B, Mobile phase, Desoges trel standard stock solution, and Ethinyl estradiol standard stock solution Prepare as directed in the Assay:

Related compounds standard stock solution-Separately dissolve aceurately weighed quantities of USP Ethinyl Es madiol Related Compound A RS, USP Desogestrel Related Compound B RS, and USP Desogestrel Related Compound GRS in Diluent, and dilute quantitatively, and stepwise if neeessary, with Diltent to obtain a solution having a known eoncentrations of about 0.006 mg per $\mathrm{mL}, 0.00375 \mathrm{mg}$ per mL , and 0.00375 mg per mL , respectively. concentration- $f$ about $50 \%$ relative to the expected concentration of ethinyl estradiol and desogestrel in the Test solution.

Standard solution Transfer 5.0 mL of Ethinyl estradiol standard stock solution and 2.0 mL of Related compeunds standed stock solution to a 100 mL volumetric flask, add an aceurately measured volume-of Desogestrel standard stock solution to obtain a final solution having a concentration, in mg per mt, correspending to the expected concentration of desogestrel in the Test solution. Dilute with Biltent to volume, and mix. Transfer 2.0 mL of Related ermpeunds standard stock solution and an aceurately mensured volume each of Ethinyl estradiol standard stock solu tion and Desogestrel standard stock solution to a $100-\mathrm{mb}$ volumetric flack to obtain a final solution having an acet rately known concentration in mg per mL , correspending
approximately to the expected concentration of desogestrel andethinyl estradiol in the Test solution. Dilute with Diltent to volume, and mix.

Fest solution Use the Assay preparation.
Chromatographic systen- Prepare as directed in the -As say. [NOTE-The related compernds $A$ and C Ethinyl estradiol related compound $A$ and desogestrel related compound $G$ are menitored using a wavelength of $230-250$ nm, and all ether compeunds are menitored at 210205 nm .] Chrematograph the Statedted solttion, and record the peak responses as-directed for Procedure: the column efficiency determined from the ethinyl estradiol peak is not less than 2500 theore tieal plates; the tailing factor for the ethinylestradiol peak is between 0.9 and 1.5; and the relative standard deviation for replicate injections determined from the desegestrel and ethimy estradiol peaks is net more than $2.0 \%$, and net more than $5.0 \%$ determine from the peaks for each related compound.

Procedure Separately inject equal volumes (about 25 $200 \mu \mathrm{H})$ of the Standard solution and the Test solution inte the ehrematograph, record the chromatograms, and measure the peak heights areas respenses for ethinyl estradiol related eompound $A$, desogestrel related compound $B$, and desogestrel related compeund C. disregarding the peak, if any, with a retention time of about 12 minutes. Calculate the pereentage of ethinyl estradiol related compound $A$ in the per tion of Tablets taken by the formula:
4166.6C( $\left.+r_{i}++_{s}\right)$,
$200(C L L)\left(r_{i}++_{s}\right)$,
in which $C$ is the concentration, in mg per mL, of USP Ethinyl Estradiol Related Compound A RS in the Standard so tution; $L$ is the labeled amount, in mg, of ethinyl estradiolin each Tablet; and $r$; and $r_{s}$-are the peak heights areas respenses for ethinyl estradiol related compound $A$ obtained from the Test solution and the Standard solution, respec tively: not more than $0.5 \% 2.0 \%$ of ethinyl estradiol related eompound $A$ is found. Calculate the pereentages of desogestrel related compound B and desogestrel related compound G in the pertion of Tablets taken by the formula:

```
666.6C(+5++s),
```


## $200(C / L)\left(+r_{i}+\underset{s}{ }\right)$

in which $C$ is the concentration, in mg per mL , of USP Des egestrel Related Compound B RS or USP Desogestrel Re-tated-Compomal C RS in the Standard solution; $L$ is the tabeled amount, in mg, of desegestrel in each Tablet; and frand $f_{\text {s }}$ are the peak heights areas respenses for desegestrel related compernd $B$ or desogestrel rełated compernd $C$, as appropriate, obtained from the Test solution and the Standard solution, respectively: not more than $0.5 \%$ each 2.0\% of desegestrel related compernd $B$ is fetnd; net mere than 3.0\% of desogestrel related compound C is found; and not more than $2.0 \%-5.0 \%$ of total related compounds is found.

Solution A-Prepare a mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 (50:50).

Solution B-Prepare a mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 ( $80: 20$ ).

Mobile phase-Use variable mixtures of Solution A and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare a mixture of acetonitrile and water (50:50).

Desogestrel standard stock solution-Dissolve an accurately weighed quantity of USP Desogestrel RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL .

Ethinyl estradiol standard stock solution-Dissolve an accurately weighed quantity of USP Ethinyl Estradiol RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL .

Standard solution-Dilute quantitative portions of Desogestrel standard stock solution and Ethinyl estradiol standard stock solution with Diluent to obtain a solution containing about $0.6 \mu \mathrm{~g}$ per mL and $0.12 \mu \mathrm{~g}$ per mL of USP Desogestrel RS and USP Ethinyl Estradiol RS, respectively.

Test solution 1-Transfer 20 Tablets to a $200-\mathrm{mL}$ volumetric flask. Add about 120 mL of Diluent, and shake for about 30 minutes. Dilute with Diluent to volume, and mix. Centrifuge a portion of the dissolution sample, and use the clear supernatant

Test solution 2-Dilute a portion of Test solution 1 with Diluent to obtain a solution containing about $0.6 \mu \mathrm{~g}$ per mL of ethinyl estradiol.
Chromatographic system (see Chromatography $\langle 621\rangle$ ) The liquid chromatograph is equipped with a programmable variable wavelength UV detector and a spectrofluorometric detector with an excitation wavelength of 285 nm and an emission wavelength of 310 nm ; a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L11; and a $4.6-\mathrm{mm} \times 12.5-$ mm guard column that also contains packing L11. The chromatograph is programmed as follows.

| Time (minutes) | Solution A (\%) | Solution B <br> (\%) | Elution | UV Detector (nm) | Flow Rate ( $\mathrm{mL} / \mathrm{min}$.) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 0 | 100 | 0 | equilibration | 210 | 2 |
| 0-4 | 100 | 0 | isocratic | 210 | 2 |
| 4-10 | 100 | 0 | isocratic | 244 | 2 |
| 10-20 | 100 | 0 | isocratic | 210 | 2 |
| 20-25 | 0 | 100 | linear gradient | 210 | 2.5 |
| 25-30 | 0 | 100 | isocratic | 210 | 3 |
| 30-32 | 100 | 0 | linear gradient | 210 | 2 |
| 32-35 | 100 | 0 | re-equilibration | 210 | 2 |

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are 0.18 for ethinyl estradiol and 1.0 for desogestrel; the resolution, $R$, between ethinyl estradiol and desogestrel is not less than 2.0; the tailing factor is not more than 2.0 for ethinyl estradiol and desogestrel; and the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Inject a volume (about $200 \mu \mathrm{~L}$ ) of Test solution 2 into the chromatograph, record the chromatograms, and measure the peak heights for the major peaks obtained within 20 minutes. Calculate the percentage of $17 \beta$-ethinyl estradiol in the portion of Tablets taken by the formula:

$$
100\left(r_{U} / r_{s}\right)
$$

in which $r_{U}$ is the height of any peak at a relative retention time of 0.20 ; and $r_{s}$ is the peak height of ethinyl estradiol obtained with the spectrofluorometric detector. Inject a volume (about $200 \mu \mathrm{~L}$ ) of Test solution 1 into the chromatograph, record the chromatograms, and measure the peak
heights for the major peaks obtained within 20 minutes. Calculate the percentage of estrone in the portion of Tablets taken by the formula:

$$
100\left(r_{U} / r_{s}\right)-E
$$

in which $r_{U}$ is the height of any peak at a relative retention time of $0.20 ; r_{s}$ is the peak height of ethinyl estradiol obtained with the UV detector at 210 nm ; and $E$ is the percentage of $17 \beta$-ethinyl estradiol obtained in the Tablets. Calculate the percentage of 3-ketodesogestrel in the portion of Tablets taken by the formula:

$$
100(1 / F)\left(r_{U} / r_{s}\right)
$$

in which $r_{U}$ is the height of any peak at a relative retention time of 0.32 obtained with the UV detector at $244 \mathrm{~nm} ; r_{s}$ is the peak height of desogestrel obtained with the UV detector at 210 nm ; and $F$ is the relative response factor, equal to 4.1. Calculate the percentage of any other impurity taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the height of any peak other than those mentioned above; and $r_{s}$ is the peak height of ethinyl estradiol obtained with the UV detector. Any peak below $0.1 \%$ is not considered. Not more than $0.5 \%$ of ethinyl estradiol impurities is found; not more than $0.5 \%$ of desogestrel impurities is found; and not more than $2.0 \%$ of total impurities is found.

Assay-
Biltent Prepare a mixture of acetonitrile methanel and water (4:1). (60:40).

Solution A Use acetonitrile.
Solution-B. Prepare a filtered and degassed mixture of acetonitrile and water $(1: 1)$.

Mebile phase Use variable mixtures of Soltution $A$ and Solution B as directed for Chromatographic system. Make adjustments if neeessary (see System Suitability under Chrematography (624) .

Pesogestrel standard stock solution- Dissolve an aeet rately weighed quantity of USP Desogestrel RS in Diluent methanol to obtain a solution having a known concentration of about $0.25-0.35 \mathrm{mg}$ per mL.

Ethinyl estradiel standard stock solution- Dissolve an aecurately weighed quantity of USP Ethinyl Estradiol RS in Diluent methanel to obtain a selution having a known eencentration of about $0.25-0.21$ mg per mL .

Standard preparation-Transfer 5.0 mL of Ethinyl estrat diol standard stack solution to a 100 mL volumetric flask, and add an aceurately measured volume of Desogestrel standard stock selution to obtain a solution having a known eencentration, im mo per mL , correspending to the expected eoncentration of desogestrel in the Assay preparation. Dilete with Diluent to voltme, and mix. Transfer an aceurately measured voltme each of Ethinyl estratiol standtard stock solution and Desogestrel standard stock solution to a-100 mL voltmetrie flask to obtain a final solution having an ac-
eurately known concentration in mg per mL, correspending approximately to the expected concentration of desogestrel and ethinyl estradiol in the Assay preparation. Dilute with Biltent to volume, and mix.

Assay preparation Transfer 101410 Tablets to $30-\mathrm{mE}$ 50 mL stoppered centriftuge tube, add $20.0-30 \mathrm{~mL}$ of Dilt ent, and sonicate for 25 minutes with intermittent mixing on a vortex mixer, until all Tablets have broken apart. Extract for 30 mintutes on a benehtop shaker. Centrifuge, anduse the elear supernatant. [NOTE-Retain apertion of this solutionto use as the Test solution in the test for Related compeunds.]

Chromatographic system (see Chromatography- $\langle 621\rangle$ The liquid chromatograph is equipped with either a pregrammable variable wavelength detector or two separate detectors capable of menitoring at $210-205$ nm and at $230-250$ 230 nm and $-4.6 \mathrm{~mm} \times 15 \mathrm{em} 25$-mmedtmm that contains stable-bended $5 \mathrm{\mu m}$ packing 41 . The flow rate is about 21.5 mL per mintte, and the column temperature is maintained at $40^{\circ}$. The chromatograph is programmed as follows. Chrematograph the Standard preparation, and record the peak respenses as directed for Preedure: the coltmmneffieieney determined from the ethinyl estradiol peak is not less than 2500 theoretical plates; the tailing factor for the ethinyles tradiol peak is between 0.9 and 1.5 ; and the relative standard deviation for replieate injections is not more than $2.0 \%$ $1.5 \%$, determined frem the desogestrel and ethinyl estradiol peaks.

| Time (minutes) | Solution 4 (\%) | Solution B (\%) | Elution |
| :---: | :---: | :---: | :---: |
| 0-4.5 | $\theta$ | 100 | isocratic |
| - 12.0 |  |  |  |
| 4.5-4.6 | $\theta \rightarrow 100$ | 100 $\rightarrow$ | linear gradient |
| 12.0-12.4 |  |  |  |
| $4.6-10.7$ | 100 | $\theta$ | isecratic |
| 12.125 .0 |  |  |  |


| Time (mintites) | Solution 4 $(\%)$ | $\begin{gathered} \text { Solution } B \\ (\%) \\ \hline \end{gathered}$ | Elution |
| :---: | :---: | :---: | :---: |
| 10.7-10.8 | $\xrightarrow{100 \rightarrow 0}$ | $\theta \rightarrow 10 \theta$ | linear gradient |
| 25.0-25.1 |  |  |  |
| 25.1 30.0 | $\theta$ | 100 | isperatic |

Proecture Separately inject equal volumes (about 25 HL) of the Standard preparation and the Assay preparation into the chromatograph, record the chrematograms, and measure the peak areas at $210-205 \mathrm{~nm}$. Separately calculate the ameunts, in $\mu \mathrm{g}$, of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{30} \Theta\right)$ andethinyles tradiol $\left(\mathrm{C}_{20} \mathrm{H}_{24} \Theta_{2}\right)$ in the pertion of Tablets taken by the for mula:-

$$
\left(L G_{s}+G_{t}\right)\left(F_{t}++_{s}\right),
$$

in which $L$ is the labeled quantity, in $\mu \mathrm{g}$, of the relewant and Hyte in each Tablet; $G_{s}$ is the concentration, in $\mu$ g per mL, of the appropriate USP Reference-Standard in the Statatard preparation; $G_{t}$ is the concentration, in $\mu$ gs per mL , of the eorrespending analyte in the Assay preparation, based on the labeled quantity per Tablet and the extent of dilution; and $r_{4}$ and $r_{s}$ are the peak respenses areas obtained from the Assay preparation and the Standard preparation, re-
spectively.

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 (50:50). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare a mixture of acetonitrile and water (50:50).

Desogestrel standard stock solution-Dissolve an accurately weighed quantity of USP Desogestrel RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL .

Ethinyl estradiol standard stock solution-Dissolve an accurately weighed quantity of USP Ethinyl Estradiol RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL .

Standard preparation-Dilute appropriate aliquots of Desogestrel standard stock solution and Ethinyl estradiol standard stock solution with Diluent to obtain a solution having a known concentration of about $0.6 \mu \mathrm{~g}$ per mL and $0.12 \mu \mathrm{~g}$ per mL of USP Desogestrel RS and USP Ethinyl Estradiol RS, respectively.

Assay preparation-Transfer 20 Tablets into a $200-\mathrm{mL}$ volumetric flask. Add about 120 mL of Diluent, and shake for about 30 minutes. Dilute with Diluent to volume, and mix. Centrifuge a portion of the sample, and transfer an accurately measured volume to a $50-\mathrm{mL}$ volumetric flask to obtain a final concentration of about $0.6 \mu \mathrm{~g}$ per mL of desogestrel. Dilute with Diluent to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ ) The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector (for desogestrel analysis), a spectrofluorometric detector (for ethinyl estradiol analysis) with an excitation wavelength of 285 nm and an emission wavelength of 310 nm ; a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L11; and a $4.6-\mathrm{mm} \times 12.5-\mathrm{mm}$ guard column that also contains packing L11. The flow rate is about 2 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention
times are about 0.2 for ethinyl estradiol and 1.0 for desogestrel; the tailing factor for both analytes is not more than 2.0; and the relative standard deviation is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 200 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}\right)$ and ethinyl estradiol $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}\right)$ in the portion of Tablets taken by the formula:

$$
(500 C / V)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Desogestrel RS or USP Ethinyl Estradiol RS in the Standard preparation; $V$ is the volume of the aliquot of solution taken for the Assay preparation; and $r_{U}$ and $r_{S}$ are the peak responses for desogestrel or ethinyl estradiol obtained from the Assay preparation and the Standard preparation, respectively.■IS (USP28)

## Briefing

Dextroamphetamine Sulfate, $U S P 27$ page 576 and page 476 of PF 30(2) [Mar.-Apr. 2004]-See briefing under Amphetamine Sulfate.
(PA3: S. Salado) RTS-39348-1
pitate, wash it with about 10 mL of cold water, and recrystallize it from diluted alcohol: the crystals of the benzoyl derivative of dextroamphetamine so obtained, after being dried at $105^{\circ}$ for 4 homr,

- 3 hours, 1 IS (USP28)
melt between $155^{\circ}$ and $160^{\circ}$.
B: A solution (1 in 10) responds to the tests for Sulfate $\langle 191\rangle$.


## Change to read:

## Chromatographic purity-

Diluent-Dilute 3.12 mL of phosphoric acid with water to 1000 mL .

Buffer solution-Dissolve 2.16 g of sodium 1-octanesulfonate in 1000 mL of water, and add 1.0 mL of $0.1 \%$ triethylamine solution ( $\mathrm{N} / \mathrm{V}$ ).
triethylamine. $\Delta$ USP28
Mix, and adjust with phosphoric acid to a pH of 2.5 .
Mobile phase-Prepare a filtered and degassed mixture of Buffer solution, acetonitrile, and methanol (144:37:19). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard stock solution-Dissolve an accurately weighed quantity of USP Dextroamphetamine Sulfate RS in Diluent to obtain a solution having a known concentration of about 0.3 mg per mL .

Standard solution-Dilute an accurately measured volume of Standard stock solution in Diluent to obtain a solution having a known concentration of about 0.003 mg per mL .

Test solution-Transfer about 30 mg of Dextroamphetamine Sulfate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in 50 mL of Diluent, sonicate for 5 minutes, dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.6-$ $\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard stock solution, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$. Chromatograph the Test solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the dextroamphetamine peak and any adjacent peak is not less than 1.5.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Dextroamphetamine Sulfate taken by the formula:

$$
10,000(C / W)\left(r_{i} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Dextroamphetamine Sulfate RS in the Standard solution; $W$ is the weight, in mg , of Dextroamphetamine Sulfate taken to prepare the Test solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the peak response for amphetamine obtained from the Standard solution: not more than $0.1 \%$ of any individual impurity is found; and not more than $0.5 \%$ of total impurities is found.

## Change to read:

## Identification-

A: Dissolve about 100 mg in 5 mL of water, add 5 mL of 1 N sodium hydroxide, cool to $10^{\circ}$ to $15^{\circ}$, add 1 mL of a mixture of 1 volume of benzoyl chloride and 2 volumes of anhydrous ethyl ether, insert the stopper, and shake for 3 minutes. Filter the preci-

## Briefing

Diatrizoate Meglumine, USP 27 page 582 and page 1868 of $P F$ 29(6) [Nov.-Dec. 2003]. In the test for Free aromatic amine, it is proposed to replace the name of the reagent methyl sulfoxide with its synonym dimethyl sulfoxide. The use of the name "dimethyl sulfoxide" is being standardized throughout the $U S P-N F$.
(BPC: M. Marques) RTS-41082-7

## Change to read:

Packaging and storage-Preserve in well-closed containers.
-Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and
$30^{\circ} \cdot \mathbf{\square} 2$ (USP27)

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of in-
jectable dosage forms. $\quad$ 2S (USP27)

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Diatrizoic Acid RS. USP Diatrizoic Acid Related Compound A RS.


## Change to read:

Free aromatic amine-Transfer 1.0 g to a $50-\mathrm{mL}$ volumetric flask, and add 5 mL of water and 10 mL of 0.1 N sodium hydroxide. To a second $50-\mathrm{mL}$ volumetric flask transfer 4 mL of water, 10 mL of 0.1 N sodium hydroxide, and 1.0 mL of a Standard solution prepared by dissolving a suitable quantity of USP Diatrizoic Acid Related Compound A RS in 0.1 N sodium hydroxide. Use 0.2 mL of 0.1 N sodium hydroxide for each 5.0 mg of Standard, and dilute with water to obtain a known concentration of 500 $\mu \mathrm{g}$ per mL . To a third $50-\mathrm{mL}$ volumetric flask add 5 mL of water and 10 mL of 0.1 N sodium hydroxide to provide a blank.

Treat each flask as follows. Add 25 mL of methyl sulfoxide,

- dimethyl sulfoxide, ${ }^{\text {n }}$ 1S (USP28)
insert the stopper, and mix by swirling gently. Chill in an ice bath in the dark for 5 minutes. [NOTE-In conducting the following steps, keep the flasks in the ice bath and in the dark as much as possible until all of the reagents have been added.] Add slowly 2 mL of hydrochloric acid, mix, and allow to stand for 5 minutes. Add 2 mL of sodium nitrite solution (1 in 50 ), mix, and allow to stand for 5 minutes. Add 1 mL of sulfamic acid solution (2 in 25), shake, and allow to stand for 5 minutes. [Caution-Considerable pressure is produced.] Add 2 mL of a 1 in 1000 solution of $N$-(1-naphthy1)ethylenediamine dihydrochloride in dilute propylene glycol ( 7 in 10), and mix.

Remove the flasks from the ice bath and from storage in the dark, and allow to stand in a water bath at $22^{\circ}$ to $25^{\circ}$ for 10 min utes. Shake gently and occasionally during this period, releasing the pressure by loosening the stopper. Dilute with water to volume, and mix.

Within 5 minutes from the time of diluting the solutions in all three flasks to 50 mL , concomitantly determine the absorbances of the solution from the substance under test and the Standard solution in $1-\mathrm{cm}$ cells at the wavelength of maximum absorbance at about 465 nm , with a suitable spectrophotometer, versus the prepared blank. The absorbance of the solution from the Diatrizoate Meglumine is not greater than that of the Standard solution (0.05\%).

## Add the following:

-Other requirements-Where the label states that Diatrizoate Meglumine is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Diatrizoate Meglumine Injection. Where the label states that Diatrizoate Meglumine must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Diatrizoate Meglumine Injection.■2S (USP27)

## Briefing

Dicyclomine Hydrochloride Capsules, USP 27 page 598 and page 1459 of $P F 29(5)$ [Sept.-Oct 2003]; Dicyclomine Hydrochloride Tablets, USP 27 page 600 and page 1462 of $P F$ 29(5) [Sept.-Oct. 2003]. It is proposed to replace the UV absorbance method in the test for Dissolution with a liquid chromatographic procedure similar to that previously proposed for the Assay. The liquid chromatographic procedure in the test for Dissolution is based on the analyses performed with the $3.5-\mu \mathrm{m}$ XTerra RP-8 brand of L7 column. The typical retention time observed for the dicyclomine peak is about 4 to 7 minutes.
(PA4: E. Gonikberg) RTS-40063-1

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: $\quad 0.01 \mathrm{~N}$ hydrochloric acid; 500 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.

Picric acid solution Transfer about 100 mg of pieric acid and 14.5 g of anhydrous sodium acetate to a 500 mL volumetric flask and dissolve in 400 mL of water. Add 20.0 mL of glacial acetic aeid, dilute with water volume, and mix.
-Determine the amount of $\mathrm{C}_{19} \mathrm{H}_{35} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ dissolved by employing the following method.

Mobile phase-Prepare as directed in the Assay.
0.04 M Phosphate buffer, pH 7.5—Dissolve 2.72 g of monobasic potassium phosphate in 450 mL of water, adjust with $10 \%$ sodium hydroxide to a pH of $7.5 \pm 0.1$, dilute with water to 500 mL , and mix.
Buffer-acetonitrile mixture—Prepare a mixture of 0.04 M
Phosphate buffer, pH 7.5 and acetonitrile ( $1: 1$ ).1s (USP28)
Standard solution-Prepare a solution in 0.01 N hydrechlorie acid

- Medium ${ }_{\text {1S }}$ (USP28)
having a known concentration of about $18 \mu$

per mL of USP Dicyclomine Hydrochloride RS.
-Transfer 25.0 mL of this solution to a suitable flask, add 25.0 mL of the Buffer-acetonitrile mixture, and mix.

Test solution-Filter a portion of the solution under test through a $0.7-\mu \mathrm{m}$ glass microfiber filter. Transfer 5.0 mL of the filtrate to a suitable flask, add 5.0 mL of the Buf-fer-acetonitrile mixture, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column containing $3.5-\mu \mathrm{m}$ packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the responses as directed for Procedure: the tailing factor for the analyte peak is not more than 2.0 , and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Determine the amount of $\mathrm{C}_{10} \mathrm{H}_{25} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ dis solved using the following procedure. Pipet 20 mL each of the se lution under test, the Standard solution, and 0.01 N hydrechloric acid to provide a blank, inte-separate suitable separaters. Add 5.0 mL of Pieric acid soldtion and 25.0 mL of chloroform to each separator, and shake for one-minute. Collect the-chloroform layer in a suitable vessel containing 2.0 g of anhydreus sodium- sulfate, shake and allow the-solutions to stand for ten minutes. Coneomiantly determine the absorbanees of the solutions at the wavelength of maximum abserbance at about 405 nm , using the blank to set the spectrophotemeter.
-Separately inject equal volumes (about $250 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in mg, of $\mathrm{C}_{19} \mathrm{H}_{35} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ dissolved. 1 IS (USP28)
Tolerances-Not less than $75 \%$ (Q) of the labeled amount of $\mathrm{C}_{19} \mathrm{H}_{35} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ is dissolved in 45 minutes.

## Change to read:

## Assay-

Internalstandardsolution Dissolveaquantity of phenacetin in methanel to obtain a selution having a concentration of about 2.5 mg per mL.

Standard preparation Dissolvenan aceurately weighed quantity of USP Dieyclomine Hydrochleride RS in methanol to obtain a solution having a known concentration of about 1 mg per mL . Transfer 2.0 mL of this solution to a $10-\mathrm{mL}$ volumetric flask, add 2.0 mL of Internal standard soldtion, dilate with methanel tovelume, and mix.

Assay preparation Remeve, as completely as pessible, the eentents of not fewer than 20-Capsules, and mix the eentents. Tramsfer an aceurately weighed pertion of the pewder, equivalent to about 10 mg of dieyclomine hydrochloride, to a 25 mL volu metric flask, add 10.0 mL of Internal standard solution, dilute with methanel to velume, and mix. Filter 15 mL of this solution, dis earding the first 5 mL , and transfer 5.0 mL to a 10 mL volametrie flask. Dilute with methanel to volume, and mix.

Chramatographic system (see-Chrematography $\langle 624\rangle$ ) The gas chromatograph is equipped with a flame ionization detector and a $15 \mathrm{~m} \times 0.5 \mathrm{~mm}$ fused silica columm coated with a 1 Hm phase G3. The column is maintained at $160^{\circ}$ for 2 minutes, then programmed at $20^{\circ}$ per minute for 4 minutes, and held at a finat temperature of $240^{\circ}$ for 5 minutes. The-injection pert and detector temperatures are maintained at $250^{\circ}$. Nitregen is used as the earrier gas at a flow rate of 2 mL per minute. Chrematograph the Standard preparation, and record the peak respenses as directed for Preee dure: the resolution, $R$, between phenacetin and dieyelemine-is net less than 2; the tailing factor for dieyelemine-is not more than 2.0; and the relativestandard deviation for replieate injections is net mere than $2.0 \%$

Proecture Separately inject equalvolumes (about $2 \mu \mathrm{H}$ ) of the Standard preparation and the Assay preparation inte the chromat tograph, record the chromatograms, and measure the respenses for the majer peaks. Caleulate the quantity, in me, of dieyclomine hy drechloride $\left(\mathrm{C}_{40} \mathrm{H}_{35} \mathrm{~N} \mathrm{NO}_{2} \cdot \mathrm{HCl}\right)$ in the pertion of Capsules taken by the formula:

$$
50 C\left(R_{t}+R_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Dieyclemine Hydrechloride RS in the Standard preparation; and $R_{5}$-and $R_{s}$ are the peak respense raties of dicyclomine to phenacetin obtained from the Asisty preparation and the Standard prepariation, respectively.

- 0.02 M Phosphate buffer, pH 7.5—Dissolve 2.72 g of monobasic potassium phosphate in 900 mL of water, adjust with $10 \%$ sodium hydroxide to a pH of $7.5 \pm 0.1$, dilute with water to 1000 mL , and mix.

Mobile phase—Prepare a mixture of acetonitrile and 0.02 M Phosphate buffer, pH 7.5 (70:30), filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare a mixture of acetonitrile and water (70:30).
Standard preparation-Dissolve an accurately weighed quantity of USP Dicyclomine Hydrochloride RS in Diluent to obtain a solution having a known concentration of about 0.4 mg per mL . [NOTE-This solution is stable for 2 days].

Assay preparation-Remove, as completely as possible, the contents of not less than 20 Capsules, and mix the contents. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg of dicyclomine hydrochloride, to a $50-\mathrm{mL}$ volumetric flask. Add 2.0 mL of water, and sonicate for at least 2 minutes to disperse the sample. Add 35 mL of acetonitrile, sonicate for at least 5 minutes, and shake on a mechanical shaker for at least 30 minutes. Add 10 mL of water, allow the preparation to equilibrate to room temperature, then dilute with water to volume, and mix. Centrifuge, for at least 5 minutes, a portion of this solution in a $15-\mathrm{mL}$ glass centrifuge tube. Use the clear supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column containing $3-\mu \mathrm{m}$ packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the Standard preparation, and record the responses as directed for Procedure: the tailing factor for the analyte peak is not more than 1.5 , and the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and
measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{19} \mathrm{H}_{35} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ in the portion of Capsules taken by the formula:

$$
50 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Dicyclomine Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the areas of the dicyclomine peak obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{D S S}^{2 S}$ (USP27)

## Briefing

Dicyclomine Hydrochloride Tablets, USP 27 page 600 and page 1462 of PF 29(5) [Sept.-Oct. 2003]-See briefing under Dicyclomine Hydrochloride Capsules.
(PA4: E. Gonikberg) RTS-40063-2

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: $\quad 0.01 \mathrm{~N}$ hydrochloric acid; 500 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Pieric acid solution and Standard solution- Prepare as direeted for Dissolution under Dieyclomine Hydrochloride Capsules.

- Mobile phase, 0.02 M Phosphate buffer, pH 7.5, Bufferacetonitrile mixture, Test solution, and Chromatographic system-Proceed as directed for Dissolution under Dicyclomine Hydrochloride Capsules.
Standard solution-Prepare a solution in Medium having a known concentration of about $40 \mu \mathrm{~g}$ per mL of USP Dicyclomine Hydrochloride RS. Transfer 25.0 mL of this solution to a suitable flask, add 25.0 mL of the Bufferacetonitrile mixture, and mix.■1S (USP28)

Procedure_Proceed as directed for Dissolution under Dicyclomine Hydrochloride Capsules. except to use 10.0 mL of the solution under test and to add 10.0 mL of 0.01 N hydrochloric acid to the separator containing the solution under test.

■ $\quad$ 1S (USP28)
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{19} \mathrm{H}_{35} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ is dissolved in 45 minutes.

## Change to read:

## Assay-

Haternd stadat solution, Standard preparation, and Chremt tographic systen- Prepare as directed in the Assay under Dieyelo mine Hyolvahleride Capsules.

Assay preparation. Weigh and finely powder not less than-20 Tablets. Transfer an aceurately weighed portion of the powder, equivalent to about 20 mg of dieyelomine hydrechloride, to a 50 mL volumetric flask, add 20.0 mL of Internal standard solution, dilute with methanol to volume, and mix. Filter 15 mL of this solution, disearding the frist 5 mL , and transfer 5.0 mL to a 10 mL volumetric flask. Dilute with methanol to volume, and mix.

Procedure Proceed as directed in the Assay under Dieyelomine Hydrochloride Capsules. Caleulate the quantity, in mer, of $\mathrm{G}_{12} \mathrm{H}_{25} \mathrm{NO}_{3}-\mathrm{HCl}$ in the pertion of Tablets taken by the formmat:

$$
100 \subset\left(R_{L}+R_{\delta}\right)
$$

in which $C$ is the concentration, in me per mL, of USP Dieyelo mine Hydrochloride $R S$ in the Stad preparation, and the other terms are as defined therein.
-0.02 M Phosphate buffer, pH 7.5, Mobile phase, Diluent, Standard preparation, and Chromatographic system-Prepare as directed in the Assay under Dicyclomine Hydrochloride Capsules.

Assay preparation-Transfer not fewer than 20 Tablets to a tared container, and determine the average Tablet weight. Grind the Tablets to a fine powder using a glass mortar and pestle. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg of dicyclomine hydrochloride, to a $50-\mathrm{mL}$ volumetric flask. Proceed as directed under Dicyclomine Hydrochloride Capsules beginning with "Add 2.0 mL of water."

Procedure—Proceed as directed in the Assay under Dicyclomine Hydrochloride Capsules. Calculate the quantity, in mg , of dicyclomine hydrochloride $\left(\mathrm{C}_{19} \mathrm{H}_{35} \mathrm{NO}_{2} \cdot \mathrm{HCl}\right)$ in the portion of Tablets taken by the formula:
in which $C$ is the concentration, in mg per mL , of USP Dicyclomine Hydrochloride RS in the Standard preparation; and the other terms are as defined therein.■2S (USP27)

Briefing

Divalproex Sodium Delayed-Release Tablets, USP 27 page 650 and page 3055 of the First Supplement. It is proposed to revise the Drug release test to provide clearer instructions on how to perform the test.
(BPC: M. Marques) RTS-40956-1

## Change to read:

Drug release, $B$
■1S (USP28)
$\langle 724\rangle-$
pH 1.2, 0.08 N Hydrechloric acid Ade 40 mL of Hydrechlorie aeid to 5000 mL of water. Adjust with 2 N hydrechloric acid to a pH-of 1.2 , dilute with water to- 6.0 liters, and mix.
pH 7.5 Phosphate buffer. Disselve-40.83 g of menebasic petassitm phesphate and 9.84 g of sodium hydroxide in 5000 mL of water. just with pH 1.2, 0.08 N Hydrechtoric acid to a pH of 7.5, dilute with water to 6.0 liters, and mix.

Medium Proceed as direeted for Method $B$, observing the-folłowing exceptions. Perform Acid Stage testing, using 900 mL of
 Stage testimg, usimg 900 mL of pH 7.5 Phesphate buffer, for net less than 1 hear.

Apparatus 2: 50 mpm
Tintes: 1 and 2 hours.
■ACID STAGE-
Medium: $\quad 0.08 \mathrm{~N}$ hydrochloric acid (prepared by adding 40 mL of hydrochloric acid to 5000 mL of water, adjusting with 2 N hydrochloric acid to a pH of 1.2 , and diluting with water to 6000 mL ); 900 mL .
Apparatus 2: 50 rpm .
Time: 1 hour.

$$
50 C\left(r_{U} / r_{s}\right)
$$

Procedure-At the end of 1 hour, carefully transfer the
Tablet to a dissolution vessel containing the Medium of the Buffer stage. [NOTE-Do not perform an analysis of the Medium in the Acid stage.]

BUFFER STAGE-
Medium: $\quad \mathrm{pH} 7.5$ phosphate buffer (prepared by dissol-
ving 40.83 g of monobasic potassium phosphate and 9.84 g of sodium hydroxide in 5000 mL of water, adjusting with 0.08 N hydrochloric acid to a pH of 7.5 , and diluting with water to 6000 mL ); 900 mL .

Apparatus 2: 50 rpm .
Time: 1 hour. ${ }^{1 S}$ (USP28)
Determine the amount of $\mathrm{C}_{8} \mathrm{H}_{16} \mathrm{O}_{2}$ dissolved

- in the Buffer stage ${ }_{\text {1S }}$ (USP28)
by employing the following method.
Citrate buffer-Dissolve 0.5 g of citric acid monohydrate and $0.4 \mathrm{~g}_{\text {IS (USP27) }}$ of dibasic sodium phosphate in 1.0 liter of water. Potassium phosphate buffer-Dissolve 6.8 g of monobasic potassium phosphate and 1.7 g of sodium hydroxide in 1.0 liter of water. Adjust with phosphoric acid to a pH of $7.4 \pm 0.1$.
Mobile phase-Prepare a mixture of Citrate buffer, Potassium phosphate buffer, and acetonitrile ( $35: 35: 30$ ). Adjust with phosphoric acid to a pH of $3.0 \pm 0.1$, and mix. Filter and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Prepare a solution of USP Valproic Acid RS in the pH 7.5 Phosphate buffer

- Medium ${ }_{\text {1S (USP28) }}$
used in the Buffer stage, having a known concentration of about 0.12 mg per mL . [NOTE-A volume of acetonitrile not exceeding the $10.0 \%$ of the total volume may be used to dissolve the USP Valproic Acid RS.]
Test solution-If necessary, dilute a portion of each filtered solution under test with the pH 7.5 Phesphete buffer
- Medium ${ }_{\text {IS }}$ (USP28)
used in the Buffer stage to obtain a solution having a concentration of about 0.12 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a 210 -nm detector and a 3.9$\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $4-\mu \mathrm{m}$ packing L11. The flow rate is about 1.2 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more that 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of valproic acid $\left(\mathrm{C}_{8} \mathrm{H}_{16} \mathrm{O}_{2}\right)$ dissolved by the formula:

$$
900 C D\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Valproic Acid RS in the Standard solution; $D$ is the dilution factor used to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak areas of val-
proic acid obtained from the Test solution and the Standard solution, respectively.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{8} \mathrm{H}_{16} \mathrm{O}_{2}$ is dissolved in 2 heurs.
-1 hour in the Buffer stage.■1S (USP28)

## BRIEFING

Doxycycline Hyclate, USP 27 page 669. Doxycycline Hyclate is doxyclycline hydrochloride hemihydrate hemiethanolate. This monograph currently provides a test for Water with limits of between $1.4 \%$ and $2.8 \%$ (theory for the hemihydrate $=1.76 \%$ ). To further characterize the compound as the hemiethanolate, it is proposed to revise this monograph by adding a test and limit for Content of ethanol. It is proposed to specify that the test for Content of ethanol is to be performed using the gas chromatographic method included in the general chapter Organic Volatile Impurities $\langle 467\rangle$, using the version proposed on page 1153 of $P F 29(4)$ [July-Aug. 2003], which is targeted for publication in the Second Supplement to USP 27-NF 22. The proposed limits for Content of ethanol are between $4.3 \%$ and $6.0 \%$ (theory for the hemiethanolate $=4.49 \%$ ).
(PA7a: W. Wright) RTS-41049-1

## Add the following:

-Content of ethanol: between $4.3 \%$ and $6.0 \%$, when tested as directed in the general chapter Organic Volatile Impurities $\langle 467\rangle$, using Procedure $A$ under Water-Soluble Articles in the section Identification, Control, and Quantification of Residual Solvents.■1S (USP28)

## Briefing

Multiple Electrolytes Injection Type 1, USP 27 page 687; Multiple Electrolytes Injection Type 2, USP 27 page 688; Multiple Electrolytes and Dextrose Injection Type 1, USP 27 page 690; Multiple Electrolytes and Dextrose Injection Type 2, USP 27 page 691; Multiple Electrolytes and Dextrose Injection

Type 3, USP 27 page 693. It is proposed to revise the Definition to remove ambiguity about the possible combinations of electrolytes. In the Multiple Electrolytes Injection Type 1 monograph, it is proposed to delete the $60^{\circ}$ temperature condition to eliminate peak tailing in the Assay for gluconate and to correct the dimensions of the guard column used in the Assay for gluconate and in the Assay for acetate.
(PA1: K. Russo) RTS-40523-1; 40698-1

## Change to read:

» Multiple Electrolytes Injection Type 1 is a sterile solution of suitable salts in Water for Injection to provide sodium, potassium, magnesium, and chloride ions. In addition, the salts may

■.1S (USP28)
provide ions of acetate, or acetate and gluconate, or acetate, gluconate, and phosphate. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of sodium ( Na ), potassium ( K ), magnesium $(\mathrm{Mg})$, chloride $(\mathrm{Cl})$, acetate $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}_{2}\right)$, gluconate $\left(\mathrm{C}_{6} \mathrm{H}_{11} \mathrm{O}_{7}\right)$, and phosphate $\left(\mathrm{PO}_{4}\right)$. It may contain Hydrochloric Acid or Sodium Hydroxide used to adjust the pH . It contains no antimicrobial agents.

## Change to read:

## Assay for acetate-

Mobile phase_Prepare a filtered and degassed solution of 0.05 N sulfuric acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of sodium acetate trihydrate in water to obtain a Standard preparation having a known concentration of about 1.2 mg of sodium acetate trihydrate (about 0.0088 mEq of acetate) per mL .

Assay preparation-Dilute an accurately measured volume of Injection quantitatively with water to obtain a solution containing about 0.0088 mEq of acetate per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector, a 7.8 mm $+4-\mathrm{cm}$
-4.6-mm $\times 3-\mathrm{cm}_{1 \mathrm{IS}(U S P 28)}$
guard column containing packing L17, and a $7.8-\mathrm{mm} \times 30-\mathrm{cm}$ analytical column containing packing L17. The column temperature is maintained at about $60^{\circ}$. The flow rate is about 0.8 mL per minute. Chromatograph the Standard preparation, and record the responses as directed for Procedure: the tailing factor for the analyte peak is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mEq per liter, of acetate $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}_{2}\right)$ in the Injection taken by the formula:

$$
(C / 136.08)(L / D)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of sodium acetate trihydrate in the Standard preparation; 136.08 is the molecular weight of sodium acetate trihydrate; $L$ is the labeled quantity, in mEq per liter, of acetate in the Injection; $D$ is the quantity, in mEq per mL , of acetate in the Assay preparation, based on the labeled quantity and the extent of dilution; and $r_{U}$ and $r_{S}$ are the acetate peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Change to read:

## Assay for gluconate (if present)-

Mobile phase-Prepare a filtered and degassed solution of 0.05 N sulfuric acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Potassium Gluconate RS in water to obtain a Standard preparation having a known concentration of about 1 mg of USP Potassium Gluconate RS (about 0.0043 mEq of gluconate) per mL .

Assay preparation-Dilute an accurately measured volume of Injection quantitatively with water to obtain a solution containing about 0.004 mEq of gluconate per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector, a 7.8 mm - 4 em
-4.6-mm $\times 3-\mathrm{cm}_{1 \mathrm{M}}$ (USP28)
guard column containing packing L17, and a $7.8-\mathrm{mm} \times 30-\mathrm{cm}$ analytical column containing packing L17., and maintined at abu $60^{\circ}$.

## - 1 IS (USP28)

The flow rate is about 0.8 mL per minute. Chromatograph the Standard preparation, and record the responses as directed for Procedure: the tailing factor for the analyte peak is not more than 2.0, and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mEq per liter, of gluconate $\left(\mathrm{C}_{6} \mathrm{H}_{11} \mathrm{O}_{7}\right)$ in the Injection taken by the formula:
$(C / 234.25)(L / D)\left(r_{U} / r_{S}\right)$,
in which $C$ is the concentration, in mg per mL, of USP Potassium Gluconate RS in the Standard preparation; 234.25 is the molecular weight of anhydrous potassium gluconate; $L$ is the labeled quantity, in mEq per liter, of gluconate in the Injection; $D$ is the quantity, in mEq per mL , of gluconate in the Assay preparation, based on the labeled quantity and the extent of dilution; and $r_{U}$ and $r_{S}$ are the gluconate peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Multiple Electrolytes Injection Type 2, USP 27 page 688See briefing under Multiple Electrolytes Injection Type 1.
(PA1: K. Russo) RTS-41010-1

## Change to read:

» Multiple Electrolytes Injection Type 2 is a sterile solution of suitable salts in Water for Injection to provide sodium, potassium, calcium, magnesium, and chloride ions. In addition, the salts may
-n1S (USP28)
provide ions of either acetate and citrate, or acetate and lactate. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of sodium $(\mathrm{Na})$, potassium $(\mathrm{K})$, magnesium $(\mathrm{Mg})$, calcium $(\mathrm{Ca})$, chloride $(\mathrm{Cl})$, acetate $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}_{2}\right)$, citrate $\left(\mathrm{C}_{6} \mathrm{H}_{5} \mathrm{O}_{7}\right)$, and lactate $\left(\mathrm{C}_{3} \mathrm{H}_{5} \mathrm{O}_{3}\right)$. It may contain Hydrochloric Acid or Sodium Hydroxide used to adjust the pH . It contains no antimicrobial agents.

## Briefing

Multiple Electrolytes and Dextrose Injection Type 1, USP 27 page 690-See briefing under Multiple Electrolytes Injection Type 1.

## Change to read:

» Multiple Electrolytes and Dextrose Injection Type 1 is a sterile solution of Dextrose and suitable salts in Water for Injection to provide sodium, potassium, magnesium, and chloride ions. In addition, the salts may

■1S (USP28)
provide ions of acetate, or acetate and gluconate, or acetate and phosphate, or phosphate and lactate, or phosphate and sulfate. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of sodium ( Na ), potassium ( K ), magnesium $(\mathrm{Mg})$, acetate $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}_{2}\right)$, gluconate $\left(\mathrm{C}_{6} \mathrm{H}_{11} \mathrm{O}_{7}\right)$, phosphate $\left(\mathrm{PO}_{4}\right)$, lactate $\left(\mathrm{C}_{3} \mathrm{H}_{5} \mathrm{O}_{3}\right)$, and sulfate $\left(\mathrm{SO}_{4}\right)$, not less than 90.0 percent and not more than 120.0 percent of the labeled amount of chloride ( Cl ), and not less than 90.0 percent and not more than 105.0 percent of the labeled amount of dextrose $\left(\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}\right)$. It may contain Hydrochloric Acid or Sodium Hydroxide used to adjust the pH . It contains no antimicrobial agents.

## BRIEFING

Multiple Electrolytes and Dextrose Injection Type 2, USP 27 page 691 -See briefing under Multiple Electrolytes Injection Type 1.
(PA1: K. Russo) RTS-41010-3

## Change to read:

» Multiple Electrolytes and Dextrose Injection Type 2 is a sterile solution of Dextrose and suitable salts in Water for Injection to provide sodium, potassium, magnesium, calcium, and chloride ions. In addition, the salts may
-. 1 SS (USP28)
provide ions of acetate, or acetate and citrate, or acetate and lactate, or gluconate and sulfate. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of sodium ( Na ), potassium $(\mathrm{K})$, magnesium ( Mg ), calcium ( Ca ), acetate $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}_{2}\right)$, citrate $\left(\mathrm{C}_{6} \mathrm{H}_{5} \mathrm{O}_{7}\right)$, lactate $\left(\mathrm{C}_{3} \mathrm{H}_{5} \mathrm{O}_{3}\right)$, gluconate $\left(\mathrm{C}_{6} \mathrm{H}_{11} \mathrm{O}_{7}\right)$, and sulfate $\left(\mathrm{SO}_{4}\right)$, and not less than 90.0 percent and not more than 120.0 percent of the labeled amount of chloride ( Cl ), and not less than 90.0 percent and not more than 105.0 percent of the labeled amount of dextrose $\left(\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}\right)$. It may contain Hydrochloric Acid or Sodium Hydroxide used to adjust the pH. It contains no antimicrobial agents.

## Briefing

Multiple Electrolytes and Dextrose Injection Type 3, USP 27 page 693 -See briefing under Multiple Electrolytes Injection Type 1.
(PA1: K. Russo) RTS-41010-4

## Change to read:

» Multiple Electrolytes and Dextrose Injection Type 3 is a sterile solution of Dextrose and suitable salts in Water for Injection to provide sodium, potassium, and chloride ions. In addition, the salts may

■ $\quad$ 1S (USP28)
provide ions of ammonium, or acetate and phosphate, or phosphate and lactate. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of sodium $(\mathrm{Na})$, potassium ( K ), ammonium $\left(\mathrm{NH}_{4}\right)$, acetate $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}_{2}\right)$, phosphate $\left(\mathrm{PO}_{4}\right)$, and lactate $\left(\mathrm{C}_{3} \mathrm{H}_{5} \mathrm{O}_{3}\right)$, not less than 90.0 percent and not more than 120.0 percent of the labeled amount of chloride $(\mathrm{Cl})$, and not less than 90.0 percent and not more than 105.0 percent of the labeled amount of dextrose $\left(\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}\right)$. It may contain Hydrochloric Acid or Sodium Hydroxide used to adjust the pH . It contains no antimicrobial agents.

## Briefing

Ephedrine, USP 27 page 707; Ephedrine Hydrochloride, USP 27 page 707; Ephedrine Sulfate, USP 27 page 708 and page 1476 of PF 29(5) [Sept.-Oct. 2003]. It is proposed to correct the concentration of ammonium hydroxide used in the procedure in the test for Ordinary impurities. Deletion of the 3.6 M designation redefines the reagent as ammonium hydroxide, which is concentrated (undiluted) ammonium hydroxide, according to the definition in the Reagents section of the $U S P$. In the absence of any adverse
comments, it is proposed to implement this revision via the Fifth Interim Revision Announcement pertaining to USP 27-NF 22, with an official date of October 1, 2004.
(PA1: K. Russo) RTS-41118-1

## Change to read:

Ordinary impurities $\langle 466\rangle$ -
Test solution: methanol.
Standard solution: methanol.
Eluant: a mixture of isopropyl alcohol, 3.6-M

- ${ }^{\circ}$
ammonium hydroxide, and chloroform ( $80: 15: 5$ ).
Visualization: 1 , followed by 4.


## Briefing

Ephedrine Hydrochloride, USP 27 page 707-See briefing under Ephedrine.
(PA1: K. Russo) RTS-41118-2

## Change to read:

Ordinary impurities $\langle 466\rangle$ -
Test solution: alcohol.
Standard solution: alcohol.
Eluant: a mixture of isopropyl alcohol, 3.6 M

- ${ }^{\circ}$
ammonium hydroxide, and chloroform ( $80: 15: 5$ ). Visualization: 1 , followed by 4.


## Briefing

Ephedrine Sulfate, USP 27 page 708 and page 1476 of $P F$ 29(5) [Sept.-Oct. 2003]-See briefing under Ephedrine.
(PA1: K. Russo) RTS-41118-3

## Change to read:

Packaging and storage-Preserve in well-closed, light-resistant containers.
-Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ} \cdot$ ■2S (USP27)

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. $\quad$ 2S (USP27)

## Change to read:

USP Reference standards $\langle 11\rangle-$

USP Ephedrine Sulfate RS.

## Change to read:

Ordinary impurities $\langle 466\rangle$ -
Test solution: alcohol.
Standard solution: alcohol.
Eluant: a mixture of isopropyl alcohol, 3.6-M
${ }^{\bullet}$ •官
ammonium hydroxide, and chloroform ( $80: 15: 5$ ).
Visualization: 1, followed by 4.

## Add the following:

-Other requirements-Where the label states that Ephedrine Sulfate is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Ephedrine Sulfate Injection. Where the label states that Ephedrine Sulfate must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Ephedrine Sulfate Injection. $\quad$ 2S (USP27)

## Briefing

Conjugated Estrogens, USP 27 page 747 and page 1478 of $P F$ $29(5)$ [Sept.-Oct. 2003]. It is proposed to revise the Definition to indicate the source of Conjugated Estrogens.
(PA1: S. Salado) RTS-41071-1

## Change to read:

» Conjugated Estrogens is a mixture of sodium estrone sulfate and sodium equilin sulfate, derived whelly or im part from equine urine or synthetically from Estrone and Equilin.

- from equine urine. ${ }^{1 S}$ (USP28)

It contains other conjugated estrogenic substances of the type
-as well as conjugated pregnanes and conjugated androstanes ${ }_{\text {1S (USP28) }}$
excreted by pregnant mares. It is a dispersion of the estrogenie

- these steroidal ${ }_{\text {1S (USP28) }}$
substances on a suitable powdered diluent.
Conjugated Estrogens contains
-as the sodium sulfate conjugates, expressed in terms of the labeled content of Conjugated Estro-
gens, 1 1s (USP28)
not less than 52.5 percent and not more than 61.5 percent of sedium estrene-sulfate and
- estrone, $\boldsymbol{m}_{1 S}$ (USP28)
not less than 22.5 percent and not more than 30.5 percent of sodium equilin sulfate, and the
-equilin, and not less than 13.5 percent and not more than 19.5 percent of $17 \alpha$-dihydroequilin.


## The ${ }_{\text {IS (USP28) }}$

total of sodium estrone sulfate and sodium equilin sulfate is not less than 79.5 percent and not more than 88.0 percent of the labeled content of Conjugated Estrogens.
-The total of the sodium sulfate conjugates of estrone, equilin, and $17 \alpha$-dihydroequilin is not less than 90.0 percent and not more than 110.0 percent of the labeled content of Conjugated Estrogens. 1 IS (USP28)
Conjugated Estrogens contains as concomitant components as sodium sulfate conjugates less than 13.5 pereent and not more than 19.5 pereent of $17 \alpha$-dihy dreequilin,

- 1 IS (USP28)
not less than 2.5 percent and not more than 9.5 percent of $17 \alpha$-estradiol, and not less than 0.5 percent and not more than 4.0 percent of $17 \beta$-dihydroequilin, of the labeled content of Conjugated Estrogens.


## Change to read:

Packaging and storage-Preserve in well-closed containers.

- Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$. 2 (USP27)


## Briefing

Fexofenadine Hydrochloride, page 1790 of PF 28(6) [Nov.Dec. 2002]. Based on comments received, revisions are proposed based on FDA approved tests and acceptance criteria: the qualitative Identification test $B$ is replaced by a requirement for retention time agreement between the Assay preparation and Standard preparation; a quantitative test for Content of chloride is added; in Identification test $C$ a range is specified between $193^{\circ}$ and $199^{\circ}$; a test for Specific surface area is also proposed; and in the test for Related compounds, the acceptance criterion for any other unknown impurity is restated as less than $0.1 \%$. Other editorial changes have been made.
(PA1: K. Russo) RTS-39653-1; 40193-1; 40512-1

## Add the following:

## ■Fexofenadine Hydrochloride


$\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl} \quad 538.13538 .12$
Benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenyl-methyl)-1-piperidinyl]butyl]- $\alpha, \alpha$-dimethyl-, hydrochloride, $( \pm)$ -
( $\pm$ )-p-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)piperidi-no]butyl]- $\alpha$-methylhydratropic acid, hydrochloride [138452-21-8].
» Fexofenadine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in well closed, light re sistaners. Preserve in tight, light-resistant containers and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Fexofenadine Hydrochloride RS. USP Fexofenadine Related Compound $A$ RS. USP Fexofenadine Related Compound B RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Dissolve 30 mg f Fevenadine Hydrochloride in 2
mL of methanel, add 30 mL of water, and acidify with nittic
acid: meets the requirements of the test for Chloride $\langle 194\rangle$ :
The retention time of the fexofenadine peak in the chroma-
togram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

C: Differential Scanning Calorimetry $\langle 891\rangle$ —Accurately weigh 2 to 6 mg of Fexofenadine Hydrochloride into an aluminum pan, and crimp the pan using a suitable sample press. Analyze the sample from $25^{\circ}$ to $225^{\circ}$ at $10^{\circ}$ per minute. The sample exhibits a single endotherm $190^{\circ}$ between $193^{\circ}$ and $199^{\circ}$. [NOTE-The pan can be sealed hermetically provided a pin hole is punched into the lid so that the sample can degas during heating.]

Water, Method Ic $\langle 921\rangle$ : not more than $0.5 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.002 \%$.
Specific surface area, Method II $\langle 846\rangle$-Outgas a portion of Fexofenadine Hydrochloride (about 0.2 to 0.5 g ), using helium flow for 1 hour at $100^{\circ}$ or vacuum for 1 hour at $100^{\circ}$. Test the sample using gas sorption: between 2.5 and $5.0 \mathrm{~m}^{2}$ per g .

## Limit of fexofenadine related compound B-

Ammonium acetate buffer solution-Add 2.3 mL of glacial acetic acid to 2000 mL of water. Adjust with 6 N ammonium hydroxide to a pH of $4.0 \pm 0.1$.

Mobile phase-Prepare a filtered and degassed mixture of Ammonium acetate buffer solution and acetonitrile (80:20).

Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
System suitability solution-Add about 1.2 mg of USP Fexofenadine Related Compound B RS, accurately weighed, to a $5-\mathrm{mL}$ volumetric flask. Dilute with Mobile phase to volume, and mix. Transfer 2.0 mL of the solution so obtained into a $100-\mathrm{mL}$ volumetric flask, add about 25 mg of USP Fexofenadine Hydrochloride RS, accurately weighed, dilute with Mobile phase to volume, and mix.

Standard solution-Dilute the System suitability solution quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $2.5 \mu \mathrm{~g}$ of USP Fexofenadine Hydrochloride RS per mL.

Test solution-Dissolve an accurately weighed quantity of Fexofenadine Hydrochloride in Mobile phase to obtain a solution having a concentration of about 0.25 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{m} 25-\mathrm{cm}$ column that contains packing L45. The column is maintained at room temperature. The flow rate is about 0.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the retention time for fexofenadine is between 15 and 23 minutes; the relative retention times are about 0.7 for fexofenadine related compound B and 1.0 for fexofenadine; and the resolution, $R$, between fexofenadine and fexofenadine related compound $B$ is not less than 1.5 3.0.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Test solution and the Standard solution into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of fexofenadine related compound B in the portion of Fexofenadine Hydrochloride taken by the formula:

$$
1.25\left(r_{I} / r_{s}\right),
$$

in which 1.25 is the response factor for fexofenadine related compound B relative to fexofenadine; $r_{I}$ is the peak response for fexofenadine related compound B obtained from the Test solution; and $r_{s}$ is the peak response for fexofenadine obtained from the Standard solution: not more than $0.1 \%$ is found.

## Related compounds-

Phosphate-perchlorate buffer, Diluting solution, Mobile phase, Sys and Chromatographic system-Prepare as directed in the Assay.

Standard solution Dissolve an aceurately weighed quantity of USP Fexofenadine-Related Compound A RS
in Diluting solution to obtain a solution having a known eoncentration of about 0.5 mg per mL. Dilute with Mobite phase quantitatively, and stepwise if neeessary, to-ebtain a selution having a known concentrat ion of about 0.005 mg permE.

Reference solution-Use the Assay preparation, prepared as directed in the Assay.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay stock preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Test solution, the Standard solution, the Reference solution, and the Mobile phase (used as the blank) into the chromatograph, record the chromatograms, and measure the peak areas, excluding the peaks corresponding to those obtained from the Mobile phase. Calculate the quat in mg, percentage of fexofenadine related compound A in the portion of Fexofenadine Hydrochloride taken by the formula:

$$
50 C\left(+\quad+r_{s}\right)
$$

$$
100\left(C_{S} / C_{T}\right)\left(r_{I} / r_{S}\right)
$$

in which $C_{S}$ is the concentration, in mg per mL, of USP Fexofenadine Related Compound A RS in the Standard solution; $C_{T}$ is the concentration, in mg per mL , of
fexofenadine in the Test solution; and $r_{I}$ and $r_{s}$ are the peak responses for fexofenadine related compound A obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of decarboxylated degradant [(+)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperi-dinyl]-butyl]-isopropylbenzene], with a relative retention time of 3.2, in the portion of Fexofenadine Hydrochloride taken by the formula

$$
(100 / 1.1)\left(C_{S} / C_{T}\right)\left(r_{U} / r_{S}\right)
$$

in which 1.1 is the response factor for the decarboxylated degradant relative to fexofenadine; $C_{s}$ is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the Standard solution; $C_{T}$ is the concentration, in mg per mL , of fexofenadine in the Test solution; $r_{U}$ is the peak response of the decarboxylated degradant obtained from the Test solution; and $r_{s}$ is the peak response of fexofenadine obtained from the Standard solution. Galeulate the pereen age of other impurities in the portion of Ferofenadine Hy drochloride taken by the formula:-

$$
100 \pi+\left(16.67 r_{s}\right)
$$

in which $r$;is the peak respense for each impurity obtained from the Test solution; andrs is the peak respense for fen efenadine obtained from the Test olution: Calculate the percentage of other impurities in the portion of Fexofenadine Hydrochloride taken by the formula:

$$
100\left(C_{S} / C_{T}\right)\left(r_{U} / r_{\mathrm{S}}\right)
$$

in which $C_{s}$ is the concentration, in mg per mL , of fexofenadine in the Reference solution; $C_{T}$ is the concentration, in mg per mL , of fexofenadine in the Test solution; $r_{U}$ is the peak response for any other impurity obtained from the Test
solution; and $r_{s}$ is the peak response of fexofenadine obtained from the Reference solution. more than $0.2 \%$ of ferofenadine related compound A is found; and not more than 0.45\% of impurities is found. Not more than $0.18 \%$ of fexofenadine related compound A is found; not more than $0.15 \%$ of decarboxylated degradant is found; not more than $0.1 \%$ of any other unknown impurity is found; and not more than $0.3 \% 0.30 \%$ of total impurities is found.

Content of chloride—Dissolve about 300 mg of Fexofenadine Hydrochloride, accurately weighed, in 50 mL of methanol. Titrate with 0.1 N silver nitrate VS, and determine the endpoint potentiometrically (see Titrimetry $\langle 541\rangle$. Each mL of 0.1 N silver nitrate VS is equivalent to 3.545 mg of chloride: not less than $6.45 \%$ and not more than $6.75 \%$ of chloride is found, calculated on the anhydrous basis.

Assay-
Phosphate-perchlorate buffer-Dissolve 6.64 g of monobasic sodium phosphate and 0.84 g of sodium perchlorate in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.0.

Diluting solution-Prepare a mixture of acetonitrile and Phosphate-perchlorate buffer (50:50).

Mobile phase-Prepare a filtered and degassed mixture of Phosphate-perchlorate buffer and acetonitrile ( $65: 35$ ). Add 3 mL of triethylamine per L, and mix. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
System sutability preatan- Standard preparationPrepare a solution of USP Fexofenadine Hydrochloride RS and USP Fexofenadine Related Compound A RS in Mobile phase having known concentrations of about 0.06 mg per mL and 0.005 mg per mL , respectively.

Standard preparation Dissolve an accurately weighed quantity of USP Fexofenadine Hydrochloride RS in Dilut ing solution to obtain a solution having a known concentration of about 0.5 mg per mL . Dilute quantitatively, and stepwise if necessary, with Mebile phase to obtain acencen tration of 0.06 mg of USP Fexofenadine Hydrechloride RS per mL.

Assay stock preparation-Transfer about 50 mg of Fexofenadine Hydrochloride, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with Diluting solution to volume to obtain a solution having a concentration of about 1.0 mg of fexofenadine hydrochloride per mL .

Assay preparation-Transfer 3.0 mL of Assay stock preparation to a $50-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume to obtain a solution having a concentration of about 0.06 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L11. The column is maintained at room temperature. The flow rate is about 1.5 mL per minute. Chromatograph the fystem suitability pration, Standard preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between fexofenadine and fexofenadine related compound A is not less than 10 ; the tailing factor is not more than 2.0 ; and the relative standard deviations for replicate injections determined from fexofenadine and fexofenadine related compound A are not more than $2.0 \%$ and $3.0 \%$, respectively.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and
measure the areas for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}$ in the portion of Fexofenadine Hydrochloride taken by the formula:

$$
833.3 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses for fexofenadine obtained from the Assay preparation and the Standard preparation, respectively.■IS (USP28)

## Briefing

Fexofenadine Hydrochloride Capsules, page 1027 of $P F$ 29(4) [July-Aug. 2003]. Based on comments received, revisions are proposed to the monograph based on FDA approved acceptance criteria. It is proposed to change the upper assay limit presented in the Definition from 107.0 percent to 105.0 percent. A limit for total other unknown impurities is proposed to be added to the Related compounds procedure. Minor editorial changes have also been made.
(PA1: K. Russo) RTS—39653-2; 40193-2; 40512-2

## Add the following:

## ■Fexofenadine Hydrochloride Capsules

» Fexofenadine Hydrochloride Capsules contain not less than 93.0 percent and not more than 107.0105 .0 percent of the labeled amount of fexofenadine hydrochloride $\left(\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}\right)$.

Packaging and storage-Preserve in tight, light-resistant containers. Store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Fexofenadine Hydrochloride RS. USP Fexofenadine Related Compound $A$
RS. USP Fex fenaline Related Compound B-RS.

## Identification-

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.
B: Infrared Absorption $\langle 197 \mathrm{~K}\rangle-$
Test specimen-Empty the contents of several Capsules, equivalent to about 60 mg of fexofenadine hydrochloride, into a suitable capped tube. Add 10 mL of a mixture of acetonitrile and methanol ( $10: 1$ ), and shake until the sample is dispersed. Allow to settle. Decant, filter, and collect the supernatant in a suitable beaker. Evaporate the solvent to near dryness by using a stream of nitrogen and with gentle heating from an appropriate source (steam, low-temperature hot plate). While still warm, add 5 mL of water and 5 drops of diluted hydrochloric acid, and stir to induce precipitation. Chill in an ice bath for about 30 minutes. Pass through a 10to $15-\mu \mathrm{m}$ filtering crucible with fritted disk. Dry the precipitate in an air oven for 1 hour at $105^{\circ}$.
Dissolution $\langle 711\rangle$ —
Medium: water; 900 mL .
Apparatus 2: 50 rpm.
Times: 15 and 45 minutes.
Determine the amount of $\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}$ dissolved by employing the following method.

Buffer solution-Dissolve 1.0 g of monobasic sodium phosphate, 0.5 g of sodium perchlorate, and 0.5 mL 0.3 mL of phosphoric acid in 300 mL of water, and mix.

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and Buffer solution (700:300), and mix. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability stock solution-[NOTE—A small amount of glacial acetic acid, not to exceed $5 \%$ of the total volume, is used, if necessary, to dissolve USP Fexofenadine Related Compound A RS.] Dissolve an accurately weighed quantity of USP Fexofenadine Related Compound A RS in water to obtain a solution having a known concentration of 0.44 mg per mL .

System suitability solution-Prepare a solution of USP Fexofenadine Hydrochloride RS in System suitability stock solution containing about 0.01 mg of USP Fexofenadine Related Compound A RS and 0.06 mg of USP Fexofenadine Hydrochloride RS per mL.

Standard solution-[NOTE-A small amount of methanol, not to exceed $0.5 \%$ of the total volume, is used, if necessary, to dissolve USP Fexofenadine Hydrochloride RS.] Dissolve an accurately weighed quantity of USP Fexofenadine Hydrochloride RS in water to obtain a solution having a known concentration of 0.07 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between fexofenadine and fexofenadine related compound A is not less than 2.0. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solution and filtered portions of the solution under test into the chromatograph, record the chromatograms, and measure the responses for the fexofenadine peaks. Calculate the quantity of $\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}$ dissolved.
Tolerances-Not less than $50 \%(Q)$ of the labeled amount of $\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}$ is dissolved in 15 minutes. Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}$ is dissolved in 45 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

Water, Method $I\langle 921\rangle$ : between $3.5 \%$ and $8.0 \%$, the titration being performed at $50^{\circ}$ and the titration vessel being kept in a heated water jacket.

## Related compounds-

Pherphate perehlorate buffer- Prepare as direeted in the Assem.

Phosphate-perchlorate buffer, Diluting solution, Mobile phase, Sysm, and Chromatographic system—Proceed as directed in the Assay under Fexofenadine Hydrochloride.

Standard solution-Use the Standard preparation, prepared as directed in the Assay under Fexofenadine Hydrochloride.

Reference solution-Use the Assay preparation, prepared as directed in the Assay.

Test solution-Use the Assay stock preparation, prepared as directed in the Assay.
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the
responses for the major peaks. Calculate the percentage of fexofenadine related compound A in the portion of Capsules taken by the formula:

$$
100\left(C_{S} / C_{T}\right)\left(r_{U} / r_{S}\right)
$$

in which $C_{S}$ is the concentration, in mg per mL, of USP Fexofenadine Related Compound A RS in the Standard solution; $C_{T}$ is the concentration of fexofenadine in the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses of fexofenadine related compound A obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of decarboxylated degradant [(+)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene], with a relative retention time of 3.2 , in the portion of Fexofenadine Hydrochloride taken by the formula:

$$
(100 / 1.1)\left(C_{S} / \mathrm{C}_{T}\right)\left(r_{U} / r_{S}\right),
$$

in which 1.1 is the response factor for the decarboxylated degradant relative to fexofenadine; $C_{S}$ is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the Standard solution; $C_{T}$ is the concentration of fexofenadine in the Test solution; $r_{U}$ is the peak response of the decarboxylated degradant obtained from the Test solution; and $r_{s}$ is the peak response of fexofenadine obtained from the Standard solution. Calculate the percentage of other impurities in the portion of Fexofenadine Hydrochloride taken by the formula:

$$
100\left(C_{R} / C_{T}\right)\left(r_{U} / r_{R}\right)
$$

in which $C_{R}$ is the concentration, in mg per mL , of fexofenadine in the Reference solution; $C_{T}$ is the concentration of fexofenadine in the Test solution; $r_{U}$ is the peak response for any other impurity obtained from the Test solution; and $r_{R}$ is
the peak response of fexofenadine obtained from the Reference solution. mere than $0.3 \%$ ferofene hydro ehloride related compound $\Lambda$ is found. Not more than $0.3 \%$ of fexofenadine related compound A , not more than $0.2 \%$ of decarboxylated degradant, and less than $0.1 \%$ of any other unknown impurity is found; not more than $0.2 \%$ total other unknown impurities, and not more than $0.5 \%$ of total impurities is found.

## Assay-

Phosphate perehlorate buffer Dissolve 6.64g of menebasie sodium phesphate and 0.84 g of sodium perchlerate in 1000 mL of water. Adjust with phospheric acid to a pH- p . 4.02.0.

Phosphate-perchlorate buffer, Diluting solution, Mobile phase, fystan, Standard preparation, and Chromatographic system-Proceed as directed in the Assay under Fexofenadine Hydrochloride.

Assay stock preparation - Remove, as completely as possible, the contents of not fewer than 20 Capsules, mix the combined contents, and finely powder by using a mortar and pestle. Transfer a portion of the powder, equivalent to about 50 mg of fexofenadine hydrochloride, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask. Add 40 mL of Diluting solution, and shake by mechanical means for 60 minutes. Sonicate for about 2 minutes. Allow to cool to room temperature, dilute with Diluting solution to volume, and mix.

Assay preparation-Transfer 3.0 mL of the Assay stock preparation to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the
quantity, in mg , of fexofenadine hydrochloride $\left(\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}\right)$ in the portion of Capsules taken by the formula:

$$
833.3 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## Briefing

Fluoxetine Hydrochloride, USP 27 page 822; Fluoxetine Tablets, USP 27 page 824. It is proposed to revise the USP Reference standards section to change the name of USP Fluoxetine Related Compound B RS to USP Fluoxetine Related Compound B Solution RS. Other sections affected by the change are revised accordingly.
(PA3: S. Salado) RTS-40938-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Fluoxetine Hydrochloride RS. USP Fluoxetine Related Compound A RS. USP Fluwine Retated Compoun B-RSM.

- USP Fluoxetine Related Compound B Solution
$R S . \square_{1 S}$ (USP28)


## Change to read:

## Related compounds-

Mobile phase-Proceed as directed in the Assay.
Test solution 1 -Transfer about 56 mg of Fluoxetine Hydrochloride, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Test solution 2-Transfer 2 mL of Test solution 1, accurately measured, to a $10-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

System suitability solution-Dissolve about 22 mg of USP Fluoxetine Hydrochloride RS in 10 mL of 1 N sulfuric acid, and heat to $85^{\circ}$ for 3 hours. Cool, transfer 0.4 mL of this solution to a $25-\mathrm{mL}$ volumetric flask, and add about 28 mg of USP Fluoxetine Hydrochloride RS, 1 mg of USP Fluoxetine Related Compound A RS, and 4 mg of USP Fluoxetine Related Compound B RS.
-0.5 mL of USP Fluoxetine Related Compound B Solution

## RS. 1 IS (USP28)

Dilute with Mobile phase to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a 4.6 $\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ base-deactivated packing L7. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.24 for $\alpha$ -[2-(methylamino)ethyl]benzenemethanol (if present), 0.27 for fluoxetine related compound B (if present), 0.94 for fluoxetine related compound A, 1.0 for fluoxetine, and 2.17 for 4 -trifluoromethylphenol; and the ratio of the height of the fluoxetine related compound A peak to the depth of the valley between the fluoxetine and fluoxetine related compound A peaks (measured from the fluoxetine related compound A peak height) is not more than 1.1.
Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of Test solution 1 and Test solution 2 into the chromatograph, record the chromatograms for not less than twice the elution time for fluoxetine, and measure the peak responses. Calculate the percentage of fluoxetine related compound A in the portion of Fluoxetine Hydrochloride taken by the formula:

$$
100 r_{A} /\left(r_{A}+r_{U}\right)
$$

in which $r_{A}$ is the peak response of fluoxetine related compound A obtained from Test solution 2; and $r_{U}$ is the peak response of fluoxetine obtained from Test solution 2.

Calculate the percentage of each of the other impurities in the portion of Fluoxetine Hydrochloride taken by the formula:

$$
100 r_{i} /\left(r_{s}+5 r_{U}\right)
$$

in which $r_{i}$ is the peak response for each impurity obtained from Test solution 1; $r_{s}$ is the sum of the responses of all the peaks, excluding fluoxetine, obtained from Test solution 1; and $r_{U}$ is as defined above: not more than $0.15 \%$ of fluoxetine related compound A is found; not more than $0.25 \%$ of $\alpha$-[2-(methylamino)ethyl]benzenemethanol is found; not more than $0.25 \%$ of fluoxetine related compound B is found; not more than $0.1 \%$ of any other individual impurity is found; and not more than $0.5 \%$ of total impurities is found.

## BRIEFING

Fluoxetine Capsules, USP 27 page 822; Fluoxetine Tablets, USP 27 page 824 . It is proposed to revise the limits in the test for Chromatographic purity so that both dosage forms reflect the typical values found in stability studies for approved products.
(PA3: S. Salado) RTS-40907-1

## Change to read:

## Chromatographic purity-

Triethylamine buffer-Proceed as directed in the Assay under Fluoxetine Hydrochloride.

Mobile phase-Prepare a filtered and degassed mixture of Triethylamine buffer and acetonitrile ( $65: 35$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve an accurately weighed quantity of USP Fluoxetine Hydrochloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.01 mg per mL .

Test solution-Remove, as completely as possible, the contents of not fewer than 20 Capsules, and mix. Transfer an accurately weighed portion of the combined contents, equivalent to about 20 mg of fluoxetine, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a 4.6 $\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L10. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution for at least 22 minutes, and record the peak responses as directed for Procedure: the column efficiency is not less than 1100 theoretical plates; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Inject a volume (about $10 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Capsules taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for each impurity; and $r_{s}$ is the sum of the responses of all of the peaks: not more than $0.25 \%$ of any individual impurity is found, and not more than $0.40 \%$

- $0.80 \%_{\text {■ }}^{1 S}$ (USP28)
of total impurities is found.

BRIEFING

Fluoxetine Delayed-Release Capsules, page 1486 of $P F$ 29(5) [Sept.-Oct. 2003]. It is proposed to add a Drug release test to this new monograph.
(BPC: M. Marques) RTS—35912-1

## Add the following:

## ■Fluoxetine Delayed-Release Capsules

## » Fluoxetine Delayed-Release Capsules contain

 an amount of Fluoxetine Hydrochloride equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fluoxetine $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~F}_{3} \mathrm{NO}\right)$.Packaging and storage-Preserve in tight containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Fluoxetine Hydrochloride RS. USP Fluoxetine Related Compound C RS.

Identification, Infrared Absorption $\langle 197 \mathrm{~F}\rangle$ -
Test specimen-Transfer the contents of 3 Capsules to a suitable container, and grind to a fine powder. Transfer an a portion of the powder, equivalent to about 40 mg of fluoxetine, to a suitable container, and dissolve in 25 mL of 0.1 N hydrochloric acid. Filter, and transfer 10 mL of the solution so obtained to a separatory funnel, add 20 mL of methylene chloride, and mix. Allow the phases to separate, and transfer the organic layer to a small glass container. Evaporate to dryness with the aid of a current of air and mild heat. Redissolve the residue with a few
drops of methylene chloride, and transfer to a potassium bromide plate. Dry or evaporate to a thin film with the aid of a stream of nitrogen.

Drug release $\langle 724\rangle$ [Tocome.]
Apparatus 3: 12 dips per minute (dpm), using a polypropylene 40 -mesh screen on the top and bottom of the reciprocating cylinder.

## ACID STAGE-

Medium: $\quad 0.1 \mathrm{~N}$ hydrochloric acid; 250 mL , deaerated. Operate the apparatus for 2 hours at 12 dpm , withdraw an aliquot of the Medium, and allow the apparatus to proceed to the Buffer stage.

Standard solution-Prepare a solution of USP Fluoxetine Hydrochloride RS in Acid stage Medium having a known concentration of about 0.036 mg per mL .

Test solution-Use portions of the solution under test passed through a filter having a $0.45-\mu \mathrm{m}$ porosity.

Procedure-Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~F}_{3} \mathrm{NO}$ dissolved from the minimum (most negative) of the first derivative of UV absorbances at about 278 nm in comparison with the Standard solution.

Tolerances-Not more than $10 \%$ of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~F}_{3} \mathrm{NO}$ is dissolved in 2 hours. BUFFER STAGE-

Medium: $\quad \mathrm{pH} 6.8$ phosphate buffer (Prepared by mixing 3 L of 0.1 N hydrochloric acid and 1 L of 0.2 M tribasic sodium phosphate, and adjusting, if necessary, with 1 N hydrochloric acid or 1 N sodium hydroxide to a pH of $6.8 \pm 0.05$ ); 250 mL , deaerated. Operate the apparatus for 45 minutes at 12 dpm , and withdraw an aliquot of the Medium.

Standard solution-Prepare a solution of USP Fluoxetine Hydrochloride RS in Buffer stage Medium, having a known concentration of about 0.36 mg per mL .

Test solution-Use portions of the solution under test passed through a filter having a $0.45-\mu \mathrm{m}$ porosity.
Procedure-Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~F}_{3} \mathrm{NO}$ dissolved from the difference between the maximum UV absorbance at about 264 nm and the absorbance at 290 nm in comparison with the Standard solution.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~F}_{3} \mathrm{NO}$ is dissolved in 45 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Chromatographic purity-

Ion-pair solution-Dissolve about 6.5 g of sodium 1-octanesulfonate and 2.9 g of anhydrous sodium acetate in 1 li ter of water, and adjust with glacial acetic acid to a pH of 5.0.

Mobile phase-Prepare a filtered and degassed mixture of Ion-pair solution and acetonitrile ( $58: 42$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Degraded fluoxetine solution-Dissolve a quantity of USP Fluoxetine Hydrochloride RS in 0.1 N hydrochlorid 1.0 N sulfuric acid to obtain a solution containing about 2.2 mg per mL . Heat to $85^{\circ}$ for 3 hours, and cool to room temperature.

Fluoxetine related compound solution-Dissolve anacewrely a quantity of USP Fluoxetine Related Compound C RS in Mobile phase to obtain a solution containing about 0.5 mg per mL .

System suitability solution-Transfer oigher about 13.5 mg of USP Fluoxetine Hydrochloride RS to a $100-\mathrm{mL}$ volumetric flask, add 2 mL of Degraded fluoxetine solution and 2 mL of Fluoxetine related compound solution, and dissolve in and dilute with

Mobile phase to volume. Transfer 10.0 mL of this solution to a $250-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Detector sensitivity solution-Transfer 1 mL of the System suitability solution to a $100-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume.

Test solution-Weigh and finely powder not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of fluoxetine, to a $250-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix. Filter before injection.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $3.5-\mu \mathrm{m}$ packing L7. The column temperature is maintained at $30^{\circ}$. The flow rate is about 1 mL per minute. Inject the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.49 for $\alpha, \alpha, \alpha$-trifluoro- $p$-cresol, 0.70 for fluoxetine related compound C , and 1.0 for fluoxetine; the resolution, $R$, between $\alpha, \alpha, \alpha$-trifluoro- $p$-cresol and fluoxetine related compound C is not less than 2.0; and the resolution, $R$, between fluoxetine related compound C and fluoxetine is not less than 6.0. Chromatograph the Detector sensitivity solution, and record the peak responses as directed for Procedure: the signal-tonoise ratio for the fluoxetine peak is not less than 10 .

Procedure-Inject a volume (about $50 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram for at least three times the retention time of the fluoxetine peak, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Capsules taken by the formula:
in which $r_{i}$ is the peak response for each impurity; and $r_{s}$ is the sum of the responses of all the peaks: not more than $0.2 \%$ of any individual impurity is found, and not more than $0.7 \%$ of total impurities is found.

## Assay-

Ion-pair solution-Dissolve about 2.9 mL of glacial acetic acid and about 7.1 g of sodium 1-pentanesulfonate in 1 liter of water. Adjust with 5 N sodium hydroxide to a pH of 5.0.
Mobile phase-Prepare a filtered and degassed mixture of methanol and Ion-pair solution ( $67: 33$ ). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

System suitability solution-Dissolve suitable quantities of USP Fluoxetine Hydrochloride RS and $\alpha, \alpha, \alpha$-trifluoro- $p$-cresol in Mobile phase to obtain a solution containing about $110 \mu \mathrm{~g}$ per mL and $20 \mu \mathrm{~g}$ per mL , respectively.
Standard preparation-Dissolve an accurately weighed quantity of USP Fluoxetine Hydrochloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.11 mg per mL .

Assay preparation-Remove, as completely as possible, the contents of not fewer than 20 Capsules, and mix. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of fluoxetine, to a $500-\mathrm{mL}$ volumetric flask, shake by mechanical means for about 10 minutes, and then sonicate for about 5 minutes. Cool the solution to room temperature, dilute with Mobile phase to volume, and mix. Transfer 5.0 mL of this solution to a $10.0-\mathrm{mL}$ volumetric flask. Dilute with Mobile phase to volume, and mix. Filter the solution before injection.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $227-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 7.5-\mathrm{cm}$ column that contains $3.5-\mu \mathrm{m}$ packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at $38^{\circ}$. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for $\alpha, \alpha, \alpha$-trifluoro- $p$-cresol and 1.0 for fluoxetine; the resolution, $R$, between $\alpha, \alpha, \alpha$-trifluoro- $p$-cresol and fluoxetine is not less than 4.0; the tailing factor for the fluoxetine peak is not more than 1.7 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L})$ of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of fluoxetine $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~F}_{3} \mathrm{NO}\right)$ in the portion of Capsules taken by the formula:

$$
1000(309.33 / 345.79) C\left(r_{U} / r_{S}\right)
$$

in which 309.33 and 345.79 are the molecular weights of fluoxetine and fluoxetine hydrochloride, respectively; $C$ is the concentration, in mg per mL , of USP Fluoxetine Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Fluoxetine Tablets, USP 27 page 824—See briefing under Fluoxetine Hydrochloride and Fluoxetine Capsules.
(PA3: S. Salado) RTS-40938-2; 40907-2

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Fluoxetine Hydrochloride RS. USP Flurine Relad Compand B-RS.
-USP Fluoxetine Related Compound B Solution
$R S$. ■1S $_{\text {(USP28) }}$

## Change to read:

## Chromatographic purity-

Ion-pair solution-Dissolve 6.5 g of sodium 1-octanesulfonate in 1000 mL of water, add 2.9 mL of phosphoric acid, and adjust with a sodium hydroxide solution ( 1 in 5) to a pH of 3.0 .

Mobile phase-Prepare a filtered and degassed mixture of Ionpair solution and acetonitrile ( $57: 43$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Resolution solution-Transfer 1 mL of USP Fltoxetine Related Gempound B-RS
-USP Fluoxetine Related Compound B Solution
$\mathrm{RS}_{\mathbf{m}_{1 S} \text { (USP28) }}$
and about 13.5 mg of USP Fluoxetine Hydrochloride RS to a 100mL volumetric flask. Add 2 mL of a solution prepared by dissolving about 22 mg of USP Fluoxetine Hydrochloride RS in 10 mL of 1 N sulfuric acid, heating at about $85^{\circ}$ for 3 hours, and cooling to room temperature. Dilute with Mobile phase to volume, and mix. Pipet 10.0 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Detector sensitivity solution-Prepare a solution of Resolution solution in Mobile phase (1 in 100).

Standard solution-Dissolve an accurately weighed quantity of USP Fluoxetine Hydrochloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.0135 mg per mL .

Test solution-Place 10 Tablets in a volumetric flask of suitable size. Dissolve in and dilute with Mobile phase to volume to obtain a solution having a concentration of about 2 mg of fluoxetine per mL . Pass a portion of the solution through a suitable filter, and use the filtrate.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a 4.6$\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $3.5-\mu \mathrm{m}$ packing L7. The column temperature is maintained at $30^{\circ}$. The flow rate is about 1.0 mL per minute. Chromatograph in the following order the Mobile phase, the Detector sensitivity solution, and the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.19 for $\alpha$-[2-(methylamino) ethyl]benzenemethanol, 0.26 for fluoxetine related compound B , and 1.0 for fluoxetine; the resolution, $R$, between $\alpha-[2-$ (methyl-amino)ethyl]benzenemethanol and fluoxetine related compound B is not less than 4.5 ; and the signal-to-noise ratio for the Detector sensitivity solution is not less than 10 .

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms for a period of time equal to three times the retention time of the main peak, and measure the areas for all the peaks. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$
100(309.33 / 345.79)\left(C_{S} / C_{U}\right)\left(r_{i} / r_{S}\right)
$$

in which 309.33 and 345.79 are the molecular weights of fluoxetine and fluoxetine hydrochloride, respectively; $C_{S}$ is the concentration, in mg per mL , of USP Fluoxetine Hydrochloride RS in the Standard solution; $C_{U}$ is the concentration, in mg per mL , of fluoxetine in the Test solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the peak response for fluoxetine obtained from the Standard solution: not more than $0.2 \%$

- $0.25 \%$ (USP28).
of any individual impurity is found; and not more than $0.8 \%$
- $0.80 \%$ (USP28)
of total impurities is found.


## Briefing

Hydrocodone Bitartrate and Homotropine Methylbromide Tablets, page 1267 of PF 28(4) [July-Aug. 2002]. This proposed new monograph, which previously appeared in Pharmacopeial Previews, is now being forwarded to In-Process Revision. Editorial style changes have been made.
(PA2: C. Anthony) RTS-40986-1

## Add the following:

## ■Hydrocodone Bitartrate and Homatropine Methylbromide Tablets

## » Hydrocodone Bitartrate and Homatropine

 Methylbromide Tablets contain not less than 90.0 percent and not more than 110.0 percent ofthe labeled amounts of hydrocodone bitartrate disesquihydrate $\left(\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{3} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6} \cdot 2^{1 / 2} \mathrm{H}_{2} \mathrm{O}\right)$ and homatropine methylbromide $\left(\mathrm{C}_{17} \mathrm{H}_{24} \mathrm{BrNO}_{3}\right)$.

NOTE-Use of silanized autosampler vials such as dimethyldichlorosilane vials* is required for the Dissolution test, the Limit tests, and the Assay to prevent drug degradation.

Packaging and storage-Preserve in tight, light-resistant containers.

USP Reference standards $\langle 11\rangle$ —USP Dihydrocodeine Bitartrate RS. USP Homatropine Methylbromide RS. USP Hydrocodone Bitartrate RS.

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -

Solution A-Dissolve 850 mg of bismuth subnitrate in a mixture of 10 mL of glacial acetic acid and 40 mL of water.
Solution $B$-Dissolve 8 g of potassium iodide in 20 mL of water.

Stock solution: a mixture of Solution $A$ and Solution B (1:1).

Solvent: a mixture of methanol and water ( $9: 1$ ).
Spray reagent 1 - [NOTE—Prepare immediately before use.] Prepare a mixture of water, glacial acetic acid, and Stock solution (50:10:5).

Spray reagent 2: hydrogen peroxide TS.
Standard solution 1-Transfer an accurately weighed quantity of about 30 mg of USP Homatropine Methylbromide RS to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Solvent to volume, and mix.

[^94]Standard solution 2-Transfer an accurately weighed quantity of about 25 mg of USP Hydrocodone Bitartrate RS to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Solvent to volume, and mix.

Test solution-Transfer a portion of 20 finely powdered Tablets, equivalent to the average Tablet weight, to a centrifuge tube, add 5.0 mL of Solvent, centrifuge, and use the supernatant.
Developing solvent system: a mixture of ethyl acetate, water, and formic acid (134:33:33).

Procedure-Apply $50 \mu$ L of Standard solution 1, Standard solution 2, and the Test solution, and proceed as directed in the chapter. Remove the plate, and dry at $105^{\circ}$. Spray the plate with Spray reagent 1 and then with Spray reagent 2. The $R_{F}$ values for the principal spots in the chromatogram of the Test solution correspond to those of the Standard solutions.

B: The retention times of the major peaks in the chromatogram of the Assay preparation correspond to those in the chromatogram of the Standard preparation, as obtained in the Assay.

Dissolution $\langle 711\rangle$ - [To come].
Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

Limit of dihydrocodeine bitartrate, hydrocodone diol, and related substances-

Ion-pair solution-Prepare 0.005 M sodium 1-octanesulfonate, and adjust with glacial acetic acid to a pH of $2.5 \pm 0.1$.

Mobile phase-Prepare a filtered and degassed mixture of Ion-pair solution and methanol (6:4). Add 0.5 mL of triethylamine per liter. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve about 2 mg each of hydrocodone diol and USP Dihydrocodeine Bitartrate RS in 35 mL of Mobile phase in a $100-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume. Dilute this solution quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of each of about $0.1 \mu \mathrm{~g}$ per mL .

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.67 for hydrocodone diol, 0.75 for dihydrocodeine bitartrate, and 1.0 for hydrocodone bitartrate; the resolution, $R$, between hydrocodone diol and dihydrocodeine bitartrate is not less than 2.0 ; and the relative standard deviation for replicate injections of each of these compounds is not more than $5.0 \%$.

Procedure-Separately inject equal volumes (about 200 $\mu \mathrm{L}$ ) of the Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentages of hydrocodone diol and dihydrocodeine bitartrate in the portion of Tablets taken by the formula:

$$
100\left(r_{D} / r_{S}\right)
$$

in which $r_{D}$ is the individual peak response of either hydrocodone diol or dihydrocodeine in the chromatogram obtained from the Test solution; and $r_{s}$ is the peak response of hydrocodone bitartrate in the chromatogram obtained from the Standard solution: not more than $0.5 \%$ of hydro-
codone diol is found, and not more than $1.0 \%$ of dihydrocodeine bitartrate is found. Calculate the percentage of each other related substance in the portion of Tablets taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for any individual related substance with a retention time greater than 5 minutes; and $r_{s}$ is the sum of the responses of all the peaks: not more than $0.5 \%$ of any individual related substance is found. The sum of all impurities is not more than $1.5 \%$.

Limit of homatropine hydrobromide and related sub-stances-

Buffer solution-Prepare a solution of 0.005 M dibasic potassium phosphate, and adjust with phosphoric acid to a pH of $6.4 \pm 0.1$.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (17:3). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Standard solution-Dissolve an accurately weighed quantity of homatropine hydrobromide in Mobile phase, and dilute quantitatively with Mobile phase to obtain a solution having a known concentration of about $0.6 \mu \mathrm{~g}$ per mL .

Test solution-Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $5.0 \%$.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the
peak responses. Calculate the percentage of homatropine hydrobromide in the portion of Tablets taken by the formula:

$$
100\left(r_{H} / r_{S}\right)
$$

in which $r_{H}$ is the individual peak response of homatropine hydrobromide in the chromatogram obtained from the Test solution; and $r_{s}$ is the peak response for homatropine methylbromide in the chromatogram obtained from the Standard solution: not more than $0.5 \%$ of homatropine hydrobromide is found. Calculate the percentage of each other related substance in the portion of Tablets taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for any individual related substance with a relative retention time less than 0.44 in relation to the retention time of hydrocodone bitartrate; and $r_{s}$ is the sum of the responses of all the peaks: not more than $0.5 \%$ of any individual related substance is found. The sum of all impurities is not more than $1.5 \%$.

## Limit of tropine-

Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic silica gel.

Diluent: diethyl ether.
Test solution: Finely powder 25 Tablets, and add to a centrifuge tube. Pipet 5.0 mL of diethyl ether into the centrifuge tube, mix on a vortex mixer for 5 minutes, centrifuge, and use the supernatant.

Standard stock solution-Dissolve an accurately weighed quantity of tropine in Diluent, and dilute quantitatively with Diluent to obtain a solution having a known concentration of about $150 \mu \mathrm{~g}$ per mL .

Stock solutions-Transfer 5.0 mL of the Standard stock solution to a $10-\mathrm{mL}$ volumetric flask, and dilute with Diluent to volume quantitatively, and stepwise if necessary, to obtain Standard solutions $A, B, C$, and $D$ having known concentrations of about $75 \mu \mathrm{~g}$ per $\mathrm{mL}, 37.5 \mu \mathrm{~g}$ per $\mathrm{mL}, 18.75$ $\mu \mathrm{g}$ per mL , and $9.38 \mu \mathrm{~g}$ per mL , respectively.

Spray reagent-Dissolve 300 mg of platinic acid in 3 mL of diluted hydrochloric acid, add 97 mL of water and 100 mL of $6 \%$ potassium iodide in water, and mix.

Developing solvent system: a mixture of alcohol and ammonium hydroxide (400:100).

Procedure-Apply equal volumes (about $500 \mu \mathrm{~L}$ ) of the Standard stock solution, Standard solutions A, B, C, and D, and the Test solution to a thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ), and proceed as directed in the chapter. After the plate has dried, position it in a chamber saturated with iodine vapor for about 30 minutes, then place it in a hood to allow the iodine to sublime from the plate, and spray the plate with Spray reagent until spots appear. Any spot from the Test solution occurring at an $R_{F}$ value corresponding to tropine is not greater in size or intensity than the corresponding spot obtained from Standard solution B $(0.5 \%)$ : not more than $0.5 \%$ of tropine is found.

Assay-
Buffer solution-Prepare a solution of 0.005 M dibasic potassium phosphate, and adjust with phosphoric acid to a pH of $6.4 \pm 0.01$.
Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (17:3).

Standard preparation-Dissolve an accurately weighed quantity of USP Hydrocodone Bitartrate RS and USP Homatropine Methylbromide RS in Mobile phase, and dilute quantitatively with Mobile phase to obtain a solution having known concentrations of about 0.2 mg per mL and 0.06 mg per mL , respectively.

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg of hydrocodone bitartrate and about 1.5 mg of homatropine methylbromide, to a $25-\mathrm{mL}$ volumetric flask. Pipet 15 mL of the Mobile phase into the volumetric flask, sonicate for 15 minutes, and then shake with a wrist-action shaker for 15 additional minutes. Pipet an additional 10 mL of Mobile phase into the volumetric flask, and mix well. Pass the solution through a filter having a $0.45-\mu \mathrm{m}$ porosity prior to injection into the chromatograph.
Chromatographic system-The liquid chromatograph is equipped with a $230-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.44 for homatropine methylbromide and 1.0 for hydrocodone bitatrate; the resolution, $R$, between hydrocodone bitartrate and homatropine methylbromide is not less than 2.5 ; and the relative standard deviation for replicate injections is not more than 3.0\% for each analyte.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the amount, in mg , of homatropine methylbromide $\left(\mathrm{C}_{17} \mathrm{H}_{24} \mathrm{BrNO}_{3}\right)$ in the portion of Tablets taken by the formula:

$$
\left(L C_{S} / C_{U}\right)\left(r_{U} / r_{s}\right)
$$

in which $L$ is the labeled quantity, in mg , of homatropine methylbromide in each Tablet; $C_{s}$ is the concentration, in mg per mL , of USP Homatropine Methylbromide RS in the Standard preparation; $C_{U}$ is the concentration, in mg per mL , of homatropine methylbromide in the Assay pre-
paration, based on the labeled amount per Tablet and the extent of dilution; and $r_{U}$ and $r_{S}$ are the homatropine methylbromide peak responses obtained from the Assay preparation and the Standard preparation, respectively. Calculate the amount, in mg, of hydrocodone bitartrate disesquihydrate $\left(\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{3} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6} \cdot 2^{1 / 2} \mathrm{H}_{2} \mathrm{O}\right)$ in the portion of Tablets taken by the formula:

$$
(494.50 / 449.46)\left(L C_{S} / C_{U}\right)\left(r_{U} / r_{S}\right)
$$

in which 494.50 and 449.46 are the molecular weights of hydrocodone bitartrate disesquihydrate and anhydrous hydrocodone bitartrate, respectively; $L$ is the labeled amount, in mg , of hydrocodone bitartrate disesquihydrate in each Tablet; $C_{S}$ is the concentration, in mg per mL, of USP Hydrocodone Bitartrate RS in the Standard preparation; $C_{U}$ is the concentration, in mg per mL , of hydrocodone bitartrate disesquihydrate in the Assay preparation, based on the labeled amount per Tablet and the extent of dilution; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## Briefing

Hyoscyamine Sulfate Elixir, USP 27 page 949. It is proposed to replace the current gas chromatographic procedure in the Assay with a stability-indicating liquid chromatographic procedure. The liquid chromatographic procedure is based on analyses performed with the Phenomenex Synergi Polar RP brand of L11. The typical retention time for hyoscyamine is about 12 minutes.
(PA4: E. Gonikberg) RTS-40539-1

## Change to read:

Assay-
Internal stadtard solution Dissolve about 25 mg of hematropine hydrobromide in water containe in a 50 mL volumetrie flask, add water to volume, and mix. Prepare fresh daily.

Standard preparation- Dissolve about 10 mg of USP Hyoseynmine Sulfate $R S$, necurately weighed, in water contrined in a 100 mL volumetric flask, add water to volume, and mix. Prepare fresh daily. Pipet 5 mL of this solution into a separator, add 2.0 mL of Internal staderd soltion, and adjust with 6 N mmmonium hydre*ide to a pH of 9 . Extract with three 10 mL pertions of methylene ehloride, filter the methylene chloride extracts through 1 g of anhy drous sodium sulfate supperted by a small cotton plug in a funmel into a suitable container, anderaporate on a steam bath with the aid ef acurrent of air to dryness. Do not heat past drymess. Dissolve the residue in 2.0 mL of methylene chloride.
Assay preparation-Transfer an aceurately measured volume of Elixir, equivalent to about 0.5 mg of hyoseyamine sulfate, to a-se parator containing 5 mL of water, add 5 mL of 1 N sulfuric acid, and extract with a 25 mL pertion of methylene chloride, disearding the extract. Add 2.0 mL of Internal standard solution. Proceed as directed under Stan preparation, beginning with " adjust with 6 N ammenitm hydroxide to a pH of 9 ."

Chromatographic system Under typical conditions, the gas ehromatograph contains a $1.8 \mathrm{~m} \times 2 \mathrm{~mm}$ glass colmmm packed with $3 \%$ liquid phase $G 3$ on- suppert S1AB, conditioned as directed (see-Chromagraphy (624)). Maintain the colmman at $225^{\circ}$, and use nitrogen as the earrier gac.

Syistem suitability Chremategraph a sufficient number of injec tions of the Standard preparation, and record peak areas as directed under Predure. The analytienl-system is suitable for eenducting this assay if the relative standard deviation for the ratio of the peak areas not $2.0 \%$, the resolution factor is not less than 4.0 , and the tailing factor does not exeed 2.0 .

Proedtre Inject appropriate pertions of the Assaly preparation and the Standad preparation suceessively into the gas chromatograph. Measure the areas under the peaks for hyoseyamine and homatropine in each chromatogram. Caleulate the ratio, $R_{t}$, of the area of the hyoseymmine peak to the area of the internal standard peak in the chromatogram from the Assay, and similarly caleulate the ratio $R_{s}$, in the ehromatogram from the Standard preparation. Ealeulate the quantity, in me, of $\left(\mathrm{C}_{42} \mathrm{H}_{23} \mathrm{NO}_{2}\right)_{2}-\mathrm{H}_{2} \mathrm{SO}_{4} \cdot \mathrm{IH}_{2} \mathrm{O}$ in each mL of the Elixir taken by the formula:

$$
0.05(1.053)(H / H)\left(R_{+}+R_{s}\right),
$$

in which 1.053 is the ratio of the molecular weight of hydrated hyoseyamine-sulfate to that of anhydrous hyoseyamine-sulfate, H- is the weight, in mg, of USP Hyoseyamine-Sulfate-RS taken for the Staded prepariation, and Vis the volume, in mb, of Elixir taken.

- Diluent-Use 0.01 N hydrochloric acid.

Buffer solution-Transfer 13.6 g of monobasic potassium phosphate to a $2000-\mathrm{mL}$ volumetric flask, dissolve in about 1800 mL of water, adjust with phosphoric acid to a pH of $3.0 \pm 0.1$, dilute with water to volume, mix, and filter.

Mobile phase-Prepare a degassed mixture containing
Buffer solution and methanol (75:25).

Standard stock preparation-Dissolve an accurately weighed quantity of USP Hyoscyamine Sulfate RS in Diluent to obtain a solution having a concentration of about 0.16 mg of anhydrous hyoscyamine sulfate per mL. [NOTE-This solution may be stored in a refrigerator for 30 days.]

Standard preparation-Transfer 3.0 mL of the Standard stock preparation into a $100-\mathrm{mL}$ volumetric flask, dilute to volume with Diluent, and mix. Calculate the concentration, $C$, in mg per mL , of anhydrous hyoscyamine sulfate in this solution.

Tropic acid solution-Dissolve an accurately weighed quantity of tropic acid in Diluent to obtain a solution having a concentration of about $4 \mu \mathrm{~g}$ of tropic acid per mL .

System suitability preparation-Transfer 3.0 mL of the Standard stock preparation into a $100-\mathrm{mL}$ volumetric flask, add 4.0 mL of the Tropic acid solution, dilute to volume with Diluent, and mix.

Assay preparation-Transfer an accurately measured volume of Elixir, equivalent to about 0.25 mg of hyoscyamine sulfate, to a $50-\mathrm{mL}$ volumetric flask; dilute with Diluent to volume; and mix. Pass an aliquot through a $0.45-\mu \mathrm{m}$ filter, discarding the first 5 mL of filtrate.

Chromatographic system-The liquid chromatograph is equipped with a $205-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $4-\mu \mathrm{m}$ packing L11 and a $3-\mathrm{mm} \times$ 4-mm guard column that contains packing L11. The flow rate is about 1.0 mL per minute. The column temperature is maintained at $30^{\circ}$. Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the elution order is tropic acid peak, followed by hyoscyamine peak; the resolution, $R$, between the tropic acid and hyoscyamine peaks is not less than 1.5 ; the tailing factor for the hyoscyamine peak is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L})$ of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg, of $\left(\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{NO}_{3}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4} \cdot 2 \mathrm{H}_{2} \mathrm{O}$ in each mL of the Elixir taken by the formula:

$$
50 \times 1.053 \times(C / V)\left(r_{U} / r_{S}\right)
$$

in which 1.053 is the ratio of the molecular weight of hydrated hyoscyamine sulfate to that of anhydrous hyoscyamine sulfate; $C$ is as defined under Standard preparation; $V$ is the volume, in mL , of the Elixir taken; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Hyoscyamine Sulfate Injection, USP 27 page 950; Hyoscyamine Sulfate Oral Solution, USP 27 page 950 and page 1904 of PF 29(6) [Nov.-Dec 2003]; Hyoscyamine Sulfate Tablets, USP 27 page 951 . It is proposed to replace the current gas chromatographic procedure in the Assay with a stability-indicating liquid chromatographic procedure. The liquid chromatographic procedure is based on analyses performed with the Phenomenex Synergi Polar RP brand of L11. The typical retention time for hyoscyamine is about 15 minutes.
(PA4: E. Gonikberg) RTS-40539-2

## Change to read:

Assay-
Internal standerd solution Dissolve about 25 mg of hematropine hydrebremide in water eontained in a 50 mL volumetrie flask, add water to volume, and mix. Prepare fresh daily.
Standard prepparation-Dissolve about 10 mg of USP Hyoseya mine-Sulfate PS, aceurately weighed, in water contained in a 100 mL volumetric flask, add water to volume, and mix. Prepare fresh daily. Pipet 10 mL of this solution into a separator, add 2.0 mL of Imternal standard solution, and adjust with 6 N ammonium hydrovide to a pH -f 9 . Extract with three 10 mL portions of methylene
ehloride, filter the methylene chloride extracts through $1 . g$ of anhy drous soditm sulfate supported by a small cotton plug in a funnel into curitable container, and everorate on a steam bath with the aid ef aceurrent of air to dryness. Do not heat past drymess. Dissolve the residue in 2.0 mL of methylene chloride.

Assay preparation- Transfer an aceurately measured volume of Injection, equivalent to about 1.0 mg of hyoseyamine sulfate, to a separator containing 5 mL of water, and add 2.0 mL of Internat standard solution. Proceed as directed under Standard preparation, beginning with "adjust with 6 N ammenium hydrexide to a pHof 9 ."

Chromatographic syistem-Under typieal conditions, the gas ehromatograph contains a $1.8 \mathrm{~m} \rightarrow 2 \mathrm{~mm}$ glass columm packed with $3 \%$ liquid phase G 3 on suppert S1AB, cenditioned directed (see-Chremagraphy (624)). Maintain the collumn at $225^{\circ}$, and use nitrogen as the carrier ges.

Syistem suitability Chromatograph a sufficient number of injec tions of the Standard preparation, and record peak areas as diree ted under Produre. The analytieal-system is suitable-for eonducting this assay if the relative standard deviation for the ratio of the peak areas does not $2.0 \%$, the resolution factor is not tess than 4.0 , and the tailing factor does not exeeed 2.0 .

Procedure Inject appropriate pertions of the Assaly preparation and the Standed preparation successively into the gas chromatograph. Mearure the areas under the peaks for hyoseyamine and homatropine in each chromatogram. Caleulate the ratio, $R_{t}$, of the are of the hyoseymmine peak to the area of the intemal- standard peak in the chromatogram from the Assay preparation, and simi tarly ealeulate the ratio $R_{s}$, in the ehromatogram from the Standed preparation. Caleulate the quantity, in me, of $\left(\mathrm{C}_{12} \mathrm{H}_{22} \mathrm{NO}_{2}\right)_{2} \cdots \mathrm{H}_{2}$ $\mathrm{SO}_{4}-2 \mathrm{H}_{3} \mathrm{O}$ in each mL of the Injection taken by the formula:-

$$
\theta .1(1.053)(H / H)\left(R_{4}+R_{s}\right)
$$

in which 1.053 is the ratio of the molecular weight of hydrated hyoseyamine-sulfate to that of anhydreus hyoseyamine sulfate, $W$ is the weight, in mg, of USP Hyoseyamine Sulfate RS taken for the Standerd preparation, and $V$ is the volume, in mL , of Injec tion taken.

## - Diluent-Use 0.01 N hydrochloric acid.

Buffer solution-Transfer 13.6 g of monobasic potassium phosphate to a $2000-\mathrm{mL}$ volumetric flask, dissolve in about 1800 mL of water, adjust with phosphoric acid to a pH of $3.0 \pm 0.1$, dilute with water to volume, mix, and filter.

Mobile phase-With continuous stirring, add 0.3 mL of triethylamine to 1800 mL of the Buffer solution. Add 200 mL of acetonitrile, mix well, and degas.

Standard stock preparation-Dissolve an accurately weighed quantity of USP Hyoscyamine Sulfate RS in Diluent to obtain a solution having a concentration of about 0.16 mg of anhydrous hyoscyamine sulfate per mL . [NOTE-This solution may be stored in a refrigerator for 30 days.]

Standard preparation-Transfer 3.0 mL of the Standard stock preparation into a $100-\mathrm{mL}$ volumetric flask, dilute to volume with Diluent, and mix. Calculate the concentration, $C$, in mg per mL , of anhydrous hyoscyamine sulfate in this solution.
Assay preparation-Transfer an accurately measured volume of Injection, equivalent to about 1.0 mg of hyoscyamine sulfate, to a $200-\mathrm{mL}$ volumetric flask; dilute with Diluent to volume; and mix. Pass an aliquot through a $0.45-\mu \mathrm{m}$ filter, discarding the first 5 mL of filtrate.
Chromatographic system-The liquid chromatograph is equipped with a $205-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $4-\mu \mathrm{m}$ packing L11 and a $3-\mathrm{mm} \times$ $4-\mathrm{mm}$ guard column that contains packing L11. The flow rate is about 1.0 mL per minute. The column temperature is maintained at $30^{\circ}$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 1.8 , and the relative standard deviation for six replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg, of $\left(\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{NO}_{3}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4} \cdot 2 \mathrm{H}_{2} \mathrm{O}$ in each mL of Injection taken by the formula:

$$
100 \times 1.053 \times(C / V)\left(r_{U} / r_{S}\right)
$$

in which 1.053 is the ratio of the molecular weight of hydrated hyoscyamine sulfate to that of anhydrous hyoscyamine sulfate; $C$ is as defined under Standard preparation; $V$ is the volume, in mL , of Injection taken; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Hyoscyamine Sulfate Oral Solution, USP 27 page 950 and page 1904 of $P F$ 29(6) [Nov.-Dec. 2003]-See briefing under Hyoscyamine Sulfate Injection.
(PA4: E. Gonikberg) RTS-40539-3

## Add the following:

- Uniformity of dosage units $\langle 905\rangle$ -

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAIN-
ERS: meets the requirements.■2S (USP27)

## Add the following:

-Deliverable volume $\langle 698\rangle$ -
FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements.■2S (USP27)

## Change to read:

## Assay-

Internal stander solution Dissolve about 25 mg of hematropine hydrobromide in water contained in a 50 mL volumetrie flask, add water to volume, and mix. Prepare fresh daily.

Standard preparation Dissolve about 10 mg of USP Hyoseya mine Sulfate PS , aceurately weighed, in water contained in a 100 mL volumetric flask, add water to volume, and mix. Prepare fresh daily. Pipet 10 mL of this solution into a separater, add 2.0 mL of finternal standard solution, and adjust with 6 N ammonimm hydrovide to a pH of 9 . Extract with three 15 mL pertions of methylene ehloride, filter the methylene ehleride extracts through 1 g of anhy drous sodium sulfate supported by a small cotton plug in a fanmel into a suitable container, and evaporate on steam bath with the aid of acurrent of air to dryness. Do not heat past drymess. Dissolve the residue in 2.0 mL of methylene chloride.

Assefy preparation. Transfer an aceurately measured volume of Oral-Solution, equivalent to about 1.0 mg of hyoseyamine-sulfate, to a separator containimg 5 mL of water, add 5 mL of 1 N sulftrie acid, and extract with a 25 mL pertion of methylene chloride, dis earding the extract. Add 2.0 mL of Internal standard solution. Proeeed as directed under Standerd preparation, beginning with "adjust with 6 N ammonimm hydroxide to a pH of 9 ."

Chromatographie syistem-Under ypieal cenditions, the gas ehromagraph contains a $1.8 \mathrm{~mm} \times 2 \mathrm{~mm}$ glass columm packed with 3\% liquid phase 63 on support S1AB, conditioned as directed (see-Chremagraph (624)). Maintain the collumn at $225^{\circ}$, and tuse nitrogen as the carrier gas.

System suitability Chromatograph a sufficient number of injec tioms of the Standurd preparation, and record peak areas as direc ted under Procdure. The analytieal system is suitable-for eondueting this assay if the relative standard deviation for the ratio of the peak areas does not $2.0 \%$, the reselution factor is not less than 4.0 , and the tailing factor does not exeed 2.0 .

Procedure Inject appropriate pertions of the Assay preparation and the Standard preparationsuccessively into the gas chromatograph. Measure the areas under the peaks for hyoscyamine and homatropine in each chromatogram. Caleulate the ratio, $R_{t}$, of the are of the hyoseymmine peak to the are of the internal- standard peak in the chromatogram from the Assay preparation, and simitarly ealeulate the ratio, $R_{s}$, in the ehromategram from the Staded preparation. Caleulate the quantity, in me, of $\left(\mathrm{C}_{12} \mathrm{H}_{23} \mathrm{NO}_{2}\right)_{2}-\mathrm{H}_{2}$ $\mathrm{SO}_{4} \cdot 2 \mathrm{H}_{2} \mathrm{O}$ in each mL of the Oral Solution taken by the formmla:

$$
0.1(1.053)(H /)\left(R_{L}+R_{s}\right),
$$

in which 1.053 is the ratio of the molecular weight of hy drated hyoscyamine sulfate to that of anhydrous hyoseyamine sulfate, $W$ is the weight, in mg, of USP Hyoscyamine Sulfate RS taken for the Standard prepatration, and $V$ is the volume, in mb , of $\Theta \mathrm{rat}$ Solution taken.
-Diluent, Mobile phase, Standard preparation, and Chromatographic system—Proceed as directed in the Assay under Hyoscyamine Sulfate Injection.

Assay preparation-Transfer an accurately measured volume of Oral Solution, equivalent to about 0.5 mg of hyoscyamine sulfate, to a $100-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix. Pass an aliquot through a 0.45$\mu \mathrm{m}$ filter, discarding the first 5 mL of filtrate.

Procedure-Separately inject equal volumes (about 50
$\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg, of $\left(\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{NO}_{3}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4} \cdot 2 \mathrm{H}_{2} \mathrm{O}$ in each mL of Oral Solution taken by the formula:

$$
100 \times 1.053 \times(C / V)\left(r_{U} / r_{S}\right)
$$

in which 1.053 is the ratio of the molecular weight of hydrated hyoscyamine sulfate to that of anhydrous hyoscyamine sulfate; $C$ is defined under Standard preparation; $V$ is the volume, in mL , of Oral Solution taken; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

Briefing

Hyoscyamine Sulfate Tablets, USP 27 page 951—See briefing under Hyoscyamine Sulfate Injection.
(PA4: E. Gonikberg) RTS-40539-4

## Change to read:

## Assay-

pH 9.0 buffer Dissolve 34.8 g of dibasic petassium phesphate in 900 mL of water, and adjust to a pH Of 9.0 , determined electrometrieally, by the addition of 3 N hydrochlerie acid or 1 N sodimm hydroxide, as neeessary, with mixing.

Imternal standard solution- Dissolve about 25 mg of homatropine hydrobremide, aceurately weighed, in water contained in a 50 mL volumetrie flack, add water to volume, and mix. Prepare fresh daily.

Standard preparation- Dissolve about 10 mg of USP Hyoseya mine Sulfate RS, cuecurately weighed, in water contained in a 100 ml volumetrie flack, add water to volume, and mix. Prepare fresh daily. Pipet 10.0 mL of this solution inte a separator, add 2.0 mL of Internal steded soltion 5.0 mL of $p H 9.0-\mathrm{buffer}$, and adjust with 1 N sodium hydroxide to a pH 0 f 9.0 . Extract with 10 mL pertions of methylene chloride, filter the methylene chloride extracts through 1 g of anhydrous sodium-sulfate-supported by a small cetten plus in a fumnel into a 50 mL beaker, and evaperate under nitrogen to dryness. Dissolve the residue in 2.0 mL of methylene chloride.

Assay preparation Weigh and finely powder not less than-20 Fablets. Transfer an aceurately weighed portion of the powder, equivalent to about 1.0 mg of hyoseyamine sulfate, to a-separator eontaining 5 mL of $p H-9.0$ buffer, and add, by pipet, 2.0 mL of faternal standard solution. Proceed as directed under Standard preparation, beginning with "'adjust with-1 N sodium hydroxide - pH of 9.0.י

Chrematographie rystem- Under ypieal conditions, the instrut ment contains a $1.8 \mathrm{~mm} \times 2 \mathrm{~mm}$ glass columm packed with $3 \% \mathrm{G} 3$ on S1AB, conditioned as direeted (see-Chromatography $\langle 624$ ). Maintain the column at $225^{\circ}$, and use nitrogen as the carrier gas at a flow rate of 25 mL per minute.

System sutitability Chromatograph six to ten injections of the Stand preparation, and reeord penk areas as directed mader Proedure. The analytienl system is suitable for conducting this assay if the relative standard deviation for the ratio of the peak areas does not exeed $2.0 \%$, the resolution factor is not less than 4.0 , and the tailing factor does not exceed 2.0 .

Precedure Inject $1 \mu \mathrm{~L}$ pertions of the Assay preparation and the Standard preparation successively int the gas chromatograph. Measure the areas under the peaks for hyoseyamine sulfate and he matropine hydrobremide in each ehrematogram. Caleulate the ratio, $A_{t}$, of the are of the hyoseyamine-sulfate peak to the area of the internal standard peak in the chromatogram frem the Assay pre paration, and similarly caleulate the ratio, $A_{s}$, in the chromatogram from the Standard preparation. Caleulate the quantity, in mg, of $\left(\mathrm{C}_{4} \mathrm{H}_{22} \mathrm{NO}_{3}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4} \cdot 2 \mathrm{H}_{2} \mathrm{O}$ in the pertion of Tablets taken by the formma:-

$$
1.053(W / 10)\left(A_{t}+A_{s}\right),
$$

in which 1.053 is the ratio of the molecular weight of hydrated hyoseyamine sulfate that of anhydreus hyoseyamine-sulfate, and Wis the weight, in me, of USP Hyoseyamine Sulfate RS taken for the Standed preparation.
-Diluent, Buffer solution, Mobile phase, Standard stock preparation, and Standard preparation-Proceed as directed in the Assay under Hyoscyamine Sulfate Injection.

Tropic acid solution-Dissolve an accurately weighed quantity of tropic acid in Diluent to obtain a solution having a concentration of about $3 \mu \mathrm{~g}$ of tropic acid per mL.
System suitability preparation-Transfer 3.0 mL of the Standard stock preparation into a $100-\mathrm{mL}$ volumetric flask, add 4.0 mL of the Tropic acid solution, dilute to volume with Diluent, and mix.

Assay preparation-Weigh and finely powder not less than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 0.125 mg of hyoscyamine sulfate, to a $25-\mathrm{mL}$ volumetric flask. Add about 20 mL of the Diluent, and sonicate for 15 minutes with occasional swirling. Allow to cool to room temperature, dilute with Diluent to volume, and mix. Pass an aliquot through a $0.45-\mu \mathrm{m}$ filter, discarding the first 5 mL of filtrate.
Chromatographic system—The liquid chromatograph is equipped with a $205-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $4-\mu \mathrm{m}$ packing L11 and a $3-\mathrm{mm} \times$ $4-\mathrm{mm}$ guard column that contains packing L11. The flow rate is about 1.0 mL per minute. The column temperature is maintained at $30^{\circ}$. Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the elution order is tropic acid peak, followed by hyoscyamine peak; the resolution, $R$, between the tropic acid and hyoscyamine peaks is not less than 1.5 ; the tailing factor for the hyoscyamine peak is not more than 1.8 ; and the relative standard deviation for six replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and
measure the area responses for the major peaks. Calculate the quantity, in mg, of $\left(\mathrm{C}_{17} \mathrm{H}_{23} \mathrm{NO}_{3}\right)_{2} \cdot \mathrm{H}_{2} \mathrm{SO}_{4} \cdot 2 \mathrm{H}_{2} \mathrm{O}$ in the portion of Tablets taken by the formula:

$$
25 \times 1.053 \times C\left(r_{U} / r_{s}\right)
$$

in which 1.053 is the ratio of the molecular weight of hydrated hyoscyamine sulfate to that of anhydrous hyoscyamine sulfate; $C$ is as defined under Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

Assay preparation-Dilute an accurately measured volume of Ophthalmic Solution quantitatively with water to obtain a solution having an equivalent concentration of about $100 \mu \mathrm{~g}$ of hypromellose per mL .

Procedure-Pipet 2 mL each of the Standard preparation, the Assay preparation, and water to provide a blank, into separate, glass-stoppered test tubes. To each tube add 5.0 mL of diphenylamine solution (prepared by dissolving 3.75 g of colorless diphenylamine crystals in 150 mL of glacial acetic acid and diluting the solution with 90 mL of hydrochloric acid), mix, and immediately insert the tubes into an oil bath at $105^{\circ}$ to $110^{\circ}$ for 30 minutes, the temperature being kept uniform within $0.1^{\circ}$ during heating. Remove the tubes, and place them in an ice-water bath for 10 minutes or until thoroughly cool. At room temperature and using a suitable spectrophotometer, concomitantly determine the absorbances of the solutions from the Standard preparation and the Assay preparation at 635 nm , using the water solution as the blank. Calculate the quantity, in mg, of hypromellose in each mL of the Ophthalmic Solution taken by the formula:

$$
0.001 C(d / V)\left(A_{U} / A_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Hydroxy propyl Methyleellulose RS
-USP Hypromellose $\mathrm{RS}_{\text {■1S (USP28) }}$
in the Standard preparation;' $V$ is the volume, in mL , of Ophthalmic Solution taken; $d$ is the dilution factor of $V$ used to obtain the Assay preparation; and $A_{U}$ and $A_{S}$ are the absorbances of the solutions from the Assay preparation and the Standard preparation, respectively.

## Briefing

Hypromellose Ophthalmic Solution, USP 27 page 952. In accordance with the implemented name change of the Reference Standard, from USP Hydroxypropyl Methylcellulose RS to USP Hypromellose RS, it is proposed to make the corresponding change in the USP Reference standard $\langle 11\rangle$ section and in the Assay. This is consistent with the change to the compendial name, Hypromellose, official on September 1, 2002.
(EMC: C. Sheehan) RTS-40937-1

## Change to read:

USP Reference standards $\langle 11\rangle$-USP Hy hatere RS.

- USP Hypromellose RS.■ (USP28)


## Change to read:

```
Assay-
    Standard preparation --Dissolve a suitable quantity of USP Hy
droxypropyl Methyleellulose RS
```

- USP Hypromellose RS, ${ }_{\text {1S (USP28) }}$
accurately weighed, in water, and dilute quantitatively with water to obtain a solution having a known concentration of about $100 \mu \mathrm{~g}$ per mL .


## Briefing

Indinavir Sulfate. This new monograph replaces the monograph that was published on page 2165 of $P F 27(2)$ [Mar.-Apr. 2001] and subsequently canceled. On the basis of information received from the sponsor, the specifications were further clarified to be consistent with the validation method.
(PA7b: B. Davani) RTS-41029-1

## Add the following:

## ■Indinavir Sulfate

$\mathrm{C}_{36} \mathrm{H}_{47} \mathrm{~N}_{5} \mathrm{O}_{4} \cdot \mathrm{H}_{2} \mathrm{SO}_{4} \quad 711.87$
D-erythro-Pentonamide, 2,3,5-trideoxy- N -(2,3-dihydro-2hydroxy -1 H-inden-1-yl) -5- [2- [[(1,1-dimethylethyl) amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-, monohydrate, $[1(1 S, 2 R), 5(S)]$-, sulfate $(1: 1)$ (salt).
$(\alpha R, \gamma S, 2 S)$ - $\alpha$-Benzyl-2-(tert-butylcarbamoyl)- $\gamma$-hydroxy-$N$-[(1S,2R)-2-hydroxy-1-indanyl]-4-(3-pyridylmethyl)-1-piperazinevaleramide sulfate (1:1) (salt) [157810-81-6].
» Indinavir Sulfate contains not less than 98.5 percent and not more than 101.5 percent of $\mathrm{C}_{36} \mathrm{H}_{47} \mathrm{~N}_{5} \mathrm{O}_{4} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$, calculated on an anhydrous, solvent-free basis.

Packaging and storage-Preserve in tight containers, protected from moisture. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle — U S P$ Indinavir $R S$. USP Indinavir System Suitability RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$. The IR absorption spectrum exhibits maxima at about $3.0-3.1,5.9,6.2$, and $13.6 \mu \mathrm{~m}$.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $+122^{\circ}$ and $+129^{\circ}$, at 365 nm , determined on the anhydrous, solvent-free basis.

Test solution: 10 mg per mL , in water.
Water, Method $I\langle 921\rangle$ : not more than $1.5 \%$, using 0.25 g .

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method $I\langle 231\rangle: \quad 0.001 \%$.

## Chromatographic purity-

Solution A-Dissolve 0.54 g of monobasic potassium phosphate and 2.79 g of dibasic potassium phosphate in 2 L of water.

Solution B-Use acetonitrile.
Diluent-Prepare a mixture of Solution $A$ and Solution B (1:1).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
System suitability solution-Transfer about 40 mg of USP Indinavir System Suitability RS to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.

Test solution-Transfer about 50 mg of Indinavir Sulfate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time $\quad$ Solution A Solution B

| (minutes) | $(\%)$ | $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0-40$ | $80 \rightarrow 30$ | $20 \rightarrow 70$ | linear gradient |
| $40-45$ | 30 | 70 | isocratic |
| $45-47$ | $30 \rightarrow 80$ | $70 \rightarrow 20$ | linear gradient |
| $47-52$ | 80 | 20 | isocratic |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times, based on the indinavir peak at about 21 to 26 minutes, are listed in Table 1; the resolution, $R$, between indinavir and related compound C is greater than 1.8; and the tailing factor, determined from the indinavir peak, is greater than 0.95 and less than 2.0 .

Table 1

| Table 1 |  |
| :---: | :---: |
| Indinavir Related | Approximate Relative |
| Compound | Retention Time |
| A | 0.18 |
| B | 0.80 |
| C | 0.98 |
| D | 1.14 |
| E | 1.30 |

Procedure-Inject about $20 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Indinavar Sulfate taken by the formula:
in which $r_{i}$ is the peak area response for each impurity; and $r_{s}$ is the sum of the responses of all the peaks: not more than $0.1 \%$ of any individual impurity specified in Table 1 is found; and not more than $0.5 \%$ of total impurities is found.

## Content of alcohol-

Standard solution-Transfer 1.0 mL of dehydrated alcohol, at $20^{\circ}$, to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Dilute an accurately measured volume of the resulting solution quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.001 mL of alcohol per mL of solution.

Test solution-Transfer about 400 mg of Indinavir Sulfate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and a $0.53-\mathrm{mm} \times 30-\mathrm{m}$ capillary column coated with a $1.0-\mu \mathrm{m}$ film of phase G14. The carrier gas is helium, flowing at a rate of 10 mL per minute. The chromatograph is programmed as follows. The temperature of the column is maintained at $35^{\circ}$, the injection port temperature is maintained at $140^{\circ}$, and the detector temperature is maintained at $220^{\circ}$. At the end of each five-minute isothermal run, the oven temperature is increased to $200^{\circ}$ before adjusting the column temperature to $35^{\circ}$ for the next injection. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 0.1 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of

$$
100\left(r_{i} / r_{s}\right),
$$

alcohol, in mg, in the portion of Indinavir Sulfate taken by the formula:

$$
79,000\left(C_{S} / C_{U}\right)\left(r_{U} / r_{S}\right)
$$

in which $C_{S}$ is the concentration, in mL per mL , of dehydrated alcohol in the Standard solution; $C_{U}$ is the concentration, in mg per mL, of Indinavir Sulfate in the Test solution; and $r_{U}$ and $r_{s}$ are the peak areas for alcohol obtained from the Test solution and the Standard solution, respectively: between $5.0 \%$ and $8.0 \%$ is found. [NOTE-The value 79,000 $=$ conversion to percent $(100 \%) \times$ density of ethanol at $20^{\circ}$ ( $790 \mathrm{mg} / \mathrm{mL}$ ).]

## Content of sulfate-

Methanolic formaldehyde solution-Transfer 1000 mL of methanol to a suitable container, add $300 \mu \mathrm{~L}$ of formaldehyde, and mix.

Diluent-Prepare a mixture of Methanolic formaldehyde solution and water (50:50).

Test solution-Dissolve about 500 mg of Indinavir Sulfate, accurately weighed, in about 80 mL of Diluent.

Procedure-Titrate with 0.1 M lead perchlorate VS, determining the endpoint potentiometrically, using a lead-specific electrode in conjunction with a suitable reference electrode. Each mL of 0.1 M lead perchlorate VS is equivalent to 9.604 mg of sulfate: between $13.2 \%$ and $14.4 \%$ is found, calculated on the anhydrous and solvent-free basis.

## Assay-

Dibutylammonium phosphate buffer-Transfer 20 mL of dibutyl ammonium phosphate to 1000 mL of water. While stirring, adjust with sodium hydroxide TS to a pH of $6.5 \pm 0.05$.

Mobile phase-Prepare a filtered and degassed mixture of Dibutylammonium phosphate buffer and acetonitrile (11:9). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve a suitable quantity of USP Indinavir RS, accurately weighed, in Mobile phase to obtain a solution having a known concentration of about 0.5 mg per mL .

Assay preparation-Transfer about 60 mg of Indinavir Sulfate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $260-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The flow rate is about 1.0 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 4000 theoretical plates; the tailing factor is less than 2.0 ; and the relative standard deviation for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{36} \mathrm{H}_{47} \mathrm{~N}_{5} \mathrm{O}_{4} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ in the portion of Indinavir Sulfate taken by the formula:

$$
(1.1598) D C\left(r_{U} / r_{s}\right)
$$

in which $D$ is the dilution factor, in mL , for the Assay preparation; $C$ is the concentration, in mg per mL , of USP Indinavir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. [NOTE-1.1598 = Indinavir Sulfate MW ( $711.87 \mathrm{~g} / \mathrm{mol}$ )/Indinavir MW $(613.80 \mathrm{~g} / \mathrm{mol})]_{\mathbf{n}}{ }^{1 S}($ USP28)

## Briefing

Indomethacin Topical Gel, page 5808 of PF 24(2) [Mar.-Apr. 1998]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded with modifications to InProcess Revision.
(CRX: C. Okeke) RTS-41004-1

## Add the following:

## ■Indomethacin Topical Gel

» Indomethacin Topical Gel contains not less than 0.90 g and not more than 1.10 g of Indomethacin in 100 mL of gel. Prepare Indomethacin Topical Gel as follows:

Indomethacin. . . . . . . . . . . . . . . . $\quad 1.0 \mathrm{~g}$
Carbomer 941 . . . . . . . . . . . . . . . $\quad 2.0 \mathrm{~g}$
Purified Water . . . . . . . . . . . . . . . 10 mL
Alcohol (95\% ethyl alcohol) a
sufficient quantity, to make.... $\quad 100 \mathrm{~mL}$
Transfer the Indomethacin to a suitable beaker, and dissolve it in 55 mL of Alcohol. Transfer this solution to a glass mortar, and slowly add the Carbomer 941 so that it is thoroughly distributed. Press out any white lumps until a smooth gel is formed. Slowly add the Purified Water with mixing. Add a sufficient quantity of Alcohol to obtain a final volume of 100 mL , and mix. Transfer the Gel to a wide-mouth container or ointment jar.

Packaging and storage-Preserve in tight, light-resistant, wide-mouth containers or ointment jars. Store at controlled room temperature.

Labeling-Label it to state that it is for topical, external use only, that it should be used only as directed, and that the container should be kept tightly closed.

Beyond-use date-Thirty days after the day on which it was compounded.

Assay-[To come.] $]_{\text {1S (USP28) }}$

## BRIEFING

Ipecac, USP 27 page 1020. In the Assay for emetine and cephaeline, it is proposed to replace the name of the reagent methyl sulfoxide with its synonym dimethyl sulfoxide. The use of the name "dimethyl sulfoxide" is being standardized throughout the $U S P-N F$. In addition, minor editorial style changes have been made.
(BPC: M. Marques) RTS-41082-6

## Change to read:

## Assay for emetine and cephaeline-

Standard preparation-Weigh accurately a suitable quantity of USP Emetine Hydrochloride RS, and dissolve in 0.5 N sulfuric acid. Dilute quantitatively and stepwise with the same dilute sulfuric acid to obtain a solution having a known concentration equivalent to about $50 \mu \mathrm{~g}$ of emetine per mL .

Assay preparation-Prepare a Test Sample as directed in Methods of Analysis under Articles of Botanical Origin $\langle 561\rangle$. Transfer to a $150-\mathrm{mL}$ beaker about 200 mg , accurately weighed, of the fine powder. Add 2 mL of methyl sulfoxide,

- dimethyl sulfoxide, $\boldsymbol{m}_{1 S}$ (USP28)
mix with a flattened stirring rod to assure complete wetting of the powder, and allow to stand for about 30 minutes. Add 2 mL of water and about 1 g of sodium bicarbonate, and mix.

Phosphate buffer-Prepare approximately 0.5 M solutions of monobasic potassium phosphate (containing 5.1 g per 75 mL ) and dibasic potassium phosphate (containing 2.2 g per 25 mL ). Mix 3 volumes of 0.5 M monobasic potassium phosphate with 1 volume of 0.5 M dibasic potassium phosphate, and adjust by the addition of one or the other of the solutions to a pH of $6.0 \pm 0.05$. Dissolve 7.5 g of potassium chloride in 100 mL of the resulting solution.

Citric acid buffer-Prepare approximately 0.5 M solutions of sodium citrate (containing 6.5 g per 50 mL ) and citric acid (containing 4.8 g per 50 mL ). Mix equal volumes of these solutions, and adjust by addition of one or the other of the solutions to a pH of $4.0 \pm 0.05$.

Chromatographic columns-For each column, pack a pledget of fine glass wool in the base of a chromatographic tube (25-×200mm test tube to which is fused a $5-\mathrm{cm}$ length of $7-\mathrm{mm}$ tubing) with the aid of a tamping rod having a disk with a diameter about 1 mm less than that of the tube.

Prepare Column I as follows. To the Assay preparation add 6 g of purified siliceous earth, mix, transfer the mixture to the column, scrub the beaker with about 1 g of the purified siliceous earth, transfer this to the top of the column, and tamp. Prepare Column II using 3 g of the purified siliceous earth and 2 mL of Phosphate buffer; prepare Column III using 2 mL of Citric acid buffer and 3 g of the purified siliceous earth; and prepare Column IV using 2 mL of sodium hydroxide solution (1 in 50) and 3 g of the purified sili-ceous earth. Pack a pledget of glass wool on the top of each column.

Procedure-[NOTE-Use water-saturated solvents throughout this procedure. Rinse the tips of the chromatographic columns before discarding them.] Mount Columns I and II so that the effluent from Column I flows onto Column II. Pass three $50-\mathrm{mL}$ portions of ether through the columns, and discard Column $I$ and the eluate. Mount Column III below Column II and pass three $50-\mathrm{mL}$ portions of a mixture of 1 volume of ether and 3 volumes of chloroform through the columns. Discard Column II and the eluate. Wash Column III with 25 mL of the ether-chloroform mixture, followed by 25 mL of a mixture of equal volumes of ether and isooctane, and discard the washings. Wash Column $I V$ with 20 mL of a 1 in 50 solution of triethylamine in the ether-isooctane mixture, and discard the washing. Mount Column IV below Column III, and place as a receiver under Column IV a $125-\mathrm{mL}$ separator containing 15 mL of 4 N sulfuric acid. Pass through the columns 10 mL of a 1 in 5 solution of triethylamine in the ether-isooctane mixture, followed by three $10-\mathrm{mL}$ portions of a 1 in 50 solution of triethylamine in the ether-isooctane mixture. Discard Column III, and pass through Column IV 20 mL of the 1 in 50 solution of triethylamine in the ether-isooctane mixture. Shake the separator, allow the phases to separate, and transfer the aqueous extract to a $50-\mathrm{mL}$ volumetric flask. Extract with two additional $10-\mathrm{mL}$ portions of 0.5 N sulfuric acid, combining the extracts in the volumetric flask. Add 0.5 N sulfuric acid to volume, and mix (emetine solution).

Elute Column IV with 75 mL of chloroform, collecting the eluate in a $250-\mathrm{mL}$ separator containing 150 mL of ether. Discard Column IV. Extract with one $20-\mathrm{mL}$ and then with two $10-\mathrm{mL}$ portions of 0.5 N sulfuric acid, collecting the extracts in a $50-\mathrm{mL}$ volumetric flask. Rinse the stem of the separator, add the acid to volume, and mix (cephaeline solution).

Concomitantly determine the absorbances of the emetine solution, the cephaeline solution, and the Standard preparation in 1cm cells at the wavelength of maximum absorbance at about 283 nm and at 350 nm , with a suitable spectrophotometer, using 0.5 N sulfuric acid as the blank.

Calculate the quantity, in mg , of emetine in the portion of Ipecac taken by the formula:

$$
0.05 C\left(A_{283}-A_{350}\right)_{U} /\left(A_{283}-A_{350}\right)_{S}
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of emetine in the Standard preparation, and the parenthetic expressions are the differences in the absorbances of the solution of emetine from the $A s$ say preparation $(U)$ and the Standard preparation $(S)$, respectively, at the wavelengths indicated by the subscripts.

Calculate the quantity, in mg , of cephaeline in the portion of Ipecac taken by the formula:

$$
0.971(0.05 C)\left(A_{283}-A_{350}\right)_{U} /\left(A_{283}-A_{350}\right)_{S}
$$

in which 0.971 is the ratio of the molecular weight of cephaeline to that of emetine; $C$ is as defined above; and the parenthetic expres-
sions are the differences in the absorbances of the solution of cephaeline from the Assay preparation $(U)$ and the Standard preparation (S), respectively, at the wavelengths indicated by the subscripts.

## Briefing

Powdered Ipecac, USP 27 page 1021. In the Assay for emetine and cephaeline, it is proposed to replace the name of the reagent methyl sulfoxide with its synonym dimethyl sulfoxide. The use of the name "dimethyl sulfoxide" is being standardized throughout the $U S P-N F$. In addition, minor editorial style changes have been made.
(BPC: M. Marques) $\quad$ RTS-41082-5

## Change to read:

## Assay for emetine and cephaeline-

Standard preparation, Phosphate buffer, Citric acid buffer, and Chromatographic columns-Prepare as directed in the Assay for emetine and cephaeline under Ipecac.

Assay preparation-Transfer to a $150-\mathrm{mL}$ beaker about 200 mg , accurately weighed, of Powdered Ipecac. Add 2 mL of exide,

- dimethyl sulfoxide, ${ }^{1 / S}$ (USP28)
mix with a flattened stirring rod to ensure complete wetting of the powder, and allow to stand for about 30 minutes. Add 2 mL of water and about 1 g of sodium bicarbonate, and mix.

Procedure-Proceed as directed for Procedure in the Assay for emetine and cephaeline under Ipecac. Calculate the quantity, in mg , of emetine in the portion of Powdered Ipecac taken by the formula:

$$
0.05 C\left(A_{283}-A_{350}\right)_{U} /\left(A_{283}-A_{350}\right)_{S}
$$

in which the parenthetic expressions are the differences in the absorbances of the solution of emetine from the Assay preparation $(U)$ and the Standard preparation (S), respectively, at the wavelengths indicated by the subscripts; and $C$ is as defined for Procedure in the Assay for emetine and cephaeline under Ipecac. Calculate the quantity, in mg , of cephaeline in the portion of Powdered Ipecac taken by the formula:

$$
0.971(0.05 C)\left(A_{283}-A_{350}\right)_{U} /\left(A_{283}-A_{350}\right)_{S}
$$

in which 0.971 is the ratio of the molecular weight of cephaeline to that of emetine; the parenthetic expressions are the differences in the absorbances of the solution of cephaeline from the Assay preparation $(U)$ and the Standard preparation $(S)$, respectively, at the wavelengths indicated by the subscripts; and $C$ is as defined above.

## Briefing

Diluted Isosorbide Mononitrate, page 1509 of $P F$ 29(5) [Sept.-Oct. 2003]. It is proposed to revise the Definition to reflect its applicability to different formulations of the drug substance and to add a caution statement. Also, it is proposed to revise the test for Water to specify that Method Ic should be used.
(PA5: A. Wilk) RTS-40380-1; 40697-1

## Add the following:

## ■Diluted Isosorbide Mononitrate


$\mathrm{C}_{6} \mathrm{H}_{9} \mathrm{NO}_{6} \quad 191.14$
d-Glucitol, 1,4:3,6-dianhydro-, 5-nitrate.

$$
\text { 1,4:3,6-Dianhydro-D-glucitol 5-nitrate } \quad[16051-77-7] .
$$

» Diluted Isosorbide Mononitrate is a dry mixture of isosorbide mononitrate $\left(\mathrm{C}_{6} \mathrm{H}_{9} \mathrm{NO}_{6}\right)$ with lactose or other suitable excipients to permit safe handling. It contains not less than 87.5 percent and not mere than- 92.5 pereent (w/w) 95.0 percent and not more than 105.0 percent of the labeled amount of isosorbide mononitrate $\left(\mathrm{C}_{6} \mathrm{H}_{9} \mathrm{NO}_{6}\right)$.

Caution-Exercise proper precautions in handling undiluted isosorbide mononitrate, which is a powerful explosive and can be exploded by percussion or excessive heat. Only exceedingly small amounts should be isolated.

Packaging and storage-Preserve in tight containers. Store at a temperature between $20^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Diluted Isosorbide Dinitrate RS. USP Isosorbide RS. USP Isosorbide Mononitrate RS. USP Isosorbide Mononitrate Related Compound A RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.
$\mathbf{p H}\langle 791\rangle$ : between 4.8 and 6.5. To prepare the test solution, dissolve 5.6 g of Diluted Isosorbide Mononitrate in 50 mL of boiling water, sonicate for 5 minutes, and allow to cool to room temperature.

Water, Method Ic $\langle 921\rangle$ : between $0.4 \%$ and $0.8 \%$. Proceed as directed for hygroscopic materials. To 1.0 g of sample, accurately weighed, add 5 mL of methanol, shake for 30 minutes, and centrifuge at about 2500 rpm for 5 minutes. Use 1.0 mL of the resulting supernatant.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Caution-Material is explosive upon heating; digest the sample thoroughly before ignition.

Heavy metals, Method $I\langle 231\rangle$ : not more than $10 \mu \mathrm{~g}$ per $g$.

Organic volatile impurities, Method $I V\langle 467\rangle$ : meets the requirements.

## Related compounds-

TEST 1-
Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture.

Standard solution 1-Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with absolute alcohol to obtain a solution having a known concentration of about 0.0125 mg of isosorbide per mL .

Standard solution 2-Weigh accurately a quantity of USP Isosorbide RS , and dilute quantitatively, and stepwise if necessary, with absolute alcohol to obtain a solution having a known concentration of about 0.025 mg of isosorbide per mL .

Standard solution 3-Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with absolute alcohol to obtain a solution having a known concentration of about 0.05 mg of isosorbide per mL .

Test solution-Transfer a portion of Diluted Isosorbide Mononitrate, equivalent to about 200 mg of isosorbide mononitrate, accurately weighed, to a suitable container, add 20.0 mL of absolute alcohol, sonicate for 10 minutes, and then centrifuge. Use the supernatant.

Application volume: $20 \mu \mathrm{~L}$.
Developing solvent system: a mixture of absolute alcohol and toluene ( $8: 2$ ).

Procedure-Proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$. After developing, dry the plate with warm air for about 10 minutes, dip the plate in a solution prepared by dissolving 1.25 g of potassium permanganate and 10.0 g of sodium hydroxide in 500 mL of water (prepared fresh for each plate), and heat at $105^{\circ}$ for 5 minutes. Any spot in the chromatogram obtained from the Test solution and corresponding to the $R_{F}$ value of the spots obtained from the Standard solutions is not more intense than the spot in the chromatogram obtained from Standard solution 3: not more than $0.5 \%$ of any individual impurity is found. If the spot in the chromatogram obtained from the Test solution is nearly as intense as the
spot obtained from Standard solution 3, further dilute the Test solution ( $1: 1$ ) with absolute alcohol, repeat the test, and compare the intensity of the isosorbide spot in the diluted Test solution with the intensity of the spots obtained from the Standard solutions, correcting the percent level for the additional dilution of the Test solution.

TEST 2-
Mobile phase, Resolution solution, and Chromatographic system-Proceed as directed in the Assay.

Isosorbide mononitrate related compound A standard so-lution-Prepare as directed for Isosorbide mononitrate related compound A standard preparation in the Assay.

Isosorbide dinitrate standard stock solution-Dissolve an accurately weighed quantity of USP Diluted Isosorbide Dinitrate RS in methanol, sonicate and warm if necessary, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.125 mg of isosorbide dinitrate per mL .

Standard solution-Transfer a quantity of USP Isosorbide Mononitrate RS, accurately weighed, to a suitable volumetric flask. Dissolve in water, quantitatively add a volume of Isosorbide mononitrate related compound A standard solution and a volume of Isosorbide dinitrate standard stock solution, and dilute with water to volume to obtain a solution having a known concentration of about 2.0 mg of USP Isosorbide Mononitrate RS per $\mathrm{mL}, 0.005 \mathrm{mg}$ of isosorbide mononitrate related compound A per mL , and 0.005 mg of isosorbide dinitrate per mL . Filter a portion of the solution, discarding the first few mL of the filtrate.
Test solution-Use the Assay preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of iso-
sorbide mononitrate related compound A and isosorbide dinitrate relative to the amount of isosorbide mononitrate in the portion of Diluted Isosorbide Mononitrate taken by the formula:

$$
5556(C / W)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of the appropriate Reference Standard, USP Isosorbide Mononitrate Related Compound A RS or USP Diluted Isosorbide Dinitrate RS, in the Standard solution; $W$ is the weight, in mg, of Diluted Isosorbide Mononitrate used to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak areas of the corresponding components obtained from the Test solution and the Standard solution, respectively: not more than $0.25 \%$ of isosorbide mononitrate related compound A is found; and not more than $0.25 \%$ of isosorbide dinitrate is found. Calculate the percentage of each other impurity (other than isosorbide mononitrate related compound A or isosorbide dinitrate) in the portion of Diluted Isosorbide Mononitrate taken by the formula:

$$
100\left(r_{i} / r_{s}\right),
$$

in which $r_{i}$ is the peak area for each other impurity obtained from the Test solution; and $r_{s}$ is the sum of the areas of all the peaks: not more than $0.5 \%$ of total impurities is found including isosorbide mononitrate related compound A and isosorbide dinitrate; and not more than $0.5 \%$ of total impurities is found, the results for Test 1 and Test 2 being considered.

Assay-
Mobile phase-Prepare a filtered and degassed mixture of water and methanol ( $95: 5$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Transfer an accurately weighed quantity of USP Isosorbide Mononitrate RS to a suitable volumetric flask, dissolve in water, add a volume of methanol equivalent to $4 \%$ of the flask volume, and dilute with water to volume to obtain a solution having a known concentration of about 2.0 mg per mL .

Isosorbide mononitrate related compound A standard preparation-Dissolve an accurately weighed quantity of USP Isosorbide Mononitrate Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 1.0 mg per mL . Quantitatively dilute a portion of this solution with water to obtain a solution having a known concentration of about 0.05 mg per mL .
Resolution solution-Transfer 10.0 mL of Isosorbide mononitrate related compound A standard preparation, 1.0 mL of Standard preparation, and 4.0 mL of methanol to a $100-\mathrm{mL}$ volumetric flask, and dilute with water to volume. Filter a portion of the solution, discarding the first few mL of the filtrate.

Assay preparation-Transfer about 110 mg of Diluted Isosorbide Mononitrate, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in about 25 mL of water, add 2 mL of methanol, dilute with water to volume, and mix. Filter a portion of the solution, discarding the first few mL of the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 12.5-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute, increasing to 3.0 mL per minute at about 8.5 minutes to ensure that the isosorbide mononitrate peak has completely eluted. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.8 for isosorbide mononitrate related com-
pound A, 1.0 for isosorbide mononitrate, and 4.1 for isosorbide dinitrate; and the resolution, $R$, between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 2.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the isosorbide mononitrate peaks. Calculate the quantity, in mg , of isosorbide mononitrate $\left(\mathrm{C}_{6} \mathrm{H}_{9} \mathrm{NO}_{6}\right)$ in the portion of Diluted Isosorbide Mononitrate taken by the formula:

$$
50 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of isosorbide mononitrate in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Isosorbide Mononitrate Extended-Release Tablets, page 1515 of $P F 29(5)$ [Sept.-Oct. 2003]. It is proposed to make further revisions in the test for Related compounds and in the Assay.
(PA5: A. Wilk) RTS-40697-3

## Add the following:

## ■Isosorbide Mononitrate ExtendedRelease Tablets

» Isosorbide Mononitrate Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of isosorbide mononitrate $\left(\mathrm{C}_{6} \mathrm{H}_{9} \mathrm{NO}_{6}\right)$.

Packaging and storage-Preserve in tight containers. Store at a temperature between $20^{\circ}$ and $30^{\circ}$.

Labeling-[To come.]
USP Reference standards $\langle 11\rangle$ —USP Diluted Isosorbide Dinitrate RS. USP Isosorbide RS. USP Isosorbide Mononitrate RS. USP Isosorbide Mononitrate Related Compound A $R S$.

Identification-
A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$-Proceed as directed for Identification test $A$ under Isosorbide Mononitrate Tablets.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Drug release $\langle 724\rangle$ — [To come.]
Uniformity of dosage units $\langle 905\rangle$ : meet the requirements for Content Uniformity. Proceed as directed in the Assay, except to use one Tablet in place of the portion of powdered Tablets used in the Assay preparation.
Water, Method $+\langle 924\rangle$ : net mere than $5.0 \%$.

Fest solution Weigh and finely powder 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to one-Tablet, aceurately weighed, to a suitable eontainer. Add 5.0 mL of methanol, shake for 45 minutes, and then centrifuge at about 4000 rpm for 10 minutes. Use 0.25 mL of the resulting supernatant, correcting for the

## blank.

## Related compounds-

TEST 1—
Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture.

Standard solution 1-Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.0125 mg of isosorbide per mL.

Standard solution 2-Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.025 mg of isosorbide per mL .

Standard solution 3-Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.05 mg of isosorbide per mL .

Test solution-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of isosorbide mononitrate to a suitable flask containing 20.0 mL of acetonitrile. Sonicate for 10 minutes, and then centrifuge. Use the supernatant.

Application volume: $\quad 20 \mu \mathrm{~L}$.
Developing solvent system: a mixture of toluene, ethyl acetate, and isopropyl alcohol ( $53: 32: 15$ ).

Procedure-Proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$. After developing, dry the plate with warm air for about 10 minutes, dip the
plate in a solution prepared by dissolving 1.25 g of potassium permanganate and 10.0 g of sodium hydroxide in 500 mL of water (prepared fresh for each plate), and heat at $105^{\circ}$ for 5 minutes. Any spot in the chromatogram obtained from the Test solution and corresponding to the $R_{F}$ value of the spots obtained from the Standard solutions is not more intense than the spot in the chromatogram obtained from Standard solution 3: not more than 1\% of any individual impurity is found. [NOTE-The $R_{F}$ values of isosorbide and isosorbide mononitrate are about 0.2 and 0.6 , respectively.] If the spot in the chromatogram obtained from the Test solution is nearly as intense as the spot obtained from Standard solution 3, further dilute the Test solution (1:1) with acetonitrile, repeat the test, and compare the intensity of the isosorbide spot in the diluted Test solution with the intensity of the spots obtained from the Standard solutions, correcting the percent level for the additional dilution of the Test solution.

TEST 2-
Mobile phase-Prepare a filtered and degassed mixture of water and methanol ( $75: 25$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Isosorbide mononitrate related compound A standard stock solution-Dissolve an accurately weighed quantity of USP Isosorbide Mononitrate Related Compound A RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.3 mg per mL .

Isosorbide dinitrate standard stock solution-Dissolve an accurately weighed quantity of USP Diluted Isosorbide Dinitrate RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.15 mg of isosorbide dinitrate per mL .

Standard stock solution-Transfer 2.0 mL of Isosorbide mononitrate related compound A standard stock solution and 4.0 mL of Isosorbide dinitrate standard stock solution to a $100-\mathrm{mL}$ volumetric flask. Dilute with water to volume, and mix.

Stat Resolution solution-Transfer about 24 mg of USP Isosorbide Mononitrate RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, add 10.0 mL of Standard stock solution, add 20 mL of methanol, and dilute with water to volume.

Restand Standard solution-Transfer 10.0 mL of Standard stock solution and 20 mL of methanol to a $100-\mathrm{mL}$ volumetric flask. Dilute with water to volume, and mix.

Test solution-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 60 mg of isosorbide mononitrate, to a $50-\mathrm{mL}$ volumetric flask, add 40 mL of methanol, and sonicate for about 30 minutes with cooling. Warm to ambient temperature, dilute with methanol to volume, and mix. Centrifuge at about 3000 rpm for 10 minutes. Quantitatively dilute the supernatant ( 10 in 50 ) with water. Pass a portion of this solution through a filter having a $0.45-\mu \mathrm{m}$ or finer porosity, and use the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the isosorbide mononitrate related compound A and the isosorbide mononitrate is not less than 1.0. [NOTE-The relative retention times are about 0.9 for isosorbide mononitrate related compound A, 1.0 for isosorbide mononitrate, and 5.6 for isosorbide dinitrate.] Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the
relative standard deviation for replicate injections is not more than $10 \%$ for the isosorbide mononitrate related compound A and isosorbide dinitrate peaks.

Procedure-Separately inject equal volumes (about 100 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of isosorbide mononitrate related compound A and isosorbide dinitrate in the portion of Tablets taken by the formula:

$$
25(C / W)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of the appropriate Standard, USP Isosorbide Mononitrate Related Compound A RS or USP Diluted Isosorbide Dinitrate RS, in the Standard solution; $W$ is the weight, in mg , of isosorbide mononitrate in the sample used to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak areas of the corresponding component obtained from the Test solution and the Standard solution, respectively: not more than $0.25 \%$ of isosorbide mononitrate related compound A is found; and not more than $0.25 \%$ of isosorbide dinitrate is found. Calculate the percentage of each other impurity (other than isosorbide mononitrate related compound A or isosorbide dinitrate) in the portion of Tablets taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak area for each other impurity obtained from the Test solution; and $r_{s}$ is the sum of the areas of all the peaks: not more than $0.25 \%$ of total other impurities is found and not more than $0.5 \%$ of total impurities is found, including isosorbide mononitrate related compound A and isosorbide dinitrate.

Assay-
Mobile phase-Prepare a filtered and degassed mixture of water and methanol ( $8: 2$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Isosorbide mononitrate related compound A standard preparation-Dissolve an accurately weighed quantity of USP Isosorbide Mononitrate Related Compound A RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.15 mg per mL .

Resolution solution-Transfer a quantity of USP Isosorbide Mononitrate RS, accurately weighed, equivalent to about 30 mg of isosorbide mononitrate, to a $250-\mathrm{mL}$ volumetric flask. Dissolve in water, add 10.0 mL of Isosorbide mononitrate related compound A standard preparation, add 50 mL of methanol, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a concentration of about 0.12 mg of isosorbide mononitrate per mL and about 0.006 mg of isosorbide mononitrate related compound A per mL.

Standard preparation-Transfer a quantity of USP Isosorbide Mononitrate RS, accurately weighed, to a suitable volumetric flask. Dissolve in water, add a portion of methanol equivalent to about $20 \%$ of the flask volume, and dilute with water to volume to obtain a solution having a known concentration of about 0.12 mg of isosorbide mononitrate per mL.

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 60 mg of isosorbide mononitrate, to a $100-\mathrm{mL}$ volumetric flask, add 50 mL of methanol, and sonicate for about 30 minutes with cooling. Warm to ambient temperature, dilute with methanol to volume, and mix. Centrifuge at about 3000 rpm for 10 minutes. Quanti-
tatively dilute the supernatant ( 10 in 50 ) with water. Pass a portion of this solution through a filter having a $0.45-\mu \mathrm{m}$ or finer porosity, and use the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—
The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 12.5-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 1.5. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L} 20 \mu \mathrm{~L})$ of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of isosorbide mononitrate $\left(\mathrm{C}_{6} \mathrm{H}_{9} \mathrm{NO}_{6}\right)$ in the portion of Tablets taken by the formula:

$$
500 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of isosorbide mononitrate in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.n1S (USP28)

## Briefing

Ivermectin, page 114 of $P F 30$ (1) [Jan.-Feb. 2004]. On the basis of comments received, the following changes are proposed for this new monograph: (1) the upper limit in the Definition is changed from 100.5 to 102.0 percent; (2) the Packaging and storage statement now includes a statement for drug substances that do not contain a suitable quantity of an antioxidant; (3) the tests for Clarity of solution and Color of solution are considered unnecessary; changes in the Chromatographic system are made in the limit test; changes in the Related compounds test are made to use the Standard preparation as directed in the Assay; (4) and changes to the Assay are made to improve the resolution between the peaks of interest and to simplify the equation of the two components, $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ and $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$. Interested parties are encouraged to submit comments to USP.
(VET: I. DeVeau) RTS-40838-1

## Add the following:

## ■Ivermectin


fvermectin [70288-86-7].
Component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ :

Avermectin $\mathrm{A}_{1 \mathrm{a}}$, 5-O-demethyl-22,23-dihydro-
( $2 \mathrm{a} E, 4 E, 8 E$ )-( $5^{\prime} S, 6 S, 6^{\prime} R, 7 S, 11 R, 13 R, 15 S, 17 \mathrm{a} R, 20 R, 20 \mathrm{a} R$, 20bS)-6'-(S)-sec-Butyl-3', $4^{\prime}, 5^{\prime}, 6,6^{\prime}, 7,10,11,14,15,17 \mathrm{a}$, 20,20a,20b-tetradecahydro-20,20b-dihydroxy[11,15-methano- $2 H, 13 H, 17 H$-furo[4,3,2-pq][2,6]benzodioxa-cyclooctadecin-13, $2^{\prime}-[2 H]$ pyran $]-7-y l ~ 2,6-d i d e o x y-~$ 4-O-(2,6-dideoxy-3-O-methyl- $\alpha$-L-arabino-hexopyra-nosyl)-3-O-methyl- $\alpha$-L-arabino-hexopyranoside
[70161-11-4].
Component $\mathrm{H}_{2} \mathrm{~B}_{\mathrm{bb}}$ :
Avermectin $\mathrm{A}_{1 \mathrm{a}}$, 5-O-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-.
( $2 \mathrm{a} E, 4 E, 8 E$ )-( $5^{\prime} S, 6 S, 6^{\prime} R, 7 S, 11 R, 13 R, 15 S, 17 \mathrm{a} R, 20-$ $R, 20 \mathrm{a} R, 20 \mathrm{~b} S)-3^{\prime}, 4^{\prime}, 5^{\prime}, 6,6^{\prime}, 7,10,11,-$ oxospiro[11,15-methano- $2 H, 13 H, 17 H$-furo[4,3,2-pq][2,6]benzodioxa-cyclooctadecin-13, $2^{\prime}[2 \mathrm{H}]$ pyran]-7-yl 2,6-dideoxy-4-O-(2,6-dideoxy-3- $O$-methyl- $\alpha$-L-arabino-hexopyrano-syl)-3-O-methyl- $\alpha$-L-arabino-hexopyranoside
[70209-81-3].
\# Ivermectin is a mixture of $5-0$ demethyl 22,23dihydreavermectin $A_{1+}$ (compenent $B_{t_{n}}$ ) and 5-O demethyl 25 -de( 1 methylpropyl) 22,23 -dihydre-25-(1 methylethyl)avermectin $\Lambda_{\text {4b }}$ (compenent $\mathrm{B}_{\mathrm{tb}}$. It contains not less than 95.0 pereent of compenent $B_{16}$ plus compenent $B_{40}$, caleulated on the water, ethanel aleehel, and formamide free basis.
$»$ Ivermectin is a mixture of Avermectin $\mathrm{A}_{1 \mathrm{a}}, 5-O-$ demethyl-22,23-dihydro-(component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ ) and Avermectin $\mathrm{A}_{1 \mathrm{a}}$, 5-O-demethyl-25-de(1- methyl-propyl)-22,23-dihydro-25-(1-methylethyl)-(component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ ). It contains not less than 90.0
percent of component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$, and the sum of component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ plus component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ is not less than 95.0 percent and not more than 100.5102 .0 percent, calculated on the anhydrous and alcoholand formamide-free basis. It may contain a small amounts of suitable antioxidant and chelating agents.

Packaging and storage-Preserve in tight containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$. Store between $2^{\circ}$ and $8^{\circ}$. Where the use of an antioxidant is allowed, store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-If it is intended for veterinary use only, it is so labeled. Label it to state the name(s) and amount(s) of any added substance(s). Label it also to state that it is for manufacturing, processing, or repackaging.

USP Reference standards $\langle 11\rangle$ —USP Ivermectin $R S$.
Clarity of solution Transfer 1 g to a 50 mL volumetric flask, dissolve in and dilute with toluene to volume, and mix: the solution is clear.

Color of solution Pass a pertion of the solution prepared in the test for Clarity of solution through a fine peresity, sim tered glass filter. Determine the abserbance of the filtrate at 440 mm in a 1 em cell using toltene as the blank: the absorbance is not more than $0.024(1-0.01 V)$, in which $V$ is the stm of the percentages of water, aleohol, and formamide in the Ivermectin taken.

## Identification-

A: The-chrematogram of the Assay preparation, obtained as directed in the $A s s a y$, exhibits major peaks for eompenent $B_{+m}$ and compenent $B_{t b}$, the retention times of which correspend to these exhibited in the chrematogram
of the Standard preparation, obtained as directed in the -As say, and the ratio of compenent $B_{+4}$ tocempenent $B_{4-6}$ is net less than-9.0:1-9.0:1.0. Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.

B: Ultaviolet Abserption $\langle 197 \mathrm{U}\rangle$ -
Soltion: $20 \mu \mathrm{~g}$ per mL.
Meditm:- methanel. The spectrum exhibits maxima at about 238 nm and 245 nm and a shoulder at about 253 fm, and the absorptivity at the wavelength of maximmm abserption at about 245 nm is between 37.2 and 39.2 , caleu tated on the water, ethanel-aleohol, and formamide-free basis. The retention times of the component $\mathrm{H}_{2} \mathrm{~B}_{1 \text { a }}$ peak and the component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ peak in the chromatogram of the Assay preparation correspond to those in the chromatogram of the Standard preparation, as obtained in the Assay. Clarity and color of solution Dissolve 1.0 g of it in to tarne to obtain 50 mL of solution: the solution is clear and its abserbance at 440 nm in a 1 -em cell is not more that 0.024 , toltene being used as the blank.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $-17^{\circ}$ and $-20^{\circ}$, determined at $20^{\circ}$ and calculated on the water-, ethanel alcohol-, and formamide-free basis.

Test solution: $\quad 255 \mathrm{mg}$ per mL , in methanol.
Water, Method $I\langle 921\rangle$ : not more than $1.0 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method $I I\langle 231\rangle$ : $0.002 \%$.
Limit of alcohol and formamide-
Standetrd solutions- Transfer 3.0 mL of dehydrated aleehel to a 100 mL volumetric flask, dilute with water to vol ume, and mix (Solution 4). Transfer 1.0 mL of formamide to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix (Solution B). Transfer 3.0 mL of Solution $A$ and 3.0 mL of Solution $B$ to a 100 mL volumetric flack, dilute with water to volume, and mix to obtain a solution having coneentrations of ethanel aleohel and formamide of 0.0009 and 0.0003 mL per mL , respectively (Solutien C). Transfer 8.0
mL of Solution 4 and 8.0 mL of Solution $B$ to a $100-\mathrm{mL}$ velumetric flask, dilute with water to volume, and mix to ebtain a selution having cencentrations of ethanel aleohel and formamide of 0.0024 and 0.0008 mL per mL , respec tively (Solution D). Transfer 4.0 mL of Solution $C$ and 4.0 mL of Solution $D$ to separate $15-\mathrm{mL}$ centrifuge tubes, add 2.0 mL of $m$ xylene to each tube, stopper, mix, centrifuge, and discard the upper maylene layers. The retained lower fayers are Standerd solutions- $C$ and $D$.

Fest solution Transfer 120 mg of Ivermectin, aceurately weighed, to a 15 mL centrifuge tube, and dissolve in 2.0 mL of m xylene. Add 2.0 mL of water, mix, and centrifuge. Transfer the m- xylene-layer to a $15-\mathrm{mL}$ centrifuge tube, and extract again with 2.0 mL of water. Discard the $m-x y$ tene layer, and combine the twe aqueous layers to obtain the

## Fest solution.

Chromatographic syistem (see Chrematography $\langle 624\rangle$ ) The gas chromatograph is equipped with a flame ionization detector and contains a $1.8 \mathrm{~m} \times 3.2 \mathrm{~mm}$ columm packed with 80-10 - 100 mesh suppert S2. The injection pert is maint tained at abeut $190^{\circ}$, and the detector is maintained at abeut $250^{\circ}$. Helium is used as the carrier gas at a flow rate of about 40 mL per mintute. The columm is maintained at about $150^{\circ}$ for 12 minttes after injection, then raised at a rate of $20^{\circ}$ per mintete to $180^{\circ}$, and then held for 20 minters.

Procedure Separately inject equal volumes (about $2 \mu \mathrm{H}$ ) of Standard solutions $C$ and $D$ and the Test solution inte the ehromatograph, record the chromatograms, and measure the ethanel aleohel and formamide peak respenses. Plot the peak respenses for ethanel aleohol and formamide versus eoncentrations, in mL per mL, of ethanol aleohol and forma mide, respectively, obtained frem Standard solutions $C$ and P. From the graphs so obtained, determine the concentrations of ethanel aleohel and formamide in the Test solution. ENOTE-In the event that the peak respenses-of the Test solt
tion-are-signifieantly outside the ranges-of peak respenses ebtained with Standard solutions $C$ and $D$, prepare additional Standard solutions, and chromatograph them to obtain peak responses bracketing those obtained with the Fest solution.]-Caleulate the pereentages of ethanol aleohel and formamide in the pertion of Ivermectin taken by the for-mula:-

$$
400,000 \mathrm{Cd} / W,
$$

in which $C$ is the concentration of ethanol alcehol or formamide, in mL per mL, of the Test solution; $d$ is the density of ethanel aleohel ( 0.79 ) or formamide-(1.13); and $W$ is the weight, in mo, of Ivermectin taken: not more than $5.0 \%$ of ethanel aleohel $\left(\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}\right)$ and $3.0 \%$ of formamide are fount.

Internal standard solution-Dilute 0.5 mL of isopropyl alcohol with water to 100 mL , and mix.

Standard solution 1—Transfer 3.02 .0 mL of dehydrated alcohol to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Standard solution 2-Transfer 1.0 mL of formamide to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Standard solution 3-Transfer 5.0 mL of Standard solution 1 and 5.0 mL of Standard solution 2 to a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of formamide and alcohol of 0.001 and 0.00330 .002 mL per mL , respectively. Transfer 2.0 mL of this solution to a $15-\mathrm{mL}$ centrifuge tube, add 2.0 mL of $m$-xylene, insert the stopper, mix, and centrifuge. Remove the upper $m$-xylene layer, and extract it with 2.0 mL of water. Discard the upper layer, combine the two retained lower aqueous layers, add 1.0 mL of Internal standard solution, and mix. Each mL of this solution contains about 0.00120 .0008 mL of alcohol and 0.0004 mL of formamide.

Standard solution 4-Transfer 10.0 mL of Standard solution 1 and 10.0 mL of Standard solution 2 to a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of alcohol and formamide of 0.0060 .004 and 0.002 mL per mL , respectively. Transfer 2.0 mL of this solution to a $15-\mathrm{mL}$ centrifuge tube, add 2.0 mL of $m$-xylene, insert the stopper, mix, and centrifuge. Remove the upper $m$-xylene layer, and extract it with 2.0 mL of water. Discard the upper layer, combine the two retained lower aqueous layers, add 1.0 mL of Internal standard solution, and mix. Each mL of this solution contains about 0.00240 .0016 mL of alcohol and 0.0008 mL of formamide.

Test solution-Transfer 120 mg of Ivermectin, accurately weighed, to a $15-\mathrm{mL}$ centrifuge tube, and dissolve in 2.0 mL of $m$-xylene, heating in a water bath at $45 \pm 5^{\circ}$, if necessary. Add 2.0 mL of water, mix, and centrifuge. Transfer the $m-$ xylene layer to a $15-\mathrm{mL}$ centrifuge tube, and extract with 2.0 mL of water. Discard the upper $m$-xylene layer, combine the two retained lower aqueous layers, add 1.0 mL of Internal standard solution, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The gas chromatograph is equipped with a flame-ionization detector and a $0.53-\mathrm{mm} \times 30-\mathrm{m}$ fused-silica analytical column coated with a $3-\mu \mathrm{m}$ G43 stationary phase. The carrier gas is helium, with a $1: 510: 1$ split ratio and a linear velocity of about 35 cm per second. The chromatograph is programmed as follows. The column temperature is maintained at about $40^{\circ}$ for 5 minutes after injection, and then increased at a rate of $20^{\circ}$ per minute to $180^{\circ}$, and maintained at $180^{\circ}$ for 2 minutes. The injection port temperature is maintained at about $440^{\circ}, 220^{\circ}$, and the detector temperature is maintained at about $250^{\circ} .280^{\circ}$.

Procedure-Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of Standard solution 3, Standard solution 4, and the Test solution into the chromatograph, record the chromatograms,
and measure the peak responses for alcohol, formamide, and isopropyl alcohol. Plot the ratios of the peak responses for alcohol and isopropyl alcohol and for formamide and isopropyl alcohol versus concentrations, in mL per mL , of alcohol and formamide, respectively, obtained from Standard solution 3 and Standard solution 4. From the graphs so obtained, and using the ratios of the peak responses for alcohol and isopropyl alcohol and for formamide and isopropyl alcohol obtained from the chromatogram of the Test solution, determine the concentrations, $C$, of alcohol and formamide in the Test solution. [NOTE-In the event that the peak responses of the Test solution are significantly outside the ranges of peak responses obtained from Standard solution 3 and Standard solution 4, prepare additional Standard solutions, and chromatograph them to obtain peak responses bracketing those obtained with the Test solution.] Calculate the percentages of alcohol and formamide in the portion of Ivermectin taken by the formula:

$$
500,000 C D / W,
$$

in which $C$ is the concentration of alcohol or formamide, as appropriate, in mL per mL , in the Test solution; $D$ is the density of alcohol ( 0.79 ) or formamide (1.13); and $W$ is the weight, in mg, of Ivermectin taken: not more than $5.0 \%$ of alcohol and $3.0 \%$ of formamide is found.

Related substanees compounds-Using the chromato gram of the Assay preparation obtained as direeted in the Assaly, caleulate the percentage of each related substance compound in the Ivermectin taken by the formmat:-

$$
100
$$

[^95]Not more than 2\% of any individual related substance com pernd is found, and the-sum of all related substances is not mere than-4\%.

Mobile phase and Chromatographic system-Proceed as directed in the Assay.

Standard solution-Proceed as directed for Standard preparation in the Assay.

Standard solution 1 Transfer $1.0-\mathrm{mL}$ of the Standard stock solution to a $100-\mathrm{mL}$ volumetric flack, dilute with methanel to veltume, and mix.

Standard solution 2 Transfer 5.0 mL of Standard solu fien 1 to a 100 mL volumetric flask, dilute with methanol to volume, and mix.

Test solution-Use the Assay preparation.
Procedure-Separately inject equal volumes (about 20 HL) of Standard solution-1, Standard solution-2, (about $50 \mu \mathrm{~L})$ of the Standard solution and the Test solution into the chromatograph, record the chromatogram of the Test solution for a period of time equivalent to twice the retention time of the prineipat main peak in the chromatogram obtained from the Standard solution 1, Standard solution, and measure the respenses for the major peaks. In the chrematogram obtained from the Test soltuion, the area of any peak with a retention time of 1.3 to 1.5 abeut 1.2 to 1.4 , relative to the prineipal peak, is not greater than twiee 2.5 times the area of the principal peak in the chromatogram-ob fained frem Standard solution - 1 ( $2.0 \%$ 2.5\%); the area of any other peak, aside from the prineipal peaks, is not greater than the area of the principal peak in the chremategram obtained frem Standard solution 1 (1.0\%); and the sum of the areas of all the peaks, apart frem the proneipal peaks, is net greater than four times the area of the prin eipal peak in the ehromatogram obtained from Standard solution $1(4.0 \%)(4 \%)$. Disregard any peak with an area less
than that of the prineipal peak in the chrematogram of Standatd solution $2(0.05 \%)$. peak areas. Calculate the percentage of each impurity by the formula:

$$
100 r_{i} /\left(r_{s}-r_{b}\right)
$$

in which $r_{i}$ is the peak area for each individual impurity in the Test solution chromatogram; $r_{s}$ is the sum of all peaks in the Test solution chromatogram; and $r_{b}$ is the total area of all peaks in a blank chromatogram: not more than $2.5 \%$ is found for the sum of all peaks with a relative retention time of about 1.3 to 1.4 (corresponding to $\mathrm{H}_{4} \mathrm{~B}_{1 \mathrm{a}}$ isomers and $\Delta^{2,3}$ $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ ); not more than $1 \%$ is found for the peak with a relative retention time of about 0.7 (corresponding to $8 \mathrm{a}-\mathrm{oxo}$ $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ ); not more than $0.7 \%$ is found for the peak with a relative retention time of about 0.5 (corresponding to Avermectin $\mathrm{B}_{1 \mathrm{a}}$ ); not more than $0.5 \%$ is found for any other individual impurity peak; not more than $1 \%$ is found for the sum of all ether individuat unidentified peaks; and not more than $4 \%$ is found for the sum of the areas of all the peaks, apart from the two main peaks $\left(\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}\right.$ and $\left.\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}\right)$. Disregard any peak with an area less than that of the two main peaks $\left(\mathrm{H}_{2} \mathrm{~B}_{4+\mathrm{an}}\right.$ and $\left.\mathrm{H}_{2} \mathrm{~B}_{4 \mathrm{~b}}\right)$ in the chromatogram- of Standated solution $2(0.05 \%)$ that is calculated to be less than $0.05 \%$.

Assay-
Mebile phase Prepare a mixture of acetenitrile, methanel, and water ( $530: 350: 120$ ), filter threugh a filter having a peresity of $1 \mu \mathrm{~m}$-r less, and degas. Make adjustments if necessary (see Systen Suitability under Chromatography $\langle 624\rangle$.

Standard preparation Dissolve an aceurately weighed quantity of USP Ivermectin RS quantitatively in Mobile phase to obtain a-solution having a knewn coneentration of about 0.5 mg per mL .

Assay preparation Transfer about 40 mg of Ivermectin, accurately weighed, to a 100 mL volumetric flask, dissolve in methanel, dilute with Mobile phase to volume, and mix. Chromatographic system (see Chromatography $\langle 621\rangle$ ) The liquid chromatograph is equipped with a 254 nm detec for and a $4.6 \mathrm{~mm} \times 25 \mathrm{~mm}$ celtumn that contains $5 \mathrm{\mu m}$ packing L1. The flow rate is about 1 mL per minute. Chrematograph the Standard preparation, and record the peak respenses as directed under Precedtre: compenent $\mathrm{B}_{4 \mathrm{~b}}$ is eluted at a retention time of about 14 minntes, followed by compenent $B_{1+}$ at a retention time of about 17 minntes. The reselution, $R$, between the peaks for component $B_{46}$ and eompenent $B_{\text {ten }}$ is not less than 3.0, the column efficiency determined from the compenent $B_{+\infty}$ peak is net less than 2000 theoretical plates, the tailing factor for the compenent $B_{\text {te }}$ peak is not more than 2.5, and the relative standard de viation of the peak respenses for compenent $B_{\text {te }}$ for replieate injections is not more than $1.0 \%$.

Proedure [NOTE-Use peak areas where peak respenses are indicated.] Separately inject equal volumes (about $50 \mathrm{\mu L}$ ) of the Standard prepatration and the Assay preparation into the-chromatograph, record the-chromategrams over a period of time that is twice the retention time of the peak for compenent $B_{t+4}$, and measure the peak respenses for compenent $B_{4 n}$ and compenent $B_{4}$. Caleulate the percentage of compenent $B_{+0}$ plus compenent $B_{4+}$ in the pertion of Ivermectin taken by the formula:-

$$
100(C P / H)\left(F_{t}+F_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Ivermectin RS in the Standerd preparation, $P$ is the designated percentage of the sum of compenent $B_{4+e}$ and compenent $B_{+6}$ in the USP Ivermectin RS, $W$ is the weight, in mg, of Iver mectin taken to prepare the $A$ ssay $p$ Peparation, and $f_{t}$ and $r_{s}$
are the sums of the peak respenses for compenent $B_{\text {ta }}$ and eompenent $B_{4}$-obtained from the Assay preparation and the Standard preparation, respectively.

Mobile phase_Prepare a mixture of acetonitrile, methanol, and water $(53: 35: 12)$, pass through a flter having a + - m or finer peresity, ( $53: 27.5: 19.5$ ), and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ). Increasing the proportion of water increases the elution times and allows better separation of impurities.

Standard preparation-Dissolve an accurately weighed quantity of USP Ivermectin RS in methanol to obtain a solution having a known concentration of about 0.8 mg per mL .0 .4 mg per mL .

Assay preparation-Transfer about 80 mg 40 mg of Ivermectin, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with methanol to volume, and mix. Sonicate, if necessary.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.80 .75 for component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ and 1.0 for component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$; the resolution, $R$, between component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ and component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ is not less than 3.0 ; the column efficiency determined from the component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ peak is not less than 2000 theoretical plates; the tailing factor for component $\mathrm{H}_{2} \mathrm{~B}_{1 \text { a }}$ peak is not more than 2.5 ; and the relative standard deviation for six replicate injections is not more than $1.0 \%$ determined from the component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ peak.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L})$ (about $50 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chroma-
tograms, and measure the peak areas for component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ and component $\mathrm{H}_{2} \mathrm{~B}_{\mathrm{b} \text { b }}$. Calculate the quantity, in mg , of component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}\left(\mathrm{C}_{48} \mathrm{H}_{74} \mathrm{O}_{14}\right)$ and component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ $\left(\mathrm{C}_{47} \mathrm{H}_{72} \mathrm{O}_{14}\right)$ in the portion of Ivermectin taken by the formula:

$$
100 \mathrm{C}\left(+_{\llcorner }+\Psi_{s}\right)
$$

$$
D C\left(r_{U} / r_{S}\right)
$$

in which $D$ is the dilution factor, in mL , used to prepare the Assay preparation; $C$ is the concentration, in mg per mL , of component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ or component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak for component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{a}}$ or component $\mathrm{H}_{2} \mathrm{~B}_{1 \mathrm{~b}}$ obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP27)

## Briefing

Lamivudine, USP 27 page 1064. It is proposed to revise the test for Limit of lamivudine enantiomer to specify the concentration of USP Lamivudine Resolution Mixture A RS used in the Resolution solution. It is also proposed in the test for Limit of residual solvents to replace the reagent methyl sulfoxide by its synonym dimethyl sulfoxide. The use of dimethyl sulfoxide will be standardized throughout $U S P-N F$.
(PA7b: B. Davani; BPC: M. Marques) RTS-40983-1; 41082-4

## Change to read:

Limit of lamivudine enantiomer-
0.1 M Ammonium acetate solution-Dissolve about 7.7 g of ammonium acetate in water, and dilute with water to 1000 mL .

Mobile phase-Prepare a suitable mixture of 0.1 M Ammonium acetate solution and methanol ( $95: 5$ ), mix, filter, and degas.
Resolution solution-Pissolve the eontents of 1 vial of USP Lamivudine Resolution Mixture $A$ RS in 5 mL of water, and quantiatavely transfer the solution to a 10 mL volumetric flask using successive 2 mL portions of water. Dilute with water to volume, and mix.
-Dissolve an accurately weighed quantity of USP Lamivudine Resolution Mixture A RS in water to obtain a solution having a known concentration of about 0.25 mg per mL . 1 (USP28)
Test solution-Transfer about 25 mg of Lamivudine, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $270-\mathrm{nm}$ detector and a $4.6-$ $\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L45. The column temperature is ${ }^{4}$ maintained at a constant temperature of between $15^{\circ}$ and $30^{\circ} \cdot \mathbf{\Delta S S P 2 7}$ The flow rate is about 1.0 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between lamivudine and lamivudine enantiomer is not less than 1.5 . [NOTE-The relative retention times are about 1.0 for lamivudine and about 1.2 for lamivudine enantiomer.]
Procedure-Inject a volume (about $10 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the responses for the major peaks. Calculate the percentage of lamivudine enantiomer in the portion of Lamivudine taken by the formula:

$$
100\left[r_{U} /\left(r_{U}+r_{S}\right)\right],
$$

in which $r_{U}$ and $r_{S}$ are the peak responses of lamivudine enantiomer and lamivudine, respectively: not more than $0.3 \%$ is found.

## Change to read:

Limit of residual solvents-
Internal standard solution-Transfer about ${ }^{\mathbf{\Delta}} 1 \mathrm{~mL}$ of 2-pentanone, accurately measured, ${ }_{\Delta U S P 27}$ to a $100-\mathrm{mL}$ volumetric flask, dilute with a mixture of methyls sulfoxide

- dimethyl sulfoxide $_{\text {IS (USP28) }}$
and water ( $1: 1$ ) to volume, and mix.
Standard solution- ${ }^{\mathbf{4}}$ Transfer 10 mL of Internal standard solution to a $100-\mathrm{mL}$ volumetric flask. To the same flask add an accurately measured quantity of about $100 \mu \mathrm{~L}$ of each of the following: dehydrated alcohol, isopropyl acetate, methanol, and triethylamine. Dilute with a mixture of methyl sulfoxide
- dimethyl sulfoxide $_{\boldsymbol{m}_{1 S} \text { (USP28) }}$
and water ( $1: 1$ ) to volume, and mix. $\Delta$ USP27
Test solution-Transfer about 5 g of Lamivudine, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, add 10 mL of Internal standard solution, dilute with a mixture of methyl sulfoxide
- dimethyl sulfoxide $_{\mathbf{n}_{1 S}(\text { USP28) }}$
and water ( $1: 1$ ) to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The gas chromatograph is equipped with a split injection port, a flame-ionization detector, and a $0.53-\mathrm{mm} \times 50-\mathrm{m}$ column coated with a $5-\mu \mathrm{m}$ film of phase G1. The carrier gas is hydrogen at a pressure of 5 psig. The split flow rate is about 320 mL per minute. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at $70^{\circ}$ for 3 minutes, then increased at a rate of $30^{\circ}$ per minute to $200^{\circ}$, and maintained at that temperature for 6.5 minutes. The injection port temperature is maintained at $150^{\circ}$ and the detector temperature is maintained at $250^{\circ}$.

Procedure-Separately inject equal volumes (about $0.5 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of each residual solvent in the portion of Lamivudine taken by the formula:

$$
10(C / W)\left(R_{i} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of the respective analyte in the Standard solution; $W$ is the weight, in $g$, of Lamivudine taken; and $R_{i}$ and $R_{S}$ are the peak response ratios of the respective analyte to the internal standard obtained from the Test solution and the Standard solution, respectively: not more than $0.2 \%$ of alcohol is found; not more than $0.2 \%$ of isopropyl acetate is found; not more than $0.1 \%$ of methanol is found; not more than $0.1 \%$ of triethylamine is found; and not more than $0.3 \%$ of total residual solvents is found.

## BRIEFING

Leuprolide Acetate, page 1412 of PF 28(5) [Sept.-Oct. 2002]. On the basis of comments received, it is proposed to make the following revisions to this new monograph: in the test for Bacterial endotoxins, the instructions for performing the test are being deleted, allowing the analyst to use any method that meets the requirements specified in the general chapter Bacterial Endotoxins Test $\langle 85\rangle$; in the test for Water, the limit is being raised from "not more than $5.0 \%$ " to "not more than $8.0 \%$ "; and in the test for Amino acid content, much of the instruction for performing the test is being deleted and a citation to Amino Acid Analysis under the general chapter Biotechnology-Derived Articles-Tests $\langle 1047\rangle$ is added, thus allowing analysts to use any suitable, validated method for performing the amino acid analysis.
(BNT: I. DeVeau) RTS-40388-5

## Add the following:

## Leuprolide Acetate


$2 \quad 1269.481209 .41$ (as free base)
Luteinizing hormone-releasing factor (pig), 6-D-leucine-9-
( $N$-ethyl-L-prolinamide)-10-deglycinamide moneaeeacetate (salt).
5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tryosyl
tyrosyl-D-leucyl-L-leucyl-L-arginyl- $N$-ethyl-L-prolinamide meneetate acetate (salt) [74381-53-6].

## » Leuprolide Acetate is a synthetic nanopeptide nonapeptide agonist analog of luteinizing hor-mone-releasing factor. It contains not less than

 97.0 percent and not more than 103.0 percent of leuprolide ( $\mathrm{C}_{59} \mathrm{H}_{84} \mathrm{~N}_{16} \mathrm{O}_{12}$ ), calculated on the anhydrous, acetic acid-free basis.NOTE-Due to the hygroscopic nature of this material, analyses are performed immediately after opening the container in a glove box under dry nitrogen purge.
Caution-Leuprolide Acetate is a potent hormonal manipulator. Avoid skin contact and inhalation of dusts and mists.

Packaging and storage-Preserve in tight containers.
Store at a temperature not higher than $30^{\circ}$.
USP Reference standards $\langle 11\rangle$ —USP Endotoxin RS. USP
Leuprolide Acetate RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
Fest specimen Use the Assay prepation.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $38^{\circ}$ and- $12^{\circ}-38.0^{\circ}$ and $-42.0^{\circ}$ expressed on an anhydrous, acetic acid-free basis.

Test solution: $\quad 10.0 \mathrm{mg}$ per mL , in $4 \mathrm{~N} 1 \%$ acetic acid. Bacterial endotoxins $\langle 85\rangle$ -

NOTE-1 Prepare the solutions quickly, and use them im mediately. Where water is specified, use Sterile-Water for Irrigation.

NOTE 2-The pH of the mixtlre of the Test solutions and the LAL reagent should be between 6.0 and 8.0 .
Star stock solutions-Mix USP Endotoxin RS vigor eusly on a vortex mixer for not less than 1 minute, and dilute stitable quantities of USP Endotoxin RS with water to obtain solutions having known coneentrations of about 1.0 , $0.50,0.10,0.05$, and 0.005 USP Endorin Unit per mL.

Horking standerd solution Dilute 2.0 mL of the 1.0 USP
Endotoxin Unit per mL Stalldard stock solution with water m 10.0 mL , and mix.

Fest stoch Dissolve 20 - 40 mg of Let prolide Acetate, aceurately weighed, in a volume of 50 mM tris(hydroxymethyl)aminemethane buffer solution, and mix en a vortex mixer for abou 1 minte to obtain a solution having a coneentration of about 2.0 mg of leuprolide acetate per mL. Dilute with water, and mix on a vortex mixer to ob tain a solution having a concentration of about 1.0 mg of lemprolide acetate per mL.

Fest solution 1 Dilute 0.1 mL of the Test stock solution with 4.9 mL of 10 mM tris(hydroxymethyl)aminemethane buffer solution. (The finaldilution factor to be entered inte the system under Procedtre is 1 in 100.)

Fest solution 2 Dilute 0.1 mL of the Test stock solution with $9.9-\mathrm{mL}$ of 10 mM -tris(hydrexymethyl)aminemethane buffer solution. (The final dilution factor to be entered inte the system under Procedtre is 1 in 200 .)

Positive product control solutions Add 50 5 L of Werk ing standard solution to $50 \mu \mathrm{~L}$ of each Test solution already placed in the mierotiter wells.

System suitability The kinetic quantitative chromogenic system is equipped with a reader set at 405 nm , an appre-priate-incubation device, and a data manipulation deviee. Chrematograph the Standard stock solutions, record the peak respenses as directed for Procedure, and plat the loga rithms of reaction endpeint times versus the logarithms of the coneentrations of the Standtard stock solutions: the abse tute value-of the correlation coefficient for the-standard eurve is not less than 0.980 ; and the coefficient of variation fer replicate wells is net mere than 10\%. Preceed with the Positive product entrolsolutions as directed for Procedtre, and calculate the percentage of spike recovery by the formt ła:

## 100R/S,

in whieh $R$ is the amount, in USP Endotoxin Units per mL, of recovered spiked sample; and $S$ is 0.1 USP Endotoxim Unit per mL: $\pm 25 \%$ of the spike value is recovered. If this pereentage is feund to be maceeptable, proceed as directed for Procedure using Test solution 2 insteat of Test solution $+$

Procedure Enter concentrations of all solutions and finat dilution factors into the datastem. Use sendotoxin free mierotiter plates andendotoxin free polystyrene-ulture tabes.

Place each of the preparations in duplieate wells. Carefally dispense $100 \mu \mathrm{~L}$ of water endetoxin negative contrel and each of the-Standard stock solutions. Carefully dispense $50 \mu \mathrm{~L}$ of water and $50 \mu \mathrm{~L}$ of Test solution 1. Carefully dispense the Positive product control solution. Preineubate the plate for 10 mintutes at $37^{\circ}$. Near the end of the 10 mintte period, reconstitute each LAL reagent vial with 2.6 mL of water. Remove the mierotiter plate from the ineubation ehamber. Add $100-\mu \mathrm{L}$ of LAL reagent to each well of the mieretiter plate. Insert the mierotiter plate into the well reat er, and initiate the reading for each well. The system-soft Ware reports the endotoxin concentration in USP Endotoxin Units per mL. If caleulating manually, Use the standard curve to calculate the average endotoxin concentration, in USP Endotoxin Units per mL, in the pertion of Leu prolide Ace ate taken. Not It contains net more than 16.67 166.7 USP Endetoxin Units per mg of leuprolide acetate. A eemputerized system may be used to calculate the endotox inconcentration in USP Endotoxin Units per mes.It contains not more than 166.7 USP Endotoxin Units per mg of leuprolide acetate.

Water, Method Ic $\langle 921\rangle$ : not more than 5.0\%. $8.0 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.3 \%$.
Chromatographic purity-
Buffer solution, Organic modifier solution, Mobile phase, Standard stock preparation, and Degradation standard pre-paration-Prepare as directed in the Assay.

Standard solution-Transfer 1.0 mL of the Standard stock preparation to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Test solution-Transfer about 100 mg of Leuprolide Acetate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system-Proceed as directed in the Assay. Chromatograph the Test solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.80 for D-Ser-leuprolide, 0.90 for D-Hisleuprolide, 1.00 for leuprolide, 1.2 for L-Leu lemprolide, LLeu ${ }^{6}$-leuprolide, and 1.5 for acetyl-leuprolide.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms for 90 minutes, and measure the peak responses. Calculate the percentage of each impurity in the portion of Leuprolide Acetate taken by the formula:

$$
0.01\left(W_{s} / W_{U}\right)\left(r_{i} / r_{s}\right) P
$$

in which $W_{s}$ is the weight of USP Leuprolide Acetate RS in the Standard stock preparation; $W_{U}$ is the weight, in mg , of Leuprolide Acetate in the Test solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; $r_{S}$ is the leuprolide peak response obtained from the Standard solution; and $P$ is the designated purity, in percentage, of USP Leuprolide Acetate RS: not more than $1.0 \%$ of acet-yl-leuprolide is found; not more than $0.5 \%$ each of D-Hisleuprolide, LLeu-leuprolide, $\mathrm{L}-\mathrm{Leu}^{6}$-leuprolide, and D-Ser-leuprolide is found; not more than $0.5 \%$ of any other individual impurity is found; and not more than $2.5 \%$ of total impurities is found.

## Content of acetic acid-

Diluent-Use methanol, and adjust with phosphoric acid to a pH of 2.5 .

Standard solution-Pipet 2.0 mL of glacial acetic acid into a $100-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix. Transfer 4.0 mL of the solution so obtained to a $100-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix. Transfer 10.0 mL of this solution to a $100-\mathrm{mL}$ vol-
umetric flask, dilute with Diluent to volume, and mix to obtain a solution having a known concentration of about 0.08 mg per mL .

Test solution-Transfer about 100 mg of Leuprolide Acetate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and a $0.53-\mathrm{mm} \times 30-\mathrm{m}$ fused-silica capillary column that contains a $1.2-\mu \mathrm{m}$ film of phase G35. The carrier gas is helium, flowing at a rate of about 10 mL per minute. The column temperature is maintained at about $100^{\circ}$, the injector port temperature is about $200^{\circ}$, and the detector port temperature is about $250^{\circ}$. Chromatograph the Standard solution, and record the peak respenses areas as directed for Procedure: the retention time of acetic acid is b.0 7.0 should be about 5 to 7 minutes; the column efficiency is not less than 15,000 theoretical plates; the tailing factor is not less than 0.8 and not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$. Chromatograph the Diluent, and record the peak areas as directed for Procedure: verify that there are no interfering peaks.

Procedure-Separately inject equal volumes (about 1.0 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph (splitless mode), record the chromatograms, and measure the responses for the acetic acid peaks. Calculate the percentage of acetic acid $\left(\mathrm{C}_{2} \mathrm{H}_{4} \mathrm{O}_{2}\right)$ in the portion of Leuprolide Acetate taken by the formula:

$$
\left(839.2 / W_{U}\right)\left(r_{U} / r_{s}\right),
$$

in which $W_{U}$ is the weight, in mg, of Leuprolide Acetate taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the acetic acid peak areas obtained from the Test solution and the Standard solution, respectively: not less than $4.87 \% 4.7 \%$ and not more than $9.0 \%$ is found.

Amino acid content-Use a suitable, validated procedure (see Amino Acid Analysis under Biotechnology-Derived Ar-ticles-Tests $\langle 1047\rangle$ ).

Buffer solution-Prepare a solution that is 0.15 N with respect to lithitm hydroxide and to cittic acid, and adjust with hydrechloric acid to pH of 2.20 .

Columan-regeneration buffer Prepare a- 0.3 N solution-of lithium hydroxide.

Ninhydrin reage Dilute 18 g of nimhydrin and 0.7 g of hydrindantin in 900 mL of dimethylsulfoxide. Sparge with nitrogen before-eapping, and mix on a-shaker for net less fhan 3 heurs.

Tryptoplat solution Prepare a fresh 5 $\times 10^{-5}$ M soltt fien of tryptophant

Mebite phase 1 Prepare asolution that is 0.2 N withre speet tolithium hydroxide and tocitric acid, and adjust with hydrechloric acid to apHof 2.83 .

Mobile phase 2 Prepare a solution that is 0.3 N with re speet to lithium hydrexide and tocitric acid, and adjust with hydrechloric acid to a pH of 3.33.

A@bite phase 3 Prepare a selution that is 0.6 N with respect tolithium hydroxide and to citric acid, and adjust with hydrochloric ceid to a pH of 3.57.

Mobite phase 4 Prepareasolution that is 0.95 N with respect tolithium hydroxide and tocitric acid, and adjust with hydrochloric acid a pH -f 3.98.

Stated solution solutions Prepare, in duplieate, a so lution having known coneentrations of about $5.0 \times 10^{-5} \mathrm{M}$ each of $L$-alanine, $L$ arginine, $L$ aspartic acid, $L$ glatamic acid, slycine, L -histidine, L -isoleurine, t leurine, L lysine,

E-methionine, E -phenylatanine, E -proline, t -serine, t -threefine, t tyrosine, and L valine and about $2.5 \times 10^{-5} \mathrm{M}$ of L eystine-

Fest solution Transfer about 64 mg of Lemprolide Acet ate, aceurately weighed, to a suitable vessel, and dissolve im 1.0 mL of water. Transfer 0.10 mL of this solution to a va entm hydrolysis tube, add 2.0 mL of 6 N hydrochloric acid, evacuate the tube, and heat for 16 hours at $120^{\circ}$. Transfer 0.10 mL of the hydrolysate so obtained to a suitable vessel, add 1 mL of water, and lyophilize. Dissolve in and dilute with Buffer solution to 10.0 mL .

Chromatographic system (see Chromatography $\langle 624\rangle$ ) The amine acid analyzer chromatograph is equipped with a $4-\mathrm{mm} \times 10$ em column that contains packing L34 and a detector set at $440 \mathrm{~nm}, 570 \mathrm{~nm}$, and 690 nm , where measurements at 690 nm are used for background corrections. The detector is placed after a pest coltumn reactor where the coltmmeffurnt and Ninhydrin reagent are heated to a temperature of about $135^{\circ}$. The flow rateof Ninhydrin re agent is about 10 mL per hour. The chrematograph-is pregrammed as follows. The flow rate is about 20 mL per hour. The coltumn temperature is programmed as follows.

| Time (minutes) | Solution |
| :---: | :---: |
| Q-30.5 | Mobile phase 1 |
| 30.5-68 | Mobile phase 2 |
| 68.78 | Mebile phase 3 |
| 78159 | Mobile phase 4 |
| 159-164 | Goluman regeneration buffer |
| 161.175 | Mobile phase 1 |

It is maintained at $34^{\circ}$ for 12 mintutes, then-inereased at a rate of $1.5^{\circ}$ per minute $6.63^{\circ}$, maintained at that temperature fer 74 mintutes, and finally inereased at a rate of $1.5^{\circ}$ per minute to $70^{\circ}$. [NOTE-During columan regeneration the cot tmm effluent is mixed with water, not with Ninhydrit re agent. After regeneration, the coltmm temperature is ehanged to $34^{\circ}$. After 5 minutes, the coltmm effluent is again mixed with Ninhydrin reagent.] Chromatograph the Standard solution solutions and the Tryptophan solution, and record the peak respenses areas as directed for Prece dure: the relative retention times are about 0.12 for serine, 0.15 for ghtatamic acid, 0.22 for proline, 0.37 for leurine, 0.40 for fyresine, 0.72 for tryptophan, 0.84 for histidine, and 1.00 for arginine; and the relative standard deviations determined from the arginine, aspartic acid, proline, and serine peaks for replieate injections are not more than- $4.0 \%$ each.

Procedure Inject equal volumes (about 50- $\mu \mathrm{L}$ ) of the Standard solution, the Tryptophan-selution, and the Test sothtion into the chrematograph, record the chromategrams, and measure the respenses areas for each amine acid peak. between 0.85 and 1.1 moles each of glatamic acid, proline, fyresine, histidine, and arginine permole of leuprolide acet ate is found; and serine and tryptophan are present. Caleut tate the average respense factor for each amine acid in the Standard solution taken by the formula:-

$$
0.5\left[\left(G_{\mathrm{st}} / R_{\mathrm{st}}\right)+\left(G_{\mathrm{sz}} / R_{\mathrm{sz}}\right)\right],
$$

in which- $G_{s+}$ and $\epsilon_{s \text { se }}$ are the concentrations-of the amine aeid, in moles per liter, in each of the duplieate-Standard
solutions, and $R_{s+}$ and $R_{s z}$ are peak area respenses areas of the amine acid in each of the duplicate Standard solutions. Caleulate the concentration of each amine acid in the Test solution, in moles per liter taken by the formala:-

$$
R_{t}\left(A_{R F s}\right),
$$

in whieh $R_{4}$ is the peak respense area of each amine acid in the Test solution; and $A_{\text {prs }}$ is the average response factor for the amine acid as caleulated above. Caleulate the relative molar ratio of each amine acid in Leuprolide Acetate taken by the formula:-

in whieh $\epsilon_{L}$ is the concentration of the amine acid in the Test solution and $G_{k}, G_{p}, G_{k}, G_{k}, G_{k}$, and $G_{k}$ are the concentra tions of glatamic acid, preline, leueine, fyrosine, histidine, and arginine, respectively, in the Test solution: between 0.85 and 1.1 moles each of glatamic acid, proline, leucine, fyrosine, histidine, and arginine per mole of Leuprolide Acetate is found; between 1.8 and 2.2 moles of leucine per mole of Leuprolide Acetate is found. Serine and tryptephan are also present.

Standard solutions-Prepare a solution having known equimolar amounts of L-alanine, L-arginine, L-aspartic acid, L-glutamic acid, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-proline, Lserine, L-threonine, L-tyrosine, and L-valine with half the equimolar amount of L-cystine. For the validation of the method, an appropriate internal standard, such as norleucine, is used. Prepare a separate, equimolar solution of Ltryptophan.

Test solution-Transfer about 64 mg of Leuprolide Acetate, accurately weighed, to a suitable vessel, and dissolve in 1.0 mL of water. Transfer 0.10 mL of this solution to a va-
cuum hydrolysis tube, add 2.0 mL of 6 N hydrochloric acid, evacuate the tube, and heat for 16 hours at $120^{\circ}$. Transfer 0.10 mL of the hydrolysate so obtained to a suitable vessel, add 1 mL of water, and lyophilize. Dissolve in and dilute to a suitable volume in a buffer solution suitable for amino acid analysis.

Procedure-Inject equal volumes of the Standard solutions and the Test solution into the amino acid analyzer, and record and measure the responses for each amino acid peak. Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids in the Test solution, taking one-seventh of the sum of the number of moles of histidine, glutamic acid, leucine, proline, tyrosine, and arginine as equal to one: between 0.85 and 1.1 moles each of glutamic acid, proline, tyrosine, histidine, and arginine per mole of Leuprolide Acetate is found; between 1.8 and 2.2 moles of leucine per mole of Leuprolide Acetate is found. Serine and tryptophan are also present.

## Assay-

Buffer solution-Dissolve about 15.2 g of triethylamine in 800 mL of water, adjust with phosphoric acid to a pH of 3.0 , and dilute with water to 1000 mL .

Organic modifier solution-Prepare a mixture of acetonitrile and $n$-propyl alcohol ( $3: 2$ ).
Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and Organic modifier solution (85:15). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard stock preparation-Transfer about 100 mg of USP Leuprolide Acetate RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Standard preparation-Transfer 5.0 mL of Standard stock preparation into a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Degradation standard preparation-Transfer 5 mL of Standard stock preparation to a $50-\mathrm{mL}$ volumetric flask, and dilute with water to volume. Transfer 5 mL of the solution so obtained to a scintillation vial. Add $100 \mu \mathrm{~L}$ of 1 N sodium hydroxide solution, tightly cap, and shake vigorously. Place in an oven at a $100^{\circ}$ for 60 minutes, remove, allow to cool, add $50 \mu \mathrm{~L}$ of 1 M phosphoric acid, recap, and shake vigorously to mix.

Assay preparation-Transfer about 100 mg of Leuprolide Acetate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix. Transfer 5.0 mL of the solution so obtained to a 100 mL volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ column that contains $3-\mu \mathrm{m}$ packing L1. The flow rate is between 1.0 and 1.5 mL per minute. Chromatograph the Degradation standard preparation, and record the peak responses as directed for Procedure: the retention time of leuprolide is between 41 and 49 minutes; the relative retention times are about 0.90 for the degradation product and 1.0 for leuprolide; and the resolution, $R$, between leuprolide and the degradation product is not less than 1.0. 1.5. Chromatograph the Mobile phase, and record the peak responses as directed for Procedure: verify that no extraneous peaks are present. Chromatograph the Standard preparation, and record the peak areas as directed for Procedure: the column efficieney is not less than 5500 theoretieal plates; the tailing factor is not less than 0.8 and not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms for 60 minutes, and measure the leuprolide peak respenses. areas. Calculate the percentage of leuprolide $\left(\mathrm{C}_{59} \mathrm{H}_{84} \mathrm{~N}_{16} \mathrm{O}_{12}\right)$ in the portion of Leuprolide Acetate taken by the formula:

$$
\left(H_{s} / H_{\downarrow}\right)\left(r_{\Delta} \downarrow \Psi_{s}\right) P,\left[\left(W_{S} / W_{U}\right)\left(r_{U} / r_{s}\right)(P)(0.9527)(100)\right] /(100-
$$

acetic acid content - water content),
in which $W_{S}$ is the weight, in mg, of USP Leuprolide Acetate RS in the Standard preparation; $W_{U}$ is the weight, in mg, of Leuprolide Acetate in the Assay preparation; $r_{U}$ and $r_{s}$ are the peak respenses areas obtained from the Assay preparation and the Standard preparation, respectively; and $P$ is the designated purity, in percentage, of USP Leuprolide Acetate RS.■1S (USP28)

## BRIEFING

Levodopa, USP 27 page 1079; Levodopa Tablets, USP 27 page 1081. A revision is proposed to modify the test for Related compounds to identify the impurities that could be present in this substance and to indicate the quantitation of these impurities using an external Standard.
(PA3: S. Salado) RTS-39524-1

## Change to read:

Related compounds-[NOTE-Protect all solutions from light and maintain them at $10^{\circ}$ until they are injected into the chromatograph.]

Diluent, Mobile phase, System suitability solution, preparation,

■ $\quad 1 \mathrm{~S}$ (USP28)
and Chromatographic system-Proceed as directed in the Assay. Test preparation Use the Assay preparation.
Proecdure Separately inject equal volumes (abeut 20- HL ) -ff the Standard preparation and the Test preparation into the ehromat tograph, record the ehromategrams, and measure the peak respenses. Caleulate the pereentage of each-impurity in the pertion of Levodepa taken by the formula:

$$
100 F(+,+r)
$$

in which $F$ is the correction facter and is equalto 2.5 for peaks with a relativeretention time of 0.9 or 1.3 , andis equal to 1 for peaks with a relativeretention time of 1.6 or for any other peak; $r$ is is the peak respense of each impurity obtained from the Test solution; andr, is the sum of the respenses of all the peaks. net mere that $0.1 \%$ of levodopa-related cempeund $A$ is found; not mere that $\theta .1 \%$ of L tyresine-is found; net mere than $0.1 \%$ of any unknown impurity is feund; net more than $0.5 \%$ of 3 methexytyresine-is found; and the sum of all impurities is not mere than $1.1 \%$.
-Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of each impurity in the portion of Levodopa taken by the formula:
in which $C$ is the concentration, in mg per mL , of USP Levodopa RS in the Standard solution; $F$ is the relative response factor of each impurity according the table below; $W$ is the weight, in mg, of Levodopa, on the dried basis, used to prepare the Test solution; $r_{i}$ is the peak area for any impurity in the Test solution; and $r_{s}$ is the peak area for levodopa in the Standard solution: the impurities meet the requirements given in the table below.

|  | Relative | Relative |  |
| :---: | :---: | :---: | :---: |
| Compound | retention | response | Limit |
| name | time | factor | $(\%)$ |


| Levodopa related |  |  |  |
| :--- | :--- | :---: | :---: |
| $\quad$compound A | about 0.9 | 2.4 | 0.1 |
| Levodopa | 1.0 | - | - |
| L-Tyrosine | about 1.3 | 2.7 | 0.1 |
| 3-Methoxytyro- | about 1.6 | 1.2 | 0.5 |
| sine |  |  |  |
| 1-Veratrylglycine | about 2.7 | 1.3 | 0.1 |
| Unknown impur- | - | 1.0 | 0.1 indi- |
| ities |  |  | vidual 0.2 <br> total |
|  |  |  | unknown |
| Total |  | - | 1.1 |

-1S (USP28)

$$
(10,000 F)(C / W)\left(r_{i} / r_{s}\right)
$$

## Briefing

Levodopa Tablets, USP 27 page 1081 —See briefing under Levodopa.
(PA3: S. Salado) RTS-39524-2

## Change to read:

Related compounds- [NOTE-Protect all solutions from light and maintain them at $10^{\circ}$ until they are injected into the chromatograph.]

Mobile phase, System suitability solution, St,

- $\quad$ 1S (USP28)
and Chromatographic system-Proceed as directed in the Assay. Fest preparation Use the Assay preparation.
Procedure Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Test preparation into the chromatograph, record the chromatograms, and measure the peak respenses. Caleulate the pereentage of each impurity in the pertion of Tablets taken by the formmla:

$$
100\left(+\Psi_{*}\right)
$$

in which $r$,is the peak respense for each impurity obtained frem the Fest solution; andr, is the sumof the respenses of all the peaks: net more than $0.1 \%$ of levodopa related compernd $A$ is found; net more than $0.5 \%$ of 3 methoxytyresine is found; not more that Q.1\% of any other individual impurity is found; and the sum of all unknown impurities is not mere than $0.3 \%$.
-Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of each impurity in the portion of Levodopa taken by the formula:

$$
(10,000 F)\left(W_{T} / W_{s}\right)(C / D)\left(r_{i} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Levodopa RS in the Standard solution; $F$ is the relative response factor of the impurity according the table below; $W_{T}$ is the average weight, in mg, of the Tablets; $W_{S}$ is the weight, in mg , of sample taken to prepare the Test solution; $D$ is the labeled amount, in mg , of Levodopa per tablet; $r_{i}$ is the peak area for any impurity in the Test solution; and $r_{s}$ is the peak area for levodopa in the Standard solution: the impurities meet the requirements given in the table below.

| Compound <br> name | Relative <br> retention time | Relative <br> Response Factor | Limit (\%) |
| :--- | :---: | :---: | :---: |
| Levodopa Related Compound A | about 0.9 | 1.2 | 0.1 |
| Levodopa | 1.0 | - | - |
| 3-Methoxytyrosine | about 2.8 | 1.2 | 0.5 |
| 5,6-Dihydroxy-indole-2-carboxylic acid | about 6.0 | 0.4 | 0.1 |
| Unknown impurities | - | 1.0 | 0.1 Individual |
| Total | - |  | 0.3 Total Unknown |

## Briefing

Loratadine, page 3065 of the First Supplement. It is proposed to revise the Related compounds procedure to include an alternative procedure (Test 2) to accommodate a different synthesis route for the loratadine drug substance. The potential related compound 4,8-dichloro-6,11-dihydro-5 H -benzo[5,6]cyclohepta[1,2-b]pyri-din-11-one can be quantitated using the proposed Test 2 procedure. The reverse-phase HPLC gradient procedure was validated using a Hypersil BDS C18 column; loratadine elutes at approximately 21 minutes on this system. It is proposed to add two reference standards, USP Loratadine Related Compound A (desloratadine) and USP Loratadine Related Compound B (8-chloro-6,11-dihydro11 [N-methyl-4-piperidinylidene]-5H-benzo[5,6] cyclohepta[1,2$b]$ pyridine), to support the proposed Related compounds procedure; and to add a Labeling section to reflect the proposed Related compounds procedure revision.
(PA1: K. Russo; NL: C. Barnstein) RTS-33950-1; 40072-1; 40292-1; 40450-1; 40812-1

## Add the following:

-Labeling-The labeling states with which Related compounds test the article complies.■1s (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle — U S P$ Loratadine $R S$.

- USP Loratadine Related Compound A RS. USP Loratadine Related Compound B RS.■1S (USP28)


## Change to read:

## Related compounds-

$\square_{\text {NOTE-O }}$ On the basis of the synthetic route, perform either Test 1 or Test 2. Test 2 is recommended if 4,8-dichloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one is a potential related compound.

TEST 1-1 1 S (USP28)
Mobile phase and Diluent-Prepare as directed in the Assay.
Standard stock solution - Prepare as directed for Standard preparation in the Assay.

Standard solution-Pipet 5.0 mL of Standard stock solution into a $100-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix. Dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about $0.8 \mu \mathrm{~g}$ per mL .

Test solution-Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a 4.6 $\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The column
temperature is maintained between $25^{\circ}$ and $35^{\circ}$. The flow rate is about 1 mL per minute. Chromatograph the Test solution, and record the peak areas as directed for Procedure: the relative retention times are about 0.79 for 4-(8-chloro-11-fluoro-6,11-dihydro- 5 H -benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl and 1.0 for loratadine. Chromatograph the Standard solution, and record the peak area of the main peak as directed for Procedure: the relative standard deviation for replicate injections is not more than $4.0 \%$.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Test solution and the Standard solution into the chromatograph, record the chromatograms, and measure all the peak areas in the Test solution and the area of the main peak in the Standard solution. Calculate the percentage of each impurity in the portion of Loratadine taken by the formula:

$$
10,000(C / F)\left(r_{i} / r_{s}\right) / W
$$

in which $C$ is the concentration, in mg per mL, of USP Loratadine RS in the Standard solution; $F$ is the relative response factor for each impurity, if known ( $F$ is 0.25 for 4-(8-chloro-11-fluoro-6,11-dihydro-5 H -benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl); $r_{i}$ is the peak area response for each impurity in the Test solution; $r_{S}$ is the peak area response of loratadine in the Standard solution; and $W$ is the quantity, in mg , of Loratadine taken to prepare the Test solution: not more than $0.2 \%$ of 4-(8-chloro-11-fluoro-6,11-dihydro-5 H -benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl is found; not more than $0.1 \%$ of any other individual impurity is found; and not more than $0.3 \%$ of total impurities is found.
${ }^{-}$TEST 2 -
Solution $A$ —Dissolve 0.96 g of 1-pentanesulfonic acid sodium salt in 900 mL of water. Adjust with phosphoric acid solution (1 in 10 ) to a pH of $3.00 \pm 0.05$, then dilute with water to 1 L . Filter and degas.

Solution B-Use acetonitrile.
Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve accurately weighed quantities of USP Loratadine RS, USP Loratadine Related Compound A RS, and USP Loratadine Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution containing about 0.1 mg per mL of each compound. Transfer 1.0 mL of this solution to a $10-\mathrm{mL}$ volumetric flask, add 2 mL of Solution $A$, then dilute with methanol to volume, and mix to obtain a solution having a known concentration of about 0.01 mg per mL of loratadine.

Test solution-Transfer about 100 mg of Loratadine, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, and dissolve in 2 mL of methanol. Add 2 mL of Solution $A$, then dilute with methanol to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column containing $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.2 mL per minute. The chromatograph is programmed as follows.

| Time <br> $(\mathrm{min})$ | Solution A <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 75 | 25 | isocratic |
| $0-20$ | $75 \rightarrow 50$ | $25 \rightarrow 50$ | linear gradient |
| $20-30$ | $50 \rightarrow 40$ | $50 \rightarrow 60$ | linear gradient |
| $30-35$ | $40 \rightarrow 30$ | $60 \rightarrow 70$ | linear gradient |
| $35-45$ | 30 | 70 | isocratic |
| $45-50$ | $30 \rightarrow 75$ | $70 \rightarrow 25$ | step gradient |

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times and response factors are as follows.

|  | Relative <br> Retention <br> Time with <br> Respect to <br> Loratadine | Relative <br> Response <br> Factor (F) <br> with Re- <br> spect to <br> Loratadine |
| :---: | :---: | :---: |
| Related Compound | 0.50 | 1.00 |
| Loratadine related <br> compound A <br> Loratadine related <br> compound B <br> 8-Chloro-6,11-dihydro-5H- <br> benzo[5,6]cyclohepta[1,2- <br> $b]$ pyridin-11-one | 0.53 | 0.89 |


of each impurity in the portion of Loratadine taken by the formula:
$(100 / F)\left(C_{S} / C_{T}\right)\left(r_{i} / r_{S}\right)$,
in which $C_{S}$ is the concentration, in mg per mL , of USP Loratadine RS in the Standard solution; $C_{T}$ is the concentration of the Test solution; $F$ is the relative response factor as indicated in the table ( $F=1.0$ for unknown impurities); $r_{i}$ is the peak area response for the individual impurity in the Test solution; and $r_{s}$ is the peak response for loratadine in the Standard solution: not more than $0.1 \%$ of loratadine related compound A is found; not more than $0.1 \%$ of loratadine related compound B is found; less than $0.1 \%$ for each individual unknown impurity is found; and not more than $0.3 \%$ total impurities is found.■1S (USP28)

## Briefing

Lypressin Nasal Solution, USP 27 page 1112. It is proposed to revise the USP Reference standards section to change the name of USP Posterior Pituitary RS to USP Vasopressin RS, as specified in the monograph for Vasopressin Injection.
(BNT: I. DeVeau) RTS-41030-1

## Change to read:

USP Reference standards $\langle 11\rangle$ USP Posterior Pituitary RS.
-USP Vasopressin RS.■1S (USP28)

## Briefing

Magnesium Chloride, USP 27 page 1121. Comments were received that the formation of magnesium hydroxide precipitate may interfere with the Identification test for Chloride. It is proposed to add a Note that the sample solution should be acidified with dilute nitric acid prior to adding 6 N ammonium hydroxide.
(PA4: E. Gonikberg) RTS-41129-1

## Change to read:

Identification-A solution (1 in 20) responds to the tests for Magnesium $\langle 191\rangle$ and for Chloride $\langle 191\rangle$.

- [NOTE-When performing the test for Chloride, acidify the sample solution with dilute nitric acid prior to adding 6 N ammonium hydroxide.] ${ }_{\text {■S }}$ (USP28)


## Briefing

Melengestrol Acetate, page 1528 of PF 29(5) [Sept.-Oct. 2003]. On the basis of comments received, in the test for Limit of residual solvents, it is proposed to increase the acceptable standard deviation of the five replicate injections of the Standard solution from $5.0 \%$ to $10.0 \%$. Additional changes are being made in the test for Related compounds to avoid confusion between melengestrol acetate related compound A and melengestrol acetate related compound B. Minor editorial style changes have also been made.
(VET: I. DeVeau) RTS-41023-1

## Add the following:

## ■Melengestrol Acetate


$\mathrm{C}_{25} \mathrm{H}_{32} \mathrm{O}_{4} \quad 396.52$
Pregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-methyl-16-methylene-

17-Hydroxy-6-methyl-16-methylenepregna-4,6-diene-3,20-dione acetate [2919-66-6].
» Melengestrol Acetate contains not less than 97.0 percent and not more than 103.0 percent of $\mathrm{C}_{25} \mathrm{H}_{32} \mathrm{O}_{4}$, calculated on the dried basis.

Packaging and storage-Preserve in tight, light-resistant containers, and store at controlled room temperature.

Labeling-Label it to indicate that it is for veterinary use only.

USP Reference standards $\langle 11\rangle$ —USP Melengestrol Acetate RS. USP Melengestrol Acetate Related Compound A RS. USP Melengestrol Acetate Related Compound B RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ -
Solution: $\quad 10 \mu \mathrm{~g}$ per mL .
Medium: alcohol.
C: The retention time of the melengestrol acetate peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Melting temperature $\langle 741\rangle$ : between $219^{\circ}$ and $226^{\circ}$.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $-132.0^{\circ}$ and $-122.0^{\circ}$, at $20^{\circ}$.
Test solution: $\quad 10.0 \mathrm{mg}$ per mL , in chloroform.
Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 3 hours: it loses not more than $0.5 \%$ of its weight.

Heavy metals, Method II $\langle 231\rangle$ : not more than $0.001 \%$.
Limit of residual solvents-
Standard solution-Separately and accurately transfer 2.5 mL of dehydrated alcohol, 5.5 mL of ethyl acetate, 0.5 mL of dichloromethane, and 0.4 mL of dioxane into a $100-\mathrm{mL}$ volumetric flask. Mix, and dilute with dimethylformamide to volume. Pipet 5 mL of this solution into another $50-\mathrm{mL}$ volumetric flask, mix well, and dilute with dimethylformamide to volume.

Test solution-Weigh accurately about 500 mg of Melengestrol Acetate, and transfer to a $5-\mathrm{mL}$ volumetric flask, add a suitable amount of dimethylformamide, and sonicate for 5 minutes until completely dissolved. Dilute with dimethylformamide to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The gas chromatograph is equipped with a flame-ionization detector and a $3-\mathrm{mm} \times 2-\mathrm{m}$ stainless steel column packed with S 3 porous polymeric beads, $60-80$ mesh size. The temperature of the injector port, column, and detector are maintained at $200^{\circ}, 155^{\circ}$, and $250^{\circ}$, respectively. The carrier gas is nitrogen, flowing at a rate of 60 mL per minute. Chromatograph the Standard solution, and record the peak areas as directed for Procedure: the elution order is alcohol, dichloromethane, ethyl acetate, dioxane, and dimethylformamide. The resolution, $R$, between each peak should be not less than 1.5 , and the relative standard deviation for five replicate injections is not more than $5.0 \%$. $10.0 \%$.
Procedure-Separately inject equal volumes (about 1.0 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the
peak areas for alcohol, dichloromethane, ethyl acetate, and dioxane. Calculate the concentration of the individual solvents, in ppm, in the portion of Melengestrol Acetate taken by the formula:

$$
C V\left(r_{U} / r_{s}\right) /(1000 W)
$$

in which $C$ is the concentration, in g per mL , of the relevant solvent in the Standard solution; $V$ is the sample volume in $\mathrm{mL} ; r_{U}$ and $r_{S}$ are the peak areas of the relevant solvent obtained from the Test solution and the Standard solution, respectively; and $W$ is the weight, in mg, of Melengestrol Acetate taken to prepare the Test solution: not more than 5000 ppm of alcohol, 5000 ppm of ethyl acetate, 600 ppm of dichloromethane, and 380 ppm of dioxane is found.

## Related compounds-

Mobile phase-Prepare a mixture of acetonitrile and water (50:50).

Standard solution-Dissolve an accurately weighed quantity of USP Melengestrol Acetate RS, USP Melengestrol Acetate Related Compound A RS, and USP Melengestrol Acetate Related Compound B RS in methanol to obtain a solution having known concentrations of about 0.005 mg of each per mL.

Test solution-Use the Assay preparation prepared as directed in the Assay.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a multiwavelength detector set at 240 and 262 nm and a $4.6-\mathrm{mm} \times$ $25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: [NOTE-Melengestrol acetate and melengestrol related compound A B will generate larger peak areas at 262 nm than at 240 nm ; melengestrol acetate related compound $B$ A will generate a larger peak area at 240 nm than at

262 nm ] the relative retention times are about $0.77,0.78$, 1.0 , and 1.05 for melengestrol acetate related compound A, melengestrol acetate, and melengestrol acetate related compound B , respectively; the resolution, $R$, between melengestrol acetate related compound A and melengestrol acetate related compound B is not less than 5.0 ; the column efficiency for the melengestrol acetate related compound A peak is greater than 1500 theoretical plates; the tailing factor is less than 2.0 ; and the relative standard deviation for replicate injections is not more than $5.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, identify the peaks, and determine which detector wavelength generates the larger peak area for each impurity. Using the larger peak area, calculate the percentage of each impurity in the portion of Melengestrol Acetate taken by the formula:

$$
100\left(C_{S} / C_{U}\right)\left(r_{i} / r_{S}\right)
$$

in which $C_{S}$ is the concentration, in mg per mL , of either melengestrol related compound A or melengestrol related compound B in the Standard solution [NOTE-If using the impurity peak area generated at $262 \mathrm{~nm}, 240 \mathrm{~nm}, C_{S}$ is the concentration of melengestrol related compound $A$; if using the impurity peak area generated at $240 \mathrm{~nm}, 262 \mathrm{~nm}, C_{S}$ is the concentration of melengestrol related compound B$] ; C_{U}$ is the concentration, in mg per mL , of melengestrol acetate in the Test solution; $r_{i}$ is the peak area of each impurity obtained from the Test solution; and $r_{s}$ is the peak area of either melengestrol related compound A or melengestrol related compound B obtained from the Standard solution [NOTEIf using the impurity peak area generated at $262 \mathrm{~nm}, 240$ $\mathrm{nm}, r_{s}$ is the peak area of melengestrol related compound A; if using the impurity peak area generated at 240 nm, $262 \mathrm{~nm}, C_{S}$ is the peak area of melengestrol related com-
pound B ]: not more than $0.5 \%$ of any identified impurity is found; not more than $0.2 \%$ of any unidentified impurity is found; and not more than $1.0 \%$ of total impurities is found.

Assay-
Mobile phase—Prepare a mixture of acetonitrile and water (50:50).

Standard preparation-Dissolve an accurately weighed quantity of USP Melengestrol Acetate RS in methanol to obtain a solution having a known concentration of about 0.5 mg per mL .

Assay preparation-Transfer about 50 mg of Melengestrol Acetate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with methanol to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $287-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the Standard preparation as directed for Procedure: the column efficiency is not less than 1500 theoretical plates; the tailing factor is not more than 2 ; and the relative standard deviation for replicate injections is not more than 2.0\%.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation in duplicate into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{25} \mathrm{H}_{32} \mathrm{O}_{4}$ in the portion of Melengestrol Acetate taken by the formula:

$$
2 C W\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of the Standard preparation; $W$ is the weight, in mg , of Melengestrol Acetate used to prepare the Assay preparation; $r_{U}$ is the average peak area of the melengestrol acetate peak obtained from the Assay preparation; and $r_{s}$ is the average peak area of the melengestrol acetate peak obtained from the Standard preparation.■1S (USP28)

## Briefing

Mesalamine Extended-Release Capsules, USP 27 page 1173. It is proposed to specify the amount of Medium to be used in the Drug release test.
(BPC: M. Marques) RTS-40933-1

## Change to read:

Drug release $\langle 724\rangle$ -
Medium: $\quad 0.05 \mathrm{M} \mathrm{pH} 7.5$ phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate and 1 g of sodium hydroxide in water to make 1000 mL of solution, and adjusting with 10 N sodium hydroxide to a pH of $7.50 \pm 0.05$;
-900 mL .-1S (USP28) Apparatus 2: 100 rpm .
Times: $1,2,4$, and 8 hours.
Procedure-Determine the amount of $\mathrm{C}_{7} \mathrm{H}_{7} \mathrm{NO}_{3}$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 330 nm of filtered portions of the solution under test suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Mesalamine RS in the same Medium.
Tolerances-The percentages of the labeled amount of $\mathrm{C}_{7} \mathrm{H}_{7} \mathrm{NO}_{3}$ dissolved at the times specified conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $5 \%$ and $25 \%$ |
| 2 | between $30 \%$ and $50 \%$ |
| 4 | between $60 \%$ and $90 \%$ |
| 8 | not less than $85 \%$ |

## Briefing

Metformin Hydrochloride Tablets, page 1927 of PF 29(6) [Nov.-Dec. 2003]. It is proposed to revise Dissolution Test 1 to change the apparatus used from Apparatus 2 to Apparatus 1. Based on the comments received, it is also proposed to change the limit of total impurities under Related compounds test to $0.6 \%$. This limit is representative of marketed products. Other changes are editorial.
(BPC: M. Marques; PA4: E. Gonikberg) RTS—40979-1; 41092-2

## Add the following:

## Metformin Hydrochloride Tablets

## »Metformin Hydrochloride Tablets contain not

 less than 95.0 percent and not more than 105.0 percent of metformin hydrochloride $\left(\mathrm{C}_{4} \mathrm{H}_{11} \mathrm{~N}_{5} \cdot \mathrm{HCl}\right)$.Packaging and storage-Preserve in tight containers. Store at controlled room temperature.

Labeling-When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.

USP Reference standards $\langle 11\rangle$ —USP Metformin Hydrochloride $R S$.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
Test specimen-Transfer a quantity of powdered Tablets, equivalent to about 20 mg of metformin hydrochloride, to a suitable flask, add 20 mL of dehydrated alcohol, and shake. Filter, evaporate the filtrate on a water bath to dryness, and dry the residue at $105^{\circ}$ for 1 hour.

B: Triturate a quantity of the powdered Tablets, equivalent to about 50 mg of metformin hydrochloride, with 10 mL of water, and filter. To 5 mL of the filtrate add 1.5 mL of 5 N sodium hydroxide solution and 1 mL of a 1-naphthol solution, prepared by dissolving 1 g of 1-naphthol in a solution containing 6 g of sodium hydroxide and 16 g of anhydrous sodium carbonate in 100 mL of water. Add 0.5 mL of sodium hypochlorite TS, dropwise, and with shaking: an or-ange-red color is produced that darkens on standing.

C: Triturate a quantity of the powdered Tablets, equivalent to about 50 mg of metformin hydrochloride, with 10 mL of water, and filter. The filtrate meets the requirements of the tests for Chloride $\langle 191\rangle$.

Dissolution $\langle 711\rangle$ -
TEST 1—
Medium: $\quad$ pH 6.8 phosphate buffer; 1000 mL .
Apparatts 2: Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure—Determine the amount of $\mathrm{C}_{4} \mathrm{H}_{11} \mathrm{~N}_{5} \cdot \mathrm{HCl}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 233 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same Medium.

Tolerances-Not less than 70\% (Q) of the labeled amount of $\mathrm{C}_{4} \mathrm{H}_{11} \mathrm{~N}_{5} \cdot \mathrm{HCl}$ is dissolved in 45 minutes.

TEST 2-If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

FOR PRODUCTS LABELED TO CONTAIN 500 MG OF METFOR-MIN-

Medium: $\quad$ pH 6.8 phosphate buffer; 1000 mL .
Apparatus 2: 50 rpm.
Time: 30 minutes.
Procedure-Proceed as directed for Test 1.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{4} \mathrm{H}_{11} \mathrm{~N}_{5} \cdot \mathrm{HCl}$ is dissolved in 30 minutes.

FOR PRODUCTS LABELED TO CONTAIN 850 MG OR 1000 MG OF METFORMIN-

Medium: $\quad \mathrm{pH} 6.8$ phosphate buffer, 1000 mL .
Apparatus 2: 75 rpm .
Time: 30 minutes.
Procedure-Proceed as directed for Test 1.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{4} \mathrm{H}_{11} \mathrm{~N}_{5} \cdot \mathrm{HCl}$ is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Related compounds-

Mobile phase, Resolution solution, Biluted test solution, and Chromatographic system-Proceed as directed in the test for Related compounds under Metformin Hydrochloride.

Test solution-Weigh and finely powder not fewer than 20 Tablets. Transfer a portion of the powder, equivalent to about 500 mg of metformin hydrochloride, to a $100-\mathrm{mL}$ volumetric flask, dissolve in Mobile phase, with shaking, dilute with Mobile phase to volume, and mix. Filter, and use the filtrate.

Diluted test solution-Proceed as directed for Metformin Hydrochloride, except to use the Test solution prepared as described herein.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Test solution and the Diluted test solution into the chromatograph, record the chromatograms for not less than twice the retention time of metformin, and measure the peak areas.

The area of any secondary peak in the chromatogram of the Test solution is not greater than the area of the major peak in the chromatogram of the Diluted test solution; and the sum of the areas of all secondary peaks in the chroma-
togram of the Test solution is not greater than five times the area of the major peak in the chromatogram of the Diluted test solution: not more than $0.1 \%$ of any impurity is found; and not more than $0.5 \% 0.6 \%$ of total impurities is found.

## Assay-

Standard preparation-Prepare a solution of USP Metformin Hydrochloride RS in water having a known concentration of about $10 \mu \mathrm{~g}$ per mL .

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of metformin hydrochloride, to a $100-\mathrm{mL}$ volumetric flask. Add 70 mL of water, shake by mechanical means for 15 minutes, dilute with water to volume, and filter, discarding the first 20 mL of the filtrate. Dilute 10.0 mL of the filtrate with water to 100.0 mL , and dilute 10.0 mL of the resulting solution with water to 100.0 mL .

Procedure-Concomitantly determine the absorbances of the Standard preparation and the Assay preparation, in 1cm cells, at the wavelength of maximum absorbance at about 232 nm , with a suitable spectrophotometer, using water as a blank. Calculate the quantity, in mg , of metformin hydrochloride $\left(\mathrm{C}_{4} \mathrm{H}_{11} \mathrm{~N}_{5} \cdot \mathrm{HCl}\right)$ in the portion of Tablets taken by the formula:

$$
10 C\left(A_{U} / A_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Metformin Hydrochloride RS in the Standard preparation; and $A_{U}$ and $A_{S}$ are the absorbances obtained from the Standard preparation and the Assay preparation, respectively.■1S (USP28)

## BriEfing

Methscopolamine Bromide. On the basis of a recent request, it is proposed to reinstate this monograph, which was omitted from the $U S P$ in 1995.
(PA4: E. Gonikberg) RTS-40958-1

## Add the following:

## ■Methscopolamine Bromide


$\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{BrNO}_{4} \quad 398.30$

3-Oxa-9-azoniatricyclo[3.3.1.0 $0^{2,4}$ ]nonane, 7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9,9-dimethyl-, bromide, [7(S)( $1 \alpha, 2 \beta, 4 \beta, 5 \alpha, 7 \beta]$-.
$6 \beta, 7 \beta$-Epoxy-3 $\alpha$-hydroxy-8-methyl-1 $\alpha H, 5 \alpha H$-tropanium bromide ( - )-tropate [155-41-9].
» Methscopolamine Bromide contains not less than 97.0 percent and not more than 103.0 percent of $\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{BrNO}_{4}$, calculated on the dried basis.

Packaging and storage-Preserve in tight, light-resistant containers.

USP Reference standards $\langle 11\rangle$ —USP Methscopolamine Bromide RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: A solution (1 in 20) responds to the tests for Bromide $\langle 191\rangle$.

Specific rotation $\langle 781\rangle$ : between $-21^{\circ}$ and $-25^{\circ}$, calculated on the dried basis, determined in a solution containing 500 mg in each 10 mL .

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 2 hours: it loses not more than $2.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Assay-
Mobile phase-Prepare a solution containing 2.6 g of decyl sodium sulfate, in 450 mL of water. Add 550 mL of methanol, adjust with 1 N sulfuric acid to a pH of 3.5 , mix, filter, and degas.

Standard preparation-Transfer about 25 mg of USP Methscopolamine Bromide RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Assay preparation-Prepare as directed under the Standard preparation, using about 25 mg of Methscopolamine Bromide, accurately weighed.
Chromatographic system (see Chromatography $\langle 621\rangle$ The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for the peak responses is not greater than 2.0\%.

Procedure—Separately inject a volume (about $50 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into a chromatograph, record the chromatogram, and measure the peak responses. Calculate the quantity, in mg , of $\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{BrNO}_{4}$ in the portion of Methscopolamine Bromide taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Methscopolamine Bromide RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses of the methscopolamine bromide obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Mirtazapine, page 529 of PF 29(2) [Mar.-Apr. 2003]; Mirtazapine Tablets, page 531 of $P F$ 29(2) [Mar.-Apr. 2003]. These new monographs, which previously appeared in Pharmacopeial Previews, are now forwarded with proposed changes to In-Process Revision. The chemical name and CAS number are corrected. Under Chromatographic purity, the Procedure indicates a run time for chromatograms, and the chemical name of the impurity specified by the relative retention time is provided. The Melting range section is deleted. The limit of water content is specified for the anhydrous and hemihydrate forms, and a Labeling section is added to reflect the anhydrous and hemihydrate forms.
(PA3: S. Salado) RTS-40470-1; 40474-1; 40157-1; 40509-1; 40540-1; 40900-1

## Add the following:

## ■Mirtazapine


$\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3} \quad 265.35$
Pyrazino[2, 1-a]pyrido[2,3-c][2]benzazepine,
1,2,3,4,10,14b-hexahydro-2-methyl-benzazepine.
1,2,3,4,10,14b-Hexahydro-2-methylpyrazino[2,1-a]pyri-do[2,3-c][2]-benzazepine
[61337-67-5 85650-52-8].
» Mirtazapine contains not less than 98.598 .0 percent and not more than 101.5102 .0 percent of $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight containers, at temperature ber $15^{\circ}$ and store at controlled room temperature.

Labeling-Label it to indicate whether it is anhydrous or hemihydrate.

USP Reference standards $\langle 11\rangle$ —USP Mirtazapine $R S$.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Melting range $\langle 744\rangle$ : between $120^{\circ}$ and $124^{\circ}$.
Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $+2^{\circ}$ and $-2^{\circ}$.
Test solution: 10 mg per mL , in denatured alcohol.
Water, Method I $\langle 921\rangle$ : not more than 3.0\%. $1.0 \%$ for the anhydrous form and between $1.0 \%$ and $3.5 \%$ for the hemihydrate form.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method $I\langle 231\rangle$ : $0.001 \%$.
Diluent: a mixture of methanol and water (85:15).
Test preparation-Dissolve 4.8 g of mirtazapine in 51 mL of methanol. Add 9 mL of water. Adjust 25 mL of this solution with 1 N acetic acid to a pH of between 3.0 and 4.0, using a short-range pH indicator paper as the internal indicator. Dilute with Diluent to 40 mL , and mix.

NOTE-Use Diluent instead of water to prepare the Standard preparation and Monitor preparation. Prepare a blank of Diluent, and use Diluent instead of water in the Procedure.

## Chromatographic purity-

Diluent, Buffer solution, and Mobile phase—Proceed as directed in the Assay.

Standard solution-Dissolve an accurately weighed quantity of USP Mirtazapine RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about $0.1515 \mu \mathrm{~g}$ per mL .

Test solution-Transfer about 150 mg of Mirtazapine, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $240-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Standard solution, and record the peak response as directed for

Procedure: the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $10.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L})$ of the Standard solution and the Test solution into the chromatograph, record the chromatograms, for about twice the retention time of Mirtazapine, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Mirtazapine taken by the formula:

$$
10,000 F(C / W)\left(r_{i} / r_{s}\right)
$$

in which $F$ is the relative response factor for the mirtazapine impurities and is equal to 0.24 for any impurity 4-methyl-1-(3-methyl-pyridin-2-yl)-2-phenyl-piperazine at a relative retention time of about 1.3 , and 1.0 for any other impurity; $C$ is the concentration, in mg per mL , of USP Mirtazapine RS in the Standard solution; $W$ is the weight, in mg , of Mirtazapine taken to prepare the Test solution; $r_{i}$ is the peak response of any impurity obtained from the Test solution; and $r_{S}$ is the mirtazapine peak response obtained from the Standard solution: not more than $0.1 \%$ of any individual impurity is found, and not more than $0.5 \%$ of total impurities is found. [NOTE-Disregard any peak representing less than $0.05 \%$ of the main peak and any peak that is due to the Di luent.]

Organic volatile impurities, Method $I V\langle 467\rangle$ : meets the requirements.

## Assay-

Diluent: a mixture of acetonitrile and water (50:50).
Buffer solution-Transfer about 36.0 g of tetramethylammonium hydroxide pentahydrate to a $2000-\mathrm{mL}$ volumetric flask, and dissolve in about 1950 mL of water. While stirring, adjust with phosphoric acid to a pH of 7.4 , dilute with water to volume, and mix.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution, acetonitrile, methanol, and tetrahydrofuran ( $65: 15: 12.5: 7.5$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Mirtazapine RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 0.3 mg per mL .
Assay preparation-Transfer about 30 mg of Mirtazapine, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $290-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Standard preparation, and record the peak response as directed for Procedure: the column efficiency is not less than 7000 theoretical plates; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L})$ of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3}$ in the portion of Mirtazapine taken by the formula:

$$
100 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Mirtazapine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.ns (USP28)

## Briefing

Mirtazapine Tablets, page 531 of PF 29(2) [Mar.-Apr. 2003]-See briefing under Mirtazapine. In the test for Chromatographic purity, it is proposed to revise the Procedure to indicate a run time for chromatograms and to provide the chemical name of the impurity specified by the relative retention time.
(PA3: S. Salado) RTS-40509-2

## Add the following:

## ■Mirtazapine Tablets

» Mirtazapine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of mirtazapine $\left(\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3}\right)$.

Packaging and storage-Preserve in tight, light-resistant containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Mirtazapine $R S$.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
Extraction mixture: a mixture of water and $n$-hexane (1:1).

Test specimen-Transfer a quantity of finely powdered Tablets, equivalent to about 30 mg of mirtazapine, to a suitable centrifuge tube. Add Extraction mixture to obtain a solution of about 1 mg of mirtazapine per mL of $n$-hexane. Shake for 5 minutes, and centrifuge. Decant, and evaporate the supernatant.

Standard specimen-Dissolve an accurately weighed quantity of USP Mirtazapine RS in Extraction mixture to obtain a solution having a concentration of about 1 mg of mirtazapine per mL of $n$-hexane. Shake for 5 minutes, and centrifuge. Decant, and evaporate the supernatant.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Dissolution $\langle 711\rangle$ -
Medium: $\quad 0.1 \mathrm{~N}$ hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm .
Time: 15 minutes.
Procedure: Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 315 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, in comparison with a Standard solution having a known concentration of USP Mirtazapine RS in the same Medium.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3}$ is dissolved in 15 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements for Content Uniformity.

## Chromatographic purity-

Diluent, Buffer solution, and Mobile phase-Proceed as directed in the Assay under Mirtazapine.

Standard stock solution-Prepare as directed for Standard preparation in the Assay under Mirtazapine.

Standard solution-Transfer 5.0 mL of Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.

Test solution-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to the weight of 1 Tablet, to a suitable conical
flask. Add Diluent to obtain a solution having a concentration of about 1.5 mg of mirtazapine per mL of Diluent. Shake vigorously for 10 minutes, centrifuge an aliquot, and use the clear supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $240-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L 1 . The flow rate is about 1.5 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Standard solution, and record the peak response as directed for Procedure: the column efficiency is not less than 7000 theoretical plates; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $10.0 \%$.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms for about twice the retention time of mirtazapine, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Mirtazapine taken by the formula:

$$
5(F V)(C / W)\left(W_{20} / L\right)\left(r_{i} / r_{s}\right),
$$

in which $F$ is the relative response factor for the mirtazapine impurities and is equal to 0.24 for impurity 4-methyl-1-(3-methyl-pyridin-2-yl)-2-phenyl-piperazine at a relative retention time of about 1.3 , and 1.0 for any other impurity; $V$ is the total volume, in mL , of the Test solution; $C$ is the concentration, in mg per mL, of USP Mirtazapine RS in the Standard solution; $W$ is the weight, in mg , of the powdered Tablets taken to prepare the Test solution; $W_{20}$ is the weight of the 20 Tablets taken; $L$ is the labeled amount, in mg, of mirtazapine in each Tablet; $r_{i}$ is the peak response of any impurity obtained from the Test solution; and $r_{s}$ is the mirtazapine peak response obtained from the Standard solution: not more than $0.2 \%$ of any individual impurity is
found, and not more than $2.0 \%$ of total impurities is found. [NOTE-Disregard any peak representing less than $0.05 \%$ of the main peak and any peak that is due to the Diluent.]

## Assay-

Diluent, Buffer solution, Mobile phase, and Standard pre-paration-Prepare as directed in the Assay under Mirtazapine.

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to the weight of 1 Tablet, to a suitable conical flask. Add Diluent to obtain a solution having a concentration of about 0.3 mg of mirtazapine per mL of Di luent. Shake vigorously for 10 minutes, centrifuge an aliquot, and use the clear supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a 290 -nm detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Standard preparation, and record the peak response as directed for Procedure: the column efficiency is not less than 7000 theoretical plates; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $1.5 \%$.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of mirtazapine $\left(\mathrm{C}_{17} \mathrm{H}_{19} \mathrm{~N}_{3}\right)$ in the portion of Tablets taken by the formula:
in which $V$ is the volume, in mL , of the Assay preparation; $C$ is the concentration, in mg per mL , of USP Mirtazapine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{1 S}$ (USP28)

## Briefing

Naproxen, USP 27 page 1283. It is proposed to replace the solvent used in the Specific rotation test with one that has a lower potential for hazardous effects.
(PA1: C. Anthony) RTS-39540-1

## Change to read:

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $+63.0^{\circ}+68.5^{\circ}$.
$-+83.0^{\circ}$ and $+89.5^{\circ} \cdot 1 \mathrm{IS}$ (USP28)
Test solution: 10 mg per mL , in ehlorm.

- methylisobutyl ketone.■1S (USP28)


## Briefing

Octisalate, USP 27 page 1354. In Identification test $B$, it is proposed to specify the wavelength at which the absorptivity is determined.
(PA6: L. Evans) RTS-41112-1

$$
V C\left(r_{U} / r_{s}\right)
$$

## Change to read:

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~F}\rangle$.
B: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ -
Solution: $\quad 5.0 \mu \mathrm{~g}$ per mL .
Medium: alcohol. Abserptivities,

- Absorptivity at 305 nm , ${ }^{15}$ (USP28) calculated on the as-is basis, de
- $^{\text {does }_{\text {日 }}^{1 S}}{ }_{\text {(USP28) }}$ not differ by more than $3.0 \%$.


## Briefing

Octocrylene, USP 27 page 1355. It is proposed to revise the test for Acidity to reflect data in the original submission.
(PA6: L. Evans) RTS-41111-1

## Change to read:

Acidity-Transfer 60 mL of alcohol to a suitable container, add 1 mL of phenolphthalein TS, and add sufficient 0.1 N sodium hydroxide to obtain a persistent pink color. Transfer 60 mL of this solution to a suitable container, add about 6 g of Octocrylene, accurately weighed, mix, and titrate with 0.1 N sodium hydroxide: not more than 0.18 mL of titrant per mg
$\mathbf{m}_{\mathrm{m}_{1 S}(U S P 28)}$
of Octocrylene is necessary to obtain a persistent pink endpoint.

## Briefing

Ondansetron Oral Solution, page 34 of $P F$ 26(1) [Jan.-Feb. 2000]. This new monograph, which previously appeared in Pharmacopeial Previews, is now being forwarded, with minor editorial revisions, to In-Process Revision.

$$
\text { (PA3: S. Salado) } \quad \text { RTS }-41103-1
$$

## Add the following:

## ■Ondansetron Oral Solution

» Ondansetron Oral Solution is a solution of Ondansetron Hydrochloride in a suitable vehicle. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of ondansetron $\left(\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}\right)$.

Packaging and storage-Preserve in well-closed, light-resistant containers.

USP Reference standards $\langle 11\rangle$ —USP Ondansetron Hydrochloride RS. USP Ondansetron Related Compound A RS. USP Ondansetron Related Compound C RS. USP Ondansetron Related Compound D RS.

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -
Test solution-Dilute a portion of Oral Solution with a mixture of methanol and water ( $50: 50$ ) to obtain a solution containing about 0.2 mg of ondansetron per mL .
Standard solution: $\quad 0.25 \mathrm{mg}$ per mL in methanol.
Developing solvent system: chloroform, ethyl acetate, methanol, and ammonium hydroxide ( $90: 50: 40: 1$ ).

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Escherichia coli. The total aerobic microbial count does not exceed 100 cfu per g, the Enterobac-
teriaceae count does not exceed 10 cfu per g, and the total combined molds and yeasts count does not exceed 50 cfu per g.

Deliverable volume $\langle 698\rangle$ : meets the requirements. $\mathbf{p H}\langle 791\rangle$ : between 3.3 and 4.0.

## Limit of ondansetron related compound D-

Mobile phase-Proceed as directed in the test for Limit of ondansetron related compound D under Ondansetron Hydrochloride.

System suitability solution-Dissolve suitable quantities of USP Ondansetron Related Compound D RS and USP Ondansetron Related Compound C RS in Mobile phase; and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution containing about $0.5 \mu \mathrm{~g}$ per mL and $2 \mu \mathrm{~g}$ per mL , respectively.

Standard solution-Dissolve an accurately weighed quantity of USP Ondansetron Related Compound D RS in Mobile phase; and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $0.5 \mu \mathrm{~g}$ per mL .
Test solution-Dilute, if necessary, an accurately measured volume of Oral Solution quantitatively with Mobile phase to obtain a solution containing about 0.8 mg of ondansetron per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $328-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between ondansetron related compound D and ondansetron related compound C is not less than 2.0; the tailing factor for ondansetron related compound D is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $4.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of ondansetron related compound D in the volume of Oral Solution taken by the formula:

$$
100 D\left(C_{S} / C_{A}\right)\left(r_{U} / r_{s}\right)
$$

in which $D$ is the dilution factor for the Oral Solution in the Test solution; $C_{S}$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Ondansetron Related Compound D RS in the Standard solution; $C_{A}$ is the concentration, in $\mu \mathrm{g}$ per mL , of ondansetron in the Oral Solution, as determined in the Assay; and $r_{U}$ and $r_{s}$ are the peak responses of ondansetron related compound D obtained from the Test solution and the Standard solution, respectively: not more than $0.1 \%$ is found.

## Related compounds-

Mobile phase, System suitability solution, Standard preparation, and Chromatographic system-Proceed as directed in the Assay under Ondansetron Hydrochloride.

Test preparation-Use the Assay preparation.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Test preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each related compound in the volume of Oral Solution taken by the formula:

$$
(293.36 / 329.82) 1000(F / V)\left(C_{S} / C_{A}\right)\left(r_{i} / r_{S}\right)
$$

in which 293.36 and 329.82 are the molecular weights of ondansetron and anhydrous ondansetron hydrochloride, respectively; $F$ is the relative response factor and is equal to 0.5 for ondansetron related compounds at relative retention times of about 0.45 and $0.58,0.75$ for ondansetron related
compounds at relative retention times of about $0.63,0.84$ and 1.1, and 1 for all other impurities; $V$ is the volume, in mL , of Oral Solution taken; $C_{S}$ is the concentration, in mg per mL , on the anhydrous basis, of USP Ondansetron Hydrochloride RS in the Standard preparation; $C_{A}$ is the concentration, in mg per mL , of ondansetron in the Oral Solution; $r_{i}$ is the peak response for any related compound obtained from the Test preparation; and $r_{s}$ is the peak response for ondansetron obtained from the Standard preparation: not more than $0.2 \%$ of any related compound is found, and the sum of all impurities is not more than $0.5 \%$.

## Assay-

Mobile phase, System suitability solution, Standard preparation, and Chromatographic system-Proceed as directed in the Assay under Ondansetron Hydrochloride.

Assay preparation-Transfer an accurately measured volume of Oral Solution, equivalent to about 9 mg of ondansetron, to a $100-\mathrm{mL}$ volumetric flask; dilute with Mobile phase to volume; and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $216-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.1 for ondansetron related compound A and 1.0 for ondansetron; and the resolution, $R$, between ondansetron related compound A and ondansetron is not less than 1.5. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 , and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and
measure the responses for the major peaks. Calculate the quantity, in mg , of ondansetron $\left(\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}\right)$ in each mL of Oral Solution taken by the formula:

$$
(293.36 / 329.82) 100(C / V)\left(r_{U} / r_{S}\right)
$$

in which 293.36 and 329.82 are the molecular weights of ondansetron and anhydrous ondansetron hydrochloride, respectively; $C$ is the concentration, in mg per mL , on the anhydrous basis, of USP Ondansetron Hydrochloride RS in the Standard preparation; $V$ is the volume, in mL , of Oral Solution taken; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BriEfing

Opium, USP 27 page 1361. In the Assay, it is proposed to replace the name of the reagent methyl sulfoxide with its synonym dimethyl sulfoxide. The use of the name "dimethyl sulfoxide" is being standardized throughout the $U S P-N F$. In addition, minor editorial style changes have been made.
(BPC: M. Marques) RTS-41082-3

## Change to read:

## Assay-

Chromatographic tubes, Citrate buffer, and Standard prepara-tion-Prepare as directed in the Assay under Paregoric.

Assay preparation-Transfer about 2 g of Opium, accurately weighed, to a $250-\mathrm{mL}$ beaker, add 20 mL of methyl-sulfoxide,
-dimethyl sulfoxide, ■ $^{1 S}$ (USP28)
and heat for 20 minutes on a steam bath, intermittently dispersing the substance with a flat-end stirring rod. Allow to stand for 15 minutes to permit undissolved material to settle, and carefully decant the supernatant into a $100-\mathrm{mL}$ volumetric flask. Add another 20 mL of methyl-sulfoxide

- dimethyl sulfoxide $_{\text {n } 1 \mathrm{~S} \text { (USP28) }}$
to the residue, rinsing the sides of the beaker with the methyl sulf exide.
- dimethyl sulfoxide. 1 IS (USP28)

Disperse and heat the substance as before, allow to settle, and decant into the volumetric flask. Repeat the dissolution one or two times, until the opium is dissolved (other than for small leaf fragments, sand-like particles, gelatinous materials, etc.). Rinse the beaker, and transfer the residue to the flask with the aid of water. Dilute with water to about 90 mL , and mix. If necessary, add 1 drop of alcohol to dispel any foam. Cool to room temperature, adjust with water to volume, and mix. Pass the resulting solution through a medium-porosity filter paper, discarding the first 20 mL of the filtrate.

Chromatographic columns-Pack a pledget of glass wool at the base of each of the three tubes, and fill with adsorbent using chromatographic siliceous earth as the base of the adsorbent, and tamping it firmly in place. Prepare the tubes as follows. Pack Column I in two layers, the lower layer consisting of 3 g of chromatographic siliceous earth mixed with 2 mL of Citrate buffer and the upper layer consisting of 3 g of chromatographic siliceous earth mixed with 2.0 mL of the Assay preparation and 0.5 mL of Citrate buffer. Dry-rinse the beaker in which the components of the two layers have been mixed with 1 g of chromatographic siliceous earth, and add it also to the top of Column I. Pack Column II with 3 g of chromatographic siliceous earth mixed with 2 mL of dibasic potassium phosphate solution ( 1 in 5.75). Pack Column III with 3 g of chromatographic siliceous earth mixed with 2 mL of sodium hydroxide solution (1 in 50). Place a small pad of glass wool above each column packing.

Procedure-Proceed as directed in the Assay under Paregoric. Calculate the percentage of anhydrous morphine in the Opium taken by the formula:

$$
0.25(C / W)\left(A_{U} / A_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of anhydrous morphine in the Standard preparation; $W$ is the weight, in g , of Opium taken; and $A_{U}$ and $A_{S}$ are the corrected absorbances of the solutions from the Assay preparation and the Standard preparation, respectively.

## Briefing

Oxybutynin Chloride, USP 27 page 1373 and page 642 of $P F$ 29(3) [May-June 2003]. On the basis of comments received, a revision is proposed in the test for Related compounds and in the Assay based on the updated liquid chromatographic procedure. The proposal for Related compounds previously published in PF 29(3) is being canceled and replaced with the updated method, and the proposal for the Assay is being published again with several changes. The procedure is based on analyses performed with the $3.5-\mu \mathrm{m}$ Zorbax C8 brand, or the $3-\mu \mathrm{m}$ Luna C8 brand of L7 col-
umn. The typical retention time for oxybutynin is about 14 minutes. The $P F 29(3)$ proposal for Packaging and storage is also being canceled.
(PA4: E. Gonikberg) RTS-41115-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Oxybutynin Chloride RS. USP Phenyleyelohexylghyeolic Aeid RS.
-USP Oxybutinin Chleride Related Cempent A RS. USP
Oxybutynin Related Compound B RS. USP Oxybutynin Re-
lated Compound C $R S_{\mathbf{■ 1 S}^{\text {(USP28) }}}$

## Delete the following:

## -Chromatographie purity-

Triethatane pherphatione 2 mL of trietha nolamine in about 900 mL of water in a 1000 mL volumetric flask, adjust with phosphoric acid to a pH of 3.5 , dilute with water to volume, and mix.

Mobile phase Prepare a degassed and filtered mixture of acet enitrile and Triethamolamine phosphate solution ( $65: 35$ ). Make adjustments if neeessary (see System Suitability under Chromato graphy (624) ).

Standard preparation- Prepare a solution containing 2.0 mg of USP Oxybuynin Chloride RS per mL and 10 Hy of USP Phenyl eyclohexylglyeolic Acid PS per mL in ace anitrile. Filter through a $0.45 \mathrm{\mu m}$ filter.

Test preparain. Transfer 200 mg of Oxybutyin Chloride, ac eurately weighed, to a 100 mL velumetric flask, dissolve in acet enitrile, dilute with acenitrile to volume, and mix.

Chromagraphic system (see-Chremography (624)) The 1iquid chromatograph is equipped with a 200 nm detector and -4.6 $\mathrm{mm} \times 25 \mathrm{~cm}$ coltumn that contains packing L7, and a shert preevlumm that contains packing 47 is used if neeessary. The columm is maintained at a temperature of $45^{\circ}$. The flow rate is about 3 mL per minute. Chromatograph a solution in acetonitrile containing 40 Hy permL each of USP OxybutyinChloride RS and USP Phenyl eycloherylglyeolic Acid $P S$, and record the peak responses as directed under Procedure: the relative-standard deviation of the respenses for replientinjections is not more than $3.0 \%$, and the resolution, $R$, of the main peaks is not less than 5.0 .

Procedure Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Test preparation into the chromatograph, and record the chromatograms. The relative retention times are about 0.2 for phenyleyelohexylglyeolic acid and 1.0 for oxybutynin. In the chromatogram of the-Test preparation, any peak correspending in retention time to phenyleyclohexylgly eolic acid has a respense not greater than that in the ehrematogram of the Standard preparation, and the sum of the respenses of all peaks, excluding the solvent front and oxybutynin, is not greater than wice that value-!1S (USP28)

## Add the following:

## -Related compounds-

Phosphate buffer and Mobile phase-Prepare as directed in the Assay.

System suitability stock solution-Dissolve accurately weighed quantities of USP Oxybutynin Related Compound B RS and USP Oxybutynin Related Compound C RS in Mobile phase to obtain a solution having known concentrations of about $100 \mu \mathrm{~g}$ of each USP Reference Standard per mL .

Standard stock solution-Dissolve an accurately weighed quantity of USP Oxybutynin Chloride RS in Mobile phase to obtain a solution having a known concentration of about 1.0 mg per mL .

System suitability solution-Transfer 10.0 mL of the System suitability stock solution to a $100-\mathrm{mL}$ volumetric flask, add 10.0 mL of the Standard stock solution, and dilute with Mobile phase to volume.

Standard solution-Transfer 15.0 mL of the Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume. Transfer 5.0 mL of the solution obtained to a separate $100-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume. This solution contains about $7.5 \mu \mathrm{~g}$ of USP Oxybutynin Chloride RS per mL.

Test solution-Transfer about 50 mg of Oxybutynin Chloride, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system-Prepare as directed in the Assay. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between oxybutynin related compound B and oxybutynin related compound C peaks is not less than 1.1; and the relative standard deviation for replicate injections, determined from the oxybutynin peak, is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms for a total time of not less than twice the retention time of the oxybutynin peak, and measure all the peak responses (see Table 1 for known impurities). Calculate the percentage of each impurity in the portion of Oxybutynin Chloride taken by the formula:

$$
(C / W)(1 / F)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Oxybutynin Chloride RS in the Standard solution; $W$ is the weight, in mg , of Oxybutynin Chloride taken to prepare the Test solution; $F$ is the relative response factor for each impurity (see Table 1 for the values); and $r_{U}$ and $r_{S}$ are the peak responses for each impurity obtained from the Test solution and for the oxybutynin peak in the Standard solution, respectively. [NOTE-For unknown impurities, use the relative response factor of the closest known impurity.]

Table 1

| Relative |  | Relative |  |
| :---: | :---: | :---: | :---: |
|  |  | response |  |
| Retention |  | factor | Limit |
| Time | Name | (F) | (\%) |
| 0.08 | Oxybutynin Related | 1.4 | 0.5 |
|  | Compound $\mathrm{A}^{1}$ |  |  |
| 0.37 | Diphenyl analog of | 2.7 | 0.1 |
|  | oxybutynin chloride ${ }^{2}$ |  |  |
| 0.65 | Oxybutynin Related | 1.3 | 1.0 |
|  | Compound B ${ }^{3}$ |  |  |
| 0.79 | Oxybutynin Related | 1.0 | 1.0 |
|  | Compound $\mathrm{C}^{4}$ |  |  |
| 1.8 | Cyclohexenyl analog of | 0.4 | 1.0 |
|  | oxybutynin chloride ${ }^{5}$ |  |  |
| 1.9 | Ethylpropyl analog of | 1.0 | 0.1 |
|  | oxybutynin chloride ${ }^{6}$ |  |  |

${ }^{1}$ phenylcyclohexylglycolic acid (cyclohexylmandelic acid, $\varrho_{2}$ CHMA);
${ }^{2}$ 4-(diethylamino)but-2-ynyl 2-hydroxy-2,2-diphenylacethate
${ }^{3}$ methyl ester of phenylcyclohexylglycolic acid (methyl ester of cyclohexylmandelic acid, or CHMME);
${ }^{4}$ methylethyl analog of oxybutynin chloride (4-(ethylmethylamino) but-2-ynyl ( $\pm$ )-2-cyclohexyl-2-hydroxy-2phenylacetate)
4-(diethylamino)but-2-ynyl ( $\pm$ )-2-(cyclohex-3-enyl)-2-cyclohexyl-2-hydroxyacetate
${ }^{6}$ 4-(ethylpropylamino)but-2-ynyl ( $\pm$ )-2-cyclohexyl-2-hy-droxy-2-phenylacetate
green endpoint. Perform a blank determination, and make any neeessary correction. Each mL of 0.1 Nperchloric acid is equivalent to 39.40 mg of $\mathrm{C}_{22} \mathrm{H}_{4+} \mathrm{NO}_{3} \cdot \mathrm{HCl}$.

- Phosphate buffer-Dissolve about 3.40 g 6.67 g of monobasic potassium phosphate and 4.35 g 8.55 g of dibasic potassium phosphate in 1 L of water, and mix.

Mobile phase-Prepare a filtered and degassed mixture of Phosphate buffer and acetonitrile ( $51: 49$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Oxybutynin Chloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.5 mg 0.1 mg per mL .
Assay preparation-Transfer about 50 mg of Oxybutynin Chloride, accurately weighed, to a $100-\mathrm{mE} 10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix. Transfer 2.0 mL of this solution to a separate $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector and a $3-\mu \mathrm{m}$, or $3.5-\mu \mathrm{m}, 4.6-\mathrm{mm} \times 7.5-\mathrm{cm}$ column or $5-$ Imm $3.9 \mathrm{~mm} \times 15 \mathrm{em}$ column that contains packing L7. The column temperature is maintained at $45^{\circ}$. The flow rate is about 1 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the
quantity, in mg, of $\mathrm{C}_{22} \mathrm{H}_{31} \mathrm{NO}_{3} \cdot \mathrm{HCl}$ in the portion of Oxybutynin Chloride taken by the formula:

$$
100 \mathrm{C}\left(+_{5}++_{s}\right)
$$

$$
C D\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Oxybutynin Chloride RS in the Standard preparation; $D$ is the dilution factor for the Assay preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\quad$ IS (USP28)

## Add the following:

■ Paroxetine Hydrochloride

$\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3} \cdot \mathrm{HCl} \quad 365.83$
Piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-, hydrochloride, (3S-trans)-.
(-)-(3S,4R)-4-(p-Fluorophenyl)-3-[(3,4-methylenedioxy)phenoxy]methyl]piperidine hydrochloride
[78246-49-8].
Hemihydrate 374.83 [GAS
» Paroxetine Hydrochloride is anhydrous or contains one-half molecule of water of hydration. It contains not less than 98.5 percent and not more than 102.0 percent of $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3} \cdot \mathrm{HCl}$, calculated on the anhydrous and solvent-free basis.

## Change to read:

Packaging and storage-Preserve the anhydrous form in tight containers. Preserve the hemihydrate form in wellclosed containers. Store $15^{\circ}$ and $30^{\circ}-$ Store at controlled room temperature. ${ }^{1 S}$ (USP28)

Labeling-Label it to indicate whether it is the anhydrous or the hemihydrate form. Label it to indicate with which impurity tests the article complies.

USP Reference standards $\langle 11\rangle$ —USP Paroxetine Hydrochloride RS. USP Paroxetine Related Compound A RS. USP Paroxetine Related Compound B RS. USP Paroxetine Related Compound C RS. USP Pawetine Related Com D RS. USP Paroxetine Related Compound E RS. USP Paroxetine Related Compound F RS. USP Paroxetine Related Compound G RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$ -
Test specimen-Dissolve a suitable portion of Paroxetine Hydrochloride in a solution of water in isopropyl alcohol (1 in 10), heat to $70^{\circ}$ to dissolve, recrystallize, and we the re sidte. and dry the residue under vacuum at $50^{\circ}$ for 3 hours.
Standard specimen: a similar preparation of USP Paroxetine Hydrochloride RS.

B: A solution (1 in 100) in a mixture of methanol and water $(1: 1)$ meets the requirements of the test for Chloride $\langle 191\rangle$.

Melting range, Class $I\langle 741\rangle$ : between $115^{\circ}$ and $126^{\circ}$ for the anhydrous form;[To come for the anhydrous form] be tween $141^{\circ}$ and $145^{\circ}$ for the hemihydrate form.

## Change to read:

Water, Method I $\langle 921\rangle$ : not more than $1.5 \%$ $1.0 \%{ }^{-1.5 \%}{ }_{1 S}$ (USP28) for the anhydrous form and between z.0\% $2.2 \%$ and $3.0 \% 2.8 \%$ for the hemihydrate form.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $0.002 \%$.
Limit of stereoisomers Limit of related compound C-
Mobile phase Prepare a filtered and degassed mixture of 0.5 M sodium chloride and methanol (4:1). Make adjust ments if necessary (see-System-Suitabilit) under Chromato (624) )
6.05 M Phesphate buffer solution Dissolve 8.7 g of di basic potassium phosphate in 1000 mL of water, and adjust with phespheric acid to a pH of 6.5 .

Mobile phase Prepare a filtered and degassed mixture of 0.05 M Phesphate buffer solution and acetonitrile (92:8). Make adjustments if neeessary (see-System Suitability under Chromatography $\langle 624$ ) .

Systen suitability solution Transfer about 5-mg of USP
Paroxetine Hydrechloride Related-Compound-C RS and about 5 mg of USP Paroxetine Hydrochloride- RS, aeeu rately weighed, to a $10-\mathrm{mL}$ volumetric flask. Dissolve in 4 mL of methanol, dilute with Mobile phase to volume, and mix.

Standard solution Dissolve-an aceurately weighed quantity of USP Parexetine-Related Compeund C RS and USP Paroxetine Hydrechloride RS in methanol, the volume of the solvent not exceeding 20\% of the final solution veftume, and dilute quantitatively with 0.5 M -soditum chloride to obtain a solution having a known concentration of about 0.01 mg of each USP Reference Standard per mL. If stepwise dilation is necessary, dilate with Mobite phatse instead.

Test solution Transfer about 100 mg of Parexetine Hy drochloride, aceurately weighed, to a 100 mL volumetric flask, dissolve in 20 mL of methanol, dilute with $0.5 \mathrm{M}-\mathrm{se}-$ ditim chloride volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ ) The liquid chrematograph is equipped with a 295 nmedetec for and a- $4-\mathrm{mm} \times 10 \mathrm{~cm}$ coltmm that contains packing L41. The flot rate is about 0.5 mL per mintte. Chremategraph the Standard System suitability solution, and record the peak respenses as directed for Procedure: the relative retention times are about 0.56 for paroxetine-related compound $C$ and 1.0 for paroxetine; the resolution, $R$, between paroxetine related compound $C$ and paroxetine is not less than 1.8, the celtumn efficiency determined from the related compeund $G$
peak is not less than 230 theoretical plates; the tailing factor for the paroxetine related compernd $C$ peak is not more than 1.6; and the relative standard deviation for replieate injec tions is not more than $2.0 \%$.

Procedtre Separately inject equal volumes Inject avo lame (about $10 \mu \mathrm{~L}$ ) of the Standard solttion and the Test solution into the chromatograph, record the chromatogram, and measture all of the peak respenses. Caleutate the percenfage of paroxetine relatedeompernd $C$ in the pertion of Par oxetine Hydrochloride taken by the formmat:

$$
\begin{gathered}
10(C / H)\left(r_{4}+\Psi_{s}\right), \\
100\left(\not+r_{n}\right),
\end{gathered}
$$

in which $C$ is the concentration, in $\mu$ g per mL , of USP Par oxetine-Related Compound C RS in the Standerd solution; Wis the quantity, in mg, of Paroxetine Hydrechloride in the Test soluion; and $r_{4}$-and $r_{s}$ are the peak responses for par oxetine related compound-C obtained from the Test solution and the Standard solution, respectively. in which-ris the peak respense for paroxetine related compound $C$, andr. is the sum of the respenses of all of the peaks: not more than $0.1 \%$ is found.

## LIMIT OF RELATED-COMPOUND D-

Phesphate buffer. Prepare a 0.05 M menebasic soditm phosphate solution-in water, adjust with phesphoric acid to a pH of 3.0 , and mix.

Mobile phatse Prepare a filtered and degassed mixture of
Phosphate buffer and acetonitrile (3:2). Make adjustments if neeessary (see System Suitability under Chromatography $\langle 624\rangle$.

Standard solution Dissolve aceurately weighed quantities of USP Paroxetine-Related Compound D-RS and USP Paroxetine Hydrochloride RS in water, and dilute quantita
tively, and stepwise if necessaty, with water to obtain a-solation having known eoneentrations of about 0.1 and 1.0 mg per mL , respectively.

Fest solution Transfer about 100 mg of Paroxetine Hy drochloride, aceurately weighed, to a $50-\mathrm{mL}$ volumetrie flask, dissolve in and dilute with water to voltume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )_ The liquid chromatograph is equipped with a 295 nm detec tor and a $4.6 \mathrm{~mm} \times 25$-mm coltmm that contains packing E13. The flow rate is about 1 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention-times are about 1.2 for parexetine related compeund $D$ and 1.0 for paroxetine; the resolution, $R$, between paroxetine related eompound $D$ and parexetine is not less than 2.2; the columm efficiency determined from the paroxetine-related compound $D$ peak is not less than- 4000 theoretical plates; the failing factor for the related compound $D$ peak is not more than 1.8; and the relative standard deviation for replicate in jections is net mere than $2.5 \%$.

Procedtre Separately inject equal volumes (about 10 HL) of the Standard solution and the Test solution into the ehromagraph, record the chromatograms, and measure the respenses for the major peaks. Caleulate the pereentage of paroxetine related compound $D$ in the portion of Paroxetine Hydrochloride taken by the formula:-

$$
5(C / H)\left(r_{t}+r_{s}\right)
$$

in which $C$ is the concentration, in $\mu$ g per mL, of USP Parexetine Related Compernd D-RS in the Standard solution; Wis the quantity, in mg, of Paroxetine Hydrochloride in the Fest solution; and $r_{t}$-and $r_{s}$ are the peak respenses for par exetine related compound $D$ obtained from the Test solutiont
and the Standard solttion, respectively: the sum of the pereentages found in the Limit of related compernd $C$ and the Limit of related compernd $D$ tests is net mere than $0.1 \%$.

Mobile phase-Prepare a mixture of $n$-hexane, alcohol, water, and trifluoroacetic acid ( $900: 100: 2: 2$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Diluent: $\quad$ a mixture of alcohol and $n$-hexane ( $1: 1$ ).
Standard solution-Dissolve an accurately weighed quantity of USP Paroxetine Related Compound C RS, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 1 mg per mL .
Test solution-Transfer about 125 mg of Paroxetine Hydrochloride, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.

System suitability solution-Dilute known volumes of the Test solution and the Standard solution with Diluent to obtain a solution having known concentrations of about 0.1 mg per mL of each of USP Paroxetine Hydrechloride RS Paroxetine Hydrochloride and of USP Paroxetine Related Compound C RS.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $295-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing E49. L51. The flow rate is about 1.0 mL per minute, and the column temperature is maintained at $30^{\circ}$. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times for paroxetine and paroxetine related compound C are 1.0 and about 0.6 , respectively; the resolution, $R$, between paroxetine and paroxetine related compound C is not less than 2.0 ; and the tailing factor for paroxetine related compound C is not greater than 2.0. Chromatograph the

Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$ for the paroxetine related compound C .

Procedure-Separately inject equal volumes (about $5 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of paroxetine related compound C in the portion of Paroxetine Hydrochloride taken by the formula:

$$
10,000(C / H)\left(+++_{s}\right)
$$

$$
2500(C / W)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Paroxetine Related Compound C RS in the Standard solution; $W$ is the weight, in mg , of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the Test solution; and $r_{i}$ and $r_{s}$ are the peak areas for paroxetine related compound C in the Test solution and the Standard solution, respectively: not more than of $0.1 \%$ of paroxetine related compound C is found.

## Change to read:

## Limit of 1-methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydro-

 pyridine-Solution A-Prepare a filtered and degassed mixture of acetonitrile and trifluoroacetic acid (1000:1).

Solution B-Prepare a filtered and degassed mixture of water and trifluoroacetic acid (1000:1).
Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Paroxetine Related Compound E RS in a mixture of Solution $B$ and Solution $A(7: 3)$, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of 1-methyl-4-( $p$-fluorophenyl)-$1,2,3,6$-tetrahydropyridine of about 0.2100 ng per mL. 20 ng per mL.■1S (USP28)

Test solution-Transfer about 20 mg of Paroxetine Hydrochloride, accurately weighed, to a suitable flask, add 1.0 mL of a mixture of Solution B and Solution $A(7: 3)$, and shake to dissolve.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a tandem mass spectrophotometric detector, monitoring the mass-to-charge ratio of 44 ã arising from the fragmentation of mass-tocharge ratio of 192 , and a $2.0-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains base-deactivated packing L1. The flow rate is about 0.15 mL per minute. The collision-induced disassociation sector is filled with sufficient argon gas to produce -20 eV collisions. Adjust the argon gas pressure as necessary. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 30 | 70 | equilibration |
| $0-10$ | 30 | 70 | isocratic |
| $10-10.5$ | $30 \rightarrow 90$ | $70 \rightarrow 10$ | linear gradient |
| $10.5-20$ | 90 | 10 | isocratic |
| $20-20.5$ | $90 \rightarrow 30$ | $10 \rightarrow 70$ | linear gradient |
| $20.5-30$ | 30 | 70 | isocratic |

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the signal-to-noise ratio for the analyte response at a mass-to-charge ratio of 44 is not less than 5 ; and the relative standard deviation for replicate injections is not more than $5.0 \%$. [NOTE-A large peak
due to paroxetine is observed at about 10 minutes in this system. Divert the flow of eluate from the mass spectrometer at about 10 minutes after injection.]

Procedure-Separately inject equal volumes (about 100 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in pg ng, of 1-methyl-4-( $p$-fluorophenyl)-1,2,3,6-tetrahydropyridine in the portion of Paroxetine Hydrochloride taken by the formula:

$$
C I\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Paroxetine Related Compound E RS in the Standard solution; I is the amount, in ng, of 1-methyl-4-( $p$-fluorophenyl)-1,2,3,6-tetrahydropyridine in each mg of USP Paroxetine Related Compound E RS in the Standard solution; and $r_{U}$ and $r_{s}$ are the peak responses for 1-methyl-4-( $p$-fluorophe-nyl)-1,2,3,6-tetrahydropyridine obtained from the Test solution and the Standard solution, respectively: not more than 200 pg 100 ng 20 ng is found ( $0.0001 \%$ ).

Chromatographic purity-[NOTE-Perform all related impurities methods unless the manufacturer has assurance, based on knowledge of the manufacturing process, that one of the tests is not relevant to their material.]

TEST 1-
Solution A-Prepare a filtered and degassed mixture of water, tetrahydrofuran, and trifluoroacetic acid (180:20:1).

Solution B-Prepare a filtered and degassed mixture of acetonitrile, tetrahydrofuran, and trifluoroacetic acid (180:20:1).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent: a mixture of water and tetrahydrofuran $(9: 1)$.
Standard solution-Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about $1 \mu \mathrm{~g}$ per mL .

System suitability solution-Dissolve, by sonication if necessary, suitable quantities of USP Paroxetine Related Compound A RS and USP Paroxetine Related Compound B RS in mixture of water and tetrahydroftran (9:1) Diluent to obtain a solution having known concentrations of about 0.01 mg of each USP Reference Standard per mL .

Test solution-Transfer about 25 mg of Paroxetine Hydrochloride, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in 20 mL of a mixture of water and tetrahydreftran $(9: 1)$, Diluent, sonicate, dilute with mixtme of water and etrahydreftran (9:1) Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $285-\mathrm{nm}$ detector eapable of menitoring at 263 and 295 nm and a $4.6-\mathrm{mm}$ $\times 25-\mathrm{cm}$ column that contains packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at $40^{\circ}$. The chromatograph is programmed as follows.

| Time (mintutes) | Solution - 4 <br> (\%) | Solution B $(\%)$ | Elution |
| :---: | :---: | :---: | :---: |
| $\theta$ | 80 | 20 | equilibration (for |
|  |  |  | 10-minutes) |
| $\theta-3 \theta$ | 88 | 20 | isperatie |
| 30-50 | $80 \rightarrow 20$ | 20, 80 | tinear gradient |
| 50-nd | 20 | 80 | isocratie |

Chromatograph the System suitability solution, and record the peak respenses as directed for Procedtre: the resolution,
$R$, between parexetine related compent $A$ and paroxetine related compeund $B$ is not less than 1.5; the coltumn eff
eieney determined from the paroxetine related compound A peak is not less than 10,000 theoretical plates; the tailing factor for the paroxetine related compound A peak is not more than 1.2; and the relative standard deviation for replieate injections is net mere than $1.0 \%$.

| Time | Solution A | Solution $B$ |  |
| :---: | :---: | :---: | :--- |
| (minutes) | $(\%)$ | $(\%)$ | Elution |
| 0 | 80 | 20 | equilibration |
| $0-30$ | 80 | 20 | isocratic |
| $30-50$ | $80 \rightarrow 20$ | $20 \rightarrow 80$ | linear gradient |
| $50-60$ | 20 | 80 | isocratic |
| $60-70$ | $20 \rightarrow 80$ | $80 \rightarrow 20$ | linear gradient |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.1 for paroxetine related compound B , and 1.0 for paroxetine related compound A ; the resolution, $R$, between paroxetine related compound A and paroxetine related compound B is not less than 2.0; and the tailing factor of the paroxetine related compound A peak is between 0.8 and 2.0 ; Chromater the Stard selution, and record the peak responses as directed for Proand the relative standard deviation for replicate injections is not more than $2.0 \%$ for paroxetine related compound A.

Procedure Inject a volume (about $20 \mu \mathrm{\mu}$ ) of the Test se thtion inte the chromatograph, record the chromatogram, and measure all of the peak respenses at both 263 and 295 nm . Calculate the percentage of each impurity in the pertion of Paroxetine Hydrochloride taken by the formula:$100(+\rightarrow+5)$,
in which $r_{i}$-is the peak response for each impurity; and $\boldsymbol{r}_{5}$ is the-sum of the respenses of all of the peaks: not more that $0.1 \%$ of any individual impurity is found, and not more than

## $0.5 \%$ of total impurities is found.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution, Test solution, and Diluent into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Paroxetine Hydrochloride taken by the formula:

$$
2500(C / W)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Paroxetine Hydrochloride RS in the Standard solution; $W$ is the weight, in mg , of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the Test solution; $r_{U}$ is the peak area of each impurity in the Test solution, excluding the peaks obtained in the chromatogram of the Diluent; and $r_{s}$ is the peak area of paroxetine obtained in the Standard solution: not more than of $0.5 \% 0.3 \%$ of any peak at a retention time of paroxetine related compound B is found; not more that $0.1 \%$ of any other individual impurity is found; and not more than $1.0 \%$ of total impurities is found.

TEST 2-
Phosphate buffer-Dissolve 3.4 g of monobasic potassium phosphate and 3.4 g of tetrabutylammonium hydrogen sulfate in 1.0 L of water.

Solution A-Prepare a filtered and degassed mixture of Phosphate buffer and acetonitrile (98:2).

Solution B—Prepare a filtered and degassed mixture of Phosphate buffer and acetonitrile (6:4).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent: a mixture of Phosphate buffer and acetonitrile (9:1).
Standard solution-Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS, USP Paroxetine Related Compound B RS, USP Paroxetine Related Compound F RS, and USP Paroxetine Related Compound G RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having known concentrations of about $4 \mu \mathrm{~g}$ per $\mathrm{mL}, 10 \mu \mathrm{~g}$ per $\mathrm{mL}, 10 \mu \mathrm{~g}$ per mL , and $4 \mu \mathrm{~g}$ per mL , respectively.

Identification solution-Dissolve an accurately weighed quantity of Paroxetine Hydrochloride, USP Paroxetine Related Compound B RS, USP Paroxetine Related Compound F RS, and USP Paroxetine Related Compound G RS in Diluent to obtain a solution having known concentrations of about 2 mg per $\mathrm{mL}, 10 \mu \mathrm{~g}$ per $\mathrm{mL}, 10 \mu \mathrm{~g}$ per mL , and 4 $\mu \mathrm{g}$ per mL , respectively.

Test solution-Transfer about 25 mg of Paroxetine Hydrochloride, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L 1 . The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-5$ | 100 | 0 | isocratic |
| $5-70$ | $100 \rightarrow 40$ | $0 \rightarrow 60$ | linear gradient |
| $70-90$ | $40 \rightarrow 0$ | $60 \rightarrow 100$ | linear gradient |
| $90-95$ | 0 | 100 | isocratic |
| $95-95.1$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $95.1-110$ | 100 | 0 | re-equilibration |

Chromatograph the Identification solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.91 for paroxetine related compound B, about 0.96 for paroxetine related compound $\mathrm{F}, 1.0$ for paroxetine, and about 1.34 for paroxetine related compound G. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $10.0 \%$ for the paroxetine related compound B, paroxetine related compound F , paroxetine hydrochloride, and paroxetine related compound G peaks.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of paroxetine related compound B , paroxetine related compound F , and paroxetine related compound G in the portion of Paroxetine Hydrochloride taken by the formula:

$$
5000(C / W)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of the appropriate USP Reference Standard in the Standard solution; $W$ is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the Test solution; and $r_{i}$ and $r_{s}$ are the peak areas for the corresponding impurity in the Test solution and the Standard solution, respectively: not more than of $0.5 \%$ of paroxetine related compound B is found; not more than $0.2 \%$ of paroxetine related compound F is found; and not more than $0.2 \%$ of paroxetine related compound G is found. Calculate the percentage of any unknown impurity in the portion of Paroxetine Hydrochloride taken by the formula:
in which $C$ is the concentration, in mg per mL , of the USP Paroxetine Hydrochloride RS in the Standard solution; $W$ is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the Test solution; $r_{i}$ is the peak area for any unknown impurity in the Test solution; and $r_{s}$ is the peak area of paroxetine in the Standard solution: not more than of $0.1 \%$ of any single unknown impurity is found, and not more than $1.0 \%$ of total impurities is found.

Organic volatile impurities, Method $V\langle 467\rangle$ : meets the requirements.

## Assay-

Acetate buffer-Prepare a 0.05 M solution of ammonium acetate in water, adjust with glacial acetic acid to a pH of 4.5 , mix, and filter.

Mobile phase-Prepare a filtered and degassed mixture of Acetate buffer, acetonitrile, and triethylamine ( $60: 40: 1$ ). Adjust with glacial acetic acid to a pH of 5.5. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve suitable quantities of USP Paroxetine Related Compound B RS and USP Paroxetine Hydrochloride RS in water to obtain a solution having known concentrations of about 0.5 mg of each USP Reference Standard per mL.

Standard preparation-Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.5 mg per mL .

Assay preparation-Transfer about 50 mg of Paroxetine Hydrochloride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix.

$$
5000(C / W)\left(r_{i} / r_{s}\right)
$$

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $295-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L13. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for paroxetine related compound B and 1.0 for paroxetine; the resolution, $R$, between paroxetine related compound $B$ and paroxetine is not less than 2.0 ; the column efficiency determined from the paroxetine peak is not less than 3000 theoretical plates; the tailing factor for the paroxetine peak is not more than 1.6 ; and the relative standard deviation for replicate injections is not more than 2.0\%.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3} \cdot \mathrm{HCl}$ in the portion of Paroxetine Hydrochloride taken by the formula:

$$
100 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Paroxetine Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP27)

## Briefing

Paroxetine Tablets, page 653 of $P F$ 29(3) [May-June 2003]. Consistent with established policy of using the same terminology in the monograph title as appears in the strength expression for a dosage form, Paroxetine Tablets has been proposed to be the title for this new monograph.

Paroxetine Tablets is proposed to be the title of this new monograph that will be included in the Second Supplement to USP 27$N F$ 22, but with an official date for the title to be February 1, 2006, which is 18 months later than the official date of the Second Supplement to USP 27-NF 22. Use of the revised name would be permitted as of August 1, 2004, the official date of the Second Supplement to USP 27-NF 22, but use of the name Paroxetine Tablets would not become mandatory until February 1, 2006. The 18month extension is intended to allow for product label changes to be made and for health practitioners and consumers to become familiar with the terminology.
(NL: C. Barnstein) RTS-41137-1

## Add the following:

## ■Paroxetine Hydrochloride Tablets

-(The title for this monograph-to become official February 1, 2006)
» Paroxetine Hydrochloride Tablets contain an amount of Paroxetine Hydrochloride equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of paroxetine hydrochloride $\left(\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3}-\mathrm{HCl}\right)$.

Packaging and storage-Preserve in tight containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Paroxetine Hydrochloride RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$ -
Test specimen-Transfer an amount of finely powdered Tablets, equivalent to about 10090 mg of paroxetine hydroehloride, to a suitable flask, add 100 mL of 0.1 N hydrochloric acid, and stir for 1 hour. Transfer the mixture to a separatory funnel, and add ammonium hydroxide until the solution is alkaline to litmus paper. Add 100 mL of ethyl ether to the funnel, and shake for 2 minutes. Transfer the organic layer into the necessary number of centrifuge tubes, and centrifuge for 10 minutes. Recombine the clarified extracts, add 1 drop of water and 0.5 mL of 0.1 N hydrochloric acid, stir, and evaporate to dryness under a stream of nitrogen. Dry the residue in an oven at $90^{\circ}$ for 1 hour.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

C: Place a quantity of finely powdered Tablets, equivalent to about 500450 mg of paroxetine hydrochloride, into a stoppered flask. Add 100 mL of alcohol, and shake for 1 hour. Centrifuge about 20 mL of the mixture, and measure the angular rotation of the supernatant at $20^{\circ}$ (see Optical Rotation $\langle 781\rangle$ ): the angular rotation is between $-75^{\circ}$ and $-115^{\circ}$.

Dissolution $\langle 711\rangle$ -
Medium: simulated gastric fluid without enzyme; 900 mL .
Apparatus 2: 60 rpm .
Time: 60 minutes.
Determine the amount of $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3} \cdots \mathrm{HC}$ dissolved by employing the following method.

Buffer solution and Mobile phase-Prepare as directed in the Assay.

Standard stock solution-Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS in an amount of methanol not exceeding $5 \%$ of the volume of the final solution, and dilute with Dissolution Medium to obtain a solution having a known concentration of about 0.63 mg per mL .

Standard solution-Quantitatively dilute the Standard stock solution with Dissolution Medium to obtain a solution having a concentration estimated to correspond to that of the filtered solution under test.

Chromatographic system-Proceed as directed in the Assay, except to prepare the Standard preparatien as directed mer Dissulth (714)= chromatograph the Standard solution.
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of a portion of the solution under test, previously passed through a suitable $0.45-\mu \mathrm{m}$ membrane filter, and the Standard solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity of $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3} \cdot \mathrm{HCl}$ dissolved based on the peak responses obtained from the solution under test and the Standard solution.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3} \cdot \mathrm{HCl}$ is dissolved in 60 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## PROCEDURE FOR CONTENT UNIFORMITY-

Buffer solution, Mobile phase, and Chromatographic sys-tem-Proceed as directed in the Assay.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Place 1 Tablet in a suitable volumetric flask, and add a volume of a hydrochloric acid solution (7 in 1000), equivalent to about $25 \%$ of the flask volume. Allow the Tablet to disintegrate, dilute with methanol to vo-
lume, and mix to obtain a solution containing about 0.1 mg of paroxetine hydrectride per mL . Centrifuge a portion of the solution.

Procedure-Proceed as directed in the Assay. Calculate the quantity, in mg , of $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3} \ldots \mathrm{HCl}$ in the Tablet taken by the formula:

```
#C(+54+s),
```

$$
V C(329.37 / 365.83)\left(r_{U} / r_{S}\right)
$$

in which $V$ is the volume of the flask used; $r_{U}$ and $r_{S}$ are the peak responses obtained from the Test solution and the Standard solution, respectively; and the other terms are as defined therein.

## Assay-

Buffer solution-Prepare a mixture of water, phosphoric acid, and triethylamine ( $100: 0.6: 0.3$ ).

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (7:3). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Standard preparation-Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL .

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of paroxetine hy drochloride, to a $200-\mathrm{mL}$ volumetric flask, dissolve in and
dilute with methanol to volume, and mix. Centrifuge a portion of this solution for 6 minutes. Transfer 20 mL of the supernatant to a $100-\mathrm{mL}$ volumetric flask, dilute with methanol to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ ) The liquid chromatograph is equipped with a $295-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 3.3-\mathrm{cm}$ column that contains $3-\mu \mathrm{m}$ packing L7. The flow rate is about 2.0 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 750 theoretical plates; the tailing factor is not more than 4 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $5 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of paroxetine hydrechloride $\left(\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3}-\mathrm{HCl}\right)$ in the portion of Tablets taken by the formula:

$$
1000 C\left(+t_{t}++_{s}\right)
$$

$$
1000 C(329.37 / 365.83)\left(r_{U} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Paroxetine Hydrochloride RS in the Standard preparation; 329.37 and 365.83 are the molecular weights for paroxetine and paroxetine hydrochloride, respectively; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\quad$ 2S (USP27)

## BRIEFING

Camphorated Phenol Topical Solution, page 1561 of $P F$ 29(5) [Sept.-Oct. 2003]. On the basis of new information received from the sponsor, it is proposed to slightly modify the acceptance criteria in the test for Specific gravity to be consistent with the product release specification. Editorial style changes have also been made.
(PA7b: B. Davani) RTS-41055-1

## Add the following:

## ■Camphorated Phenol Topical Solution

» Camphorated Phenol Topical Solution is a solution of camphor and phenol in Eucalyptus Oil and Light Mineral Oil. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of camphor $\left(\mathrm{C}_{10} \mathrm{H}_{16} \mathrm{O}\right)$ and phenol $\left(\mathrm{C}_{6} \mathrm{H}_{6} \mathrm{O}\right)$.

Packaging and storage-Preserve in tight containers. Store at room temperature, avoid excessive heat, and close cover after each use.

USP Reference standards $\langle 11\rangle —$ USP Camphor RS. USP Phenol RS.

Identification-The retention times of the camphor and phenol peaks in the chromatograms of the Assay preparation correspond to those of the Standard preparation, obtained as directed in the Assay.

Specific gravity $\langle 841\rangle$ : between 0.8640 .840 and 0.865 .

## Assay-

Internal standard solution-Transfer 250 mg , accurately weighed, of $n$-dodecane to a $25-\mathrm{mL}$ volumetric flask, dilute with chloroform to volume, and mix.

Standard preparation-Transfer about 96 mg of USP Phenol RS, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask. Add about 224 mg of USP Camphor RS, accurately weighed, to the flask. Dilute with chloroform to volume, and mix. Combine 5.0 mL of this solution with 5.0 mL of Internal standard solution in a $50-\mathrm{mL}$ volumetric flask, dilute with chloroform to volume, and mix.

Assay preparation-Transfer about 1 g of Topical Solution, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask. Add 5.0 mL of Internal standard solution, dilute with chloroform to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector, maintained at a temperature of $200^{\circ}$, and a $2-\mathrm{mm}$ $\times 1.8$-m glass column packed with $100-$ to 120 -mesh S 1 A , coated with $15 \%$ G44. The carrier gas is helium. Adjust the column temperature to about $140^{\circ}$ so that the relative retention times are 0.3 for phenol, 0.8 for camphor, and 1.0 for the internal standard. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between the camphor peak and the internal standard peak is not less than 2.0, and between the phenol peak and the camphor peak not less than 5.0; and the relative standard deviation of the peak response ratio of the camphor peak and the phenol peak to the internal standard peak for five consecutive injections of the Standard preparation is not more than $2.0 \%$.

Procedure-Separately inject 1 to $2 \mu \mathrm{~L}$ of the Assay preparation and the Standard preparation into the gas chromatograph, record the chromatograms, and determine the peak
response ratios. Calculate the percentage of camphor (w/w) and the percentage of phenol ( $\mathrm{w} / \mathrm{w}$ ) in the portion of Topical Solution taken by the formula:

$$
\left(50 W_{R} / W\right)\left(R_{U} / R_{S}\right)
$$

in which $W_{R}$ is the weight, in mg , of the appropriate USP Reference Standard in the Standard preparation; $W$ is the weight of Topical Solution, in mg, taken to prepare the $A s$ say preparation; and $R_{U}$ and $R_{S}$ are the response ratios of the corresponding analyte peaks in the Assay preparation and the Standard preparation, respectively. $\quad$ IS (USP28)

## Briefing

Phenylephrine Bitartrate. Because there is no existing USP monograph for this drug substance, a new monograph is being proposed. The liquid chromatographic procedures in the test for Chromatographic purity are based on analyses performed with the Symmetry brand of L1 column. The typical retention times are about 2.0 for norphenylephrine, about 2.2 for (-)-phenylephrine, about 2.6 for phenylephrone, about 6.4 for 1-benzylphenylepherine, and about 6.9 for benzylphenylepherine HCl .
(PA1: C. Anthony) RTS—39860-1

## Add the following:

## ■Phenylephrine Bitartrate

## $\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6} \quad 317.3$

R-2-(Methylamino)-1-(3-hydroxyphenyl)ethanol, hydrogentartrate.
(-)-1-(3-Hydroxyphenyl)-2-methylaminoethanol, hydrogentartrate.
(-)-3 Hydroxy- $\alpha$ [(methylamino) methyl] benzenemethanol, hydrogentartrate.
$1-m$-Hydroxy- $\alpha-[($ methylamino $)$ methyl $]$ benzylalcohol, hydrogentartrate [17162-39-0].
» Phenylephrine bitartrate contains not less than 99.0 percent and not more than 100.5 percent of $\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$, calculated on the dried basis.

## Packaging and storage-Preserve in tight, light-resistant

 containers. Store at controlled room temperature.USP Reference standards $\langle 11\rangle$ —USP Phenylephrine Hydrochloride RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The alkaline of tartrate from the test for Specific rotation responds positively to the test for Tartrate $\langle 191\rangle$.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $-53^{\circ}$ and $-57^{\circ}$ for the prepared sample.

Test solution-Prepare a sample solution of about 24 mg per mL in water. Make the solution slightly alkaline by adding concentrated ammonium hydroxide dropwise. Rub the wall of the vessel with a glass rod so that the base precipitates out. Filter the base under suction, wash with a little water and acetone, and dry at $105^{\circ}$ for 2 hours. Prepare and measure a 50 mg per mL solution of base precipitate in 1 M hydrochloric acid.
$\mathbf{p H}\langle 791\rangle$ : between 3.0 and 4.0 in $10 \% \mathrm{w} / \mathrm{v}$ aqueous solution.

Loss on drying $\langle 731\rangle$ —Dry at $105^{\circ}$ to a constant weight: it loses not more than $0.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.

## Chromatographic purity-

Buffer solution-Dissolve 3.25 g of 1-octanesulfonic acid sodium salt monohydrate in 1 L of water. Adjust slowly with 3 M phosphoric acid to a pH of 2.8 .
Solution A-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (9:1).
Solution B—Prepare a filtered and degassed mixture of acetonitrile and Buffer solution (9:1).

Diluent-Prepare a mixture of Solution $A$ and Solution B (8:2).
System suitability solution-Dissolve accurately weighed quantities of USP Phenylephrine Hydrochloride RS, norphenylephrine hydrochloride, 1-benzylphenylepherine base, and benzylphenylepherine hydrochloride in Diluent, and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 0.06 mg per $\mathrm{mL}, 0.09 \mathrm{mg}$ per $\mathrm{mL}, 0.07 \mathrm{mg}$ per mL , and 0.05 mg per mL , respectively.
Test solution-Transfer 78 mg of phenylephrine bitartrate, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $5.5-\mathrm{cm} \times 4-\mathrm{mm}$ column that contains packing L1. The column temperature and injector temperature are maintained at $45 \pm 2^{\circ}$. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows:

| Time | Solution $A$ | Solution B |  |
| :---: | :---: | :---: | :---: |
| (minutes) | $(\%)$ | $(\%)$ | Elution |
| 0 | 93 | 7 | equilibration |
| $0-10$ | $93 \rightarrow 30$ | $7 \rightarrow 70$ | linear gradient |
| $10-18$ | 30 | 70 | isocratic |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for norphenylephrine, about 1.0 for ( - -phenylephrine, about 1.2 for phenylephrone, about 2.9 for 1-benzylphenylepherine, and about 3.1 for benzylphenylepherine HCl .

The resolution, $R$, between norphenylephrine and $(-)$-phenylephrine is not less than 1.5 . The tailing factor of $(-)$-phenylephrine is less than 1.8 . The relative standard deviation for replicate injections is not more than $6 \%$.

Procedure-Inject about $10 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Phenylephrine Bitartrate taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for each impurity, and $r_{s}$ is the sum of the responses of all the peaks: not more than $0.2 \%$ of any individual impurity is found, and not more than $0.5 \%$ of total impurities is found.

Assay-Transfer about 280 mg of Phenylephrine Bitartrate, accurately weighed, to a $100-\mathrm{ml}$ beaker, and dissolve by stirring in 60 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrically. Perform a blank titration and make the necessary correction (see Titrimetry $\langle 541\rangle$ ). Each mL of $0.1 \mathrm{~N} \mathrm{HClO}_{4}$ is equivalent to 31.73 mg of $\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6} \cdot \mathbf{1 S}$ (USP28)

## Briefing

Propoxyphene Hydrochloride, USP 27 page 1578 and page 529 of PF 30(2) [Mar.-Apr. 2004]; Propoxyphene Napsylate, USP 27 page 1582 and page 662 of PF 29(3) [May-June 2003]. On the basis of comments received, it is proposed to make further revisions to modify the System suitability solution in the test for Related compounds.
(PA2: C. Anthony) RTS-40678-1

## Change to read:

USP Reference standards $\langle 11\rangle$-USP Propoxyphene Hydrochloride RS. USP x-d-2 Aeex-4 dimethyme 1,2 dipheny-子 methyllat RS.
${ }^{\star}$ USP Propoxyphene Related Compound B RS. $\mathbf{\Delta S P 2 8}$ USP Propoxyphene Related Compound $A R S$.

## Change to read:

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~S}\rangle$ -
Solution: 1 in 20.
Medium: chloroform.
B: It respends to the tests for Chloride- $\langle 194\rangle=$
${ }^{\Delta}$ Dissolve 0.25 g of Propoxyphene Hydrochloride in 15 mL of Purified Water, and treat 3 mL of this solution with 1 mL of 6 N ammonium hydroxide to precipitate the propoxyphene base. Filter to remove the precipitate, acidify the filtrate with 2 mL of nitric acid, and add 1 mL of silver nitrate TS: a white, curdy precipitate that is soluble in an excess of 6 N ammonium hydroxide confirms the presence of silver chloride. $\Delta U S P 28$

## Change to read:

## Related compounds-

Mobile phase and Chromatographic system-Proceed as directed in the Assay.

Standard solution Proceed as directed for the Standard preparation in the Assat:

Related compeands standard solution-
$\square$ Standard stock solution-■1S (USP28)
Pissolve

- Accurately weigh ■IS (USP28)
about 10 mg each of USP Propoxyphene Related Compound A RS and USP $x$ d 2 a butane RS

■USP Propoxyphene Related Compound $\mathrm{B} \mathrm{RS}_{\mathbf{1 S}}$ (USP28) in 20 mL of methanl in a 50 mL volumetric flask,

■into a $50-\mathrm{mL}$ volumetric flask, dissolve using 2 mL of methanol, ${ }^{1 S}$ (USP28)
dilute with Mobile phase to volume, and mix.
■Standard solution-Transfer 5.0 mL of the Standard stock solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. 1 IS (USP28)

Test solution-Use the Assay preparation.
System suitability solution Combine 1.0 mL of the Related empernds stated solution containing about 0.2 mg per mL of each related eompernd with 10.0 mL of the Standetrd solution, and mix.

Transfer 1.0 mL of the Standard stock solution to a 10.0 mL veltumetric flack, dilute with Mobile phate to volume, and mix.
-Dissolve an accurately weighed quantity of USP Propoxyphene Hydrochloride RS in Standard solution, and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 4.5 mg per mL of USP Propoxyphene Hydrochloride RS, about 0.02 mg per mL of USP Propoxyphene Related Compound A RS, and about 0.02 mg per mL of USP Propoxyphene Related Compound B RS. ${ }^{1 S}$ (USP28)

Chromatographic system (see Chromatography $\langle 621\rangle$ )—Proceed as directed in the Assay. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.63 for propoxyphene related compound $\mathrm{A}, 0.78$ for -2 2 2 - dimethylamine- 1,2 diphe nyl-3-methylbutane,
■propoxyphene related compound B, ■ $_{1 \mathrm{~S}}$ (USP28)
and 1.0 for propoxyphene hydrochloride; the resolution, $R$, between $\alpha d 2$ acetoxy 4 dimethylamino 1,2 diphenyl 3 methylbur me,
$\square_{\text {propoxyphene related compound }} \mathrm{B}_{\mathbf{m}_{1 S} \text { (USP28) }}$ and propoxyphene
$\square_{\text {related compound }} \mathrm{A}_{\square 1 \text { IS (USP28) }}$
is not less than 4.4 ;
-2.0; 1S (USP28)
and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure- tajecta
-Separately inject equal $_{\mathbf{1 S}_{1 S} \text { (USP28) }}$
volumes (about $50 \mu \mathrm{~L}$ ) of the Test solution
$\square_{\text {and the }}$ Standard solution $_{1 S}$ (USP28)
into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the
$\square_{\text {quantity, in }} \mathrm{mg}$, ${ }^{1 S}$ (USP28)
of propoxyphene related compound A in the portion of Propoxyphene Hydrochloride taken by the formula:

$$
\begin{aligned}
& 100(+\underset{+}{4}) \\
& \text {-50C }\left(r_{U} / r_{S}\right) \text {, }{ }^{1 S} \text { (USP28) }
\end{aligned}
$$

in which 7 , is the individual peak response of propoxyphene related eompound $A$ in the Test solution; andr, is the sum of the respenses for all of the peaks:

- $C$ is the concentration, in $m g$ per $m L$, of USP Propoxyphene Related Compound A RS in the Standard solution; and $r_{U}$ and $r_{S}$ are the propoxyphene related compound A peak responses obtained from the Test solution and Stan-
dard solution, respectively. 1 IS (USP28)
Not more than $0.5 \%$ of propoxyphene related compound $A$ as the hydrechloride
- $\quad 1 \mathrm{IS}$ (USP28)
is found. Calculate the pereentage
- quantity, in mg, ${ }^{1 S}$ (USP28)
of $\alpha-d$ - 2 aeetoxy 4 -dimethylamine-1,2 diphenyl-3-methylbutane,
${ }_{\square}$ propoxyphene related compound B as the $\mathbf{m}_{1 S}$ (USP28) hydrochloride in the portion of Propoxyphene Hydrochloride taken by the formula:

$$
\left.100(1.112)(+\ldots+)_{t}\right)
$$

$$
■ 50 C(361.93 / 325.45)\left(r_{U} / r_{S}\right)_{,}{ }^{1 S}(U S P 28)
$$

in which 1.112 is the ratio of the melecular weight of $\alpha d 2$ aeet exy 4 dimethylamino 1,2 diphenyl -3 methylbutane hydrochloride to that of $x d 2$ acetoxy 4 dimethylamine 1,2 diphenyl 3 methyl butane free base; + , is the individual peak respense of $\alpha d-2$ acet exy 4 dimethylamine 1,2 diphenyl 3 methylbutane in the Test solution; andrs, is the stm of the respenses for all of the peaks:

- $C$ is the concentration, in mg per mL , of USP $\alpha d 2$ Aeet
oxy 4-dimethylamine 1,2 diphenyl 3-methylbutane RS
USP Propoxyphene Related Compound B RS in the Standard solution; 361.93 and 325.45 are the molecular weights of $\alpha d 2$ acetoxy 4-dimethylamine-1,2 diphenyl 3-methyl butane, propoxyphene related compound $B$ as the hydrochloride and a-d-2 acetoxy-4-dimethylamine-1,2 diphenyl-3-methylbutane, propoxyphene related compound B , respectively; and $r_{U}$ and $r_{S}$ are the $\alpha-d 2$ acetoxy 4 di
methylamine-1,2-diphenyl-3-methylbutane,propoxyphene related compound B peak responses obtained from the Test solution and the Standard solution, respectively.■1S (USP28) Not more than $0.6 \%$ of 2 - 2 - dimethylamine 1,2 diphe-nyl-3-methylbutane,
$\square_{\text {propoxyphene related compound } \mathrm{B} \text { as the } \mathbf{m}_{1 S} \text { (USP28) }}$ hydrochloride is found.


## Change to read:

Assay-
0.01 M
-0.1 $M_{\square 1 \mathrm{~S}}$ (USP28)
Monobasic ammonium phosphate buffer, pH 6.3-Dissolve 11.5 g of monobasic ammonium phosphate and 1.0 mL of triethylamine in 1000 mL of water, adjust with $10 \%$ sodium hydroxide to a pH of $6.3 \pm 0.05$, and mix.

Mobile phase-Prepare a filtered and degassed mixture of methanol and 0.01 M
-0.1 $M_{\text {■1S (USP28) }}$
Monobasic ammonium phosphate buffer, pH 6.3 (67:33). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard preparation-Dissolve an accurately weighed quantity of USP Propoxyphene Hydrochloride RS in Mobile phase to obtain a solution having a known concentration of about 5.0 mg per mL .

Assay preparation-Transfer about 250 mg of Propoxyphene Hydrochloride, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a 3.9$\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the retention time of propoxyphene hydrochloride is about $9 \mathrm{~min}-$ utes; the resolution, $R$, between a d 2 aeetoxy 4 dimethylamine 1,2 diphenyl 3 methylbutane and propoxyphene is not less that +4;
-the tailing factor for the propoxyphene hydrochloride peak
is not more than 3.5 ; is (USP28)
and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ in the portion of Propoxyphene Hydrochloride taken by the formula:

$$
100 C\left(x_{t}+r_{s}\right)
$$

$$
\text { ■ } 50 C\left(r_{U} / r_{S}\right), \llbracket 1 \mathrm{~S}(U S P 28)
$$

in which $C$ is the concentration, in mg per mL , of USP Propoxyphene Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Propoxyphene Napsylate, USP 27 page 1582 and page 662 of PF 29(3) [May-June 2003]-See briefing under Propoxyphene Hydrochloride.
(PA2: C. Anthony) RTS-40688-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Propoxyphene Napsylate RS. USP x d 2 Aeexy dimethylanin-1,2 diphenyl 3 methyl RS RS.
${ }^{\Delta}$ USP Propoxyphene Related Compound B RS. $\quad$ USP28 USP Propoxyphene Related Compound A RS.

## Change to read:

Related compounds-
Mobile phase and Chromatographic system-Proceed as directed in the Assay.

Standard solution-Proceed as direeted for Standard preparat tion in the Assay.

Related empents standerd solution-
-Standard stock solution-■1S (USP28)
Pissolve

- Accurately weigh ${ }_{\text {1S (USP28) }}$
about 10 mg each of USP Propoxyphene Related Compound A RS and USP $x d-2$ Aeetoxy - 4 dimethylamine 1,2 diphenyl 3 methyl butane RS
$\square^{\bullet U S P}$ Propoxyphene Related Compound $\mathrm{B} \mathrm{RS}_{\mathbf{\square 1 S}}$ (USP28) in 20 mL of methanel in a -50 mL velumetric flack,

■into a $50-\mathrm{mL}$ volumetric flask, dissolve using 2 mL of methanol, 1 1S (USP28)
dilute with Mobile phase to volume, and mix.

## ■Standard solution-Transfer 5.0 mL of the Standard

 stock solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.■1S (USP28)System suitability solution Combine 1.0 mL of the Related emprads stald soltion containing about 0.2 mg per mL of each relatedempound with 10.0 mL of the Standurdsolution, and mix.

Transfer 1.0 mL of the Standard stock solution to a 10.0 mL velumetric flask, dilute with Mobile phase to volume, and mix.

■Dissolve an accurately weighed quantity of USP Propoxyphene Napsylate RS in Standard solution, and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 4.5 mg per mL of USP Propoxyphene Napsylate RS, about 0.02 mg per mL of USP Propoxyphene Related Compound A RS, and about 0.02 mg per mL of USP Propoxyphene Related Compound B RS.■1S (USP28)

Test solution-Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—Proceed as directed in the Assay. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.63 for propoxyphene related compound A, 0.78 for ad- 2 acetoxy - 4 dimethylamine-1,2 diphemyl 3 -methylbutane,
■propoxyphene related compound B, $\boldsymbol{■ 1 S}_{1 S}$ (USP28) and 1.0 for propoxyphene napsylate; the resolution, $R$, between $\not \approx$ d2 acetoxy 4 dimethylamine - 1,2 diphenyl 3 methylbutane
$\square_{\text {propoxyphene related compound }} \mathrm{B}_{\mathbf{■}^{1 S}}$ (USP28) and propoxyphene
$\square_{\text {related compound }} \mathrm{A}_{\square}$ IS (USP28)
is not less than 1.4 ;
-2.0; ${ }_{1 S}$ (USP28)
and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the
-Standard solution $^{\text {Sand }} \mathbf{m 1 S}_{\text {(USP28) }}$
Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the pereene

- quantity, in mg, 1 IS (USP28) $^{\text {m }}$
of propoxyphene related compound A as the napsylate salt
- $\quad$ IS (USP28)
in the portion of Propoxyphene Napsylate taken by the formula:

$$
\left.100(491.67 / 319.88) r_{4}+r_{4}\right)
$$

in which 491.67 and 319.88 are the melecular weights of properyphene related compound $\Lambda$ napsylate and propoxyphene related compound $A$, respectively; $;$, is the individual peak respense of propoxyphene related compound $\Lambda$; and $x$, is the sum of the re sponses for all the peaks: net more than $0.5 \%$ of propexyphene re tated compernd $A$ is found.

$$
\cdot 50 C(491.67 / 319.88)\left(r_{U} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Propoxyphene Related Compound A RS in the Standard solution; 491.67 and 319.88 are the molecular weights of propoxyphene related compound A napsylate and propoxy-
phene related compound A, respectively; and $r_{U}$ and $r_{S}$ are the propoxyphene related compound A peak responses obtained from the Test solution and the Standard solution, respectively: not more than $0.5 \%$ of propoxyphene related
compound A napsylate is found. 1 (USP28)
Calculate the pere
-quantity, in $\mathrm{mg}_{\text {, }}^{\text {nIS }}$ (USP28)
of $\operatorname{*d2}$ aeetoxy 4 dimethylamine-1,2 dipheny13 methylbutane
${ }^{\square}$ propoxyphene related compound $\mathrm{B}_{\square 1 S}$ (USP28)
napsylate in the portion of Propoxyphene Napsylate taken by the formula:

$$
100(533.71 / 325.45)\left(+++_{t}\right)
$$

in which-533.71 and 325.45 are the molecular weights of $\alpha d 2$ acetoxy 4 dimethylamine 1,2 diphenyl-3 methylbutane napsylate and $\alpha d 2$ acetoxy 4 dimethylamine 1,2 diphenyl 3 methylbut ane, respectively; $r$ is the individual peak respense of $\alpha$ d 2 aeet өxy 4-dimethylamine 1,2 diphenyl 3-methylbutane napoylate; and $r$ is stam of the respenses for all the peaks:

$$
\text { - } 50 C(533.71 / 325.45)\left(r_{U} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP $\alpha$ 2.Aeetoxy-4-dimethylamine-1,2-diphenyl-3-methylbutane RS USP Propoxyphene Related Compound B RS in the Standard solution; 533.71 and 325.45 are the molecular weights of $d$ - 2 - 4 dimethylamine-1,2 diphenyl
 late and ad-2 ace 4 dimethylamino-1,2 diphenyl 3athylbe propoxyphene related compound B , respectively; and $r_{U}$ and $r_{s}$ are the ne-1,2-diphenyl-3 methylbutane propoxyphene related compound B peak responses obtained from the Test solution and the Standard solution, respectively. $\quad$ 1S (USP28)

Not more than $0.6 \%$ of $\propto d 2$ acetoxy - 4 dimethylamine 1,2 diphe-nyl-3-methylbutane
$\square_{\text {propoxyphene related compound } \mathrm{B}_{\mathbf{I V S}^{1 S}} \text { (USP28) }}$ napsylate is found.

## Change to read:

Assay-
0.01M

- $0.1 M_{\mathbf{n}}$ 1S (USP28)

Monobasic ammonium phosphate buffer, pH 6.3-Dissolve 11.5 g of monobasic ammonium phosphate and 1.0 mL of triethylamine in 1000 mL of water, adjust with $10 \%$ sodium hydroxide to a pH of $6.3 \pm 0.05$, and mix.
Mobile phase-Prepare a filtered and degassed mixture of methanol and 8.014
-0.1 $M_{\text {■1S (USP28) }}$
Monobasic ammonium phosphate buffer, pH 6.3 (67:33). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard preparation-Dissolve an accurately weighed quantity of USP Propoxyphene Napsylate RS in Mobile phase to obtain a solution having a known concentration of about 5.0 mg per mL .
Assay preparation-Transfer about 250 mg of Propoxyphene Napsylate, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a 3.9$\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the retention time of propoxyphene napsylate is about 9 minutes; the resolution, $R$, betwen $x d 2$ aeetoxy 4 dimethylamine 1,2 diphenyl 3 - methylbutane and propoxyphene napsylate is net less than-1.4;
-the tailing factor for the propoxyphene napsylate peak is not more than 3.5 ; 1 s (USP28) and the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{22} \mathrm{H}_{29} \mathrm{NO}_{2}$. $\mathrm{C}_{10} \mathrm{H}_{8} \mathrm{O}_{3} \mathrm{~S}$ in the portion of Propoxyphene Napsylate taken by the formula:

$$
100 C\left(r_{t}+r_{s}\right)
$$

$$
\pm 50 C\left(r_{U} / r_{S}\right), \square_{1 \mathrm{~S}}(U S P 28)
$$

in which $C$ is the concentration, in $m g$ per mL , of USP Propoxyphene Napsylate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Pyrimethamine Tablets, USP 27 page 1611. It is proposed to change the concentration of the Dissolution Medium from 0.01 N to 0.1 N hydrochloric acid, in accordance with the original submission.
(BPC: M. Marques) RTS-40882-1

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: $\quad 0.01 \mathrm{~N}$ hydrechleric acid;
$\square 0.1 \mathrm{~N}$ hydrochloric acid; ${ }^{1 \mathrm{~S}}$ (USP28)
900 mL .
Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-Determine the amount of $\mathrm{C}_{12} \mathrm{H}_{13} \mathrm{ClN}_{4}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 273 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Pyrimethamine RS in the same Medium.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{12} \mathrm{H}_{13} \mathrm{ClN}_{4}$ is dissolved in 45 minutes.

## Briefing

Riboflavin, USP 27 page 1645. It is proposed to revise the test for Specific rotation by replacing the current procedure with the method given in the European Pharmacopoeia ( $E P$ ). In the current procedure the sample under test is dissolved in hydrochloric acid. However, it has been reported that along with handling difficulties associated with using concentrated hydrochloric acid, false readings were obtained due to interactions between the acid and the optical cell materials. It was found that these problems were not observed when 0.05 M sodium hydroxide is used as is described in the $E P$.
(DSN: L. Evans) RTS-40944-1

## Change to read:

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $+56.5^{\circ}$ and $+59.5^{\circ}$.

- $-115^{\circ}$ and $-135^{\circ} \cdot$ ■1S (USP28)

Test solution: 5 mg per mL , in hydrechloric acid.
${ }^{-} 0.05 \mathrm{M}$ sodium hydroxide free from carbonate. Measure the specific rotation within 30 minutes of preparat-
ion.■1S (USP28)

## Briefing

Sorbitol Solution, USP 27 page 1715, page 3083 of the First Supplement, and page 1078 of PF 29(4) [July-Aug. 2003]-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-19

## Change to read:

Packaging and storage--Preserve in well-closed containers. De net store below $20^{\circ} . \square 1 \mathrm{~S}$ (USP27)
${ }^{\bullet}$ No storage requirements specified. ${ }^{\circ}$

## Briefing

Spironolactone Oral Suspension, page 5813 of PF 24(2) [Mar.-Apr. 1998]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded with modifications to In-Process Revision.
(CRX: C. Okeke) RTS-41005-1

## Add the following:

## ■Spironolactone Oral Suspension

## » Spironolactone Oral Suspension contains not

 less than 0.18 g and not more than 0.22 g of Spironolactone in 100 mL of Oral Suspension.Use Spironolactone, or the number of Spironolactone Tablets that contain the designated amount of Spironolactone, and prepare Spironolactone


Transfer the Spironolactone, or Spironolactone Tablets, to a glass mortar. [NOTE-If Tablets are used, finely powder the Tablets such that they pass through a 40- or 45 -mesh sieve, and place the sieved powder in a glass mortar. If the Tablets have a waxy coating that will not pass through a 40- or $45-\mathrm{mesh}$ sieve, transfer the unsieved portion to another glass mortar (holding the sieved portion to be added later), add 0.5 mL of alcohol ( $95 \%$ ethyl alcohol), and make a smooth paste; then transfer the sieved portion to the mortar containing the paste.] Dissolve the Cetylpyridinium Chloride in 10 mL of Purified Water, transfer this solution in divided portions to the mortar containing the spironolactone powder or paste, and mix to form a smooth paste. Place 20 mL of Purified Water in a beaker. Using moderate heat, stir to form a vortex, and slowly sprinkle the Xanthan Gum into the vortex to produce a uniform dispersion. Add the dispersion to the wetted powder paste, and mix until smooth. Add a sufficient
quantity of the Suspension Structured Vehicle (plain or sugar free) to obtain a final volume of 100 mL , and mix.

NOTE-Do not add flavors or colors to the formulation for oral syringe dosing of infants and younger children or for dosing by intubation. For older children, incorporate a suitable flavor and/or color just prior to bringing the product to final volume with the structured vehicle.

Packaging and storage-Preserve in tight, light-resistant containers. Store in a refrigerator, and avoid freezing.

Labeling-Label it to state that it should be stored in a refrigerator and should not be frozen; that it should be warmed to room temperature before filling oral syringes or dispensing; and that it is to be well shaken before using.

Beyond-use date-Fourteen days after the day on which it was compounded.

Assay-[To come.] $]^{1 S}$ (USP28)

## Briefing

Spironolactone and Hydrochlorothiazide Oral Suspension, page 5814 of PF 24(2) [Mar.-Apr. 1998]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded with modifications to In-Process Revision.
(CRX: C. Okeke) RTS-41006-1

## Add the following:

## ■Spironolactone and Hydrochlorothiazide Oral Suspension

» Spironolactone and Hydrochlorothiazide Oral Suspension contains not less than 0.18 g and not more than 0.22 g of Spironolactone and not less than 0.18 g and not more than 0.22 g of Hydrochlorothiazide in 100 mL of Oral Suspension.

Use Spironolactone and Hydrochlorothiazide, or the number of Spironolactone and Hydrochlorothiazide Tablets that contain the designated amounts of Spironolactone and Hydrochlorothiazide, and prepare Spironolactone and Hydrochlorothiazide Oral Suspension as follows (see Pharmaceutical Compounding-Nonsterile Preparations $\langle 795\rangle$ ):

| Spironolactone. . . . . . . . . . . . . . | 0.20 g |
| :--- | :--- | :--- |
| Hydrochlorothiazide. . . . . . . . . . | 0.20 g |
| Cetylpyridinium Chloride . . . . . . | 0.01 g |
| Xanthan Gum . . . . . . . . . . . . . . | 0.20 g |
| Purified Water . . . . . . . . . . . . . . | 30.0 mL |
| Suspension Structured Vehicle |  |
| (plain or sugar free), a sufficient  <br> quantity, to make . . . . . . . . . . 100 mL |  |

Transfer the Spironolactone and Hydrochlorothiazide, or Spironolactone and Hydrochlorothiazide Tablets, to a glass mortar. [NOTE-If Tablets are used, finely powder the Tablets such that the powder passes through a 40- or 45-mesh sieve, and place the sieved powder in a glass mortar. If the Tablets have a waxy coating that will not pass through a 40- or 45-mesh sieve, transfer the unsieved portion to another glass mortar (holding the sieved portion to be added later), add 0.5 mL of alcohol (95\% ethyl alcohol), and make a smooth paste; then transfer the sieved portion to the mortar containing the paste.] Dissolve the Cetylpyridinium Chloride in 10 mL of the Purified Water, transfer this solution in divided portions to the mortar containing the powder or paste, and mix to form a smooth paste. Place 20 mL of Purified Water in a beaker. Using moderate heat, stir to form a vortex, and slowly sprinkle the Xanthan Gum into the vortex to produce a uniform dispersion. Add the dispersion to the wetted powder paste, and mix until smooth. Add a sufficient quantity of the Suspension Structured Vehicle (plain or sugar free) to obtain a final volume of 100 mL , and mix.

NOTE-Do not add flavors or colors to the formulation for oral syringe dosing of infants and younger children or for dosing by intubation. For older children, incorporate a suitable flavor and/or color just prior to bringing the product to final volume with the structured vehicle.

Packaging and storage-Preserve in tight, light-resistant containers. Store in a refrigerator, and avoid freezing.

Labeling-Label it to state that it should be stored in a refrigerator and should not be frozen; that it should be warmed to room temperature before filling oral syringes or dispensing; and that it is to be well shaken before using.

Beyond-use date-Fourteen days after the day on which it was compounded.

Assay-[To come.] $]_{1 S}$ (USP28)

## Briefing

Stavudine; Stavudine Capsules; Stavudine for Oral Solution. Because there are no existing USP monographs for this drug substance and dosage forms, new monographs based on submitted data are being proposed. The liquid chromatographic procedures in the Related compounds test and in the Assay are based on analyses performed with the Supelcosil LC-18-DB brand of L1 column.
(PA7b: B. Davani) RTS-40185-1

## Add the following:

## ©Stavudine


$\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4} \quad 224.21$
Thymidine, 2', 3'-didehydro-3'-deoxy-.
1-(2,3-Dideoxy- $\beta$-D-glycero-pent-2-enofuranosyl)thymine. [3056-17-5].
» Stavudine contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4}$, calculated on an anhydrous and solvent-free basis.

Packaging and storage-Store protected from light and humidity. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Stavudine RS. USP
Stavudine System Suitability Mixture RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Specific rotation $\langle 781\rangle$ : between $-45^{\circ}$ and $-40^{\circ}$, calculated on the anhydrous basis, determined in a solution in water containing 10 mg per mL .

Water, Method $1\langle 921\rangle$ : not more than $0.5 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.3 \%$.
Heavy metals, Method $I\langle 231\rangle: \quad 0.002 \%$.
Related compounds-
NOTE—All testing solutions must be prepared immediately prior to use and remain refrigerated until use.
0.01 M Ammonium acetate-Prepare as directed in the Assay.
Solution A-Prepare a filtered and degassed mixture of 0.01 M Ammonium acetate and acetonitrile (96.5:3.5).

Solution B—Prepare a filtered and degassed mixture of 0.01 M Ammonium acetate and acetonitrile ( $75: 25$ ).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Prepare a 0.50 mg per mL solution of USP Stavudine System Suitability Mixture RS in water.

Test solution-Prepare a solution of Stavudine, accurately weighed, in water, and having a concentration of about 0.5 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 2.1 mL per minute. The chromatograph is programmed as follows.

## Time $\quad$ Solution $A \quad$ Solution $B$

| (minutes) | $(\%)$ | $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-10$ | 100 | 0 | isocratic |
| $10-20$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| $20-30$ | 0 | 100 | isocratic |
| $30-35$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $35-40$ | 100 | 0 | re-equilibration |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the retention time of the main stavudine peak is $10.5 \pm 2$ minutes; the relative retention times are about 1.0 for stavudine and 0.28 for thymine; the resolution, $R$, between thymidine epimer and thymidine is greater than or equal to 1.15 and between stavudine and $\alpha$-stavudine is greater than or equal to 1.0 ; the capacity factor, $k^{\prime}$, is greater than 4 ; and the column efficiency is greater than 9500 theoretical plates.

Procedure-Inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the System suitability solution and the Test solution into the chromatograph, record the chromatograms for twice the retention time of the major peak, or at least until the last impurity has eluted, and measure the area of the responses for
all the peaks. Determine the percentage of thymine in the portion of Stavudine taken by the formula:

$$
\left.(100)(F) r_{U} / r_{s}\right),
$$

in which $F$ is the relative response factor and is equal to 0.69; $r_{U}$ is the peak response of thymine obtained from the Test solution; and $r_{s}$ is the sum of the responses of all the related peaks in the chromatogram of the Test solution, including that of the main stavudine peak: not more than $0.5 \%$ of thymine is found. Calculate the percentage of all other impurities in the portion of Stavudine taken by the formula:

$$
100\left(r_{U} / r_{s}\right)
$$

in which $r_{U}$ is the peak area response of each impurity obtained from the Test solution; and $r_{s}$ is the sum of the area responses of all the related peaks in the chromatogram of the Test solution, including that of the main stavudine peak and disregarding any peak observed in the blank: not more than $0.1 \%$ of any impurity is found; and not more than $1.0 \%$ of total impurities is found, including thymine. The quantitation limit is $0.03 \%$ of the total sample related peak areas.

## Assay-

NOTE-All testing solutions must be prepared immediately prior to use and remain refrigerated until use.
0.01 M Ammonium acetate-Dissolve 0.77 g of ammonium acetate in about 900 mL of water in a $1000-\mathrm{mL}$ volumetric flask. Dilute with water to volume, and mix.

Mobile phase-Prepare a filtered and degassed mixture of 0.01 M Ammonium acetate and acetonitrile (95:5).

Standard preparation-Transfer about 10 mg of USP Stavudine RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with water to volume. Pipet 10.0 mL of this solution into a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Assay preparation-Transfer about 10 mg of the Stavudine to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Pipet 10.0 mL of this solution into a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 3.3-\mathrm{cm}$ column that contains $3-\mu \mathrm{m}$ packing L1. The flow rate is about 0.7 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the retention time of the stavudine peak is between 2.8 and 5.0 minutes; the column efficiency is not less than 800 theoretical plates; the tailing factor is less than or equal to 1.6 ; and the relative standard deviation for replicate injections is not more than 2.0\%.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4}$ in the portion of Stavudine taken by the formula:

$$
500 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Stavudine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## Briefing

Stavudine Capsules-See briefing under Stavudine.
(PA7b: B. Davani; BPC: M. Marques) RTS-40185-2

## Add the following:

## ■Stavudine Capsules

»Stavudine Capsules contain not less than 90.0 percent and not more than 105.0 percent of the labeled amount of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4}$.

Packaging and storage-Store in tightly closed containers at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Stavudine $R S$.

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -

Test solution-Using sonication, dissolve a portion of Capsule contents in enough water to obtain a solution having a concentration of 0.2 mg of stavudine per mL , filter, and mix. Use the filtrate as the Test solution.

Application volume: $\quad 10 \mu \mathrm{~L}$, applied in two $5-\mu \mathrm{L}$ portions.

Developing solvent system: a mixture of chloroform, alcohol, and water (100:50:2).

Procedure-Proceed as directed in the chapter. Allow the spots to dry, and develop the chromatogram in the Developing solvent system until the solvent front has moved about

10 cm from the origin. Remove the plate from the developing chamber, mark the solvent front, and allow to air dry for 5 to 10 minutes.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $-40^{\circ}$ and $-45^{\circ}$, determined in a solution in water containing 10 mg of stavudine per mL . Disperse a sufficient quantity of Capsule content, equivalent to 200 mg of stavudine, in 50 mL of acetone. Bring to a boil, and pass through a fine-porosity filter. Precipitate the stavudine with 150 mL of heptane, filter the crystals, wash with heptane, and dry in air.

## Dissolution $\langle 711\rangle$ -

Medium: water; 900 mL .
Apparatus 2: 75 rpm .
Time: 30 minutes.
Determine the amount of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4}$ dissolved by employing the following method.
0.01 M Ammonium acetate and Mobile phase-Prepare as directed in the Assay.

Standard solution-Dissolve an accurately weighed quantity of USP Stavudine RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration corresponding to that of the solution under test.

Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay except that the liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency is not less than 800 theoretical plates; the tailing factor is not more than 2 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Determine the amount of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4}$ dissolved, employing the procedure set forth in the Assay, making any necessary modifications. The injection volume is about $10 \mu \mathrm{~L}$.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4}$ is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

Water, Method $I\langle 921\rangle$ : not more than $3.5 \%$.

## Related compounds-

0.01 M Ammonium acetate and Mobile phase-Prepare as directed in the Assay.

Resolution solution-Proceed as directed in the Assay.
Standard solution-Using sonication, dissolve an accurately weighed quantity of thymine in water, and dilute quantitatively, and stepwise if necessary, with water, to obtain a solution having a known concentration of about $1 \mu \mathrm{~g}$ per mL.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Chromatographic system-Proceed as directed in the Assay. The relative standard deviation for replicate injections of the Standard solution is not more than $3.0 \%$.

Procedure-Proceed as directed in the Assay, recording the chromatograms for a period of time that is 2.5 times the retention time of stavudine, and measure the responses of all the peaks. Calculate the quantity of thymine in each Capsule taken by the formula:

$$
(C V D / N)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of the Standard solution; $V$ is the volume, in mL , used to prepare the Test solution; $D$ is the dilution factor of the Test solution; $N$ is the number of Capsules taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Test
solution and the Standard solution, respectively. Not more than $1.0 \%$ of thymine is found. Calculate the percentage of unknown impurities, not including thymine, in the portion of Capsules taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for each impurity; and $r_{s}$ is the sum of the responses of all the peaks: not more than $0.2 \%$ of any individual impurity is found; and not more than $2.0 \%$ of total impurities, including thymine, is found. The quantitation limit is $0.05 \%$ of the total sample related peak response.

## Assay-

NOTE-All solutions must be prepared immediately prior to use and remain refrigerated until use.
0.01 M Ammonium acetate-Dissolve 0.77 g of ammonium acetate in about 900 mL of water in a $1000-\mathrm{mL}$ volumetric flask. Dilute with water to volume, and mix.

Mobile phase-Prepare a filtered and degassed mixture of 0.01 M Ammonium acetate and acetonitrile (95:5).

Resolution solution-Dissolve accurately weighed quantities of thymine and thymidine in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of $0.1 \mu \mathrm{~g}$ per mL of each component.

Standard preparation-Transfer about 50 mg of USP Stavudine RS, accurately weighed, to a $500-\mathrm{mL}$ volumetric flask, and dissolve in about 200 mL of water, sonicate, dilute with water to volume, and mix.
Assay preparation-Open not fewer than 3 Capsules, and dissolve the contents quantitatively in water. Dilute quantitatively, and stepwise if necessary, with water, to obtain a solution having a concentration of about 0.1 mg of stavudine per mL.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a 268 -nm detector and a $4.6-\mathrm{mm} \times 3.3-\mathrm{cm}$ column that contains packing L1. The flow rate is about 0.7 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between thymine and thymidine is not less than 2.0 , and thymine is resolved from the void volume. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the retention time for the stavudine peak must be between 2.8 and 5.0 minutes; the column efficiency is not less than 800 theoretical plates; the tailing factor is not more than 1.8 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of stavudine $\left(\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4}\right)$ in each Capsule taken by the formula:

$$
C(V / N)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Stavudine RS in the Standard preparation; $V$ is the volume, in mL , used to prepare the Assay preparation; $N$ is the number of Capsules taken to prepare the Assay preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■IS (USP28)

## Briefing

Stavudine for Oral Solution-See briefing under Stavudine. (PA7b: B. Davani) RTS-40187-1

## Add the following:

## Stavudine for Oral Solution

» Stavudine for Oral Solution, when reconstituted as directed in the labeling, yields a 1 mg per mL solution that contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of stavudine $\left(\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4}\right)$. It may contain suitable flavors, preservatives, sweeteners, and stabilizers.

Packaging and storage-Preserve in tightly closed containers, protected from excessive moisture. Store at controlled room temperature. After constitution, store the Oral Solution in tightly closed containers under refrigeration. Discard unused portion after 30 days.

Labeling-The label contains directions for constitution of the powder and states the equivalent amount of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4}$ in a given volume of the Oral Solution obtained after constitution.

USP Reference standards $\langle 11\rangle-U S P$ Stavudine RS.
Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Deliverable volume $\langle 698\rangle$ : meets the requirements.
$\mathbf{p H}\langle 791\rangle$ : between 5 and 7 when constituted as directed in the labeling.

Water, Method $I\langle 921\rangle$ : not more than $2.0 \%$

## Related compounds-

NOTE—All testing solutions must be prepared immediately prior to use and remain refrigerated until use.
Solution A, Solution B, Resolution solution, and Chromatographic system-Proceed as directed in the Assay.
Standard solution-Prepare as directed for Standard preparation in the Assay.

Test solution-Prepare as directed for Assay preparation in the Assay.

Procedure-Noting the retention times of the impurities relative to that of stavudine, calculate the percentage of all other impurities in the portion of Stavudine for Oral Solution taken by the formula:

$$
100\left(F r_{i} / r_{s}\right),
$$

in which $F$ is the relative response factor and is equal to 0.69 for thymine (relative retention time of about 0.24 ) and equal to 1.0 for all other peaks; $r_{i}$ is the peak area response of each impurity obtained from the Test solution; and $r_{s}$ is the sum of the area responses of all the sample-related peaks in the chromatogram including that of the main stavudine peak: not more than $1.0 \%$ of thymine is found, not more than $0.2 \%$ of any other individual impurity is found, and not more than $1.5 \%$ of total impurities is found.

Assay-
NOTE-All testing solutions must be prepared immediately prior to use and remain refrigerated until use.

25 mM Ammonium acetate—Dissolve 1.93 g of ammonium acetate in about 900 mL of water in a $1000-\mathrm{mL}$ volumetric flask. Dilute with water to volume, and mix.

Solution A-Prepare a filtered and degassed mixture of 25 mM Ammonium acetate and methanol (94: 6).

Solution B-Prepare a filtered and degassed mixture of 25 $m M$ Ammonium acetate and methanol (1:1).

Resolution solution-Prepare a solution in water of thymidine and thymine containing $2.5 \mu \mathrm{~g}$ of each per mL .

Standard preparation-Prepare a solution of USP Stavudine RS in water having a concentration of 0.1 mg per mL . Assay preparation-Transfer to a suitable volumetric flask an accurately measured volume of Oral Solution, constituted as directed in the labeling, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a concentration of 0.1 mg of stavudine per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $268-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 3.3-\mathrm{cm}$ column that contains packing L1 and a $4-\mathrm{mm} \times 20-\mathrm{mm}$ guard column (L1). The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-12$ | 100 | 0 | isocratic |
| 12.1 | $100 \rightarrow 0$ | $0 \rightarrow 100$ | step gradient |
| $12.1-17$ | 0 | 100 | isocratic |
| 17.1 | $0 \rightarrow 100$ | $100 \rightarrow 0$ | step gradient |
| $17.1-35$ | 100 | 0 | re-equilibration |

Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between thymine and thymidine is not less than 8.4. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 2000 theoretical plates; the tailing factor for the stavudine peak is not more than 2 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of stavudine $\left(\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4}\right)$ in each mL of Oral Solution taken by the formula:

$$
(L / D)(C)\left(r_{U} / r_{s}\right)
$$

in which $L$ is the labeled quantity, in mg , of stavudine $\left(\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{4}\right)$ in each mL of the Oral Solution; $D$ is the concentration, in mg, of stavudine per mL of the Assay preparation, based on the labeled quantity of stavudine in the portion of Oral Solution taken; $C$ is the concentration, in mg per mL , of USP Stavudine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak area responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## Briefing

Tiamulin Fumarate, USP 27 page 1842 and page 190 of $P F$ 30(1) [Jan.-Feb. 2004]. To improve reproducibility, it is proposed to revise Identification test $A$ to provide additional instructions for preparing the test material for analysis of the IR absorption spectrum.
(VET: I. DeVeau) RTS-41025-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Tiamulin Fumarate $R S$. USP Tosyl Pleurmutilin RS.
${ }^{\Delta}$ USP Tiamulin Related Compound A RS. $\mathbf{\Delta U S P 2 8}$

## Change to read:

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$ -

- [NOTE-Intimately mix Tiamulin Fumarate with potassium
bromide, but do not grind.] $]_{1 S}$ (USP28)
B: The retention time of the tiamulin fumarate peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.


## Change to read:

## Chromatographic purity-

Dilute perchloric acid solution, Buffer solution, Mobile phase, System suitability solution, and Chromatographic system-Proceed as directed in the Assay.

Standard solution-Use the Standard preparation prepared as directed in the Assay.

Test solution-Use the Assay preparation prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, identify the tiamulin fumarate peak, and measure all of the peak responses. [NOTE-Possible tiamulin fumarate impurities include, but are not limited to, pleuromutilin, mutilin, 14-acetyl mutilin, 11-monoacetyl mutilin, plememe tilin,
©tiamulin related compound $\mathrm{A}, \mathbf{1}$ USP28
11,14-diacetyl mutilin, 8-dimethylderivative, bisdimethylderivative, and 11-ketoderivative, their retention times, relative to tiamulin fumarate, being about $0.25,0.3,0.5,0.6,0.8,1.1,1.3,1.4$, and 2.3 , respectively.] Calculate the area percentage of each impurity, relative to tiamulin fumarate, in the portion of Tiamulin Fumarate taken by the formula:

$$
100\left(r_{i} / r_{U}\right)
$$

in which $r_{i}$ and $r_{U}$ are the peak responses of each impurity and tiamulin fumarate, respectively: not more than $1.0 \%$ of any identified impurity is found; not more than $0.5 \%$ of any unidentified impurity is found; and not more than $2.0 \%$ of total impurities is found.

## Change to read:

Assay-
Dilute perchloric acid solution-Prepare a solution containing $6 \%$ of perchloric acid.

Buffer solution-Transfer 10 g of ammonium carbonate to a $1000-\mathrm{mL}$ volumetric flask, and dissolve in about 800 mL of water. Add 24 mL of Dilute perchloric acid solution, dilute with water to volume, mix, and filter.

Mobile phase-Prepare a mixture of methanol, Buffer solution, and acetonitrile ( $49: 28: 23$ ), filter, and degas.

System suitability solution-Dissolve accurately weighed quantities of USP Tiamulin Fumarate RS and USP Tesyl Pleuremutilin RS
${ }^{\boldsymbol{\Delta}}$ USP Tiamulin Related Compound A RS $\mathbf{\Delta U S P 2 8}$
in Mobile phase to obtain a solution having known concentrations of about 0.08 mg of each per mL .
Standard preparation-Dissolve an accurately weighed quantity of USP Tiamulin Fumarate RS in Mobile phase to obtain a solution having a known concentration of about 4 mg per mL .
Assay preparation-Transfer about 200 mg , accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $212-\mathrm{nm}$ detector and a 4.6 $\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at $30 \pm 3^{\circ}$. Chromatograph the Standard preparation and the System suitability solution, and record the peak responses as directed for Procedure: plemmetilim
$\Delta_{\text {the tiamulin related compound }} \mathrm{A}_{\mathbf{\Delta U S P 2 8}}$ peak elutes prior to the tiamulin fumarate peak; the resolution, $R$, between plewremetilin
$\Delta_{\text {tiamulin related compound }} \mathrm{A}_{\mathbf{\Delta} U S P 28}$
and tiamulin fumarate is not less than 2.0; the capacity factor, $k^{\prime}$, determined from the tiamulin fumarate peak, is not less than 2.0 ; the column efficiency is not less than 14,000 ; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{28} \mathrm{H}_{4} \mathrm{NO}_{4} \mathrm{~S} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$ in the portion of Tiamulin Fumarate taken by the formula:

$$
50 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Tiamulin Fumarate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the tiamulin fumarate peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Tolcapone, page 836 of PF 29(3) [May-June 2003]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded to In-Process Revision with no changes.
(PA3: S. Salado) RTS-39849-1

## Add the following:

## ■Tolcapone

$\mathrm{C}_{14} \mathrm{H}_{11} \mathrm{NO}_{5} \quad 273.24$
Methanone, (3,4-dihydroxy-5-nitrophenyl)(4-methyl-
phenyl).

3,4-Dihydroxy-4'-methyl-5-nitrobenzophenone
[134308-13-7].
» Tolcapone contains not less than 98.5 percent and not more than 101.5 percent of $\mathrm{C}_{14} \mathrm{H}_{11} \mathrm{NO}_{5}$, calculated on dried and solvent-free basis.

Packaging and storage—Preserve in tight, light-resistant containers between $20^{\circ}$ and $25^{\circ}$.

USP Reference standards $\langle 11\rangle —$ USP Tolcapone RS. USP Tolcapone Related Compound A RS. USP Tolcapone Related Compound B RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

## Absorptivity-

Test Preparation-Prepare a solution of Tolcapone having a concentration of 0.01 mg per mL in 0.1 N alcoholic hydrochloric acid.

Procedure-Proceed as directed under Spectrophotometry and Light-Scattering $\langle 851\rangle$, and measure the absorbance: the maximum is between 265.2 and 269.3 , and the absorptivity is between 752.9 and 799.3.

Water, Method $I\langle 921\rangle$ : not more than $0.1 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.002 \%$.

## Limit of residual solvents-

Alcohol stock solution-Transfer $6.3 \mu \mathrm{~L}$ of absolute alcohol, using a microsyringe, to a $50-\mathrm{mL}$ volumetric flask containing dimethylformamide, and mix.

Methylene chloride stock solution-Transfer $3.8 \mu \mathrm{~L}$ of methylene chloride, using a microsyringe, to a $50-\mathrm{mL}$ volumetric flask containing dimethylformamide, and mix.
Standard solution-Transfer 10.0 mL of Alcohol stock solution and 1.0 mL of Methylene chloride stock solution to a $50-\mathrm{mL}$ volumetric flask. Dilute with dimethylformamide to volume, and mix.

Test solution-Transfer about 200 mg of Tolcapone, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, add 7 mL of dimethylformamide, and sonicate to dissolve. Dilute with dimethylformamide to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector, a $0.53-\mathrm{mm} \times 30-\mathrm{m}$ fused silica column coated with $3.0-\mu \mathrm{m}$ G43 stationary phase, and a $0.53-\mathrm{mm} \times 5-\mathrm{m}$ fused silica column coated with $3.0-\mu \mathrm{m}$ G3 stationary phase. The carrier gas is helium, flowing at a rate of 5 mL per minute. The column is maintained at $35^{\circ}$. The temperatures of the injection port and the detector are maintained at $120^{\circ}$ and $260^{\circ}$, respectively. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention time is about 0.7 for alcohol and 1.0 for methylene chloride; and the relative standard deviation for replicate injections is not more than $10.0 \%$.

Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentages (w/w) of alcohol and methylene chloride in the portion of Tolcapone taken by the formula:

$$
(1000 D)(C / W)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{L}$ per mL , of each solvent in the Standard solution; $D$ is the density, in mg per $\mu \mathrm{L}$, of each solvent at $20^{\circ} ; W$ is the weight, in mg , of Tolcapone taken to prepare the Test solution; and $r_{U}$ and $r_{s}$ are the peak areas of the appropriate analyte obtained from the Test solution and the Standard solution, respectively: not more than $0.25 \%$ of alcohol is found; and not more than $0.01 \%$ of methylene chloride is found. [NOTE-Condition the column at $220^{\circ}$ for 15 minutes after each injection.]

## Related compounds-

TEST 1-
Adsorbent- $0.25-\mathrm{mm}$ layer of chromatographic $5-\mu \mathrm{m}$ silica gel mixture with a suitable fluorescing substance (see Chromatography $\langle 621\rangle$ ).

Standard solution 1-Dissolve an accurately weighed portion of USP Tolcapone RS in chloroform, and dilute quantitatively, and stepwise if necessary, with chloroform to obtain a solution having a known concentration of 0.4 mg per mL .

Standard solution 2-Transfer 2.0 mL of Standard solution 1 to a $10-\mathrm{mL}$ volumetric flask, dilute with chloroform to volume, and mix.

Standard solution 3-Transfer 1.0 mL of Standard solution 1 to a $10-\mathrm{mL}$ volumetric flask, dilute with chloroform to volume, and mix.

Standard solution 4-Transfer 5.0 mL of Standard solution 3 to a $100-\mathrm{mL}$ volumetric flask, dilute with chloroform to volume, and mix.

Test solution-Transfer about 200 mg of Tolcapone, accurately weighed, to a $5-\mathrm{mL}$ volumetric flask, dissolve in and dilute with chloroform to volume, and mix. [NOTE-Prepare this solution last and chromatograph immediately.]

Application volume: $\quad 10 \mu \mathrm{~L}$.
Developing solvent system: a mixture of chloroform, formic acid, and ethyl acetate ( $83: 15: 2$ ).

Procedure-Apply the Test solution and each of the Standard solutions as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$. Dry the plate in a current of cold air, and view it under short wavelength UV. The $R_{F}$ values of analytes are as follows:

| Compound | $R_{F}$ |
| :--- | :---: |
| Tolcapone related compound A | about 0.2 |
| Tolcapone | about 0.5 |
| Tolcapone related compound B | about 0.7 |

Compare any spot at $R_{F}$ of 0.0 in the chromatogram obtained from the Test solution with the main spot of the Standard solution 2, Standard solution 3, and Standard solution 4, and obtain the approximate amount: not more than $0.1 \%$ of any impurity at $R_{F}$ of 0.0 is found. [NOTE-The $R_{F}$ of tolcapone related compound A and tolcapone related compound B are given just for reference. They are quantified in Test 2.]

TEST 2-
Diluent, System suitability solution, Mobile phase, and Chromatographic system-Proceed as directed in the Assay.
Standard solution-Use the Standard preparation, prepared as directed in the Assay.
Test solution-Use the Assay preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of each impurity in the portion of Tolcapone taken by the formula:

$$
(50,000 F)(C / W)\left(r_{i} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Tolcapone RS in the Standard solution; $F$ is the relative response factor of the impurity according to the table below; $W$ is the weight, in mg , of Tolcapone, calculated on the sol-vent- and water-free basis, used to prepare the Test solution; $r_{i}$ is the peak area for any impurity in the Test solution; and $r_{s}$ is the peak area for tolcapone in the Standard solution: the impurities meet the requirements given in the table below.

|  | Relative <br> Retention <br> Time | Relative <br> Response <br> Factor | Limit (\%) |
| :--- | :---: | :---: | :---: |
| Compound Name | about 0.6 | 1.14 | 0.1 |
| Tolcapone related <br> compound A | 1.0 | - | - |
| Tolcapone | 1.36 | 0.98 | 0.2 |
| Tolcapone related <br> compound B |  |  |  |
| Unknown impuri- <br> ties | - | 1.0 | 0.1 indivi- |
| dual, 0.2 |  |  |  |
| Total impurities | - | - | known <br> 0.5 |

## Assay-

Diluent-Prepare a mixture of methanol and acetonitrile (24:15).

System suitability solution-Dissolve an accurately weighed quantity of USP Tolcapone Related Compound A RS, USP Tolcapone RS, and USP Tolcapone Related Compound B RS in Diluent; and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about $5 \mu \mathrm{~g}$ per $\mathrm{mL}, 5 \mu \mathrm{~g}$ per mL , and $10 \mu \mathrm{~g}$ per mL , respectively. Transfer 2.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, add about 63 mL of Diluent, dilute with water to volume, and mix.

Mobile phase-Prepare a filtered and degassed mixture of methanol, 0.05 M monobasic potassium phosphate having a pH of $2.0 \pm 0.1$, and acetonitrile ( $8: 7: 5$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Tolcapone RS in Diluent; and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 1.0 mg per mL . Transfer 5.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, add about 27.5 mL of Diluent, dilute with water to volume, and mix.

Assay preparation-Transfer about 50 mg of Tolcapone, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix. Transfer 5.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, add about 27.5 mL of Diluent, dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a $230-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.6 for tolcapone related compound A, 1.0 for tolcapone, and about 1.4 for tolcapone related compound B ; and the resolution, $R$, between tolcapone related com-
pound $B$ and tolcapone is not less than 4.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major tolcapone peaks. Calculate the quantity, in mg, of $\mathrm{C}_{14} \mathrm{H}_{11} \mathrm{NO}_{5}$ in the portion of Tolcapone taken by the formula:

$$
500 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Tolcapone RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## Briefing

Tolcapone Tablets, page 839 of PF 29(3) [May-June 2003]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded to In-Process Revision with no changes.
(PA3: S. Salado) RTS—39849-2

## Add the following:

## ■Tolcapone Tablets

» Tolcapone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of tolcapone $\left(\mathrm{C}_{14} \mathrm{H}_{11} \mathrm{NO}_{5}\right)$.

Packaging and storage-Preserve in tight containers between $20^{\circ}$ and $25^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Tolcapone RS. USP Tolcapone Related Compound A RS. USP Tolcapone Related Compound B RS.

## Identification-

A: Infrared Absorption-Grind 10 Tablets to a fine powder. Transfer an amount of powder, equivalent to 3 mg of tolcapone, into a polystyrene vial containing two mixing beads. Add 300 mg of infrared grade potassium bromide, and disperse the material in the matrix by agitating the capped vial in a grinding mill for 2 minutes. Transfer a portion of the sample to a sample cup. Record the diffuse reflectance IR spectrum between 2200 and $1090 \mathrm{~cm}^{-1}$ (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). The spectrum thus obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP Tolcapone RS, concomitantly measured.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

## Dissolution $\langle 711\rangle$ -

Medium: pH 6.8 phosphate buffer containing $1 \%$ of sodium lauryl sulfate; 900 mL .

Apparatus 2: 75 rpm .
Time: 30 minutes.
Procedure-Determine the amount of $\mathrm{C}_{14} \mathrm{H}_{11} \mathrm{NO}_{5}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 271 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Tolcapone RS in the same Medium. Calculate the amount of $\mathrm{C}_{14} \mathrm{H}_{11} \mathrm{NO}_{5}$ dissolved in each Tablet.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{14} \mathrm{H}_{11} \mathrm{NO}_{5}$ is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Chromatographic purity-

Diluent 1, Diluent 2, System suitability solution, Mobile phase, and Chromatographic system-Proceed as directed in the Assay.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major tolcapone peaks. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:
in which $C$ is the concentration, in mg per mL , of USP Tolcapone RS in the Standard solution; $A$ is the average weight, in mg , of the Tablets; $W$ is the weight, in mg , of tablet powder taken to prepare the Test solution; $D$ is the labeled quantity, in mg , of tolcapone per Tablet; $r_{i}$ is the peak area for any impurity in the Test solution; and $r_{s}$ is the peak area for tolcapone in the Standard solution: not more than $0.1 \%$ of any individual impurity is found, and not more than $0.5 \%$ of total impurities is found.

## Assay-

Diluent 1-Prepare a mixture of methanol and acetonitrile (24:15).
Diluent 2-Prepare a mixture of methanol, water, and acetonitrile $(8: 7: 5)$.

System suitability solution-Dissolve an accurately weighed quantity of USP Tolcapone RS, USP Tolcapone Related Compound A RS, and USP Tolcapone Related Compound B RS in Diluent 2, and dilute quantitatively, and stepwise if necessary, with Diluent 2 to obtain a solution having a known concentration of about $104 \mu \mathrm{~g}$ per $\mathrm{mL}, 10.4$ $\mu \mathrm{g}$ per mL , and $10.4 \mu \mathrm{~g}$ per mL , respectively.

Mobile phase-Prepare a filtered and degassed mixture of methanol, 0.05 M monobasic potassium phosphate having a pH of $2.0 \pm 0.1$, and acetonitrile ( $8: 7: 5$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Tolcapone RS in Diluent 1, and dilute quantitatively, and stepwise if necessary, with Diluent 1 to obtain a solution having a known concentration of about 1.0 mg per mL . Transfer 5.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, add about 27.5 mL of Diluent 1, dilute with water to volume, and mix.

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of tolcapone, to a $100-\mathrm{mL}$ volumetric flask, add 10 mL of water, and sonicate for about 10 minutes. Add 65 mL of Diluent 1, and sonicate for about 15 minutes. Allow the sample to settle. If the material is still undispersed, sonicate for an additional 5 minutes. Dilute with water to volume, and mix. Centrifuge a portion of this solution, and transfer 5.0 mL of the supernatant to a $50-\mathrm{mL}$ volumetric flask. Dilute with Diluent 2 to volume, and mix. Pass a portion of this solution through a $0.45-\mu \mathrm{m}$ filter, and use the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $230-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.6 for tolcapone related compound A, 1.0 for tolcapone, and about 1.4 for tolcapone related compound B ; the resolution, $R$, between tolcapone related compound B and tolcapone is not less than 6.0; and the tailing factor is not more than 1.5 for the tolcapone peak. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of tolcapone $\left(\mathrm{C}_{14} \mathrm{H}_{11} \mathrm{NO}_{5}\right)$ in the portion of Tablets taken by the formula:

$$
1000 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Tolcapone RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Triamcinolone Acetonide, USP 27 page 1875 and page 1588 of PF 29(5) [Sept.-Oct. 2003]. In order to achieve better peak shape and resolution, it is proposed in the test for Chromatographic purity to change the solvent and specify the quantity and ratio used in the Test solution.
(PA1: C. Anthony) RTS-41027-1

## Change to read:

Packaging and storage-Preserve in well-closed containers.
-Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ} \cdot{ }^{-2 S}$ (USP27)

## Add the following:

${ }^{\boldsymbol{4}}$ Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. $\Delta$ USP28

## Change to read:

USP Reference standards $\langle 11\rangle$ -
${ }^{\Delta}$ USP Endotoxin RS. $\mathbf{\Delta U S P 2 8}$
USP Triamcinolone Acetonide RS.

## Change to read:

## Chromatographic purity-

Mobile phase-Prepare a filtered and degassed mixture of water and acetonitrile ( $17: 8$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Test solution-Transfer about 25 mg of Triamcinolone Acetonide, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask; dissolve in enitrile,

- 25 mL of methanol, ${ }_{1 S}$ (USP28)
shake vigorously to aid dissolution; dilute with
- Mobile phase ${ }_{\text {■1S (USP28) }}$
to volume; and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a 3.9$\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Test solution, and record the peak responses as directed for Procedure: the resolution, $R$, between triamcinolone acetonide and any impurity peak is not less than 1.0.

Procedure-Inject about $20 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram for not less than four times the retention time of triamcinolone acetonide, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Triamcinolone Acetonide taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for each impurity and $r_{S}$ is the sum of the responses of all peaks: not more than $0.3 \%$ of any individual impurity is found, and not more than $0.8 \%$ of total impurities is found.

## Add the following:

${ }^{\Delta}$ Other requirements-Where the label states that Triamcinolone Acetonide is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Triamcinolone Acetonide Injectable Suspension. Where the label states that Triamcinolone Acetonide must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under
Triamcinolone Acetonide Injectable Suspension. $\mathbf{4 S P 2 8}$
name "dimethyl sulfoxide" is being standardized throughout the $U S P-N F$. In addition, minor editorial style changes have been made.
(BPC: M. Marques) $\quad$ RTS-41082-2

## Change to read:

Limit of residual solvents-
Internal standard solution-Prepare a solution of $n$-propyl alcohol in methyl sulfoxide

- dimethyl sulfoxide $_{\mathbf{m}_{1 S} \text { (USP28) }}$
having a concentration of about $0.05 \mu \mathrm{~L}$ per mL .
Standard solution-Prepare a solution in Internal standard solution having a concentration of $2.5 \mu \mathrm{~g}$ of chloroform, $5.0 \mu \mathrm{~g}$ of dehydrated alcohol, $5.0 \mu \mathrm{~g}$ of acetone, $5.0 \mu \mathrm{~g}$ of butyl alcohol, $5.0 \mu \mathrm{~g}$ of dioxane, $10.0 \mu \mathrm{~g}$ of methylene chloride, $15.0 \mu \mathrm{~g}$ of diisopropyl ether, $20.5 \mu \mathrm{~g}$ of acetonitrile, $50 \mu \mathrm{~g}$ of pentane, and $100 \mu \mathrm{~g}$ of methanol in each mL, and sonicate.

Test solution-Dissolve about 200 mg of Valrubicin, accurately weighed, in 4.0 mL of Internal standard solution, and sonicate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The gas chromatograph is equipped with a flame-ionization detector and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ fused-silica capillary column coated with a $5-\mu \mathrm{m}$ film of G2 stationary phase. The carrier gas is helium, flowing at a rate of 30 mL per minute. The column temperature is maintained at $220^{\circ}$. The injection port temperature and the detector block temperature are maintained at $250^{\circ}$. Chromatograph the Standard solution, and record the responses as directed for Procedure: the relative retention times are about 0.48 for methanol, 0.66 for dehydrated alcohol, 0.71 for acetonitrile, 0.76 for acetone, 0.86 for pentane, 0.92 for methylene chloride, 1.0 for $n$-propyl alcohol, 1.19 for diisopropyl ether, 1.22 for chloroform, 1.35 for butyl alcohol, and 1.52 for dioxane; the component solvent peaks are resolved; and the relative standard deviation of the ratios of the peak area of each solvent to the peak area of $n$-propyl alcohol is not more than $10 \%$.
Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the concentration, in $\mu \mathrm{g}$ per g , of each residual solvent in the portion of Valrubicin taken by the formula:

$$
4000(C / W)\left(R_{i} / R_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of the respective individual solvent in the Standard solution; $W$ is the quantity, in mg , of Valrubicin taken to prepare the Test solution; and $R_{i}$ and $R_{S}$ are the peak area ratios of the respective individual solvent to $n$-propyl alcohol obtained from the Test solution and the Standard solution, respectively: not more than $50 \mu \mathrm{~g}$ per g of chloroform, $100 \mu \mathrm{~g}$ per g of dehydrated alcohol, $100 \mu \mathrm{~g}$ per g of acetone, $100 \mu \mathrm{~g}$ per g of butyl alcohol, $100 \mu \mathrm{~g}$ per g of dioxane, $300 \mu \mathrm{~g}$ per $g$ of methylene chloride, $410 \mu \mathrm{~g}$ per g of acetonitrile, $500 \mu \mathrm{~g}$ per $g$ of diisopropyl ether, $1000 \mu \mathrm{~g}$ per g of pentane, and $2000 \mu \mathrm{~g}$ per $g$ of methanol are found.

Valrubicin, USP 27 page 1928. In the test for Limit of residual solvents, it is proposed to replace the name of the reagent methyl sulfoxide with its synonym dimethyl sulfoxide. The use of the

## BRIEFING

Verteporfin, USP 27 page 1938. It is proposed to add a Sensitivity check solution in the Related compounds test to ensure detectability at the limit of quantitation. It is also proposed to replace the test for Limit of methylene chloride with a test for Organic volatile impurities to control additional solvents present in the approved drug product application.
(PA6: L. Evans) RTS-40002-2

## Change to read:

## Related compounds-

Solution A, Solution B, and Mobile phase—Proceed as directed in the Assay.
-Standard solution-Prepare as directed for the Standard preparation in the Assay.

Sensitivity check solution-Dilute the Standard solution with water to obtain a solution having a concentration of $0.25 \mu \mathrm{~g}$ per mL . 1 is (USP28)

Test solution-Prepare as directed for Assay preparation in the Assay.

Chromatographic system-
-Chromatograph the Sensitivity check solution at 410 nm , and record the peak heights: the ratio of the verteporfin peak height to the noise height is not less than 10 , the noise height
being determined by a suitable procedure. 1 (USP28)
Proceed as directed in the Assay. To evaluate the system suitability requirements, use the Standard preparation prepared as directed in the Assay.

Procedure—Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each related compound in the portion of Verteporfin taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the individual peak response of each related compound; and $r_{s}$ is the sum of the responses of all the peaks. Not more than $0.6 \%$ of the peak having a retention time of about 0.56 relative to that of the first verteporfin isomer peak is found; not more than $0.8 \%$ of any other individual related compound is found; and the sum of all impurities is not more than $4.0 \%$.

Test solution: 10 mg of Verteporfin per mL in dimethylformamide.

Limit: not more than 5000 - s , per of of Verteporfin ( $0.5 \%$ )

## Add the following:

-Organic volatile impurities Method $I\langle 467\rangle$ : meets the requirements.■1S (USP28)

## BRIEFING

Sterile Purified Water, USP 27 page 1950 and page 3089 of the First Supplement. It it proposed to revise the test for Ammonia to make a correction in the calculation for the added ammonia. The calculation, which was previously added to make the procedure more definitive, lacks a dilution step that would bring the control to the $30 \mu \mathrm{~g}$ of added ammonia in 100 mL . This proposed revision would correct the oversight and make the procedure more practical for the user.
(PW: F. Barletta) RTS-41116-1

## Change to read:

Ammonia-For containers having a fill volume of less than 50 mL , dilute 50 mL of it with 50 mL of High-Purity Water (see Reagents under Containers $\langle 661\rangle$ ), and use this dilution as the test solution; where the fill volume is 50 mL or more, use 100 mL of it as the test solution. To 100 mL of the test solution add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing $30 \mu \mathrm{~g}$ of added ammonia $\quad$ (fumished by adding 1.76 mL of 1.0 N amme

-(furnished by adding 1 mL of the final solution prepared by diluting 3.0 mL of ammonia TS with High-Purity Water to $100 \mathrm{~mL} ; 1.0 \mathrm{~mL}$ of this solution is further diluted to 100 $\mathrm{mL})_{1 \mathrm{IS}(U S P 28)}$
in 100 mL of High-Purity Water. This corresponds to a limit of 0.6 mg per L for containers having a fill volume of less than 50 mL and 0.3 mg per L where the fill volume is 50 mL or more.

## Delete the following:

ELimit of methylene chloride-Use the procedure for Method 1 under $O$ geanic Volatile Impurities $(467$ ), with the following exeeptions.

Standedrdsolution: $50 \mu \mathrm{~g}$ of methylene chloride per mL in dimethylformamide.

## BRIEFING


#### Abstract

Zileuton, USP 27 page 1965 and page 2006 of $P F 29(6)$ [Nov.Dec. 2003]. Based on comments received, the monograph is being revised. Procedures and acceptance criteria for Specific surface area, Arsenic, Limit of boron, Limit of Pyridine, and Organic volatile impurities are added, and the acceptance criteria in Test 1 in the test for Chromatographic purity are revised in compliance with FDA-approved submissions.


(PA1: K. Russo) RTS-40214-1; 40564-1

## Add the following:

■Specific surface area, Method $I\langle 846\rangle$ : Outgas a portion of the test sample, about 100 mg , at $90^{\circ}$ for 1 hour at ambient pressure using 0.001 mole fraction of krypton in helium as the adsorbate gas: between 0.9 and 3.1. $\mathrm{m}^{2}$ per g .■1S (USP28)

## Add the following:

■Arsenic, Method II $\langle 211\rangle$ : $\quad 2 \mu \mathrm{~g}$ per g.■1S (USP28)

## Add the following:

## -Limit of boron-

Sulfuric acid solution-Carefully add 50 mL of sulfuric acid to 450 mL of water, and mix.

Standard solution-Prepare a solution in Sulfuric acid solution having a concentration of about $2.0 \mu \mathrm{~g}$ of boron per mL . Use of a commercially prepared boron ICP standard solution is recommended.

Test solution-Accurately weigh approximately 1.0 g of Zileuton into a $125-\mathrm{mL}$ conical flask. Add 1 to 1.5 mL of sulfuric acid, and digest in a fume hood on a hot plate until charring begins. Add 2 mL of nitric acid to the cooled sample to aid digestion, and heat until brown fumes are not evolved. Cautiously add 30 percent hydrogen peroxide, dropwise, allowing the reaction to subside, and heating between drops. Add the first few drops very slowly with sufficient mixing in order to prevent a rapid reaction. Discontinue heating if foaming becomes excessive. When
the reaction has abated, heat cautiously, rotating the flask occasionally to prevent the sample from caking on glass exposed to the heating unit. Maintain oxidizing conditions at all times during the digestion by adding small quantities of the 30 percent hydrogen peroxide, whenever the mixture turns brown or darkens. Approximately 1 to 2 mL of nitric acid can be added, if necessary, which will create a refluxing effect to wash down any particles adhering to the neck of the flask. Continue the digestion until the organic matter is destroyed, gradually raising the temperature of the hot plate until fumes of sulfur trioxide are copiously evolved and the solution becomes colorless or retains only a light straw color. Transfer the solution to a $25-\mathrm{mL}$ volumetric flask using about 7 mL of water. Repeat the washing twice more, and combine the washings in the volumetric flask. Dilute with water to volume, and mix.

Procedure-The inductively coupled plasma-atomic emission spectrometer is set up with wavelength of 249.7 nm , RF power of 1.25 KW , argon torch flow of about 13 L per minute, argon nebulizer flow of about 1 L per minute, and argon auxillary flow of about 0.5 L per minute. Analyze the Standard solution and the Test solution, using Sulfuric acid solution as the blank. Calculate the quantity, in $\mu \mathrm{g}$ of boron per g , in the portion of Zileuton taken by the formula:

## $25 C / W$,

where $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of boron in the Test solution determined from the instrument; and $W$ is the weight, in g , of the zileuton: not more than $10 \mu \mathrm{~g}$ per g is found.1S (USP28)

## Add the following:

## - Limit of pyridine-

Standard solution-Dissolve an accurately weighed quantity of pyridine, approximately 250 mg , in dimethyl sulfoxide, and dilute to 50 mL . Transfer $5 \mu \mathrm{~L}$ to a $100-$ mL sealed headspace vial.

Test Solution, Chromatography System, and ProcedureProceed as directed under Organic Volatile Impurities, Method IV, 〈467〉. Separately inject the Standard solution and the Test Solution into the gas chromatograph, and record the peak responses. Calculate the quantity, in ppm, of pyridine in the portion of Zileuton taken by the formula:

$$
100\left(r_{U} / r_{s}\right)\left(W_{S} / W_{U}\right)
$$

where $r_{U}$ and $r_{S}$ are the peak responses for pyridine in the Test solution and the Standard solution, respectively; $W_{S}$ is the weight, in mg, of pyridine used to prepare the Standard solution; and $W_{U}$ is the weights, in mg , of zileuton: not more than 100 ppm is found. ${ }^{1 S}$ (USP28)

## Change to read:

## Chromatographic purity-

$\mathbf{-}_{\text {NOTE-For Test }} 1$ and Test 2 the System suitability solution, Standard solution, and Test solution are to be refrigerated at or below $5^{\circ}$ immediately after preparation and during analysis using a refrigerated autosampler. The solutions are stable at or below $5^{\circ}$ for about 36 hours. $\mathbf{L S S}^{2 S}$ (USP27) TEST 1-
Buffer solution-Prepare as directed in the Assay.
Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $82: 18$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve accurately weighed quantities of USP Zileuton RS and USP Zileuton Related Compound A RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 5 $\mu \mathrm{g}$ of each USP Reference Standard per mL.

Standard solution-Dissolve an accurately weighed quantity of USP Zileuton RS in acetonitrile to obtain a solution having a known concentration of about $10 \mu \mathrm{~g}$ per mL .

Test solution-Transfer about 125 mg of Zileuton, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with acetonitrile to volume, and mix.

Chromatographic system-Prepare as directed in the Assay, except to use a flow rate of 2.2 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between zileuton and zileuton related compound A is not less than 1.5 ; and the relative standard deviation for replicate injections is not more than $5.0 \%$.
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, and measure the areas for the major peaks. Calculate the percentage of each impurity in the portion of Zileuton taken by the formula:

$$
100 F\left(C_{S} / C_{U}\right)\left(r_{i} / r_{S}\right)
$$

in which $F$ is the relative response factor for each impurity, which is 1.0 for any peak with a relative retention time of $0.5,0.7,1.2$, 1.6, 3.2, or 3.4 , and is $1.2,1.4$, and 1.7 for peaks with relative retention times of $0.8,2.1$, and 2.8 , respectively; $C_{s}$ is the concentration, in mg per mL, of USP Zileuton RS in the Standard solution; $C_{U}$ is the concentration, in mg per mL , of zileuton in the Test solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{s}$ is the peak response for zileuton obtained from the Standard solution: not more than $0.1 \%$ of any individual impurity with a relative retention time of 0.7 ,
$\square_{\text {n } 15}$ (USP28)
$0.8,1.6$, or 2.13 .2 , or 3.4
${ }^{-15}$ (USP28)
is found;
-not more than $0.10 \%$ of any individual impurity with a re-
lative retention time of $0.7,3.2$, or 3.4 is found; ${ }_{1 S}$ (USP28) not more than $0.2 \%$

- $0.20 \%_{\text {MS }}$ (USP28).
of any individual impurity with a relative retention time of 0.5 or 1.2 is found; and not more than $0.3 \%$

of any individual impurity with a relative retention time of 2.8 is found.

TEST $2-$
Perchloric acid solution-Dissolve 5.0 mL of perchloric acid in 1000 mL of water.
Mobile phase-Prepare a filtered and degassed mixture of Perchloric acid solution and acetonitrile ( $1: 1$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard stock solution-Dissolve an accurately weighed quantity of USP Zileuton Related Compound B RS in acetonitrile to obtain a solution having a known concentration of about 0.25 mg per mL . Transfer 5.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix.

System suitability solution-Dissolve an accurately weighed quantity of USP Zileuton Related Compound C RS in acetonitrile to obtain a solution having a known concentration of about $10 \mu \mathrm{~g}$ per mL. Transfer 5.0 mL of this solution and 5.0 mL of the Standard stock solution to a $50-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix.

Standard solution-Transfer 5.0 mL of the Standard stock solution to a $50-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix.
Test solution-Proceed as directed for Test solution under Test 1.
Chromatographic system-Prepare as directed in the Assay. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between zileuton related compound B and zileuton related compound C is not less than 20. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $5.0 \%$.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of each impurity in the portion of Zileuton taken by the formula:

$$
100\left(C_{S} / C_{U}\right)\left(r_{i} / r_{S}\right)
$$

in which $C_{S}$ is the concentration, in mg per mL , of USP Zileuton Related Compound B RS in the Standard solution; $C_{U}$ is the concentration, in mg per mL , of zileuton in the Test solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the peak response for zileuton related compound B obtained from the Standard solution: not more than $0.1 \%$ of any individual impurity is found; and not more than $0.7 \%$ of total impurities is found, the results for Test 1 and Test 2 being added.

## Add the following:

-Organic volatile impurities Method IV $\langle 467\rangle$ :
meets
the requirements.■1S (USP28)

## Change to read:

## Assay

$\square_{\text {NOTE-The }}$ Standard preparation and the Assay preparation are to be refrigerated at or below $5^{\circ}$ immediately after preparation and during analysis using a refrigerated autosampler. The solutions are stable at or below $5^{\circ}$ for about 36 hours. $\quad$ 2S (USP 27

Buffer solution-Dissolve 7.7 g of ammonium acetate and 0.25 g of acetohydroxamic acid in about 900 mL of water in a $1000-\mathrm{mL}$ volumetric flask, adjust with perchloric acid to a pH of 2.0 , dilute with water to volume, and mix.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $72: 28$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard preparation-Transfer about 30 mg of methylparaben, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with acetonitrile to volume, and mix.

Standard stock preparation-Dissolve an accurately weighed quantity of USP Zileuton RS in acetonitrile to obtain a solution having a known concentration of about 1 mg per mL .

Standard preparation-Transfer 5.0 mL of the Standard stock preparation and 4.0 mL of the Internal standard preparation to a $50-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix.

Assay preparation-Transfer about 100 mg of Zileuton, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with acetonitrile to volume, and mix. Transfer 5.0 mL of this solution and 4.0 mL of the Internal standard preparation to a $50-$ mL volumetric flask, dilute with acetonitrile to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $260-\mathrm{nm}$ detector and a 4.6$\mathrm{mm} \times 30-\mathrm{cm}$ column that contains $10-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between zileuton and methylparaben is not less than 5.0; the tailing factor is not more than 1.3 ; and the relative standard deviation for replicate injections is not more than $0.6 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Assay preparation and the Standard preparation into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the quantity, in mg, of $\mathrm{C}_{11} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{O}_{2} \mathrm{~S}$ in the portion of Zi leuton taken by the formula:

$$
1000 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Zileuton RS in the Standard preparation; and $R_{U}$ and $R_{S}$ are the peak area ratios obtained from the Assay preparation and the Standard preparation, respectively.

## DIETARY SUPPLEMENTSMONOGRAPHS

## BRIEFING

Choline Bitartrate, USP 27 page 1979. On the basis of comments received, it is proposed to revise the Mobile phase and the derivatization procedure in the test for Chromatographic purity to improve separation.
(DSN: L. Evans) RTS-41054-1

## Change to read:

## Chromatographic purity-

Buffer solution, Mobile phase, Standard solution, and Chromatographic system-Proceed as directed for Chromatographic purity under Choline Chloride.

Test solution-Transfer about 500 mg of Choline Bitartrate, accurately weighed, to a centrifuge tube; add 2.0 mL of water; and swirl to dissolve. Add 0.5 mL of potassium chloride solution ( 7.5 in 25), centrifuge, and transfer 1.0 mL of the supernatant to a 24 mL screw-capped vial. Dry at $120^{\circ}$ for 2 hours. Add 400 mg of 3,5dinitrobenzoyl chloride and 10 mL of acetonitrile, and mix. Cap the vial, and heat at $55^{\circ}$ for + hemr.

- 2 hours.■1S (USP28)

Cool to room temperature, add 5 mL of water, and allow to stand for 2 minutes.

- 5 minutes. 1 (USP28)

Quantitatively transfer this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

- Pipet 2.0 mL of the solution to a $25-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.■1S (USP28)

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of each impurity in the portion of Choline Bitartrate taken by the formula:

$$
(253.25 / 139.62) 5000(\mathrm{C} / \mathrm{H})\left(++_{5}+5\right)
$$

$$
\mathbf{\square}_{(253.25 / 139.62) 62,500(C / W)\left(r_{i} / r_{S}\right), ■ 1 \mathrm{SS}(U S P 28)}
$$

in which 253.25 and 139.62 are the molecular weights of choline bitartrate and choline chloride, respectively; $C$ is the concentration of USP Choline Chloride RS, in mg per mL, in the Standard solution; $W$ is the weight, in mg , of Choline Bitartrate taken to prepare the Test solution; $r_{i}$ is the peak response for each impurity, other than that of the choline bitartrate derivative and 3,5-dinitrobenzoic acid; and $r_{s}$ is the peak response for the choline chloride derivative in the Standard solution: not more than $0.3 \%$ of any individual impurity is found; and not more than $2.0 \%$ of total impurities is found.

## Briefing

Choline Chloride, USP 27 page 1979. On the basis of comments received, it is proposed to revise the Mobile phase and the derivatization procedure in the test for Chromatographic purity to improve separation.
(DSN: L. Evans) RTS-41054-2

## Change to read:

## Chromatographic purity-

Buffer solution-Dissolve 7.1 g of anhydrous dibasic sodium phosphate in 1 L of water. Adjust with phosphoric acid to a pH of 2.5 .

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (50:50).

■(70:30).■1s (USP28)
Standard solution-Transfer an accurately weighed amount, not more than 100 mg , of USP Choline Chloride RS to a $24-\mathrm{mL}$ screwcapped vial, and add 400 mg of 3,5-dinitrobenzoyl chloride and 10 mL of acetonitrile. Cap the vial, heat to $55^{\circ}$, and continue heating for $1+$ hemf

- 2 hours.■1S (USP28)

Cool to room temperature, and add 5 mL of water. Allow to stand for $z$ mintutes.
-5 minutes.■1S (USP28)

Quantitatively transfer the solution to a $25-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix. Dilute a volume of this solution with Mobile phase to obtain a solution having a known concentration of $2.0 \mu \mathrm{~g}$ of USP Choline Chloride RS per mL .

Test solution-Transfer about 110 mg of Choline Chloride, accurately weighed, to a $24-\mathrm{mL}$ screw-capped vial. Dry at $120^{\circ}$ for 2 hours. Add 400 mg of 3,5 -dinitrobenzoyl chloride and 10 mL of acetonitrile. Cap the vial, heat to $55^{\circ}$, and continue heating for 4 hetr.

- 2 hours.■1S (USP28)

Cool to room temperature, and add 5 mL of water. Allow to stand for $z$ minutes.
-5 minutes. 1 IS (USP28)
Quantitatively transfer the solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

- Pipet 2.0 mL of the solution to a $25-\mathrm{mL}$ volumetric flask,
dilute with Mobile phase to volume, and mix.■1S (USP28)
Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $208-\mathrm{nm}$ detector and a $4.6-$ $\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L7. The column temperature is maintained at $30^{\circ}$. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is not less than 2 ; and the relative standard deviation determined from the choline chloride derivative peak is not more than $5 \%$.
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of each impurity in the portion of Choline Chloride taken by the formula:

$$
5000(C H)\left(x_{i}+x_{s}\right)
$$

$$
\mathbf{■}^{62500(C / W)\left(r_{i} / r_{S}\right), \boldsymbol{■}_{1 \mathrm{~S}}(U S P 28)}
$$

in which $C$ is the concentration, in mg per mL , of USP Choline Chloride RS in the Standard solution; $W$ is the weight, in mg , of Choline Chloride taken to prepare the Test solution; $r_{i}$ is the peak response for each impurity, other than that for the choline chloride derivative and 3,5-dinitrobenzoic acid obtained from the Test solution; and $r_{s}$ is the peak response for the choline chloride derivative obtained from the Standard solution: not more than $0.3 \%$ of any individual impurity is found; and not more than $2.0 \%$ of total impurities is found.

## Briefing

Cranberry Liquid Preparation, USP 27 page 1986. In the test for Content of organic acids, it is proposed to revise the Chromatographic system and the system suitability requirements to more accurately represent the actual practices in some laboratories. The proposed changes are supported by data obtained with the YMC120A ODS-AQ brand of guard column and an L1 analytical col-
umn. Typical retention times for quinic, malic, citric, and fumaric acids are $4.8,5.8,10.8$, and 13.0 minutes, respectively. Editorial style changes have also been made.
(DSB: G. Giancaspro) RTS-30853-1

## Change to read:

Content of organic acids-
Mobile phase-Transfer about 27.2 g of monobasic potassium phosphate, accurately weighed, to a $1000-\mathrm{mL}$ volumetric flask, and dissolve in 950 mL of water. Adjust with phosphoric acid to a pH of 2.4 , dilute with water to volume, mix, and filter.

Standard preparation-Dissolve accurately weighed quantities of USP Citric Acid RS, USP Malic Acid RS, and USP Quinic Acid RS in water to obtain a solution having known concentrations of about 1.0 mg of each Reference Standard per mL .

Test preparation-Use the filtered Liquid Preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $214-\mathrm{nm}$ detector, a 4.6 mm $\times 15 \mathrm{~mm}$,
-4.6-mm $\times 25-\mathrm{cm}_{\mathbf{1}_{1 S}}$ (USP28)
analytical column containing packing L1, and a guard column containing
$-5-\mu \mathrm{m}_{\text {■1S (USP28) }}$
packing L1. The flow rate is about 0.8 mE
$\mathbf{- n}_{0} .6 \mathrm{~mL}_{1 \mathrm{~S}}{ }_{\text {(USP28) }}$
per minute. Prior to use, condition the column with methanol, with water, and finally with Mobile phase. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.4 for quinic acid, 0.5 for malic acid, and 1.0 for citric acid; the resolution, $R$, between quinic acid and malic acid is not less than 7.0 ;
-2.5; 1 IS (USP28)
and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Test preparation into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the percentages of quinic acid, malic acid, and citric acid in the Liquid Preparation by the formula:
in which $C$ is the concentration, in mg per mL , of the appropriate Reference Standard in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak area responses of the appropriate analyte obtained from the Test preparation and the Standard preparation, respectively: not less than $0.9 \%$ each of quinic acid and citric acid is found; not less than $0.7 \%$ of malic acid is found; and the ratio of quinic acid to malic acid is not less than 1.0.

## Briefing

Goldenseal, USP 27 page 2013 and page 2255 of $P F$ 27(2) [Mar.-Apr. 2001]; Powdered Goldenseal, USP 27 page 2014; Powdered Goldenseal Extract, USP 27 page 2014. Adulteration of goldenseal with other plants has been detected. A common adulteration appears with Coptis sp., and it has been reported that an indicator of such adulteration is the presence of significant amounts of the alkaloid palmatine. Therefore, it is proposed to add a limit of palmatine in the USP monographs for Goldenseal. In addition, a simpler procedure for preparation of the Test solution, yielding results similar to those in the official procedure, is proposed in the test for Content of berberine and hydrastine and limit of palmatine.
(DSB: G. Giancaspro) RTS—32818-1; 34299-1

## Change to read:

## » Goldenseal consists of the dried roots and rhizomes

 of Hydrastis canadensis (Linné)-L.■1S (USP28)
(Fam. Ranunculaceae). It contains not less than 2.0 percent of hydrastine $\left(\mathrm{C}_{21} \mathrm{H}_{21} \mathrm{NO}_{6}\right)$ and not less than 2.5 percent of berberine $\left(\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{NO}_{4}\right)$, calculated on the dried basis.

## Add the following:

-Microbial limits $\langle 2021\rangle$-The total aerobic microbial count does not exceed $1 \theta^{7} 10^{5}$ cfu per $g$, the total combined molds and yeasts count does not exceed $10^{5} 10^{4}$ cfu per $g$,
the coliform count does noteveed $10^{4}$ efu per $g$, and the enterobacterial count does not exceed $10^{4} 10^{3}$ cfu per g . It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. and Staphylococcus aut eHs.nis (USP28)

## Change to read:

## Content of berberine and hydrastine-

-Content of berberine and hydrastine and limit of pal-matine-■1S (USP28)

Mobile phase-Dissolve 9.93 g of monobasic potassium phosphate in 730 mL of distilled water. Add 270 mL of acetonitrile, mix, filter, and degas. Make other adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
-System suitability solution-Prepare a solution of palmatine in a mixture of water and methanol ( $1: 1$ ) having a known concentration of about 0.05 mg per mL . Mix equal
volumes of this solution and the Standard solution.■1S (USP28), Standard solution-Dissolve accurately weighed quantities of USP Berberine Chloride RS and USP Hydrastine Hydrochloride RS in a mixture of water and methanol ( $1: 1$ ),
-and dilute quantitatively, and stepwise if neces-
sary, 1 1S (USP28)
to obtain a solution containing about 0.2 mg
$\square^{-} 0.05 \mathrm{mg}^{1 \mathrm{IS}}$ (USP28)
of each USP Reference Standard per mL. [note-Concentrations of berberine and hydrastine in this solution are calculated by multiplying the concentration of each of the USP Reference Standards by correction factors of 0.905 and 0.913 , respectively.]

Test solution-Finely powder a quantity of Goldenseal, and transfer 4.0 。
-0.12 g , ${ }^{1 S}$ (USP28)
accurately weighed, to a 500 mL round bettom flask.

- $50-\mathrm{ml}$ volumetric flask. Add 40 mL of a mixture of 0.1 M monobasic potassium phosphate and acetonitrile ( $60: 40$ ). Sonicate for 5 minutes, and shake for 10 minutes on a rotation shaker. Dilute with the mixture of 0.1 M monobasic potassium phosphate and acetonitrile ( $60: 40$ ), mix, and
filter. 1 IS (USP28)
Treat the Geldenseat with 150 mL of methanel, and extract for $\theta$ hours, or until the-solvent is clear. The-volume-of the thimble should be at least one half that of the-volume of methanel. Coet toroom temperature, and transfer the methanelextract to a-200mL volumetric flack. Rinse the extraction unit with methanel, quantitatively transfer the eontents the wolumetric flask, and ditute with methand to velume.


## -. ${ }^{1 S}$ (USP28)

- 1 SUROMatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a 235 -nm detector and a 4.6 $\mathrm{mm} \times 150-\mathrm{mm}$ column that contains packing L 1 . The flow rate is about 1.8 mL per minute. Chromaghe the Stallitan,
-Inject the Standard solution into the chromatograph, ${ }_{\text {IS }}^{1 \text { S (USP28) }}$
and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, determined from the hydrastine and berberine peaks is not less than 3.0 ; the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.5 \%$.
-Inject the System suitability solution into the chromatograph, and record the peak responses as directed for Procedure: identify the locus for palmatine, and calculate the resolution, $R$, with respect to hydrastine and berberine: the
resolution, $R$, between berberine and palmatine is not less than 1.5 , and the resolution, $R$, between hydrastine and palmatine is not less than 1.5 .nis (USP28)
[note- The ratal ime is 10 minules.]
-. 1 (USP28)
1 IS (USP28)
Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentages of berberine and hydrastine in the portion of Goldenseal taken by the formula:

$$
100(C V / W)\left(r_{U} / r_{S}\right),
$$

in which $C$ is the concentration, in mg per mL , of berberine or hydrastine in the respective USP Reference Standard in the Standard solution, using the correction factors as noted above; $V$ is the final volume, in mL, of the Test solution; $W$ is the weight, in mg , of Goldenseal taken; and $r_{U}$ and $r_{S}$ are the peak areas for berberine and hydrastine obtained from the Test solution and the Standard solution, respectively: mess than $2.0 \%$ of hydrastine is found, and not less than $2.5 \%$ of berberine is found.
-Using the values obtained from the chromatogram of the Test solution, divide the peak area of berberine by the peak area of any peak at the locus for palmatine (if present): the ratio is more than $50: 1$. 1 (USP28)

## BriEfing

Powdered Goldenseal, USP 27 page 2014—See briefing under Goldenseal. Editorial changes have also been made.
(DSB: G. Giancaspro) RTS-34299-2

## Change to read:

» Powdered Goldenseal is Goldenseal reduced to a fine or very fine powder.
-It contains not less than 2.0 percent of hydrastine $\left(\mathrm{C}_{21} \mathrm{H}_{21} \mathrm{NO}_{6}\right)$ and not less than 2.5 percent of berberine $\left(\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{NO}_{4}\right)$, calculated on the dried ba-
sis. ${ }^{1 S}$ (USP28)

## Change to read:

Other requirements-It meets the requirements of the Thin-layer chromatographic identification test and the tests for Loss on drying, Foreign organic matter, Total ash, Acid-insoluble ash, Pesticide residues, Heavy metals, Con ber ber hydrastine

- Microbial limits and Content of berberine and hydrastine and limit of palmatine $\mathbf{1 S}_{1 \mathrm{~S}}$ (USP28) under Goldenseal.


## Briefing

Powdered Goldenseal Extract, USP 27 page 2014—See briefing under Goldenseal. Editorial changes have also been made.
(DSB: G. Giancaspro) RTS-34299-3

## Change to read:

» Powdered Goldenseal Extract is prepared from the pulverized dried roots and rhizomes of Hydrastis canadensis L. (Fam. Ranunculaceae) using suitable solvents. It contains not less than 5 percent of hydrastine $\left(\mathrm{C}_{21} \mathrm{H}_{21} \mathrm{NO}_{6}\right)$ and not less than 10 percent of alkatoids.
-the sum of berberine and hydrastine, calculated
on the dried basis.п1S (USP28)
The ratio of starting crude plant material to Powdered Extract is 2:1.

## Change to read:

## Content of totalalkntoids-

-Content of berberine and hydrastine and limit of pal-
matine-1S (USP28)
Mobile phase, Standard solution, and Chromatographic sys-tem-Proceed as directed for Content of berberine and hydrastine
$\mathbf{- a n d}_{\text {and limit of palmatine }} 1 \mathrm{1S}$ (USP28)
under Goldenseal.
Test solution-Transfer about 100 mg of Powdered Extract, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, and dilute with a mixture of water and methanol $(1: 1)$. Sonicate for 20 minutes, cool to room temperature, mix, and filter.

Procedure_Proceed as directed for Content of berberine and hydrastine
$\mathbf{- a n d}$ limit of palmatine $\boldsymbol{\square 1 S}$ (USP28)
under Goldenseal, except to calculate the percentages of hydrastine and berberine in the portion of Powdered Extract taken by the formula:

$$
\begin{gathered}
100(C / R)(H / M)\left(\Psi_{L}+r_{s}\right), \\
-100 C(V / W)\left(r_{U} / r_{S}\right), \square_{1 S}(U S P 28)
\end{gathered}
$$

in which $R$ is the fraction of the test sample left after undergeing the test for Less on drying (see-Notebelou);

- 1 IS (USP28)
$W$ is the weight, in mg , of Powdered Extract taken for the Test solution; and the other terms are as defined therein: not less than 5\% of hydrastine is found; and not less than $10 \%$ of hydrastine plus berberine is found.
-Using the values obtained from the chromatogram of the Test solution, divide the peak area of berberine by the peak area of any peak at the locus for palmatine (if present): the ratio is more than $50: 1$. 1 S (USP28)
[NOTE $R$ is defined as the residue, in drying divided by the quantity, in of, of the original sample under going the test for Less on drying.
- $\quad$ 1S (USP28)

The sample to be used in the

- this $_{\text {■1S (USP28) }}$
test for Content of total alleatoids
-n.1S (USP28)
should not be subjected to the conditions specified in the test for Loss on drying. A separate sample is used to determine the of R.
$\mathbf{m}_{\text {content }}$ on the dried basis.] $]_{\text {1S (USP28) }}$


## BRIEFING

Pygeum, page 1317 of $P F$ 29(4) [July-Aug. 2003]; Pygeum Extract, page 1318 of $P F 29$ (4) [July-Aug. 2003]; Pygeum Capsules, page 1322 of $P F$ 29(4) [July-Aug. 2003]. These new monographs, which previously appeared in Pharmacopeial Previews, are now forwarded to In-Process Revision, with changes to Pygeum Extract and Pygeum Capsules. The chromatographic procedure for the Content of sterols is based on determinations performed with a capillary column HP-5 brand of G27 silica bonded stationary phase. Typical retention times are 12.5 minutes
for $5 \alpha$-cholestanol, 17.8 minutes for campesterol, 18.7 minutes for stigmasterol, and 19.0 minutes for $\beta$-sitosterol. The chromatographic procedure for the Content of docosyl ferulate is based on determinations performed on a Supersphere 60, RP-8 brand column of packing L7. The typical retention time for docosyl ferulate is about 12.5 minutes.
(DSB: G. Giancaspro) RTS-37249-1

## Add the following:

## © Pygeum

» Pygeum consists of the bark of Prunus africana (Hook f.) Kalkman (Pygeum africanum Hook f.) Rosaceae. It contains not less than 9.0 percent of extractable matters.

Packaging and storage-Preserve in well-closed containers, and store at room temperature.

Labeling-The label states the Latin binomial and, following the official name, the parts of the plant contained in the article.

USP Reference standards $\langle 11\rangle$ —USP Pygeum Extract $R S$. USP $\beta$-Sitosterol RS.

## Botanic characteristics-

Macroscopic-Bark pieces consist of long fragments of variable dimensions, from only a few cm to $1-\mathrm{m}$ long with a thickness varying from a few mm to $1-2 \mathrm{~cm}$. The color is brown, more or less dark on the external surface; light brown to red-brown on the internal surface. The external part of the bark presents a very dark and fissured rhytidome that in the samples of old trees is fragmented in more or less square plaques of about 1 to 5 cm . The thickness varies from 1 mm in young plants or branches to $5-8 \mathrm{~mm}$ in old plants. The outer surface may also be covered with whitish lichens
or thin filamentous moss. The internal bark, under the rhytidome, is clearer and has a more reddish coloration, with a long fibrous break, from reddish to light brown and dark brown in color, often presenting concentrical stratification cracks. The internal surface is more clear and presents small wrinkles.

Microscopic-The transverse section of the bark presents a suberized bed having a thickness depending on the age of the plant, consisting of multiple layers of small, square cells with the walls of moderate thickness. It presents a cortical parenchyma of more or less round cells, with a few apparent formations of very thin-walled selerites, sclereids, definitely sharp. Often, in the parenchyma, there are groups of cells containing oxalate druses; a few bigger cells with highly thickened walls can also be observed. It shows a liber with phloem zones and presenting medulary rays. The phloemical portions contain groups of fibrous cells with highly thickened walls as well as phloemical and parenchymal elements sometimes containing druses of oxalate. The medulary rays are of conical shape, larger on the external surface and thinner on the internal side; they can also contain druses of oxalate.

Thin-layer chromatographic identification test $\langle 201\rangle$ -
Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture.

Test solution-Transfer about 10 g of the powdered plant material to a soxhlet apparatus. Extract with 150 mL of methylene chloride for 4 hours. Evaporate the extract under vacuum to dryness. Dissolve the residue with 10 mL of methylene chloride. Apply $10 \mu \mathrm{~L}$ to the plate.
Standard solution 1-Prepare a solution of USP Pygeum Extract RS in chloroform having a concentration of about 10 mg per mL .

Standard solution 2-Prepare a solution of USP $\beta$-Sitosterol RS in chloroform having a concentration of about 1 mg per mL.

Developing solvent system: methylene chloride in a saturated chamber.

Spray reagent-Prepare a solution of sulfuric acid and water ( $1: 1$ ).

Procedure-Develop the chromatogram to a length of not less than 15 cm , and dry the plate in a current of air. Spray the plate with Spray reagent, and heat the plate at $100^{\circ}$ for 10 minutes. Examine the plate under white light: the chromatogram obtained with the Test solution shows one redviolet zone turning to grayish-brown near the origin that corresponds in color and $R_{F}$ value to that in the chromatogram of Standard solution 1; one red-violet zone turning to grayish brown at an $R_{F}$ about 0.08 , corresponding in color and $R_{F}$ value to that in the chromatogram of the Standard solution 2; above these spots a grayish-brown zone may be present, corresponding in color and $R_{F}$ value to that in the chromatogram of the Standard solution 1; and other colored zones of varying intensities may be observed in the chromatogram of the Test solution.

Total ash $\langle 561\rangle$ : not more than $10.0 \%$.
Loss on drying $\langle 731\rangle$ —Dry it at $60^{\circ}$ for 15 hours: it loses not more than $10.0 \%$ of its weight.

Foreign organic matter $\langle 561\rangle$ : not more than $5.0 \%$. Pesticide residues $\langle 561\rangle$ : meets the requirements.

Heavy metals $\langle 231\rangle$ : not more than $20 \mu \mathrm{~g}$ per g.
Extractable matter-Extract 2.00 g of the powdered material in a soxhlet apparatus with 150 mL of alcohol for 6 hours. Evaporate the solution to dryness under vacuum, and dry the residue at $105^{\circ}$ for 24 hours. ${ }^{1 S}$ (USP28)

## Briefing

Pygeum Extract, page 1318 of PF 29(4) [July-Aug. 2003]See briefing under Pygeum.
(DSB: Giancaspro) RTS—37249-2

## Add the following:

## Pygeum Extract

» Pygeum Extract is prepared from the pulverized Pygeum using suitable solvents. It contains not less than 90 percent and not more than 110 percent of the labeled amount of docosyl ferulate and not less than 90 percent and not more than 110 percent of the labeled amount of total sterols as $\beta$-sitosterol, calculated on the dried basis.

Packaging and storage-Store in tight containers, protected from light.

Labeling-The label states the Latin binomial and, following the official name, the part of the plant from which the article was prepared. Label the content in percentage of total sterols as $\beta$-sitosterol and the content in percentage of docosyl ferulate. It also meets the requirements for labeling in the chapter Extracts $\langle 565\rangle$.

USP Reference standards $\langle 11\rangle — U S P$ Docosyl Ferulate
RS. USP Pygeum Extract RS. USP $\beta$-Sitosterol RS.

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -

Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture.

Test solution-Dissolve about 150 mg of Extract in 10 mL of chloroform. Apply $10 \mu \mathrm{~L}$ to the plate.

Standard solution 1-Prepare a solution of USP Pygeum Extract RS in chloroform having a concentration of about 15 mg per mL .

Standard solution 2-Prepare a solution of USP $\beta$-Sitosterol RS in chloroform having a concentration of about 2 mg per mL.

Developing solvent system: methylene chloride in a saturated chamber.

Spray reagent-Prepare a solution of sulfuric acid and water ( $1: 1$ ).

Procedure-Develop the chromatogram to a length of not less than 15 cm , and dry the plate in a current of air. Spray the plate with Spray reagent, and heat the plate at $100^{\circ}$ for 10 minutes. Examine the plate under white light: the chromatogram obtained with the Test solution shows one redviolet zone turning to grayish brown near the origin that corresponds in color and $R_{F}$ value to that in the chromatogram of Standard solution 1; one red-violet zone turning to grayish brown at an $R_{F}$ of about 0.08 corresponding in color and $R_{F}$ value to that in the chromatogram of Standard solution 2; above these spots a grayish-brown zone may be present, corresponding in color and $R_{F}$ value to that in the chromatogram of Standard solution 1; and other colored zones of varying intensities may be observed in the chromatogram of the Test solution.

B: The retention time of the peak for docosyl ferulate in the chromatogram of the Test solution, correspond to that in the chromatogram of the Standard solution as obtained in the Content of docosyl ferulate.

Loss on drying $\langle 731\rangle$-Dry about 1.0 g of Extract, accurately weighed, for 3 hours at $110^{\circ}$ : it loses not more than $10 \%$ of its weight.

Ash content $\langle 561\rangle$ : not more than $0.5 \%$.
Heavy metals $\langle 565\rangle$ : meets the requirement.
Residual solvents $\langle 565\rangle$ : meets the requirement.
Pesticide residue $\langle 561\rangle$ : meets the requirement.
Aflatoxins $\langle 561\rangle$ : not more than $4 \mu \mathrm{~g}$ per kg of total aflatoxins B1, B2, G1, and G2; not more than $2 \mu \mathrm{~g}$ per kg of aflatoxin B1.

Microbial limits $\langle 2021\rangle$ - The total aerobic microbial count does not exceed $10^{4}$ per g , the total combined molds and yeasts count does not exceed $10^{3}$ per g , and it meets the requirements of the tests for absence of Salmonella species, and Escherichia coli.

## Content of sterols-

Derivatizing solution: a mixture of bis(trimethylsilyl)acetamide and trimethylchlorosilane ( $9: 1$ ).

Internal standard solution-Prepare a solution containing 2 mg per mL of $5 \alpha$-cholestane in chloroform.

System suitability solution-Prepare a solution containing about 2 mg per mL each of campesterol, stigmasterol, and USP $\beta$-Sistosterol RS. Transfer 2.0 mL of this solution and 2.0 mL of Internal standard solution to a $10-\mathrm{mL}$ volumetric flask, and dilute with chloroform to volume. Evaporate about $500 \mu \mathrm{~L}$ of this solution to dryness using a stream of nitrogen. Dissolve the residue in $80 \mu \mathrm{~L}$ of Derivatizing solution and $20 \mu \mathrm{~L}$ of pyridine. Allow to stand for not less than 10 minutes at room temperature.

Standard stock solution-Prepare a solution of USP $\beta$-Sitosterol RS in chloroform having a known concentration of about 2.0 mg per mL .

Standard solution-Transfer 2.0 mL of the Standard stock solution and 2.0 mL of the Internal standard solution to a $10-\mathrm{mL}$ volumetric flask, and dilute with chloroform to volume. Evaporate about $500 \mu \mathrm{~L}$ of this solution to dryness using a stream of nitrogen. Dissolve the residue in $80 \mu \mathrm{~L}$ of Derivatizing solution and $20 \mu \mathrm{~L}$ of pyridine. Allow to stand for not less than 10 minutes at room temperature.

Test solution-Transfer an accurately weighed quantity of about 100 mg of Extract into a $100-\mathrm{mL}$, round-bottomed flask. Add 2.0 mL of Internal standard solution and 20 mL of diluted hydrochloric acid. Attach a condenser, and reflux in a bath at $100^{\circ}$ for 30 minutes. Cool the solution to room temperature, and adjust by the addition of about 5 mL of 10 N sodium hydroxide to a pH of 8 . Extract twice using 50 mL of ether each time, wash the collected organic phases with 50 mL of water, and evaporate the organic phase to dryness under vacuum. Dissolve the residue with 4 mL of chloroform, and transfer to a cartridge containing 500 mg of packing L8 that has been conditioned with a 2 column volume of $n$-hexane [NOTE-A suitable cartridge is Chromabond NH2, manufactured by Macheray Nagel, or equivalent.] Collect the eluate. Elute twice with a 1 -column volume of a mixture of chloroform and isopropanol (2:1). Combine the eluates, and evaporate to dryness. Dissolve the residue in 10 mL of chloroform. Evaporate about $500 \mu \mathrm{~L}$ of this solution to dryness under a stream of nitrogen. Dissolve the residue with $80 \mu \mathrm{~L}$ of Derivatizing solution and $20 \mu \mathrm{~L}$ of pyridine. Allow to stand for not less than 10 minutes at room temperature.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a split injection system, a flame-ionization detector, and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$
capillary column coated with a G27 phase of $0.25-\mu \mathrm{m}$ thickness. The chromatograph is programmed as follows. Initially the temperature of the column is equilibrated at $250^{\circ}$ for 5 minutes, then the temperature is increased at a rate of $5^{\circ}$ per minute to $320^{\circ}$. The injection port temperature and detector temperature are both maintained at $285^{\circ}$. The carrier gas is helium, with a flow rate adjusted to obtain a retention time of about 19 minutes for $\beta$-sitosterol, a split ratio of $1: 50$, and the make up is helium. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about $0.66,0.94,0.96$, and 1.00 for $5 \alpha$-cholestane, campesterol, stigmasterol, and $\beta$-sitosterol, respectively; the resolution, $R$, between campesterol and stigmasterol is not less than 2 ; the column efficiency is not less than 150,000 for the $5 \alpha$-cholestane peak; and the tailing factor for each relevant peak is not more than 2.0 .
Procedure-Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Identify the signals corresponding to the relevant analytes by comparison with the chromatograms obtained with the System suitability solution.

Separately calculate the percentages of campesterol, stigmasterol, and $\beta$-sitosterol respectively in the portion of Extract taken by the formula:

$$
200 C / W\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration of $\beta$-sitosterol, in mg per mL , in the Standard solution; $W$ is the weight, in mg , of the Extract taken to prepare the Test solution; $R_{U}$ is the ratio of the appropriate sterol peak to the internal standard in the chromatogram of the Test solution; and $R_{S}$ is the ratio of the $\beta$-sitosterol peak to the $5 \alpha$-cholestane internal standard in
the chromatogram of the Standard solution. Calculate the total content of sterols in percentage by adding the individual percentages.

## Content of docosyl ferulate-

Solution $A$-Use mixture of methanol and water (95:5).
Solution B-Use a filtered and degassed mixture of Solution $A$ and acetonitrile.

Mobile phase-Use variable mixtures of Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Standard solution-Dissolve an accurately weighed quantity of USP Docosyl Ferulate RS with chloroform and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.02 mg per mL . Filter with a $0.45-\mu \mathrm{m}$ membrane or finer porosity.

Test solution-Weigh approximately 250 mg of Extract. Add 5 mL of chloroform, and quantitatively transfer to a $25-\mathrm{mL}$ volumetric flask. Dilute with acetonitrile to volume, and mix. Filter with a $0.45-\mu \mathrm{m}$ membrane or finer porosity discarding the first 4 mL of the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $323-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L7, and is maintained at a temperature of $25^{\circ}$. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency for the peak of docosyl ferulate is not less than 1700 theoretical plates; and the tailing factor for docosyl ferulate is not more than 2.0.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution, and the Test solution into the chromatograph, record the chromatograms, and measure
the areas of the analyte peaks. Calculate the percentage of docosyl ferulate in the portion of Extract taken by the formula:

$$
2500 C / W\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Docosyl Ferulate RS in the Standard solution; $W$ is the weight, in mg , of the portion of Extract taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses for docosyl ferulate in the Test solution and the Standard solution, respectively. $\quad$ IS (USP28)

Briefing

Pygeum Capsules, page 1322 of PF 29(4) [July-Aug. 2003]See briefing under Pygeum.
(DSB. G. Giancaspro) RTS-37249-3

## Add the following:

## ■Pygeum Capsules

## » Pygeum Capsules contain Pygeum Extract.

 Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Extract, calculated as sterols and docosyl ferulate.Packaging and storage-Preserve in tight containers at controlled room temperature.

Labeling-The label states the Latin binomial and, following the official name, the article from which the Capsules were prepared. The label also indicates the amount of Extract, in mg per Capsule. Label the Capsules to indicate the amount of sterols and docosyl ferulate in percentage of the Extract contained in the Capsules.

USP Reference standards $\langle 11\rangle — U S P$ Docosyl Ferulate RS. USP Pygeum Extract RS. USP $\beta$-Sitosterol RS.

## Identification-

A: The retention times of the peaks for campesterol, stigmasterol and $\beta$-sitosterol, in the chromatogram of the Test solution, correspond to these in the chromatograms of the Standard solution, as obtained in the Content of sterols.

B: The retention time of the peak for docosyl ferulate in the chromatogram of the Test solution corresponds to that in the chromatogram of the Standard solution, as obtained in the Content of docosyl ferulate.

Disintegration $\langle 2040\rangle$ : meet the requirements for disintegration of botanical dosage forms.

RUPTURE TEST-[NOTE-See Dissolution $\langle 711\rangle$ for Apparatus.]

Medium: simulated gastric fluid TS; 500 mL .
Apparatus 2: 50 rpm.
Time: 15 minutes.
Procedure-Place 1 Capsule in each vessel, and allow the Capsule to sink to the bottom of the vessel before starting rotation of the blade. Observe the Capsules, and record the time taken for each capsule shell to rupture.

Tolerances-The requirements are met if all of the Capsules tested rupture in not more than 15 minutes. If 1 or 2 of the Capsules rupture in more than 15 but not more than

30 minutes, repeat the test on 12 additional Capsules. Not more than 2 of the total of 18 Capsules tested rupture in more than 15 but not more than 30 minutes.

Weight variation $\langle 2091\rangle$ : meet the requirements.
Microbial limits $\langle 2021\rangle$ —The total bacterial count does not exceed 1000 cfu per $g$. The total combined molds and yeasts count does not exceed 100 cfu per $g$. It meets the requirements of the tests for absence of Salmonella species and Escherichia coli.

## Content of sterols-

Derivatizing solution, Internal standard solution, System suitability solution, Standard stock solution, Standard solution, and Chromatographic system-Proceed as directed in Pygeum Extract.

Test solution-Transfer an accurately weighed quantity of Capsules, equivalent to about 100 mg of the labeled amount of Extract, into a $100-\mathrm{mL}$, round-bottomed flask. Add 2.0 mL of Internal standard solution and 20 mL of diluted hydrochloric acid. Attach a condenser, and reflux in a bath at $100^{\circ}$ for 30 minutes. Cool the solution to room temperature, and adjust by the addition of about 5 mL of 10 N sodium hydroxide to a pH of 8 . Extract twice using 50 mL of ether each time, wash the collected organic phases with 50 mL of water, and evaporate the organic phase to dryness under vacuum. Dissolve the residue with 4 mL of chloroform, and transfer to a cartridge containing 500 mg of packing L8 that has been conditioned with a 2 -column volume of $n$-hexane. [NOTE-A suitable cartridge is Chromabond NH2, manufactured by Macheray Nagel, or equivalent.] Collect the eluate. Elute twice with a 1 -column volume of a mixture of chloroform and isopropanol (2:1). Combine the eluates, and evaporate to dryness. Dissolve the residue in 10 mL of chloroform. Evaporate about $500 \mu \mathrm{~L}$ of this solution to dry-
ness under a stream of nitrogen. Dissolve the residue with $80 \mu \mathrm{~L}$ of Derivatizing solution and $20 \mu \mathrm{~L}$ of pyridine. Allow to stand for not less than 10 minutes at room temperature.

Procedure-Proceed as directed in Pygeum Extract. Separately calculate the content, in mg, of campesterol, stigmasterol, and $\beta$-sitosterol, respectively in the portion of Capsules taken by the formula:

$$
2 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration of $\beta$-sitosterol, in mg per mL , in the Standard solution; $W$ is the weight, in mg , of the Extract taken to prepare the Test solution; $R_{U}$ is the ratio of the appropriate sterol peak to the internal standard in the chromatogram of the Test solution; and $R_{S}$ is the ratio of the $\beta$-sitosterol peak to the $5 \alpha$-cholestane internal standard in the chromatogram of the Standard solution. Calculate the total content of sterols, in mg, by adding the individual contents.

## Content of docosyl ferulate-

Solution A, Solution B, Mobile phase, and Chromatographic system-Proceed as directed for the Content of docosyl ferulate in Pygeum Extract.

Standard solution-Dissolve an accurately weighed quantity of USP Docosyl Ferulate RS with chloroform, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.01 mg per mL . Filter with a $0.45-\mu \mathrm{m}$ membrane or finer porosity.

Test solution-Accurately weigh the contents of not fewer than 20 Capsules, and transfer an accurately weighed quantity of the material, equivalent to 0.2 mg of the labeled amount of docosyl ferulate, to a $50-\mathrm{mL}$ beaker. Add 5 mL of chloroform, and dissolve in an ultrasonic bath. Transfer to
a $20-\mathrm{mL}$ volumetric flask with the aid of not more than 2 mL of chloroform. Dilute with acetonitrile to volume, and mix. Filter through a $0.45-\mu \mathrm{m}$ membrane or finer porosity.

Procedure-Proceed as directed for the Procedure under Content of docosyl ferulate in Pygeum Extract, except to inject about $30 \mu \mathrm{~L}$ into the chromatograph. Calculate the content of docosyl ferulate, in mg , in the portion of Capsules taken by the formula:

$$
20 C\left(r_{U} / r_{S}\right)
$$

in which the terms are as defined therein. ${ }^{15}$ (USP28)

## Briefing

Excipients, USP and NF Excipients, Listed by Category, $N F$ 22 page 2809, page 3168 of the First Supplement, and page 587 of PF 30(2) [Mar.-Apr. 2003]. The proposed revisions complement the following proposed new monographs that appear elsewhere in this number of PF: Palmitic Acid and Maltol.
(EMC) RTS-40947-1; 40951-1

## Change to read:

Acidifying Agent
Acetic Acid
Acetic Acid, Glacial
Gitric Acid
${ }^{\boldsymbol{\Delta}}$ Citric Acid, Anhydrous ${ }_{\Delta N F 23}$
${ }^{\mathbf{4}}$ Citric Acid Monohydrate $\mathbf{\Delta N F 2 3}$
Fumaric Acid
Hydrochloric Acid
Hydrochloric Acid, Diluted
Malic Acid
Nitric Acid
Phosphoric Acid
Phosphoric Acid, Diluted
Propionic Acid
Sulfuric Acid
Tartaric Acid

| Change to read: | Change to read: |
| :---: | :---: |
| Antifoaming Agent | Buffering Agent |
| Dimethicone | Acetic Acid |
|  | $\triangle_{\text {Adipic Acid }}^{\text {ANF23 }}$ |
| -Palmitic Acid ${ }_{\text {1S (NF23) }}$ | Ammonium Carbonate |
| Simethicone | Ammonium Phosphate |
|  | Boric Acid |
|  | Eitric Asid |
| Change to read: | ${ }^{\triangle}$ Citric Acid, Anhydrous ${ }_{\Delta N F 23}$ |
| Antimicrobial Preservative | ${ }^{\text {© }}$ Citric Acid Monohydrate ${ }_{\mathbf{\Delta N F 2 3}}$ |
| Benzalkonium Chloride | Lactic Acid |
| Benzalkonium Chloride Solution | Phosphoric Acid |
| Benzethonium Chloride | Potassium Citrate |
| Benzoic Acid | Potassium Metaphosphate |
| Benzyl Alcohol | Potassium Phosphate, Monobasic |
| Butylparaben | Sodium Acetate |
| ${ }^{\text {a }}$ Cetrimonium Bromide ${ }_{\text {ANF22 }}$ | Sodium Citrate |
| Cetylpyridinium Chloride | Sodium Lactate Solution |
| Chlorobutanol | Sodium Phosphate, Dibasic |
| Chlorocresol | Sodium Phosphate, Monobasic |
| Cresol Ethylparaben |  |
| Methylparaben | ${ }^{\text {Succinic Acid }}{ }_{\text {ANF23 }}$ |
| Methylparaben Sodium |  |
| Phenol | Change to read: |
| 2-Phenoxyethanol ${ }_{\text {2S }}$ (NF22) | Coating Agent |
| Phenylethyl Alcohol |  |
| Phenylmercuric Acetate Phenylmercuric Nitrate | -Ammonio Methacrylate Copolymer Dispersion ²S (NF22) $^{\text {a }}$ |
| Phenylmercuric Nitrate Potassium Benzoate | Carboxymethylcellulose, Sodium |
| Potassium Sorbate | Cellacefate (formerly Cellulose Acetate Phthalate) |
| Propylparaben | Cellulose Acetate |
| Propylparaben Sodium | Gellure Acetate Buyrate |
| Sodium Benzoate |  |
| Sodium Dehydroacetate |  |
| Sodium Propionate | Cellulose Acetate Phthalate (see Cellacefate) |
| Sorbic Acid |  |
| Thimerosal |  |
| Thymol | - Corn Syrup Solids ${ }_{\text {2S }}$ (NF22) |
|  | Ethylcellulose |
|  | Ethylcellulose Aqueous Dispersion |
| Change to read: | Gelatin |
|  | Glaze, Pharmaceutical |
| Antioxidant | Hydroxypropyl Cellulose |
| Ascorbic Acid | Hydroxypropyl Methylcellulose ${ }^{\mathbf{4}}$ (see Hypromellose) $\mathbf{\Delta N F 2 2}$ |
| Ascorbyl Palmitate | Hydroxypropyl Methylcellulose Phthalate (see Hypromellose |
| Butylated Hydroxyanisole Butylated Hydroxytoluene | © Phthalate) (formerly Hydroxypropyl Methylcellu |
| Hypophosphorous Acid | Hypromellose (formerly Hydroxypropyl Methylcellu- lose) |
| Monothioglycerol |  |
| Potassium Metabisulfite | -Hypromellose Acetate Succinate ${ }_{\text {2S }}^{\text {(NF22) }}$ |
| Propyl Gallate | Hypromellose Phthalate (formerly Hydroxypropyl Methylcellu- |
| Sodium Formaldehyde Sulfoxylate | lose Phthalate) |
| Sodium Metabisulfite | Methacrylic Acid Copolymer |
|  | Methacrylic Acid Copolymer Dispersion |
| Sodium Thiosulfate | Methylcellulose |
| Sulfur Dioxide | Polyvinyl Acetate Phthalate |
| Tocopherol | Shellac |
| Tocopherols Excipient |  |
|  | -Starch, Pregelatinized Modified ${ }_{\text {■S }}$ (NF22) Sucrose |
|  | Titanium Dioxide |
|  | Wax, Carnauba |

## Change to read:

Antifoaming Agent
Dimethicone
-Palmitic Acid $_{\text {■1S (NF23) }}$
Simethicone

## Change to read:

Antimicrobial Preservative
Benzalkonium Chloride
Benzalkonium Chloride Solution
Benzoic Acid
Benzyl Alcohol
Butylparaben
Cetrimonium Bromide $\mathbf{A N F 2 2}$
Chlorobutanol
Chlorocresol

Enylparaben
Methylparaben
Phenol
2-Phenoxyethanol ${ }_{\text {2S (NF22) }}$
Penylethyl Alcoho
Phenylmercuric Acetate
Potassium Benzoate
Potassium Sorbate
Propylparaben
Sodium Benzoate
Sodium Dehydroacetate
Sodium Propionate
Sorbic Acid
Thimerosal
Thymol

## Change to read:

## Antioxidant

Ascorbic Acid
Ascorbyl Palmitate
Butylated Hydroxyanisole
Hypophosphorous Acid
Monothioglycerol
Potassium Metabisulfite
Propyl Gallate
Sodum Formaldehyde Sulfoxylate
${ }^{\mathbf{4}}$ Sodium Sulfite $_{\mathbf{\Delta N F 2 3}}$
odium Thiosulfate
Sulfur Dioxide
Tocopherol
Tocopherols Excipient

## Change to read:

Buffering Agent
Acetic Acid
${ }^{\boldsymbol{4}}$ Adipic Acid ${ }_{\mathbf{A N F 2 3}}$
Ammonium Carbonate
Ammonium Phosphate
Eitric Acid
${ }^{\boldsymbol{4}}$ Citric Acid, Anhydrous $\mathbf{\Delta N F 2 3}$
${ }^{\boldsymbol{4}}$ Citric Acid Monohydrate $\boldsymbol{\Delta N F 2 3}$
Lactic Acid
sphoric Acid
Potassium Citrate
Potassium Phosphate, Monobasic
Sodium Acetate
Sodium Citrate
Lactate Solution
Sodium Phosphate, Dibasic
${ }^{\Delta}$ Succinic Acid ${ }_{\mathbf{\Delta N F 2 3}}$

## Change to read:

## Coating Agent

-Ammonio Methacrylate Copolymer Dispersion ${ }_{\text {■ }}$ (NF22)
Carboxymethylcellulose, Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
Coltuose Aeeta Butyra

Cellulose Acetate Phthalate (see Cellacefate)

- Copovidone $_{\text {■2S (NF22) }}$
${ }^{-}$Corn Syrup Solids ${ }_{\text {■2S (NF22) }}$
luose
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose) $\mathbf{\Delta N F 2 2}$
Phoxypropyl Methylcellulose Phthalate (see Hypromenose
${ }^{\Delta}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) ${ }_{\mathbf{A F F 2 2}}$
-Hypromellose Acetate Succinate $_{\text {m }}{ }^{2 S}$ (NF22)
Hypromellose Phthalate (formerly Hydroxypropyl MethylcelluPhthalate)
Methacrylic Acid Copolymer
Methylcellulose
Polyethylene Glycol
Shellac

Titanium Dioxide
Wax, Carnauba

Wax, Microcrystalline
Zein

## Change to read:

## Emollient

Alkyl (C12-15) Benzoate
-Hydrogenated Soybean Oil■1S (NF22)

## Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Cholesterol
Diethanolamine (Adjunct)
${ }^{-}$Diethylene Glycol Stearates_1S (NF22)

- Ethylene Glycol Stearates. 1 (NF22)
${ }^{\Delta}$ Glyceryl Distearate ${ }_{\mathbf{A} N F 22}$
${ }^{\Delta}$ Glyceryl Monolinoleate ${ }_{\text {ANF22 }}$
${ }^{\Delta}$ Glyceryl Monooleate $\mathbf{A N F 2 2}^{\text {N }}$
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 40 Stearate
-Polyoxyl Lauryl Ether ${ }_{\text {1S (NF22) }}$
-Polyoxyl Stearyl Ether ${ }_{\text {IS (NF22) }}$
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
■Sodium Cetostearyl Sulfate $_{\text {■1S (NF22) }}$
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Stearic Acid
Trolamine
Wax, Emulsifying


## Change to read:

Flavors and Perfumes
Anethole
Benzaldehyde
Ethyl Vanillin
-Maltol_1S (NF23)
Menthol
Methyl Salicylate
Monosodium Glutamate
Peppermint
Peppermint Oil
Peppermint Spirit
Rose Oil
Rose Water, Stronger

Thymol
Vanillin

## Change to read:

## Humectant

${ }^{\text {- Corn }}$ Syrup Solids ${ }_{\text {■ } 2 \text { S (NF22) }}$
Glycerin
Hexylene Glycol
Propylene Glycol
Sorbitol
$\bullet_{\text {-Sorbitol, Anhydrized Liquid }}^{\mathbf{m}^{2 S}(\text { NF22 }}$

## Change to read:

Ointment Base
Gaprylocaproyl Macrogelglycerides

- Caprylocaproyl Polyoxylglycerides $_{\text {■2S (NF22) }}$

Diethylene Glycol Monoethyl Ether
-Lauroyl Macrogolglycerides $_{\mathbf{m}_{2 S}(\text { NF22 }}$
Lineoyl Macrogolglyeerides
■Lineoyl $^{\text {Polyoxylglycerides }}{ }_{\text {■2S (NF22) }}$
Lanolin
Ointment, Hydrophilic
Ointment, White
Oleoy/ Macrogelglycerides

Ointment, Yellow
Polyethylene Glycol Ointment
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White
Rose Water Ointment
Squalane
Stearoyl Macrogelgy yeerides
-Stearoyl Polyoxylglycerides $\mathbf{n 2 S}_{\text {(NF22) }}$ Vegetable Oil, Hydrogenated, Type II

## Change to read:

Plasticizer
Acetyltributyl Citrate
Acetyltriethyl Citrate
Castor Oil
Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin
Polyethylene Glycol
Propylene Glycol
$\square_{\text {Sorbitol, Anhydrized Liquid }}^{\mathbf{m}_{2 S}(N F 22)}$
Triacetin
Tributyl Citrate
Triethyl Citrate

## Change to read:

Polymer Membrane
Cellulose Acetate
Cellulose Acetate Butyrate
${ }^{\boldsymbol{\Delta}}$ Cellaburate $_{\mathbf{A N F 2 3}}$

## Change to read:

Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)
${ }^{\boldsymbol{\Delta}}$ Sodium Tartrate $\mathbf{A N F 2 3}$

Change to read:

## Solvent

Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol
Caprylocaproyl Macrogelgyyeerides
${ }^{\text {■ Caprylocaproyl Polyoxylglycerides }} \mathbf{■ 2 S}^{\text {(NF22) }}$
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
■Lauroyl Macrogolglycerides $_{\text {■2S (NF22) }}$
Eineoyl Macrogolglyeerides
■Lineoyl Polyoxylglycerides $_{\mathbf{n}^{2 S}(\text { NF22 }}$
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Oleoyl Macrogelglycerides
■Oleoyl Polyoxylglycerides $_{\mathbf{■}_{2 S} \text { (NF22) }}$
Peanut Oil
Polyethylene Glycol
Propylene Glycol
Sesame Oil
Stearoyl Macrogolglyeerides
${ }^{\text {-Stearoyl Polyoxylglycerides }} \mathbf{m}^{\text {2S (NF22) }}$
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

## Change to read:

Suspending and/or Viscosity-increasing Agent
Acacia
Agar
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated

Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
${ }^{\text {- Carbomer Homopolymer }}{ }_{\text {2S }}{ }^{\text {(NF22) }}$
Carboxymethylcellulose Calcium Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium
${ }^{\text {■ }}$ Corn Syrup Solids ${ }_{\mathbf{■ 2 S}}$ (NF22)
Dextrin
Gelatin

Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose ${ }^{\Delta}$ (see Hypromellose) $\Delta_{\Delta N 22}$
${ }^{\Delta}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) $\mathbf{A N F 2 2}^{\text {an }}$
Magnesium Aluminum Silicate
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
${ }^{\mathbf{4}}$ Starch, Corn $_{\mathbf{\Delta N F 2 3}}$
${ }_{\Delta}$ Starch, Potato $_{\mathbf{\Delta} N F 23}$
${ }^{\mathbf{4}}$ Starch, Tapioca $\mathbf{\Delta N F 2 2}$
${ }^{\mathbf{\Delta}}$ Starch, Wheat ${ }_{\Delta N F 23}$
Tragacanth
Xanthan Gum

## Change to read:

Sweetening Agent
${ }^{\Delta}$ Acesulfame Potassium $\mathbf{\Delta N F 2 3}$
Aspartame
${ }^{\Delta}$ Aspartame Acesulfame $\mathbf{\Delta N F 2 2 ~}$
${ }^{\text {■ }}$ Corn Syrup Solids $\mathbf{m}^{\text {2S (NF22) }}$
Dextrates
Dextrose
Dextrose Excipient
Fructose
${ }^{\boldsymbol{4}}$ Galactose $\mathbf{\Delta N F 2 3}$
${ }^{-}$Maltose ${ }_{\text {■2S }}$ (NF22)
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium

Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

## Change to read:

## Tablet Binder

Acacia
Alginic Acid

- Carbomer Homopolymer ${ }_{\text {2S }}$ (NF22) $^{\text {( }}$

Carboxymethylcellulose, Sodium
Cellulose, Microcrystalline

${ }^{-}$Corn Syrup Solids ${ }_{\text {■ }}{ }^{\text {S (NF22) }}$
Dextrin
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
Hydroxypropyl Methylcellulose $^{\mathbf{\Delta}}$ (see Hypromellose) $\mathbf{\Delta N F 2 2}^{2}$
${ }^{\Delta}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) $\mathbf{\Delta N F 2 2 ~}^{\text {a }}$
${ }^{\text {-Hypromellose Acetate Succinate }} \mathbf{m}_{\mathbf{2 S}}$ (NF22)

- Maltose ${ }_{\text {n2S }}{ }^{\text {(NF22) }}$

Methylcellulose
Polyethylene Oxide
Povidone
${ }^{\Delta}$ Starch, Corn $_{\Delta N F 23}$
${ }^{\mathbf{4}}$ Starch, Potato ${ }_{\mathbf{\Delta} N F 23}$
Starch, Pregelatinized
-Starch, Pregelatinized Modified $\mathbf{I S S}_{\text {2S }}{ }_{\text {(NF22) }}$
${ }^{\boldsymbol{4}}$ Starch, Tapioca ${ }_{\mathbf{A F F 2 2}}$
${ }^{\mathbf{4}}$ Starch, Wheat ${ }_{\mathbf{A} N F 23}$
Syrup

## Change to read:

Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered
${ }^{\text {- }}$ Corn Syrup Solids ${ }_{\text {■ }}{ }^{\text {S (NF22) }}$
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose

- Maltose $_{\text {■2S (NF22) }}$

Mannitol
Sorbitol
Stareh
${ }^{\boldsymbol{\Delta}}$ Starch, Corn $_{\mathbf{\Delta N F 2 3}}$
${ }^{\mathbf{4}}$ Starch, Potato ${ }_{\mathbf{\Delta} N F 23}$
Starch, Pregelatinized
$\square_{\text {Starch, Pregelatinized Modified }}^{\text {(2S (NF22) }}$
${ }^{\star}$ Starch, Tapioca $\mathbf{A N F 2 2}$
${ }^{\Delta}$ Starch, Wheat ${ }_{\Delta N F 23}$
Sucrose
Sugar, Compressible
Sugar, Confectioner's

## Change to read:

Tablet Disintegrant
Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone

- Maltose $_{\text {n2S }}{ }^{\text {(NF22) }}$

Polacrilin Potassium
Sodium Starch Glycolate Stareh
${ }^{\mathbf{\Delta}}$ Starch, Corn $_{\mathbf{\Delta N F 2 3}}$
${ }^{\Delta}$ Starch, Potato ${ }_{\mathbf{\Delta N F 2 3}}$
Starch, Pregelatinized
$\square_{\text {Starch, Pregelatinized Modified }}^{\text {(2S (NF22) }}$
${ }^{\boldsymbol{\Delta}}$ Starch, Tapioca $\mathbf{\Delta N F 2 2}$
${ }^{\Delta}$ Starch, Wheat ${ }_{\Delta N F 23}$

## Change to read:

Tonicity Agent
${ }^{\text {■ }}$ Corn Syrup Solids ${ }_{\text {■ }}$ 2S (NF22)
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Change to read:

## Vehicle

FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound
${ }^{-}$Corn Syrup Solids ${ }_{\text {■ } 2 \text { S (NF22) }}$
Peppermint Water
Sorbitol Solution
Syrup

OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
Safflower Oil
Sesame Oil
Soybean Oil
Squalane
SOLID CARRIER
Sugar Spheres
STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

## MONOGRAPHS (NF)

## Briefing


#### Abstract

Ammonium Sulfate, $N F 22$ page 2822; Candelilla Wax, $N F 22$ page 2836; Low-Substituted Carboxymethylcellulose Sodium, page 3169 of the First Supplement and page 1095 of PF 29(4) [July-Aug. 2003]; Cetrimonium Bromide, NF 22 page 2848; Hydrogenated Cottonseed Oil, NF 22 page 2854; Dibutyl Phthalate, page 3170 of the First Supplement; Diethylene Glycol Stearates, page 3171 of the First Supplement; Ethylene Glycol Stearates, page 3171 of the First Supplement; Glyceryl Distearate, $N F 22$ page 2872; Glyceryl Monolinoleate, $N F 22$ page 2873; Glyceryl Monoleate, $N F 22$ page 2874; Hymetellose, page 3172 of the First Supplement and page 1100 of PF 29(4) [JulyAug. 2003]; Maltitol Solution, NF 22 page 2891 and page 3173 of the First Supplement; Polyisobutylene, page 3175 of the First Supplement; Sodium Cetostearyl Sulfate, page 3177 of the First Supplement and page 1122 of PF 29(4) [July-Aug. 2003]; Tribasic Sodium Phosphate, NF 22 page 2932; Sorbitol, $N F 22$ page 2937 and page 3178 of the First Supplement; Sorbitol Solution, USP 27 page 1715, page of 3083 of the First Supplement, and page 1078 of PF 29(4) [July-Aug. 2003]; Noncrystallizing Sorbitol Solution, NF 22 page 2938 and page 3180 of the First Supplement; Hydrogenated Soybean Oil, page 3180 of the First Supplement; and Medium-Chain Triglycerides, page 3181 of the First Supplement.

It is proposed to revise the Packaging and storage requirements for the above $U S P-N F$ excipient monographs in accordance with the Packaging, Storage, and Distribution Expert Committee's decision to consider the storage conditions for excipients on a case-bycase basis, based on available scientific knowledge and stability


data. Excipients generally recognized as stable may not require any storage statement or may require a limited storage statement, as appropriate. In the absence of any significant adverse comment, it is proposed to implement these revisions via the Fifth Interim Revision Announcement pertaining to USP 27-NF 22, with an official date of October 1, 2004.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-1

## Change to read:

Packaging and storage-Preserve in well-closed containers. Store at room temperattre, and avoid excessive heat and freezing. Protect from moisture.
${ }^{\bullet}$ No storage requirements specified.es

## Briefing

Candelilla Wax, NF 22 page 2836-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-2

## Change to read:

Packaging and storage-Preserve in well-closed containers. Store at roem temperattre, and avoid exeessive heat and freezing. Protect from moisture.
${ }^{\bullet}$ No storage requirements specified.es

## Briefing

Low-Substituted Carboxymethylcellulose Sodium, page 3169 of the First Supplement and page 1095 of PF 29(4) [JulyAug. 2003]-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-14

## Add the following:

${ }^{\bullet}$ Packaging and storage-Preserve in a tight containers.
Store at up to $25^{\circ}$, exeursions permitted between $15^{\circ}$ and
$30^{\circ}$. Avoid exeessive heat and freezing. Protect from moist tre. No storage requirements specified.es

Cellulose, acetate butanoate.

Cellulose, acetate butyrate.

Acetylbutyrylcellulose.

Cellulose butyrate acetate.

Cellulose acetate butyrate [9004-36-8].
» Gellutese Acetate Butyrate Cellaburate is a reaction product of cellulose, acetic anhydride or acetic acid, and butyric acid or butyric anhydride.
It contains not less than 1.0 percent and not more than 41.0 percent acetyl $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}\right)$ groups, by weight, and not less than 5.0 percent and not more than 57.356 .0 percent butyryl $\left(\mathrm{C}_{4} \mathrm{H}_{7} \mathrm{O}\right)$ groups, by weight, calculated on the mhydrous, previously dried, acid-free basis.

Packaging and-storage-Preserve in tight containers.
Labeling-The labeling indicates the nominal percentage ranges of acetyl and butyryl groups.

USP Reference standards $\langle 11\rangle$ USP Cellulose Acetate Bumate RS. USP Cellaburate RS.

Identification, Infrared Absorption $\langle 197 \mathrm{~F}\rangle$ —Dissolve 150 mg in 1 mL of acetone. Evenly cast 1 drop of the solution on a sodium chloride plate. Heat the plate at $105^{\circ}$ for 10 minutes.

Water, Method $I\langle 921\rangle$ : not more than $5.0 \%$, a mixture of methylene chloride and methanol (2:1) being used in place of the methanol solvent.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.002 \%$.


## $\triangle$ Cellulose Acetate Buthyrate Cellaburate

-(Title for this new monograph-to become official January 1, 2010) ${ }^{4}$

Cellaburate, page 597 of PF 30(2) [Mar.-Apr. 2004]. It is proposed to adopt Cellaburate as the title of this proposed new monograph. This nomenclature is desirable because it would result in harmonization with the terminology recommended by a World Health Organization (WHO) committee for use in pharmacopeias. There is no USAN at this time, but Cellaburate is an International Nonproprietary Name (INN) for this excipient.

A monograph on this proposed new $N F$ excipient first appeared in Pharmacopeial Previews in PF 23(4) [Jul.-Aug. 1997] and, subsequently, under In-Process Revision in PF 23(6) [Nov.-Dec. 1997], and PF 25(2) [Mar.-Apr. 1999] under the name Cellulose Acetate Butyrate.

Cellaburate is proposed by the Expert Committee on Nomenclature and Labeling to be the title of the monograph for this excipient monograph, which is proposed for inclusion in USP 28-NF 23, but with an official date of January 1, 2010, which is 60 months later than the January 1, 2005 official date of USP 28-NF 23. Use of the revised name would be permitted as of the January 1, 2005, the official date of $U S P$ 28-NF 23, but use of the name Cellaburate would not become mandatory until January 1, 2010. The 60 -month extension will provide the time deemed necessary for labeling changes to be made for the article and the numerous preparations in which it is an ingredient, and for practitioners, consumers, and regulatory agencies to become familiar with the terminology.
(NL: C. Barnstein) RTS-41135-1

## Add the following:

## Limit of free acid-

Indicator solution-Transfer about $0.54 \theta 0.675 \mathrm{~g}$ of bromocresol purple, accurately weighed, to a 1-L volumetric flask. Dissolve in 20025 mL of 0.0100 .10 N sodium hydroxide, dilute with water to volume, and mix.

Calibration solutions-Pipet 1, 2, 3, and 4 mL of 0.001 N acetic acid VS into four $100-\mathrm{mL}$ volumetric flasks, respectively. Pipet 4 mL of the Indicator solution into each flask and into an empty $100-\mathrm{mL}$ volumetric flask, and dilute each flask with water to volume to obtain solutions containing $0.0,0.60,1.20,1.80$, and $2.40 \mu \mathrm{~g}$ of acetic acid per mL.

Control solution-Place 96 mL of water in a suitable bottle, add a stirring bar, cap the bottle, and stir for 75 minutes at room temperature. Pipet 4 mL of Indicator solution into the bottle, and mix.

Test solution-Transfer about 1 to 2 g of Gellulese Aeet Be, Cellaburate, accurately weighed, to a bottle, and add 96 mL of water. Add a stirring bar, cap the bottle, and stir for 75 minutes at room temperature. Pipet 4 mL of Indicator solution into the bottle, stir to mix, and allow the solid to settle for 2 minutes.

Calibration-Determine the absorbances of the Calibration solutions in a $1-\mathrm{cm}$ cell at the wavelength of maximum absorption of the basic form of bromocresol purple at about 589 nm , with a suitable spectrophotometer, using water as the blank. The absorbance difference, $A_{S}$, between the $0.0 \mu \mathrm{~g}$ per mL solution and the other solutions is byessed the formma:

$$
a b G_{s}+\left(60 \times 10^{6}\right)
$$

in which $a$ is the absorptivity of the basic form of bremeresel purple, in mL per em mole; $b$ is the cell path length, in $\mathrm{em} ; \mathrm{C}_{\mathrm{s}}$ is the concentration of the acetic acid, in $\mu \mathrm{g}$ per mL ; and $60 \times 10^{6}$ is the molecular weight of acetic acid in $\mu \mathrm{g}$ per mole. Plot $A_{s}$ ersus $G_{s}$ adheres to Beer's law over the range
stated under Calibration solutions. Plot $A_{S}$ versus $C_{S}$ (the concentration of the acetic acid in $\mu \mathrm{g}$ per mL ) on linear graph paper, and draw the straight line best fitting the points including the origin.

Procedure-Pass 10 mL of the Test solution through a polytef syringe filter that has been presoaked in isopropyl alcohol. Determine the absorbance of the filtered Test solution in a $1-\mathrm{cm}$ cell at about 589 nm on the same spectrophotometer, using water as the blank. In the same manner, determine the absorbance of the Control solution. Calculate the percentage of free acid, as acetic acid, in the portion of Gellulose Acetate Buyrate Cellaburate taken by the formula:

$$
\left(100 C_{U} / W_{U}\right) / 10,000,
$$

in which 100 is the total volume, in mL , of the Test solution; $C_{U}$ is the concentration of free acid, calculated as acetic acid, in $\mu \mathrm{g}$ per mL , based on the absorbance difference between the Control solution and the Test solution read directly from the calibration plot; and $W_{U}$ is the weight, in g , of Cellulose Ace Bellaburate taken to prepare the Test solution. [NOTE-If the $C_{U}$ value is greater than $2.42 .8 \mu \mathrm{~g}$ per mL , reduce the test sample size by half in the Test solution, and repeat the determination.] Not more than $0.1 \%$ is found.

## Acetyl and butyryl content-

Internal standard solution-Prepare a solution of isovaleric acid in pyridine containing about 4.6 mg per mL , and store it in a tightly closed container.

Saponification solution-Place 250 mL of $n$-propyl alcohol in a $500-\mathrm{mL}$ volumetric flask, add 65.5 g of potassium hydroxide, and mix to dissolve. Dilute with $n$-propyl alcohol to volume, and mix.

Acid solution-Place 250 mL of $n$-propyl alcohol in a $500-\mathrm{mL}$ volumetric flask, add 166 mL of hydrochloric acid, and mix. Dilute with $n$-propyl alcohol to volume, and mix.

Standard preparation-Transfer about 0.20 g of glacial acetic acid and 0.31 g of butyric acid, each accurately weighed, to a $50-\mathrm{mL}$ volumetric flask. Dilute with Internal standard solution to volume, and mix.

Test preparation-Transfer about 0.15 g of Cellulese Ace, Cellaburate, previously dried at $105^{\circ}$ for 1 hour and accurately weighed, into a $25-\mathrm{mm} \times 160-\mathrm{mm}$ test tube. Pipet 10 mL of Internal standard solution into the test tube, and dissolve by stirring and heating at $110^{\circ}$ for 30 minutes. While stirring, add 5 mL of Saponification solution slowly into the tube. Heat at $110^{\circ}$ for 10 minutes. Cool, and add 5 mL of the Acid solution. Mix on a vortex mixer, and allow the precipitate to settle.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector, a $0.53-\mathrm{mm} \times 30-\mathrm{m}$ fused silica column bonded with a $1-\mu \mathrm{m}$ layer of phase G35, and a split injection system with a split ratio of about $35: 1$. Helium is used as the carrier gas flowing at a rate of about 8 mL per minute. The injection port, column, and detector block temperatures are maintained at $250^{\circ}, 125^{\circ}$, and $250^{\circ}$, respectively. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.45 for acetic acid, 0.85 for butyric acid, and 1.00 for isovaleric acid; the tailing factor for the butyric acid peak is not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $3.0 \%$.

Calibration-Inject about $1 \mu \mathrm{~L}$ of the Standard preparation into the chromatograph, and record the chromatogram as directed for Procedure. Repeat two more times. Calculate the average unit weight response, $F_{S 4}$, of acetic acid per 10 mL of the Internal standard solution by the formula:
in which $10 / 50$ is the volume ratio of the Internal standard solution in the Test preparation and in the Standard preparation; $q_{R A}$ is the weight, in g , of acetic acid in the Standard preparation; and $R_{S A}$ is the average peak response ratio of acetic acid and isovaleric acid. Similarly, calculate the average unit weight response, $F_{S B}$, of butyric acid per 10 mL of the Internal standard solution by the formula:

$$
(10 / 50) q_{R B} / R_{S B}
$$

in which $10 / 50$ is the volume ratio of the Internal standard solution in the Test preparation and in the Standard preparation; $q_{R B}$ is the weight, in g , of butyric acid in the Standard preparation; and $R_{S B}$ is the average peak response ratio of butyric acid and isovaleric acid.
Procedure-Inject about $1 \mu \mathrm{~L}$ of the upper clear solution from the Test preparation into the chromatograph, record the chromatogram, and measure the peak area responses. Calculate the percentage of acetyl in the portion of Cellulese Ace Burate Cellaburate taken by the formula:

$$
(43 / 60)(100) R_{U A} F_{S A} / W_{U},
$$

in which $43 / 60$ is the ratio of the formula weights of acetyl and acetic acid; $R_{U A}$ is the peak area response ratio of acetic acid and isovaleric acid in the Test preparation; $F_{S A}$ is as defined under Calibration; and $W_{U}$ is the weight, in g, of Eet lulese Ace Burate Cellaburate taken to prepare the Test preparation. Similarly, calculate the percentage of butyryl in the portion of Cellule Ace Burate taken by the formula:

$$
(71 / 88)(100) R_{U B} F_{S B} / W_{U}
$$

$$
(10 / 50) q_{R A} / R_{S A},
$$

in which $71 / 88$ is the ratio of the formula weights of butyryl and butyric acid; $R_{U B}$ is the peak area response ratio of butyric acid and isovaleric acid in the Test preparation; $F_{S B}$ is as defined under Calibration; and $W_{U}$ is the weight, in g , of Gelluse Ae Butaburate taken to prepare the Test preparation. $\mathbf{\Delta N F 2 3}$

## BRIEFING

Cetrimonium Bromide, NF 22 page 2848—See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-3

## Change to read:

Packaging and storage-Preserve in well-closed containers. Store at rom temperattre, and avoid eveessive heat and freezing. Protect from moisture.
${ }^{\bullet}$ No storage requirements specified.es

## Briefing

Cetyl Alcohol, NF 22 page 2849. On the basis of comments received, it is proposed to revise the System suitability solution in the Assay to use dehydrated alcohol instead of alcohol to be consistent with the use of dehydrated alcohol in the Assay preparation.
(EMC: C. Sheehan) RTS-41133-1

## Change to read:

## Assay-

System suitability solution-Dissolve accurately weighed quantities of USP Cetyl Alcohol RS and USP Stearyl Alcohol RS in

- dehydrated ${ }_{\text {■S }}^{\text {(NF23) }}$
alcohol to obtain a solution having known concentrations of about 9 mg per mL and 1 mg per mL , respectively.

Assay preparation-Dissolve 100 mg of Cetyl Alcohol in 10.0 mL of dehydrated alcohol, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The gas chromatograph is equipped with a flame-ionization detector and a $3-\mathrm{mm} \times 2-\mathrm{m}$ column packed with $10 \%$ liquid phase G2 on support S1A. The carrier gas is helium. The column temperature is maintained at about $205^{\circ}$, the injection port at about $275^{\circ}$, and the detector at about $250^{\circ}$. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between cetyl alcohol and stearyl alcohol is not less than 4.0; and the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Inject about $2 \mu \mathrm{~L}$ of the Assay preparation into the chromatograph, record the chromatogram, and measure the areas for the major peaks. Calculate the percentage of $\mathrm{C}_{16} \mathrm{H}_{34} \mathrm{O}$ in the portion of Cetyl Alcohol taken by the formula:

$$
100\left(r_{U} / r_{s}\right)
$$

in which $r_{U}$ is the peak area for cetyl alcohol obtained from the Assay preparation; and $r_{s}$ is the sum of the areas of all the peaks except the solvent peak.

## BRIEFING

Copovidone, page 1097 of PF 29(4) [July-Aug. 2003]; Hypromellose Acetate Succinate, page 1102 of $P F$ 29(4) [July-Aug. 2003]; Maltose, page 1113 of $P F$ 29(4) [July-Aug. 2003]; Phenolsulfonphthalein, page 2018 of PF 29(6) [Nov.-Dec. 2003]; Anhydrized Liquid Sorbitol, page 1128 of $P F$ 29(4) [July-Aug. 2003]; Modified Starch, page 1132 of $P F$ 29(4) [July-Aug. 2003]; Pregelatinized Starch, NF 22 page 2939, page 3181 of the First Supplement, and page 1601 of $P F$ 29(5) [Sept.-Oct. 2003]; Pregelatinized Modified Starch, page 1133 of $P F$ 29(4) [JulyAug. 2003]; Tapioca Starch, $N F 22$ page 2940, page 3181 of the First Supplement, and page 1134 of PF 29(4) [July-Aug. 2003]. It is proposed to revise the Packaging and storage requirements for the above excipients in accordance with the Packaging, Storage, and Distribution Expert Committee's decision to consider the storage conditions for excipients on a case-by-case basis, based on available scientific knowledge and stability data. Excipients generally recognized as stable may not require a storage statement or may require a limited storage statement, as appropriate.

The revision of the Packaging and storage requirement for Pregelatinized Modified Starch is covered by a cross-reference to Modified Starch in the section Other requirements under Pregelatinized Modified Starch.

In addition, on the basis of comments received and for further clarification, it is proposed to revise the monograph for Copovidone to include a starch indicator solution in the test for Limit of monomers as a more accurate means of endpoint determination.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40873-1

## Add the following:

## Copovidone


$\left(\mathrm{C}_{6} \mathrm{H}_{9} \mathrm{NO}\right)_{n}+\left(\mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{2}\right)_{m}$
Acetic acid ethenyl ester polymer with 1-ethenyl-2-pyrrolidone.

1-Vinyl-2-pyrrolidone polymer with vinyl acetate
[25086-89-9].
» Copovidone is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in the mass proportion of $3: 2$. The nominal K -value of Copovidone as stated in the labeling is not less than 90.0 percent and not more than 110.0 percent.

Packaging and storage-Preserve in tight containers. protected from moisture. Storeat $25^{\circ}$, exeursion permittedupto $40^{\circ}$. No storage requirements specified.

Labeling-Label it to indicate its nominal K-value.
USP Reference standards $\langle 11\rangle —$ USP Copovidone RS.
Clarity and color of solution-Dissolve 1.0 g in 10 mL of water: the solution is clear or slightly opalescent and colorless to pale yellow or pale red.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: $\quad$ To 5 mL of a solution $(1 \mathrm{in} 50)$ add a few drops of iodine TS: a deep red color is produced.

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 3 hours: it loses not more than $5.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.

## Limit of aldehydes-

Phosphate buffer-Transfer 8.7 g of monobasic potassium phosphate to a $500-\mathrm{mL}$ volumetric flask, and dissolve in 400 mL of water. Adjust, if necessary, with 1 N potassium hydroxide to a pH of 9.0 , dilute with water to volume, and mix.

Aldehyde dehydrogenase solution-Transfer a quantity of lyophilized aldehyde dehydrogenase equivalent to 70 units to a glass vial, dissolve in 10.0 mL of water, and mix. [NOTE-This solution is stable for 8 hours at $4^{\circ}$.]
NAD solution-Transfer 40 mg of nicotinamide adenine dinucleotide to a glass vial, dissolve in 10.0 mL of Phosphate buffer, and mix. [NOTE-This solution is stable for 4 weeks at $4^{\circ}$.]

Blank solution-Use water.
Standard solution-Transfer about 2 mL of water at $4^{\circ}$ to a glass weighing bottle, and weigh accurately. Add about 100 mg of freshly distilled acetaldehyde, and weigh accurately. Transfer this solution to a $100-\mathrm{mL}$ volumetric flask. Rinse the weighing bottle with several portions of water at $4^{\circ}$, and transfer each rinsing to the $100-\mathrm{mL}$ volumetric flask. Dilute the solution in the $100-\mathrm{mL}$ volumetric flask with water at $4^{\circ}$ to volume. Store at $4^{\circ}$ for about 20 hours. Pipet 1 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, dilute with Phosphate buffer to volume, and mix.

Test solution-Transfer about 1 g of Copovidone, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in 50 mL of Phosphate buffer, dilute with Phosphate buffer to volume, and mix. Insert a stopper into the flask, heat at $60^{\circ}$ for 1 hour, and cool to room temperature.

Procedure-Pipet 0.5 mL each of the Standard solution, the Test solution, and the Blank solution into separate $1-\mathrm{cm}$ cells. Add 2.5 mL of Phosphate buffer and 0.2 mL of NAD solution to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 2 to 3 minutes at $22 \pm 2^{\circ}$. Determine the absorbances of the solutions at a wavelength of 340 nm . Add 0.05 mL of Aldehyde dehydrogenase solution to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 5 minutes at $22 \pm 2^{\circ}$. Determine the absorbances of the solutions at a wavelength of 340 nm . Calculate the percentage of aldehydes, expressed as acetaldehyde, in the portion of Copovidone taken by the formula:

$$
10(C / W)\left[\frac{\left(A_{U 2}-A_{U 1}\right)-\left(A_{B 2}-A_{B 1}\right)}{\left(A_{S 2}-A_{S 1}\right)-\left(A_{B 2}-A_{B 1}\right)}\right],
$$

in which $C$ is the concentration, in mg per mL , of acetaldehyde in the Standard solution; $W$ is the weight, in g, calculated on the dried basis, of Copovidone taken to prepare the Test solution; $A_{U 1}, A_{S 1}$, and $A_{B 1}$ are the absorbances of the solutions obtained from the Test solution, the Standard solution, and the Blank solution, respectively, before the addition of the Aldehyde dehydrogenase solution; and $A_{U 2}, A_{52}$, and $A_{B 2}$ are the absorbances of the solutions obtained from the Test solution, the Standard solution, and the Blank solution, respectively, after addition of the Aldehyde dehydrogenase solution: not more than $0.05 \%$ is found.

## Limit of hydrazine-

Standard solution-Dissolve an accurately weighed quantities of salicylaldazine and salicylaldehyde in toluene, and dilute quantitatively, and stepwise if necessary, with toluene to obtain a solution having a known concentrations of $9 \mu \mathrm{~g}$ per mL and 10 mg per mL , respectively.

Test solution-Transfer the equivalent of 2.5 g of dried Copovidone, accurately weighed, to a $50-\mathrm{mL}$ centrifuge tube, add 25 mL of water, and mix to dissolve. Add 500 $\mu \mathrm{L}$ of a 1 in 20 solution of salicylaldehyde in methanol, adjust the solution with 0.25 N sulfuric acid to a pH of about 2, swirl, and heat in a water bath at $60^{\circ}$ for 15 minutes. Allow to cool, add 2.0 mL of toluene, insert a stopper in the tube, shake vigorously for 2 minutes, and centrifuge. Use the clear upper toluene layer as the Test solution.

Procedure-Separately apply $10 \mu \mathrm{~L}$ of the Test solution and the Standard solution to a suitable thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ) coated with a $0.25-\mathrm{mm}$ layer of dimethylsilanized chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of methal and ( $2: 1$ ) acetonitrile and water ( $85: 15$ ) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by examination under UV light at a wavelength of 365 nm : salicylaldazine appears as a fluorescent spot having an $R_{F}$ value of about 0.3 , 0.6 to 0.7 , and the fluorescence of any salicylaldazine spot from the Test solution is not more intense than that produced by the spot obtained from the Standard solution: not more than $1 \mu \mathrm{~g}$ per g is found.

## Limit of peroxides-

Copovidone solution-Transfer the equivalent of 2.0 g of dried Copovidone, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix.

Test solution-Transfer 25.0 mL of Copovidone solution to a $50-\mathrm{mL}$ beaker, add 2 mL of titanium trichloride-sulfuric acid TS, and mix. Allow to stand for 30 minutes at room temperature.

Blank solution-Transfer 25.0 mL of Copovidone solution to a $50-\mathrm{mL}$ beaker, add 2 mL of $13 \%$ sulfuric acid, and mix.

Procedure-Determine the absorbance of the Test solution in a $1-\mathrm{cm}$ cell at the wavelength of maximum absorbance at about 405 nm , with a suitable spectrophotometer, using the Blank solution as the blank: the absorbance is not more than 0.35 (corresponding to not more than $0.04 \%$, expressed as hydrogen peroxide).

Limit of monomers-Dissolve the equivalent of 5.0 g of dried Copovidone in 20 mL of methanol, and slowly add 20.0 mL of iodobromide TS. Allow to stand for 30 minutes, protected from light, with repeated shaking. Add 5 mL of potassium iodide solution (1 in 10), and titrate the liberated iodine with 0.1 N sodium thiosulfate VS until the solution is yellow. Continue the titration dropwise until the solution is colorless, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination (see Residual Titrations under Titrimetry $\langle 541\rangle$ ): the difference between the volumes of 0.1 N sodium thiosulfate consumed in the blank and the specimen titrations is not more than 0.9 mL , corresponding to not more than $0.1 \%$ of monomers calculated as vinylpyrrolidone.

K-value-Transfer an accurately weighed quantity of undried Copovidone, equivalent to about 1.0 g on the dried basis, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 1 hour. Determine the viscosity, using a capillary-tube viscosimeter (see Viscosity $\langle 911\rangle$ ), of this solution at $25 \pm 0.2^{\circ}$. Calculate the K -value of Copovidone by the formula:

$$
\frac{\sqrt{300 c \log z+(c+1.5 c \log z)^{2}}+1.5 c \log z-c}{0.15 c+0.003 c^{2}}
$$

in which $c$ is the weight, in g , on the dried basis, of the specimen tested in each 100.0 mL of solution, and $z$ is the viscosity of the test solution relative to that of water: the K-value is not less than $90.0 \%$ and not more than $110.0 \%$ of the Kvalue stated on the label.

Content of copolymerized vinyl acetate-Determine the saponification value as directed for Saponification Value under Fats and Fixed Oils $\langle 401\rangle$. Calculate the percentage of copolymerized vinyl acetate in the Copovidone taken by the formula:

$$
0.1(86.09 / 56.11)(S)
$$

in which 86.09 and 56.11 are the molecular weights of vinyl acetate and potassium hydroxide, respectively, and $S$ is the saponification value: not less than $35.3 \%$ and not more than $41.4 \%$ of the copolymerized vinyl acetate component, calculated on the dried basis, is found.

Nitrogen, Method II $\langle 461\rangle$-Proceed as directed using about 0.1 g of Copovidone, accurately weighed. In the procedure, use 5 g of a powdered mixture of potassium sulfate, cupric sulfate, and titanium dioxide ( $33: 1: 1$ ) instead of potassium sulfate and cupric sulfate ( $10: 1$ ), omit the use of hydrogen peroxide, and heat until the solution has a clear, yellow-green color and the sides of the flask are free from carbonaceous material. Then heat for a further 45 minutes, add 20 mL of water, instead of 70 mL , after the second heating, and use bromocresol green-methyl red TS instead of methyl red-methylene blue TS. Titrate the distillate with 0.05 N sulfuric acid VS until the color of the solution changes from green through pale grayish blue to pale grayish red-purple: the nitrogen content, on the dried basis, is not less than $7.0 \%$ and not more than $8.0 \%$.■ 1 S (NF23)

## Briefing

Hydrogenated Cottonseed Oil, NF 22 page 2854—See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-4

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers. Store at room temperature, and avoid excessive heat and freez ing. Pretect frem meisture.
${ }^{\bullet}$ No storage requirements specified.es

## Briefing

Diethylene Glycol Stearates, page 3171 of the First Supple-ment-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-10

## Change to read:

Packaging and storage-Preserve in tight containers. Storeat reom temperattre and protect from light, freezing, and exeessive heat.
${ }^{\bullet}$ No storage requirements specified.es

## Briefing

Dibutyl Phthalate, page 3170 of the First Supplement-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-9

## Change to read:

Packaging and storage-Preserve in tight containers. Store at room-temperatrre, and avoid exeessive heat and freezing. Protect frem meisture.
${ }^{\bullet}$ No storage requirements specified.es

## BRIEFING

Ethylene Glycol Stearates, page 3171 of the First Supple-ment-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-11

## Change to read:

Packaging and storage-Preserve in tight containers. Storeat roem temperattre and protect from light, freezing, and exeessive heat.
${ }^{\bullet}$ No storage requirements specified. ${ }^{\text {s }}$
BRIEFING

| Glyceryl Distearate, $N F 22$ page $2872 —$ See briefing under |
| :--- |
| Ammonium Sulfate. |

(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-6

## Change to read:

Packaging and storage-Preserve in tight containers. Store at room temperature. Protect from light, freezing, and excessive heat.
${ }^{\bullet}$ No storage requirements specified.es

## BRIEFING

Glyceryl Monolinoleate, NF 22 page 2873—See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-7

## Change to read:

Packaging and storage-Preserve in tight containers. Storeat foom temperature. Protect from light, freezing, and exeessive heat.
${ }^{\bullet}$ No storage requirements specified.es

## Change to read:

Packaging and storage-Preserve in tight containers. Stere at room temperatre. Protec from light, freezing, and exeessive heat.

- No storage requirements specified. ${ }^{\text {os }}$ BRIEFING

Glyceryl Monostearate, $N F 22$ page 2875 . On the basis of comments received, it is proposed to revise the Hydroxyl value and the Saponification value because the current specifications do not reflect the inclusion of material derived from plant sources. It is also proposed to revise the description statement in the $D e$ scription and Solubility section in this $P F$, for the same reason.
(EMC: D. Bempong) RTS-40241-1; 40908-1

## Change to read:

Hydroxyl value $\langle 401\rangle$ : between 300

- 290 $_{\text {IS (NF23) }}$
and 330 .


## Change to read:

Saponification value $\langle 401\rangle$ : between 155
$\mathbf{- 1 5 0}_{\text {■1S (NF23) }}$
and 165 .

Glyceryl Monooleate, NF 22 page 2874—See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-8

## Briefing

Hymetellose, page 3172 of the First Supplement and page 1100 of PF 29(4) [July-Aug. 2003]-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-13

## Add the following:

${ }^{\bullet}$ Packaging and storage-Preserve in well-closed containers. Store at $25^{\circ}$, exerrsion permitted between $15^{\circ}$ and $30^{\circ}$. Avoid excessive heat and freezing. Protect frem moisture. No storage requirements specified. 。

## Briefing

Hypromellose Acetate Succinate, page 1102 of $P F$ 29(4) [July-Aug. 2003]-See briefing under Copovidone.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40873-7

## Add the following:

## -Hypromellose Acetate Succinate

Hydroxypropyl methylcellulose acetate succinate.

Cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate.

Cellulose, 2-hydroxypropyl methyl ether, acetate succinate [71138-97-1].
» Hypromellose Acetate Succinate is a mixture of acetic acid and monosuccinic acid esters of hydroxypropyl methylcellulose. When dried at $105^{\circ}$ for 1 hour, it contains not less than 12.0 percent and not more than 28.0 percent of methoxy groups $\left(-\mathrm{OCH}_{3}\right)$, not less than 4.0 percent and not more than 23.0 percent of hydroxypropoxy
groups ( $-\mathrm{OCH}_{2} \mathrm{CHOHCH}_{3}$ ), not less than 2.0 percent and not more than 16.0 percent of acetyl groups ( $-\mathrm{COCH}_{3}$ ), and not less than 4.0 percent and not more than 28.0 percent of succinoyl groups ( $-\mathrm{COC}_{2} \mathrm{H}_{4} \mathrm{COOH}$ ).

Packaging and storage-Preserve in tight containers. Store at room temperature. Avoid excessive heat and freez ing. Protect from meistere. No storage requirements specified.

Labeling-Label it to indicate its nominal viscosity type.
USP Reference standards $\langle 11\rangle$ —USP Hypromellose Acetate Succinate RS.

Identification, Infrared Abserption- $\langle 197 \mathrm{~K}\rangle$, on undried specimen. Infrared Absorption $\langle 197 \mathrm{~A}\rangle$ —Do not dry specimens. Use a Fourier transform infrared spectrometer fitted with a suitable accessory for single bounce attenuated total reflectance (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) with a diamond crystal. Acquire a background sin-gle-beam spectrum with a clean diamond crystal sampling plate in place. Place the sample on the diamond crystal sampling surface with a microspatula or equivalent. For best results, the sample should cover the crystal surface under the pressure point tip. Using the pressure device, apply pressure to the sample, making sure the sample remains centered under the pressure tip. Acquire a single-beam spectrum of the sample, and make the necessary corrections for the background. Release the pressure device, and clear it from the sample area. Wipe the sample off the crystal and pressure device tip, and rinse both with acetone. The IR spectrum so obtained exhibits maxima only at the same wavelengths as a similarly obtained spectrum of USP Hypromellose Acetate Succinate RS.

Viscosity $\langle 911\rangle$ -
Sodium hydroxide solution-Immediately before use, dissolve 4.3 g of sodium hydroxide in carbon dioxide-free water to make 1000 mL .

Procedure-To 2.00 g of Hypromellose Acetate Succinate, previously dried, add Sodium hydroxide solution to make 100.0 g , insert a stopper into the vessel, and dissolve by constant shaking for 30 minutes. Adjust the temperature of the solution to $20 \pm 0.1^{\circ}$, and determine the viscosity in a suitable viscometer, as directed for Procedure for Cellulose Derivatives under Viscosity $\langle 911\rangle$. Its viscosity is not less than $80 \%$ and not more than $120 \%$ of that stated on the label.

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 1 hour: it loses not more than $5.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.20 \%$, determined at $600 \pm 50^{\circ}$.

Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.001 \%$.
Limit of freestecinic acid-Transfer 1.5 g of Нургmellese Acetate Stecinate, previeusly dried at $105^{\circ}$ for 1 hour and aceurately weighed, to a separator, dissolve in 50 mL of a mixture of dehydrated aleohol and dichloremethane $(3: 2, \mathrm{v} / \mathrm{v})$, add 75 mL of water with shaking, and then add 50 mL of hexane and 1 gof sodium chloride. Shake-well, and separate the lower water layer. Extract the erganic layer with 50 mL of water, and combine the wash ing and the water layer. Ade 3 dreps of phenolphthatein TS, and titrate with 0.1 N soditm hydroxide VS. Perferm at blank determination, and make any necessary eorrection. Each mL of 0.1N sodium hydroxide is equivalent to 5.904 mg of $\mathrm{C}_{4} \mathrm{H}_{6} \Theta_{4} \div$ net mere than $1.0 \%$ is feunt.

## Limit of free acetic and succinic acids-

Phosphoric acid solution-Transfer 1.0 mL of 1.25 M phosphoric acid into a $50-\mathrm{mL}$ volumetric flask, and dilute with water to volume.
0.02 M Phosphate buffer—Dissolve 5.44 g of monobasic potassium phosphate in 2 L of water.

Diluent-Adjust 0.02 M Phosphate buffer with 1 N sodium hydroxide to a pH of 7.5 .

Acetic acid stock solution-Add approximately 20 mL of water to a stoppered, $100-\mathrm{mL}$ volumetric flask, place the flask on a balance, and tare. Transfer 2.0 mL of the glacial acetic acid to the flask, and record the weight of the acid added. Fill the flask with water to volume. Transfer 6.0 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, and dilute with water to volume.

Succinic acid stock solution-Accurately weigh about 130 mg of succinic acid into a $100-\mathrm{mL}$ volumetric flask. Add about 50 mL of water, and swirl the contents until the succinic acid is fully dissolved. Fill the flask with water to volume.

Mobile phase—Adjust the 0.02 M Phosphate buffer to a pH of 2.8 by dropwise addition of 6 M phosphoric acid. Filter through a $0.22-\mu \mathrm{m}$ nylon filter.

Standard solution-Transfer 4.0 mL of the Acetic acid stock solution into a $25-\mathrm{mL}$ volumetric flask. To the same flask, transfer 4.0 mL of the Succinic acid stock solution, dilute with Mobile phase to volume, and mix. Prepare this solution in duplicate.

Test solution-Accurately weigh about 102 mg of Hypromellose Acetate Succinate into a glass vial. Transfer 4.0 mL of Diluent to the vial, and stir the content for 2 hours. Then, transfer 4.0 mL of the Phosphoric acid solution to the same vial to bring the pH of the Test solution to 3 or less. Invert
the vial several times to ensure complete mixing, centrifuge, and use the clear supernatant as a Test solution. Prepare this solution in duplicate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.6 \mathrm{~mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The column temperature is maintained between $20^{\circ}$ to $30^{\circ}$. The flow rate is about 1 mL per minute, and the run time is about 15 minutes. Chromatograph the first preparation of the Standard solution, and record the peak responses as directed for Procedure: the column efficiency, determined from the succinic acid peak, is not less than 8000 theoretical plates; the tailing of this peak is between 0.9 and 1.5 ; and the relative standard deviation for six replicate injections is not more than $2.0 \%$ for each peak. Chromatograph the second preparation of the Standard solution: the difference in peak areas between the two standard solutions for both acetic and succinic acid peaks does not exceed $2 \%$. [NOTE-After each run sequence, the column should be flushed first by $50 \%$ water and $50 \%$ acetonitrile for 60 minutes and then by $100 \%$ methanol for 60 minutes. The column should be stored in $100 \%$ methanol.]

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas corresponding to acetic and succinic acids. Calculate the percentage of free acetic acid, $A_{\text {free }}$, in the portion of Hypromellose Acetate Succinate taken by the formula:

$$
0.0768\left(W_{A} / W\right)\left(R_{U A} / R_{S A}\right)
$$

in which $W_{A}$ is the weight of glacial acetic acid, in mg, used to prepare the Acetic acid stock solution; $W$ is the weight of Hypromellose Acetate Succinate, in mg, used to prepare the Test solution; and $R_{U A}$ and $R_{S A}$ are the peak responses for acetic acid obtained from the Test solution and the Standard
solution, respectively. Calculate the percentage of free succinic acid, $S_{\text {free }}$, in the Hypromellose Acetate Succinate taken by the formula:

$$
1.28\left(W_{S} / W\right)\left(R_{U S} / R_{S S}\right)
$$

in which $W_{S}$ is the weight of succinic acid, in mg , used to prepare the Succinic acid stock solution; $R_{U S}$ and $R_{S S}$ are the peak responses for succinic acid obtained from the Test solution and the Standard solution, respectively; and $W$ is as defined above: the sum of free acetic acid and free succinic acid found does not exceed $1.0 \%$.

## Content of acetyl and succinoyl groups-

Phosphoric acid solution, Acetic acid stock solution, Succinic acid stock solution, Mobile phase, Standard solution, and Chromatographic system-Proceed as directed in the test for Limit of free acetic and succinic acids.

Test solution-Accurately weigh about 12.4 mg of Hypromellose Acetate Succinate into a glass vial. Transfer 4.0 mL of 1.0 N sodium hydroxide to the vial, and stir the solution for 4 hours. Then, add 4.0 mL of 1.25 M phosphoric acid to the same vial to bring the pH of the solution to 3 or less. Invert the test sample solution vial several times to ensure complete mixing, and filter through a $0.22-\mu \mathrm{m}$ filter. Use the clear filtrate as the Test solution.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas corresponding to acetic and succinic acids. Calculate the percentage of acetic acid, $A$, in the portion of Hy promellose Acetate Succinate taken by the formula:

$$
0.0768\left(W_{A} / W_{U}\right)\left(R_{U A} / R_{S A}\right),
$$

in which $W_{A}$ is the weight of acetic acid, in mg , used to prepare the Acetic acid stock solution; $W_{U}$ is the weight of Hypromellose Acetate Succinate, in mg, used to prepare the Test solution; and $R_{U A}$ and $R_{S A}$ are the peak responses for acetic acid obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of acetyl groups $\left(-\mathrm{COCH}_{3}\right)$ in the portion of Hydroxypropyl Methylcellulose Acetate Succinate taken by the formula:

$$
0.717\left(A-A_{\text {free }}\right)
$$

in which $A_{\text {free }}$ is the percentage of free acetic acid, as determined in the test for Limit of free acetic and succinic acid; and $A$ is as defined above. Calculate the percentage of succinic acid, $S$, in the portion of Hypromellose Acetate Succinate taken by the formula:

$$
1.28\left(W_{S} / W_{U}\right)\left(R_{U S} / R_{S S}\right),
$$

in which $W_{S}$ is the weight of succinic acid, in mg, used to prepare the Succinic acid stock solution; $W_{U}$ is as defined above; and $R_{U S}$ and $R_{S S}$ are the peak responses for succinic acid obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of succinoyl groups $\left(-\mathrm{COC}_{2} \mathrm{H}_{4} \mathrm{COOH}\right)$ in the portion of Hydroxypropyl Methylcellulose Acetate Succinate taken by the formula:

$$
0.856\left(S-S_{\text {free }}\right)
$$

in which $S$ is as defined above; and $S_{\text {free }}$ is the percentage of free succinic acid, as determined in the test for Limit of free acetic and succinic acids.

## Content of methoxy and hydroxypropoxy groups-

fCamtion Hydriodic acid and its reaction byproducts are highly toxic. Perfom all steps in the preparation f the Test solution and the Standerd solution in aproperly functioning hood. Specific safety practices to be followed are be iden tifed the andys performing this test.?
Hydrid Use a reagent having a specific gravily of at least 1.69 , equivalent to $55 \% \mathrm{HH}$.

Internal standerd solution- Transfer about 2.5 g of to tuene, aceurately weighed, to a $100-\mathrm{mL}$ volumetric flask eontaining 10 mL of $\theta$ xylene, dilute with $\theta$ xylene to vo fume, and mix.

Stenderd solution Into suitable serum vial weigh about 135 mg of adipic acid and 4.0 mL of Hydriadic acd, pipet 4 mL of Interal stad solution int the vial, and close the vial seetrely with a stitable septum stopper. Weigh acet rately the vial and contents, add $30 \mu \mathrm{~L}$ - of isopropyl iodide through the septum with a syringe, weigh again, and calet tate the weight of isopropyl iodide added, by difference. Similarly, add $90-\mu \mathrm{L}$ of methyliodide weigh again, and ealeulate the weight of methyl iodide added, by difference. Shake, and allow the layers to separate.

Fest solution Transfer about 0.065 g of Hypromellose Acetate Suceinate, previously dried at $105^{\circ}$ for 1 hour and aceurately weighed, to a 5 mL thick walled reaction vial equippe with a pressure tight septum yype clostre, add an amount of adipic acid equal to the weight of the test spe eimen, and pipet 2 mL of Internal standard solution into the vial. Cautiously pipet 2 mL of Hydriodic aid into the mix ture, immediately eap the vial tightly, and weigh aceurately. Mix the contents of the vial continuously while heating at $150^{\circ}$ for 60 minttes. Allow the vial to cool for about 45 mintes, and weigh again. If the weight loss is greater than 10 -mg, discard the mixture, and prepare another Test preparation.

Chromatographic systen The gas chromatograph is equipped with a thermal conductivity detector and a-4 mm * 1.8 m glass coltum packed with 20\% liquid phase-G28 on 100 to 120 mesh support SIC that is not silanized. Hetimm is used as the carrier gas, and the temperature of the celtamm is maintained at $130^{\circ}$. Chrematograph the Standard solution, and record the peak respenses as directed for Proedure: the relative retention times of methyl iodide, isepropyliodide, toluene, ande-xylene are approximately 1.0,2.2, 3.6, and 8.0, respectively; and the resolution, $R$, between the tolnene and isopropyl iodide peaks is not less than 2.0 .

Galibration Inject about $2 \mu \mathrm{~L}$ of the upper layer of the Standerd solution inte the gas ehromatograph, and record the-chromatograms. Caleulate the relative respense factor, $F_{4}$, of equal weights of toluene and methyl iodide taken by the formula:-

$$
Q_{+4}+R_{\text {sert }}
$$

in which $Q_{4}$ is the quantity ratio of methyliodide to toltene in the Standard soltution, and $R_{\text {sur }}$-is the peak area ratio- of methyl iodide to toltuene obtained from the Stathdard soltttion. Similarly, calculate the relative respense factor, $F$, of equal weights of toluene and isopropyliodide taken by the formata:
$\qquad$

$$
Q_{0}+R_{s}
$$

in which $Q$.is the quantity ratio of isepropyl iodide to to thene in the Standard solution, and $R_{s i}$ is the peak area ratio of isopropyl iodide to toltene obtained from the Standard solution.

Procedure Inject about $2 \mu \mathrm{~K}$ of the upper layer of the Test solution inte the gas chromatograph, and record the ehrematograms. Caleulate the percentage of methoxy groups ( $\mathrm{OCH}_{3}$ ) in the portion of Hypromellose Acetate Succinate taken by the formula:-

$$
2(31 / 142) F_{\#} R_{14}\left(H_{7}+H_{t}\right),
$$

in which $31 / 142$ is the ratio of the formula weights of the methoxy group and methyl iodide; $F_{4}$-is defined under $C a-$ libration; $R_{\text {nu }}$ is the ratio of the area of the methyl iodide peak to that of the toluene peak obtained from the Test solt tion; $W_{7}$ is the weight, in f , of toluene used to prepare the Internal standard solution; and $\mathrm{H}_{+}$is the weight, in g, of Hypromellose Acetate Succinate taken to prepare the Test solution. Similarly, caleulate the pereentage of hydroxyprepexy groups ( $\mathrm{OCH}_{2} \mathrm{CHOHCH}_{3}$ ) in the pertion of Hypremellose Acetate Succinate taken by the formula:-

$$
z(75 / 170) F_{d} R_{u}\left(H_{\mp}+W_{\downarrow}\right)
$$

in which $75 / 170$ is the ratio of the formula weights of the hydroxypropoxy group and isopropyliodide; $F_{f}$ is defmed tader Catibration; $R_{\psi}$ is the ratio of the area of the isoprepyl iodide peak to that of the tolnene peak obtained from the Test solution; $W_{f}$ is the weight, in ge of toluene used to pre pare the Internat standetrd solution; and $H_{t}$ is the weight, in g, of Hypromellose Ace Sutecinate taken to prepare the Fest solution.

Gontent of streinoyl groups Transfer about 1 g of Hy promellose Aretate-Strecinate, previously dried at $105^{\circ}$ for Thour and acemately weighed, to aconical flask, dissolve in 50 mL of a mixture of aleohol, acetone, and water $(2: 2: 1$, WV), add 2 dreps of phenelphthalein TS, and titrate with
Q. 1 N soditm hydroxideVS. Perform a blank determination, and make any neeessary corrections. Caleulate the pereenage of suceinoyl groups by the formula:-
in whieh $V$ is the volume, in mL , of 0.1 N soditm hydroxide eensumed after correction for the blank; $W$ is the weight, in g, of Hypremellose Acetate Stuecinate taken; and $S$ is the percentage of free succinic acid found as directed in the test for Limit of free suceinic acid.

## Content of acetyl groups-

Apparatus Use the apparatus illustrated in Figutre 1.


Figure 1: Apparatus for Determination of Content of AcetylGroups

Internal standad solution-Transfer 1.0 mL of propionie acid into a 250 mL volumetrie flask, and dilute with Diluent volume-

Piltent Use dilute phespherie acid ( 1 in 5000 ).
Standard solution Transfer about 100 mg of glacial acetic acid, aceurately weighed, into a 100 mL velumetric flask, and dilute with Diluent to volume. Transfer 15 mL
of this selution to another $100-\mathrm{mL}$ volumetric flack, add 5.0 mL of the Internat standard solttion, and dilute with Dilt ent to volume.

Fest solution Transfer about 150 me of Hypromellose Acetate Suceinate, previously dried at $105^{\circ}$ for 1 hour and aceurately weighed, to decempesition flask D , add 5 mL of sodium hydroxide TS, dissolve by shaking, and decompose in a water bath at $60^{\circ}$ for 2 hours. After cooling, add 5 mL of diluted phosphoric acid ( 1 in 6 ), and immediately construct the apparatus as shown in Figute 1. Dip the decomposition flask and steam generator $B$ in the oil bath at $155^{\circ}$, while passing nitrogen from nitrogen induction tube H at a rate of 1 to 2 bubbles per second, continte the distillation at the same temperature, and collect the distillate in measuring eylinder $G$. Take 60 mL of the distillate, wash the inside of eendenser $F$ with 10 mL of water, combine the washing with the distillate in a $100-\mathrm{mL}$ volumetric flask, add 5.0 mL of the Internal standard solution, and dilute with water to ve tame.

Chromatographic system The gas chromatograph is equipped with a flame-ionization detector and a-3-mm $*$ Z m-glass columm packed with-60-10-80 mesh suppert S2. The carrier gas is helium, and the temperature of the coltamm is maintained at $180^{\circ}$. Adjust the flow rate so that the inter nal standard peak elutes in about 5 minutes. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the elution order is acetic acid, fot towed by the internal standard peak. The resolution, $R$, between these peaks is not less than 2.0; and the relative standard deviation for replicate injections is net mere than $2.0 \%$ for each of the peaks.

## Procedtre Separately inject equal volumes (about $2 \mu \mathrm{~L}$ )

of the Standerd solution and the Test solution inte the chromatograph, record the chromatograms, and measure the re spenses for the major peaks. Caleulate the ratio, $R_{t}$, of the
area of the acetic acid peak to the area of the internal-standard peak in the chromatogram obtained frem the Test solt tion, and similarly ealeulate the ratio, $R_{s}$, in the ehrematogram obtained from the Standard solution. Caleu tate the pereentage of acetylgroups ( $\mathrm{COCH}_{3}$ ) in the pertion of Нурromellose Acetate-Strecinate taken by the formata:-

$$
\left(R_{4}+R_{s}\right)\left(H H_{s}+H\right) \times 0.15 \times 71.68
$$

in whieh $W_{s}$ is the weight, in mg, of glacial acetic acid used to prepare the Standard solution; Wis the weight, in mg, of the pertion of Hypromellose Acetate Suecinate taken; and the other terms are as defined therein.

Content of methoxy and 2-hydroxypropoxy groups-[Caution-Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps in the preparation of the Test solution and the Standard solution in a properly functioning hood. Specific safety practices to be followed are to be identified to the analyst performing this test.]

Hydriodic acid-Use a reagent having a specific gravity of at least 1.69 , equivalent to $55 \%$ hydrogen iodide.

Solution $A$-Prepare a mixture of water and methanol (90:10).

Solution B-Prepare a mixture of methanol and water (85: 15).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard stock solution-Transfer 2 mL of $o$-xylene into a stoppered, $10-\mathrm{mL}$ volumetric flask, place the flask on a balance, and tare. Add about $200 \mu \mathrm{~L}$ of methyl iodide, insert the stopper into the flask, and accurately weigh: the weight of methyl iodide is about 350 mg . Tare the flask again, add
about $34 \mu \mathrm{~L}$ of isopropyl iodide, and accurately weigh the flask: the recorded weight of isopropyl iodide is about 50 mg . Dilute with $o$-xylene to volume, and mix.

Standard solution-Transfer about 85 mg of adipic acid into an $8-\mathrm{mL}$ vial (or other suitable container), add 2 mL of Hydriodic acid, and add 2.0 mL of the Standard stock solution. Shake and allow the phases to separate. Carefully transfer approximately 1.5 mL of the $o$-xylene (top) layer to a small vial, making sure that the bottom aqueous layer is not disturbed. Transfer 1.0 mL of this solution into a $10-$ mL volumetric flask, and dilute with methanol to volume. [NOTE-This solution is stable for 8 hours at $5^{\circ}$.]

Test solution-Accurately weigh about 65 mg of Hypromellose Acetate Succinate into a $5-\mathrm{mL}$ reaction vial, add 2.0 mL of $o$-xylene and about 100 mg of adipic acid. Add 2.0 mL of Hydriodic acid, and close the vial tightly with a cap. [Caution-Use a cap that has a top safety relief valve, such as a Minniert valve, to prevent accidental explosion of the vial under high pressure when heated.] Weigh the vial before heating, and place the vial into a heating block at $150^{\circ}$. Shake the vial after 5 minutes and after 30 minutes of heating. Remove the vial from the heating block after 1 hour of heating, and cool. Weigh the vial. If the weight loss is greater than 10 mg , discard the mixture, and prepare another reaction solution. Carefully transfer approximately 1.5 mL of the top $o$-xylene layer into a small glass vial, making sure that the bottom aqueous layer is not disturbed. Transfer 1.0 ml of this solution into a $10-\mathrm{mL}$ volumetric flask, and dilute with methanol to volume. [NOTE-This solution is stable for 8 hours at $5^{\circ}$.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6 \mathrm{~mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ pack-
ing L1. The column temperature is maintained at $30^{\circ}$. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Time | Solution A | Solution B |  |
| :---: | :---: | :---: | :--- |
| (minutes) | $(\%)$ | $(\%)$ | Elution |
| 0 | 70 | 30 | equilibration |
| $0-8$ | $70 \rightarrow 40$ | $30 \rightarrow 60$ | linear gradient |
| $8-10$ | $40 \rightarrow 15$ | $60 \rightarrow 85$ | linear gradient |
| $10-17$ | 15 | 85 | isocratic |

[NOTE-These gradient elution times are established on an HPLC system with a dwell volume of approximately 2.0 mL . The injection time can be adjusted relative to the start of a run to accommodate the change in dwell volume from one HPLC system to another to achieve the separation described.] Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency, determined from the methyl iodide peak, is not less than 10,000 theoretical plates; the tailing factor of this peak is between 0.9 and 1.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$ for each peak.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas corresponding to methyl iodide and isopropyl iodide. Calculate the percentage of methoxy groups $\left(-\mathrm{OCH}_{3}\right)$ in the portion of Hypromellose Acetate Succinate taken by the formula:

$$
4.38\left(W_{M} / W\right)\left(R_{U M} / R_{S M}\right),
$$

in which $W_{M}$ is the weight of methyl iodide, in mg, used to prepare the Standard stock solution; $W$ is the weight of Hypromellose Acetate Succinate, in mg, used to prepare the Test solution; and $R_{U M}$ and $R_{S M}$ are the peak responses for
methyl iodide obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of 2hydroxypropoxy groups $\left(-\mathrm{OCH}_{2} \mathrm{CHOHCH}_{3}\right)$ in the portion of Hypromellose Acetate Succinate taken by the formula:

$$
8.84\left(W_{I} / W\right)\left(R_{U I} / R_{S I}\right)
$$

in which $W_{I}$ is the weight of isopropyl iodide, in mg, used to prepare the Standard stock solution; $R_{U I}$ and $R_{S I}$ are the peak responses for methyl iodide obtained from the Test solution and the Standard solution, respectively; and $W$ is as defined above. 1 S (NF23)

## Briefing

Hypromellose Phthalate, NF 22 page 2879. In accordance with the implemented name change of the Reference Standard, from USP Hydroxypropyl Methylcellulose Phthalate RS to USP Hypromellose Phthalate RS, it is proposed to make the corresponding change in the USP Reference standards $\langle 11\rangle$ section of the monograph.
(EMC: C. Sheehan) RTS-40945-1

## Change to read:

USP Reference standards $\langle 11\rangle$ USP Hydreyproyl Methyteel tatose Phthatate RS.

- USP Hypromellose Phthalate $R$.n. $_{\text {1S (NF23) }}$


## BRIEFING

Maltitol Solution, NF 22 page 2891 and page 3173 of the First Supplement-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-20

## Change to read:

Packaging and storage--Preserve in well-closed containers. Đe not store below $20^{\circ}$. 1 S (NF22)
${ }^{\bullet}$ No storage requirements specified.es

## Briefing

Maltol. Because there is no existing $N F$ monograph for this product, a new monograph, based on the Maltol monograph on page 273 of the Food Chemicals Codex, Fifth Edition, is being proposed.
(EMC: D. Bempong) RTS-40947-1

## Add the following:

## ■ Maltol

» Maltol contains not less than 99.0 percent of $\mathrm{C}_{6} \mathrm{H}_{6} \mathrm{O}_{3}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight containers, protected from light.

USP Reference standards $\langle 11\rangle —$ USP Maltol $R S$.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle-$
Solution: 0.01 mg per mL.
Medium: $\quad 0.1 \mathrm{~N}$ hydrochloric acid.
Melting range, Class $1 a\langle 741\rangle$ : between $160^{\circ}$ and $164^{\circ}$.
Water, Method $I\langle 921\rangle$ : not more than $0.5 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.2 \%$, determined on 1.0 g .

Lead $\langle 251\rangle$ : $\quad 10 \mu \mathrm{~g}$ per g.
Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.002 \%$.
Assay-
Standard preparation-Dissolve an accurately weighed quantity of USP Maltol RS in 0.1 N hydrochloric acid, and dilute quantitatively, and stepwise if necessary, with 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 0.01 mg per mL .
Assay preparation-Transfer about 50 mg of Maltol, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask, dissolve in and dilute with 0.1 N hydrochloric acid to volume, and mix. Pipet 5 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix.
Procedure-With a suitable spectrophotometer, using 0.1 N hydrochloric acid as a blank, concomitantly determine the absorbances of the Standard preparation and the Assay preparation at the wavelength of maximum absorbance at
about 274 nm . Calculate the quantity, in mg , of $\mathrm{C}_{6} \mathrm{H}_{6} \mathrm{O}_{3}$ in the portion of Maltol taken by the formula:

$$
5000 C\left(A_{U} / A_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Maltol RS in the Standard preparation; and $A_{U}$ and $A_{S}$ are the absorbances obtained from the Assay preparation and the Standard preparation, respectively.■1S (NF23)

## Briefing

Maltose, page 1113 of PF 29(4) [July-Aug. 2003]—See briefing under Copovidone.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40873-4

## Add the following:

## -Maltose


$\mathrm{C}_{12} \mathrm{H}_{22} \mathrm{O}_{11} \cdot \mathrm{H}_{2} \mathrm{O} \quad 360.31$
$\mathrm{C}_{12} \mathrm{H}_{22} \mathrm{O}_{11} \quad 342.30$
4-O- $\alpha$-D-Glucopyranosyl- $\beta$-D-glucopyranose.
» Maltose is a sugar. It contains one molecule of water of hydration or is anhydrous. It contains not less than 92.0 percent of maltose, calculated on the anhydrous basis. The amounts of other sugars, if detected, are not included in the requirements or the calculated amount under Other Impurities.

## Change to read:

Packaging and storage-Preserve in tightentainers. Preserve in well-closed containers. Store at room tempera-(tre-No storage requirements specified. ${ }^{1 S}$ (NF23)

USP Reference standards $\langle 11\rangle$ —USP Maltose Monohydrate $R S$.

## Identification-

A: Add 2 to 3 drops of a solution of Maltose $(1$ in 20$)$ to 5 mL of hot alkaline cupric tartrate TS. A red precipitate is formed.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the chromatogram of the Standard preparation, as obtained in the Assay.
$\mathbf{p H}\langle 791\rangle$ —Prepare a 1 in 10 solution in carbon dioxide-free water. For the anhydrous form, it is between 3.7 and 4.7 and for the monohydrate form, it is between 4.0 and 5.5.

Water, Method I $\langle 921\rangle$ —The anhydrous form contains not more than $1.5 \%$. The monohydrate form contains not less than $5.0 \%$ and not more than $6.5 \%$.

Residue on ignition $\langle 281\rangle$ : not more than $0.05 \%$, determined on a $2-\mathrm{g}$ portion, accurately weighed.

Heavy metals, Method I 231$\rangle$ : not more than $5 \mu \mathrm{~g}$ per g.

Dextrin, starch, and sulfite-Dissolve 1.0 g of Maltose in 10 mL of water, and add 1 drop of iodine TS: a yellow color develops. Then add 1 drop of starch TS to this portion: a blue color develops.

## Assay-

Mobile phase-Use degassed water.
Resolution solution-Dissolve accurately weighed quantities of maltotriose, maltose, and glucose in water, to obtain a solution having concentrations of about 10 mg of each per g.

Standard preparation-Dissolve an accurately weighed quantity of USP Maltose Monohydrate RS in water, to obtain a solution having a concentration of about 10 mg ef per g . Calculate the exact concentration on the anhydrous basis.
Assay preparation-Dissolve about 0.10 g of Maltose, accurately weighed, in water, and dilute with water to about 10 g . Accurately record the final solution weight, and mix thoroughly.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatographic system is equipped with a refractive index detector maintained at a constant temperature of about $40^{\circ}$, and a $7.8-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing $\mathrm{L} 54 \mathrm{~L} \# \#$ (See Chromatography $\langle 621\rangle$ ). The column temperature is maintained at about $80^{\circ}$, controlled to within $\pm 2^{\circ}$. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure. Adjust the flow rate to about 0.35 mL per minute such that the resolution, $R$, between maltotriose and maltose is not less than 1.6. and that between maltose and glueese is not less than 4.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for maltotriose, 1.0 for maltose, and 1.2 for glucose; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of Maltose on the anhydrous basis, taken by the formula:

$$
\left[10,000\left(C_{S} / C_{U}\right)\left(r_{U} / r_{s}\right)\right] /(100-W)
$$

in which $C_{S}$ is the concentration, in mg per g , on the anhydrous basis of USP Maltose Monohydrate RS in the Standard preparation; $C_{U}$ is the concentration, in mg per g , of Maltose in the Assay preparation; $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively; and $W$ is the percentage obtained in the test for Water. $\mathbf{U S S}_{\text {(NF22) }}$

## BRIEFING

Palmitic Acid. Because there is no existing $N F$ monograph for this product, a new monograph, based on the Palmitic Acid monograph in the European Pharmacopoeia, Fourth Edition, Supplement 1 , page 2507 , is being proposed.
(EMC: D. Bempong) RTS-40951-1

## Add the following:

## Palmitic Acid

$\mathrm{C}_{16} \mathrm{H}_{32} \mathrm{O}_{2} \quad 256.43$
Hexadecanoic acid [57-10-3].
» Palmitic Acid is a mixture of solid organic acids obtained from fats or oils of animal or vegetable origin. The content of $\mathrm{C}_{16} \mathrm{H}_{32} \mathrm{O}_{2}$ is not less than 92.0 percent and the content of stearic acid $\left(\mathrm{C}_{18} \mathrm{H}_{36} \mathrm{O}_{2}\right)$ is not more than 6.0 percent.

Packaging and storage-Preserve in well-closed containers, and store at room temperature.

Labeling-Label it to indicate whether it is derived from animal or vegetable sources.

USP Reference standards $\langle 11\rangle$ —USP Palmitic Acid $R S$.
USP Stearic Acid RS.
Color-Heat it to about $75^{\circ}$. The resulting liquid is not more intensely colored than a solution prepared by mixing 1.2 mL of ferric chloride CS and 0.3 mL of cobaltous chloride CS with 0.3 N hydrochloric acid to make 10 mL , and diluting 5 mL of this solution with 0.3 N hydrochloric acid to make 100 mL . Make the comparison by viewing the solutions downward in matched color-comparison tubes against a white surface (see Color and Achromicity $\langle 631\rangle$ ).

Identification-The chromatogram of the Assay preparation obtained as directed in the Assay exhibits a major peak for palmitic acid, the retention time of which corresponds to that exhibited by palmitic acid in the chromatogram of the Standard preparation, obtained as directed in the Assay.

Congealing temperature $\langle 651\rangle$ : between $60^{\circ}$ and $66^{\circ}$.
Acid value $\langle 401\rangle$ : between 216 and 220 , using about 1 g , accurately weighed.

Iodine value $\langle 401\rangle$ : not more than 1. Proceed as directed in Method I except to use 35 mL of chloroform.

Mineral acid—Shake 5 g of melted Palmitic Acid with an equal volume of hot water for 2 minutes, cool, and filter: the filtrate is not reddened by the addition of 1 drop of methyl orange TS.

Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.001 \%$.
Organic volatile impurities, Method $V\langle 467\rangle$ : meets the requirements.

Solvent-Use dimethyl sulfoxide.

## Assay-

Standard preparation-Prepare the Standard preparation in the same manner as the Assay preparation, using a mixture of 50 mg of USP Palmitic Acid RS and 50 mg of USP Stearic Acid RS instead of the substance to be examined.

Assay preparation-Proceed as directed for Test Solution in Fatty Acid Composition under Fats and Fixed Oils $\langle 401\rangle$.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— Prepare as directed for Fatty Acid Composition under Fats and Fixed Oils $\langle 401\rangle$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for methyl palmitate and 1.0 for methyl stearate; the resolution, $R$ between methyl stearate and methyl palmitate is not less than 3.0.

Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Assay preparation and the Standard preparation into the chromatograph, record the chromatograms, identify the methyl palmitate peak in the chromatogram obtained from the Assay preparation by comparing the retention times of the peaks in that chromatogram with those in the chromatogram obtained from the Standard preparation, and measure the responses for all of the peaks, excluding the solvent peak. Calculate the percentage of $\mathrm{C}_{16} \mathrm{H}_{32} \mathrm{O}_{2}$ in the portion of Palmitic Acid taken by the formula:

100A/B,
in which $A$ is the methyl palmitate peak response; and $B$ is the sum of the responses of all the peaks in the chromatogram, except the solvent peak. Similarly, calculate the percentage of stearic acid in the portion of Palmitic Acid taken. 1 S (NF23)

## Briefing

Phenolsulfonphthalein, page 2018 of $P F$ 29(6) [Nov.-Dec. 2003]-See briefing under Copovidone.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40873-6

## Add the following:

## ■Phenolsulfonphthalein


$\mathrm{C}_{19} \mathrm{H}_{14} \mathrm{O}_{5} \mathrm{~S} \quad 354.38$
Phenol Red
Phenol, 4,4'-(3H-2,1-benzoxathiol-3-ylidene)bis-,( $S, S$-dioxide).

3,3-bis(4-hydroxyphenyl)-3H-2,1-benzoxathiole 1,1-dioxide [143-74-8].

## » Phenolsulfonphthalein contains not less than

 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{19} \mathrm{H}_{14} \mathrm{O}_{5} \mathrm{~S}$, calculated on the dried basis.Packaging and storage-Preserve in well-closed containers. Store at $25^{\circ}$, exeursions permitted between $15^{\circ}$ and $30^{\circ}$.

No storage requirements specified.
Labeling-Where it is intended for use in nistered either intramuseularly or subeutaneously, articles administered parenterally, it is so labeled.

USP Reference standards $\langle 11\rangle$ —USP Endotoxin RS.

## Identification-

A: Transfer 5 mg of Phenolsulfonphthalein to a 100mL volumetric flask, dissolve in and dilute with sodium carbonate solution (1 in 100) to volume, and mix. Dilute 5.0 mL of the solution so obtained to 100.0 mL with sodium carbonate solution (1 in 100). Examined between 400 and 630 nm , the solution exhibits an absorption maximum at 558 nm . The specific absorbance at the maximum is between 1900 and 2100.

B: Dissolve about 10 mg of Phenolsulfonphthalein in 2 mL of 1 N sodium hydroxide, and add 8 mL of water. To 5 mL of the solution so obtained add 1 mL of 0.1 N potassium bromide-bromate and 1 mL of diluted hydrochloric acid, shake, and allow to stand for 15 minutes. Render the solution alkaline with 1 N sodium hydroxide: an intense violetblue color is produced.

Visual transition interval-Dissolve 1.0 g of potassium chloride in 100 mL of water, and adjust with 0.01 N hydrochloric acid or sodium hydroxide to a pH of 6.8 . Dissolve 0.1 g of Phenolsulfonphthalein in 100 mL of alcohol, and add 0.15 mL of this solution to the potassium chloride solution. The color of the resulting solution is yellow, with not more than a faint trace of green color. Titrate the solution with 0.01 N sodium hydroxide to a pH of 7.0 : the color of the solution becomes orange. Continue the titration to pH 8.2: the color of the solution becomes red. Not more than 0.20 mL of 0.01 N sodium hydroxide is consumed in the entire titration.

Microbial limit $\langle 61\rangle$ —The total aerobic microbial count does not exceed 1000 cfu per $g$, and the total combined molds and yeasts count does not exceed 100 cfu per g .

Bacterial endotoxins $\langle 85\rangle$-Where it is intended for use in vaceines administered either intramuseularly or subeuta nemsly, articles administered parenterally, it contains not more than 600 USP Endotoxin Units per mg.

Loss on drying $\langle 731\rangle$ —Dry 1 g of the powdered Phenolsulfonphthalein at $105^{\circ}$ to constant weight: it loses not more than $1.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.2 \%$, determined on a $0.5-\mathrm{g}$ portion.

Insoluble substances-To about 1 g of the finely powdered Phenolsulfonphthalein, accurately weighed, add a solution of 0.50 g of sodium bicarbonate in 12 mL of water. Allow to stand for 1 hour, shaking frequently. Dilute with sufficient water to make 100 mL , and allow to stand for 15 hours. Centrifuge at 2000 to $3000 g$ for 30 minutes, and decant the supernatant. Wash the residue first with 25 mL of sodium bicarbonate solution ( 1 in 100), then with 25 mL of water, and dry at $105^{\circ}$ : the weight of the insoluble residue does not exceed $0.5 \%$ of the weight of Phenolsulfonphthalein taken.

## Chromatographic purity-

Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture.

Application volume: $\quad 10 \mu \mathrm{~L}$
Developing solvent system: a mixture of tert-amyl alcohol, glacial acetic acid, and water ( $100: 25: 25$ ).

Test solution-Transfer about 100 mg of Phenolsulfonphthalein to a $5-\mathrm{mL}$ volumetric flask, dissolve in and dilute with 0.1 N sodium hydroxide to volume, and mix.

Diluted test solution-Transfer 0.5 mL of the Test solution to a $100-\mathrm{mL}$ volumetric flask, dilute with 0.1 N sodium hydroxide to volume, and mix.

Procedure-Proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$. Allow the plate to air-dry until the solvent has evaporated, and expose the plate to ammonia vapor. Examine the plate under short-wavelength UV light. Not more than one spot, apart from the principal spot, appears in the chromatogram obtained from the Test solution. This spot is not more intense than the spot in the chromatogram obtained from the Diluted test solution: not more than $0.5 \%$ is found.

Assay-Transfer about 0.9 g of Phenolsulfonphthalein, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask, dissolve in 15 mL of 1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 10.0 mL of the solution so obtained to a glass-stoppered flask, add 25 mL of glacial acetic acid, 20.0 mL of 0.1 N potassium bromate $\mathrm{VS}, 5 \mathrm{~mL}$ of potassium bromide solution ( 1 in 10 ), and 5 mL of hydrochloric acid, and immediately insert the stopper into the flask. Allow to stand protected from light for 15 minutes. Quickly add 10 mL of potassium iodide solution (1 in 10), taking care to avoid the escape of bromine vapor, immediately insert the stopper in the flask, and shake vigorously. Rinse the stopper and the neck of the flask with a small quantity of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, using starch TS as the indicator. Perform a blank determination (see Residual Titrations under Titrimetry $\langle 541\rangle$ ), and note the difference in volumes required. Each mL of the difference in volumes of 0.1 N sodium thiosulfate is equivalent to 4.43 mg of $\mathrm{C}_{19} \mathrm{H}_{14} \mathrm{O}_{5} \mathrm{~S}$.■1S (NF23)

## Briefing

Polyisobutylene, page 3175 of the First Supplement-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-16

## Change to read:

Packaging and storage-Store in well-closed containers. Storeat room temperature, and avoid excessive heat and freezing. Protect from moisture.
${ }^{\bullet}$ No storage requirements specified. $\bullet$

## Briefing

Sodium Caprylate. Because there is no existing NF monograph for this excipient, a new monograph, based on the Sodium Caprylate monograph in the European Pharmacopoeia, Fourth Edition, page 1904, is being proposed.
(EMC: E. Gonikberg) RTS-40973-1

## Add the following:

## ■Sodium Caprylate


» Sodium Caprylate contains not less than 99.0 percent and not more than 101.0 percent of sodium octanoate $\left(\mathrm{C}_{8} \mathrm{H}_{15} \mathrm{O}_{2} \mathrm{Na}\right)$, calculated on the anhydrous basis.

Packaging and storage-Store in well-closed containers. USP Reference standards $\langle 11\rangle$ —USP Caprylic Acid RS. Appearance of solution-Dissolve 2.5 g of Sodium Caprylate in 25.0 mL of freshly boiled and cooled water: the resulting solution is clear and colorless.

## Identification-

A: The retention time of the major peak in the chromatogram of Test solution 1 corresponds to the major peak in the chromatogram of the Reference solution, as directed in the test for Chromatographic purity.

B: Proceed as directed below.
Methoxyphenylacetic reagent-Dissolve 2.7 g of methoxyphenylacetic acid in 6 mL of $10 \%$ tetramethylammonium hydroxide solution in methanol, and add 20 mL of alcohol. Store in a polyethylene container.

Procedure-Dissolve about 20 mg of Sodium Caprylate in 0.5 mL of water, add 1.5 mL of Methoxyphenylacetic reagent, and cool in ice water for 30 minutes. A voluminous, white, crystalline precipitate is formed. Place in water at $20^{\circ}$, and stir for 5 minutes. The precipitate does not disappear. Add 1 mL of ammonia TS. The precipitate dissolves completely. Add 1 mL of ammonium carbonate solution (16 in 100): no precipitate is formed.
$\mathbf{p H}\langle 791\rangle$ : between 8.0 and 10.5, in a solution obtained in the test for Appearance of solution.

Water, Method $I\langle 921\rangle$ : not more than 3.0\%.
Heavy metals, Method II $\langle 231\rangle$ —Dissolve 2.0 g of Sodium Caprylate in 10 mL of glacial acetic acid, add 10 mL of alcohol, and use 12 mL of the solution obtained as the Test

Preparation. Prepare the Standard Preparation using 1 mL of Standard Lead Solution and 9 mL of a mixture of glacial acetic acid and alcohol ( $1: 1$ ). The limit is $5 \mu \mathrm{~g}$ per g .

## Chromatographic purity-

Reference solution-Transfer 10 mg of USP Caprylic Acid RS to a $10-\mathrm{mL}$ volumetric flask, and dilute with ethyl acetate to volume.

Test solution 1-Dissolve 116 mg of Sodium Caprylate in 5 mL of water, add 1 mL of dilute sulfuric acid ( 1 in 35 ), and extract with 10 mL of ethyl acetate. Separate the organic layer, and dry it over anhydrous sodium sulfate.

Test solution 2-Dilute 1.0 mL of Test solution 1 with ethyl acetate to 100 mL , transfer 5.0 mL of the solution obtained, and dilute with ethyl acetate to 50 mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The gas chromatograph is equipped with a flame-ionization detector, a split injection system with a split ratio of about $1: 100$, and a $0.25-\mathrm{mm} \times 30-\mathrm{m}$ fused silica column coated with a $0.25-\mu \mathrm{m}$ layer of phase G25. The carrier gas is helium, flowing at a rate of 1.5 mL per minute. The chromatograph is programmed as follows. Initially the temperature of the column is equilibrated at $100^{\circ}$, then, 1 minute after the injection, the temperature is increased at a rate of $5^{\circ}$ per minute to $220^{\circ}$, and maintained at $220^{\circ}$ for another 10 minutes. The injection port temperature and the detector temperature are maintained at $250^{\circ}$. Chromatograph Test solution 2, and record the peak responses as directed for Procedure: the signal-to-noise ratio of the principal peak is not less than 5 .

Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Reference solution, Test solution 2, and Test solution 1 into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Disregard any peaks with an area less than half of the area of the principal
peak from Test solution 2, and any peak due to the solvent. Calculate the percentage of each impurity in the portion of Sodium Caprylate taken by the formula:

$$
100\left(r_{i} / r_{s}\right),
$$

in which $r_{i}$ is the peak response of the individual impurity, and $r_{s}$ is the sum of the responses of all the peaks: not more than $0.3 \%$ of any impurity is found, and the sum of all the impurities found is not greater than $0.5 \%$.

Assay-Transfer an accurately weighed quantity of about 150 mg of Sodium Caprylate to a $125-\mathrm{mL}$ volumetric flask, dissolve in 50 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 16.62 mg of $\mathrm{C}_{8} \mathrm{H}_{15} \mathrm{O}_{2} \mathrm{Na}$.■1S (NF23)

## Briefing

Sodium Cetostearyl Sulfate, page 3177 of the First Supplement and page 1122 of $P F$ 29(4) [July-Aug. 2003]-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-17

## Add the following:

-Packaging and storage-Preserve in well-closed containers. Store at temperature $25^{\circ}$, exetrsions permitted between $15^{\circ} 30^{\circ}$. No storage requirements specified.

## Briefing

Tribasic Sodium Phosphate, NF 22 page 2932—See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-5

## Change to read:

Packaging and storage-Preserve in tight containers. Store at room temperature, and avoid excessive heat and freezing. Protect from moisture.
${ }^{\bullet}$ No storage requirements specified. ${ }^{\circ}$

## BRIEFING

Sorbitol, NF 22 page 2937 and page 3178 of the First Supple-ment-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-18

## Change to read:

Packaging and storage--Preserve in well-closed containers.
Store at roem temperature:-1S (NF22)
${ }^{\bullet}$ No storage requirements specified. ${ }^{\circ}$

## Briefing

Anhydrized Liquid Sorbitol, page 1128 of $P F$ 29(4) [JulyAug. 2003]-See briefing under Copovidone.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40873-5

## Add the following:

## ■Anhydrized Liquid Sorbitol

» Anhydrized Liquid Sorbitol is a water solution containing, on the anhydrous basis, not less than 25.0 percent of D-sorbitol $\left(\mathrm{C}_{6} \mathrm{H}_{14} \mathrm{O}_{6}\right)$ and not less than 15.0 percent of 1,4 -sorbitan $\left(\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{5}\right)$. The amounts of total sugars, other polyhydric alcohols, and any other hexitol anhydrides, if detected, are not included in the requirements or in the calculated amount under Other Impurities.

Packaging and storage-Preserve in tightenters. Preserve in well-closed containers. Pe net stere below $20^{\circ}$. No storage requirements specified.

Labeling-The labeling indicates the percentage content, on the anhydrous basis, of D-sorbitol and 1,4-sorbitan.

USP Reference standards $\langle 11\rangle$ —USP Sorbitol RS. USP 1, 4-Sorbitan RS.

## Identification-

A: Dissolve 1.4 g of Anhydrized Liquid Sorbitol in 75 mL of water. Transfer 3 mL of this solution to a $15-\mathrm{cm}$ test tube, add 3 mL of freshly prepared catechol solution (1 in
10), and mix. Add 6 mL of sulfuric acid, mix again, then gently heat the tube in a flame for about 30 seconds: a deep pink or wine-red color appears.

B: The retention times of the major peaks in the chromatogram of the Assay preparation correspond to those in the chromatogram of the Standard preparation, as obtained in the Assay.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count using the Plate Method is not more than $10^{3}$ cfu per mL . The total combined molds and yeasts count is not more than $10^{2}$ cfu per mL .
$\mathbf{p H}\langle 791\rangle$ : between 4.0 and 7.0 , in a $14 \%(\mathrm{w} / \mathrm{w})$ solution of Anhydrized Liquid Sorbitol in carbon dioxide-free water.

Water, Method $I\langle 921\rangle$ : not more than $31.5 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.20 \%$, calculated on the anhydrous basis. Determine on a $2-\mathrm{g}$ portion, accurately weighed.

Reducing sugars-To an amount of Anhydrized Liquid Sorbitol, equivalent to 3.3 g , on the anhydrous basis, add 3 mL of water, 20.0 mL of cupric citrate TS, and a few glass beads. Proceed as direeted in the test for Reduing sugans tader Mannitol, beginning with "Heat so that boiling be gins." Heat so that boiling begins after 4 minutes, and maintain boiling for 3 minutes. Cool rapidly, and add 40 mL of diluted acetic acid, 60 mL of water, and 20.0 mL of 0.05 N iodine VS. With continuous shaking, add 25 mL of a mixture of 6 mL of hydrochloric acid and 94 mL of water. When the precipitate has dissolved, titrate the excess of iodine with 0.05 N sodium thiosulfate VS using 2 mL of starch TS, added towards the end of the titration, as an indicator. Not less than 12.8 mL of 0.05 N sodium thiosulfate VS is required, corresponding to not more than $0.3 \%$ of reducing sugars, on the anhydrous basis, as glucose. The amount determined in this test is not included in the calculated amount under Other Impurities.

## Limit of nickel-

Test solution-Dissolve 20.0 g of Anhydrized Liquid Sorbitol in diluted acetic acid, and dilute with diluted acetic acid to 100.0 mL . Add 2.0 mL of a saturated solution of ammonium pyrrolidine dithiocarbamate (about 10 g of ammonium pyrrolidine dithiocarbamate per L) and 10.0 mL of methyl isobutyl ketone, and shake for 30 seconds. Protect from bright light. Allow the two layers to separate, and use the methyl isobutyl ketone layer.

Blank solution-Prepare as directed for the Test solution, except to omit the use of Anhydrized Liquid Sorbitol. Quantities should be increased five fold to ensure that a sufficient volume of Blank solution is available.

Standard solutions-Prepare as directed for the Test solution, except to prepare three solutions by adding $0.5 \mathrm{~mL}, 1.0$ mL , and 1.5 mL of nickel standard solution TS.

## Procedure-Proceed as directedin the test for Niekel an

der Mamitol. Set the instrument to zero using the Blank solution. Concomitantly determine the absorbances of the Standard solutions and the Test solution at least three times each, at the wavelength of maximum absorbance at 232.0 nm , with a suitable atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) equipped with a nickel hollow-cathode lamp and an airacetylene flame. Record the average of the steady readings for each of the Standard solutions and the Test solution. Between each measurement, aspirate the Blank solution, and ascertain that the reading returns to zero. Plot the absorbances of the Standard solutions and the Test solution versus the added quantity of nickel. Extrapolate the line joining the points on the graph until it meets the concentration axis. The distance between this point and the intersection of the axes represents the concentration of nickel in the Test solution. Not more than $1 \mu \mathrm{~g}$ per g , calculated on the anhydrous basis, is found.

## Assay-

Mobile phase-Use degassed water.
Resolution solution-Dissolve sorbitol, 1,4-sorbitan, isosorbide, and mannitol in water to obtain a solution having concentrations of about 10 mg per $\mathrm{g}, 4 \mathrm{mg}$ per $\mathrm{g}, 4 \mathrm{mg}$ per g , and 1 mg per g , respectively.

Standard preparation-Dissolve accurately weighed quantities of USP Sorbitol RS and USP 1,4-Sorbitan RS in water to obtain a solution having concentrations of about 10 mg per g and 4 mg per g , respectively.

Assay preparation-Dissolve about 0.40 g of Anhydrized Liquid Sorbitol, accurately weighed, in water, and dilute with water to about 20 g . Accurately record the final solution weight, and mix thoroughly.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a refractive index detector that is maintained at a constant temperature of about $35^{\circ}$, and a $7.8-\mathrm{mm} \times 10-\mathrm{cm}$ column that contains packing L34. The column temperature is maintained at about $50^{\circ}$, controlled within $\pm 2^{\circ}$, and the flow rate is about 0.6 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the 1,4 -sorbitan and isosorbide is not less than 2.0. Chromatograph the Standard preparation, and record the peak responses for 1,4 -sorbitan and sorbitol as directed for Procedure: the relative retention times are about 0.35 for 1,4 -sorbitan, 0.43 for isosorbide, 0.7 for mannitol, and 1.0 for sorbitol; and the relative standard deviation for replicate injections is not more than $2.0 \%$ for each analyte.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Separately cal-
culate the percentages, on the anhydrous basis, of 1,4-sorbitan and sorbitol in the portion of Anhydrized Liquid Sorbitol taken by the formula:

$$
\left[10,000\left(C_{s} / C_{U}\right)\left(r_{U} / r_{s}\right)\right] /(100-W)
$$

in which $C_{S}$ is the concentration, in mg per g , of the appropriate USP Reference Standard in the Standard preparation; $C_{U}$ is the concentration, in mg per g , of the Anhydrized $\mathrm{Li}-$ quid Sorbitol in the Assay preparation; $r_{U}$ and $r_{S}$ are the peak responses of the corresponding analyte obtained from the Assay preparation and the Standard preparation, respectively; and $W$ is the percentage obtained in the test for Water:-1S (NF23)

| BRIEFING |
| :--- |
| Noncrystallizing Sorbitol Solution, NF 22 page 2938 and page |
| 3180 of the First Supplement-See briefing under Ammonium Sul- |
| fate. |
| (EMC: C. Sheehan; PSD: C. Okeke) $\quad$ RTS-40871-21 |

## Change to read:

Packaging and storage--Preserve in well-closed containers. Đe net stere belew 20. . 1 IS (NF22)
${ }^{\bullet}$ No storage requirements specified.es


## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers. Store at room temperature, and avoid excessive heat and freez ing. Protect from moisture.
${ }^{\bullet}$ No storage requirements specified.es

## Briefing

Modified Starch, page 1132 of PF 29(4) [July-Aug. 2003]See briefing under Copovidone.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40873-2

## Add the following:

## ■Modified Starch

» Modified Starch is Starch modified by chemical means. Food Starch may be acid-modified, bleached, oxidized, esterified, or etherified, or treated enzymatically to change the functional properties (21 CFR 172.892).

## Packaging and storage-Preserve-Store-in-well-elesed <br> eontainers at temperattres ranging from $0^{\circ}$ to $55^{\circ}$. Preserve

 in well-closed containers. No storage requirements specified.
## Botanic characteristics-

Corn starch-Polygonal, rounded or spheroidal granules up to about $35 \mu \mathrm{~m}$ in diameter and usually having a circular or several-rayed central cleft.
Tapioca starch-Spherical granules with one truncated side, typically 5 to $35 \mu \mathrm{~m}$ in diameter and usually having a circular or several-rayed central cleft.
Potato starch-Irregularly shaped, ovoid, or pear-shaped granules, usually 30 to $100 \mu \mathrm{~m}$ in size but occasionally exceeding $100 \mu \mathrm{~m}$; or rounded, 10 to $35 \mu \mathrm{~m}$ in size. There are occasional compound granules having two to four components. The ovoid and pear-shaped granules have an eccentric hilum, and the rounded granules have accentric or slightly eccentric hilum. All granules show clearly visible concentric striations.

Wheat starch-Large and small granules, usually 10 to 60 $\mu \mathrm{m}$ in diameter. The central hilum and striations are visible or barely visible.

## Identification-

A: Prepare a smoeth mixture of 1 g of Modified Stareh
with 2 mL of cold water, stir into 15 mL of beiling water, beilgently for 2 minutes, and coolto room temperature: the product is translucent to clear. Prepare a $2 \%(\mathrm{w} / \mathrm{w})$ sodium hydroxide solution. Weigh 0.6 g of Modified Starch, and transfer to a $25-\mathrm{mL}$ glass vial with a plastic cap. Add 9.4 g of water, cap, and shake vigorously to evenly disperse
the starch. Add 10 g of $2 \%$ sodium hydroxide solution, cap, and shake vigorously for 1 minute to create a smooth mixture. Evaluate within 1 minute. The final solution is translucent to opaque with a fluid consistency. A yellow tint of the final solution is acceptable.

B: A water slurry of the Modified Starch is colored red dish violet orange-red to deep blue by iodine TS.

Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total aerobic microbial count does not exceed 1000 cfu per g ; the total combined molds and yeasts count does not exceed 100 cfu per $g$.
$\mathbf{p H}\langle 791\rangle$ —Weigh $20.0 \pm 0.1 \mathrm{~g}$ of Modified Starch, transfer to a suitable nonmetallic container, and add 100 mL of water to obtain a slurry. Stir using a magnetic stirrer at a moderate rate for about 5 minutes, and determine the pH to the nearest 0.1 unit: between 4.5 and 8.0. 3.0 and 9.0. Loss on drying $\langle 731\rangle$ —Dry it at $120^{\circ}$ for 4 hours. it loses not more than $14 \%$ its weight. Corn starch, Wheat starch, and Tapioca starch: not more than $15.0 \%$; Potato starch: not more than $21.0 \%$.

Residue on ignition $\langle 281\rangle$ : not more than $0.5 \%$, a test specimen of $2.0 \pm 0.1 \mathrm{~g}$ being used.

Iron $\langle 241\rangle$ : $0.002 \%$, the Test Preparation being prepared as follows. Dissolve the residue obtained in the test for Re sidue on ignition in 8 mL of hydrochloric acid with the aid of gentle heating. Dilute with water to 100 mL in a volumetric flask, and mix. Dilute 25 mL of this solution with water to $47 \pm 1 \mathrm{~mL}$.

Oxidizing substances-To 5g of Modiffed Stareh add 20 mL of a mixture of methanel and water ( $1: 1$ ), then add 4 mL of 6 N acetic acid, and stir untila hemogeneous suspension is obtained. Add 0.5 mL of a freshly prepared saturated selution of potassium iodide, mix, and allow to stand for 5 mintes: no distinct blte, brown, or purple color is obsed. Transfer 4.0 g to a glass-stoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 12.6 mL of 0.002 N sodium thiosulfate is required ( $180 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ): not more than $0.018 \%$ of oxidizing substances is found.

Limit of sulfur dioxide-Mix $20.0 \pm 0.1 \mathrm{~g}$ of Modified Starch with 200 mL of $5 \%$ alcohol until a smooth suspension is obtained, and vacuum filter through paper (Whatman No. 1 or equivalent). To 100 mL of the filtrate add 3 mL of starch TS, and titrate with 0.10 N iodine to the first perma-
nent blue color. Not more than 2.7 mL is consumed: not more than $0.008 \% 0.005 \%$ of sulfur dioxide is found.■1S (NF23)

## Briefing

Pregelatinized Starch, $N F 22$ page 2939, page 3181 of the First Supplement, and page 1600 of PF 29(5) [Sept.-Oct. 2003]-See briefing under Copovidone.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40873-8

## Change to read:

APackaging and storage-Preserve in well-closed containers. $\quad$ NF22 Store at $25^{\circ}$, excursions permitted up-to-40.

- No storage requirements specified.■1s (NF23)


## Change to read:

${ }^{\mathbf{4}}$ Identification-A water slurry of it is colored redish violet
$\boldsymbol{■}_{\text {orange }} \operatorname{red}_{\text {■2S }}{ }_{(N F 22)}$
to deep blue by iodine TS. $\mathbf{\Delta N F 2 2}$

## Change to read:

${ }^{\mathbf{4}}$ Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. $\mathbf{\Delta N F 2 2}$

- The total aerobic microbial count does not exceed 1000 cfu per g , and the total combined molds and yeasts count does not exceed 100 cfu per g. $\quad$ 2S (NF22)


## Briefing

Tapioca Starch, NF 22 page 2940, page 3181 of the First Supplement, and page 1134 of PF 29(4) [July-Aug. 2003]-See briefing under Copovidone.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40873-9

## Change to read:

Packaging and storage-Preserve in well-closed containers.
Store at $25^{\circ}$, exeursion permitted up $10-40^{\circ}$.

- No storage requirements specified.■1S (NF23)


## Briefing

Medium-Chain Triglycerides, page 3181 of the First Supple-ment-See briefing under Ammonium Sulfate.
(EMC: C. Sheehan; PSD: C. Okeke) RTS-40871-15

## Change to read:

Packaging and storage-Preserve in tight containers, protected from light. Store at temperatures not exceeding $25^{\circ}$.
${ }^{\bullet}$ No storage requirements specified.es

## GENERAL CHAPTERS

## General Tests and Assays

## General Requirements for Tests and Assays

## Briefing

$\langle 11\rangle$ Reference Standards, USP 27 page 2111, page 3099 of the First Supplement, the First Interim Revision Announcement on page 31 of PF 30(1) [Jan.-Feb. 2004], the Second Interim Revision Announcement on page 416 of PF 30(2) [Mar.-Apr. 2004], page 5180 of PF 23(6) [Nov.-Dec. 1997], page 6925 of PF 24(5) [Aug.-Sept. 1998], page 8222 of $P F$ 25(3) [May-June 1999], page 8561 of $P F 25(4)$ [July-Aug. 1999], page 8893 of $P F 25(5)$ [Sept.Oct. 1999], page 218 of $P F$ 26(1) [Jan.-Feb. 2000], page 793 of $P F$ 26(3) [May-June 2000], page 1101 of $P F$ 26(4) [July-Aug. 2000], page 1369 of $P F 26(5)$ [Sept.-Oct. 2000], page 1832 of PF 27(1) [Jan.-Feb. 2001], page 2268 of PF 27(2) [Mar.-Apr. 2001], page 3071 of $P F 27(5)$ [Sept.-Oct. 2001], page 3348 of $P F 27(6)$ [Nov.Dec. 2001], page 433 of PF 28(2) [Mar.-Apr. 2002], page 839 of PF 28(3) [May-June 2002], page 1224 of PF 28(4) [July-Aug. 2002], page 1468 of $P F 28(5)$ [Sept.-Oct. 2002], page 1913 of PF 28(6) [Nov.-Dec. 2002], page 163 of PF 29(1) [Jan.-Feb. 2003], page 483 of $P F$ 29(2) [Mar.-Apr. 2003], page 710 of $P F$ 29(3) [May-June 2003], page 1137 of $P F$ 29(4) [July-Aug. 2003], page 1601 of $P F$ 29(5) [Sept.-Oct. 2003], page 2022 of PF 29(6) [Nov.-Dec. 2003], page 211 of $P F$ 30(1) [Jan.-Feb. 2004], and page 613 of $P F 30(2)$ [Mar.-Apr. 2004].
(HDQ) RTS—33950-1; 39849-3; 39860-1; 40072-1; 40292-1; 40450-1; 40509-3; 40812-1; 40947-1; 40973-1; 41023-1; 41023-3; 41023-4

Add the following:
-USP Caprylic Acid RS.■1S (USP28)

## Add the following:

-USP Loratadine Related Compound A RS
［8－chloro－6，11－dihydro－11（4－piperidylidene）－5H－benzo［5，6］ cyclohepta［1，2－b］pyridinel（ $\mathrm{C}_{19} \mathrm{H}_{19} \mathrm{ClN}_{2}$ $\diamond$ 310．83）．■1S（USP28）

## Add the following：

－USP Loratadine Related Compound B RS
［8－chloro－6，11－dihydro－11（ N －methyl－4－piperinylidene）－5 H － benzo［5，6］cyclohepta［1，2－b］pyridine］$\left(\mathrm{C}_{20} \mathrm{H}_{21} \mathrm{ClN}_{2}\right.$ $\diamond 324.88) \cdot \mathbf{1 S}($ USP28）

## Add the following：

－USP Maltol RS．－［To come．］$]_{1 S}$（USP28）

## Add the following：

－USP Melengestrol Acetate Related Compound A RS
［16－methylene－17 $\alpha$－hydroxy－4－pregnene－3，20－dione 17－ acetate］．［To come．］IS（USP28）

## Add the following：

－USP Melengestrol Acetate Related Compound B RS
［17 $\alpha$－hydroxy－6，16－dimethyleneprogna－4－ene－3，20－dione 17－acetate］．［To come．］${ }_{\text {IS }}$（USP28）

## Add the following：

－USP Methscopolamine Bromide RS—Dry at $105^{\circ}$ for 3 hours before using．${ }^{1 S}$（USP28）

## Add the following：

－USP Mirtazapine RS－Do not dry；determine the water content titrimetrically at the time of use．Keep container tightly closed．Protect from light．${ }^{1 S}$（USP28）

## Add the following：

－USP Phenylephrine Bitartrate RS—Keep container tightly closed．Protect from light and oxygen．Store at room temperature．$\quad$ IS（USP28）

## Add the following：

－USP Stavudine RS．■1S（USP28）

## Add the following：

－USP Stavudine System Suitability Mixture RS．■1S（USP28）

## Add the following：

－USP Tolcapone RS－［To come．］$]_{1 S}$（USP28）

## Add the following：

－USP Tolcapone Related Compound A RS［4＇－methyl－
3，4－dihydrobenzophenone］$\left(\mathrm{C}_{14} \mathrm{H}_{12} \mathrm{O}_{3} \triangleleft 228.24\right)$ ．■1S（USP28）

## Add the following：

－USP Tolcapone Related Compound B RS［4＇－hydroxy－ 3－methoxy－4＇－methyl－5－nitrobenzophenone］$\left(\mathrm{C}_{15} \mathrm{H}_{13} \mathrm{NO}_{5} \diamond\right.$ 287．27）．■1S（USP28）

## Briefing

〈41〉 Weights and Balances，USP 27 page 2148．In this pro－ posed revision，based in part on correspondence received，the proof of trueness of the weighing（systematic errors）is distinguished from the proof of precision（uncertainty）．The former is an issue of the calibration of the balance，while the latter is a measure of the uncertainty of the weighing．Together，they determine the ac－ curacy of the weighing．The concept of minimum weight is also introduced．
（PA4：H．Pappa）RTS－41034－1

## Change to read：

## 〈41〉 WEIGHTS AND BALANCES

The intent of this section is to bring the requirements for weights into confermity with Ameriean Natienal Standard ANSI／ASTM E617，＂Laberatery Weights and Precision Mass－Standards．＂This standard is ineorperated by reference and should be consulted for fall deseriptions and information on the tolerances and construt－ tion of weights．${ }^{+}$

Pharmacepeial tests and assays require balanees that vary in ea pacity，sensitivity，and reproducibility．Unless otherwise－speeifled， when substances are to be＂aceurately weighed＂for Assay the weighing is to be perfermed with a weighing deviee whose mea
${ }^{4}$ Copies of ASTM Standard E617 81（Reapproved 1985）may be ebtained from the American．Society for Testing and Materiats， 1916 Pace－Street，Philadelphia，PA 19103．
surement uncertainty (random plus systematic error) does not ex eeed $0.1 \%$ of the reading. Meastrement uncertainty is satisfactory if three times the standard deviation of not less than ten replicate weighings divided by the ameunt weighed, does not exeed 0.001 . Unless otherwise speeified, for titrimetrie limits tests, the weighing shall be performed to provide the number of signifiean figures in the weight of the analyte that correspends to the number of signiff ieant figures in the concentration of the titrant.

The class designations below are in order of increasing toler ances.

Class 1.1 weights are used for calibration of low eapacity, hight sensitivity balanees. They are available in various denominations from 1 to 500 mg . The toleranee for any denemination in this class is $5 \mu \mathrm{~g}$. They are recommended for calibration of balanee using eptienlor electrieal methods for aceurately weighing quantities be 1ow 20 me.

Class 1 weights are designated as high precision-standards for ealibration. They may be used for weighing aecurately quantities below 20 mg . (For weights of 10 s or less, the requirements of class 1 are met by USP KXI class M.)

Glass 2 weights are used as working standards for calibration, built in weights for analytieal balanees, and laboratory weights for routine analytical-work. (The requirements of class 2 are met by USP XXI class S. ${ }^{2}$

Glass 3 and class 4 weights are used with moderate precision taboratory balanees. (Class 3 requirements are met by USP XXI elass S 1; class-4 requirements are met by USP XXI elass P.) ${ }^{2}$

A weight class is chosen so that the tolerance of the weights used does not exeeed $0.1 \%$ of the amount weighed. Generally, class 2 may beused for quantities greater than 20 mes, class 3 for quantities of greater than 50 mg, and class 4 for quantitie of greater than 100 m. Weights should be calibrated periodically, preferably against an absolute standard weight.

## -INTRODUCTION

Measurement processes are generally subject to a wide variety of influences. Weighing is no exception and may get distorted by many factors that introduce bias and uncertainty into the results. The distortions may be caused by properties of the weighing object, the balance, the environment, and the procedure used to weigh the object.

Influences originating from the balance, itself, are manifold. They include effects introduced by the following properties of the balance: quantized digital display, limited capability to repeat, nonlinear characteristic, sensitivity to eccentric loading, deviation of sensitivity from the correct value, and temperature dependence. Among the factors that affect the weighing object, the most prominent is buoyancy,

[^96]which is caused by the fact that weighings are usually being carried out in air instead of empty space (i.e., a vacuum). Determination of the weight of objects with large surface areas is also affected by air drafts (even in the presence of draft shields), by electrostatic charge buildup (e.g., glass, plastic, or other electrically insulating materials), and by magnetic forces (e.g., stirring magnets or magnetically permeable objects).
Ambient conditions such as air temperature, humidity, pressure, and air velocity will also have an effect on the weighing object and the balance. In addition, effects caused by vibration, inclination, or other conditions may also be present.

In the following sections the requirements for weights and balances are described.

## WEIGHTS

ASTM standard E617, "Standard Specification for Laboratory Weights and Precision Mass Standards" is incorporated by reference and is to be consulted for full descriptions and information on the tolerances and construction of weights. ${ }^{1}$

Weights are periodically calibrated against standard masses. The mass of each weight thus determined is referred to as its calibration mass value, and the difference between the nominal mass value and the calibration mass value is referred to as its calibration error.

When weights are used with beam balances to weigh materials, the weight class is chosen so that the tolerances of the weights do not exceed $0.1 \%$ of the net amount weighed. If the weights meet the tolerances of the corresponding ASTM class (currently 8 classes, numbered $0-$

[^97]7), corrections for calibration errors are not required. If, however, weights are used to calibrate beam or electronic balances, different criteria apply.

The class designations below are listed in order of increasing tolerances.

- Class 0 and Class 1 weights are designated as high-precision standards for calibration. Use of Class 0 and Class 1 weights requires careful control of relative humidity and temperature and accurate monitoring of barometric pressure, as specified by the weight manufacturer.
- Class 1 and Class 2 weights may be used as laboratory weights for routine analytical work. Weights in Class 0 through Class 3 are available in denominations from 1 mg to 50 kg , and their tolerances vary with class and nominal values.
- Class 4, Class 5, and Class 6 weights may be used with moderate-precision balances, trip balances, dial scales, and platform scales; they are available in denominations from 1 mg to 5000 kg , and their tolerances vary with nominal values.
- Class 7 weights are used in rough weighing operations.


## BALANCES

Pharmacopeial procedures require balances that vary in capacity, readability, and repeatability. When substances are to be "accurately weighed", weighings have to be performed with an expanded relative uncertainty, $U_{\text {rel }}$, equal to or smaller than $0.1 \%$, observing a coverage factor, $k$, of
three. The expanded relative uncertainty is thus given by the following expression:

$$
\begin{equation*}
U_{r e l}=k u_{r e l}=3 u_{r e l}, \tag{1}
\end{equation*}
$$

in which the relative standard uncertainty, $u_{r e l}$, is given by the formula:

$$
\begin{equation*}
u_{r e l}=u / m \tag{2}
\end{equation*}
$$

in which $u$ is the (absolute) standard uncertainty of the weighing; and $m$ is the weighed sample (or net) mass to which this uncertainty applies. From statements (1) and (2) we get the following:

$$
\begin{equation*}
U_{r e l}=k u / m \tag{3}
\end{equation*}
$$

The smallest possible amount of mass that meets the aforementioned requirement is known as the "minimum weight", which can be obtained from the following formula:

$$
\begin{equation*}
m_{\text {min }}>\left(k / U_{r e l}\right) u=(3 / 0.1 \%) u=3000 u \tag{4}
\end{equation*}
$$

For cases in which a small mass (compared to the maximum capacity of the balance) is considered, it is generally sufficient to represent the standard uncertainty, $u$, of the weighing by its repeatability, $S_{R P}$, because other contributors to uncertainty (from sources such as linearity deviation, eccentric load deviation, or sensitivity offset) are much smaller and thus may be neglected. This leads to a simple
expression for $m_{\text {min }}$, whereby the minimal sample mass depends only on one property of the weighing, namely its repeatability:

$$
\begin{equation*}
m_{m i n}>\left(k / U_{r e l}\right) S_{R P}, \tag{5}
\end{equation*}
$$

in which $S_{R P}$ represents the standard deviation of not less than 10 replicate weighings obtained from the individual net readings, $R_{i}$, as follows:

$$
\begin{equation*}
S_{R P}=\sqrt{\frac{1}{n-1} \sum_{i=1}^{n}\left(R_{i}-\bar{R}\right)^{2}} \tag{6}
\end{equation*}
$$

in which

$$
\begin{equation*}
\bar{R}=\frac{1}{n} \sum_{i=1}^{n} R_{i} \tag{7}
\end{equation*}
$$

The test weighings must be performed with a weighing setup under conditions similar to those expected for later use, including the following: configuration of the balance, type of weighing object (sample and/or container), weighing procedure, environmental conditions, and the site of use. If weights are used to simulate the sample mass, they need not be calibrated.

As the standard deviation, $S_{R P}$, is reduced to a value equal or even less than the readability, $d$, of a digital balance, then the influence of the necessary rounding between two indication steps on the weighing value becomes predominant. Similarly, the standard deviation estimated from repeated weighings is influenced by the average weighing value, and it may accidentally vanish altogether, i.e., have
a value of zero. To prevent this, a replacement value for the standard uncertainty of no less than $0.4 d$ must be observed, as shown below:

$$
\begin{equation*}
S_{R P} \geq 0.4 d \tag{8}
\end{equation*}
$$

Thus the minimal weight, $m_{\text {min }}$, is greater than $3000 S_{R P}$ or greater than 1200 d , whichever is larger.

This suitability test differs from routine calibrations of the balance. It is used to determine the suitability of a weighing device initially and at established intervals thereafter. Measurement uncertainty may be determined as part of the balance maintenance and calibration, and need not be repeated with every weighing. The frequency of testing, as well as the measurement conditions, are established by the balance user and form a part of the laboratory standard operating procedures.■1S (USP28)

## Briefing

<81 $\rangle$ Antibiotics-Microbial Assays, USP 27 page 2163. In the Turbidimetric Method section under Procedure, it is proposed to replace the name of the reagent methyl sulfoxide with its synonym "dimethyl sulfoxide". The use of "dimethyl sulfoxide" will be standardized throughout the $U S P-N F$.
(HDQ: M. Marques) RTS-41082-1

## Change to read:

## PROCEDURE

## Assay Designs

Microbial assays gain markedly in precision by the segregation of relatively large sources of potential error and bias through suitable experimental designs. In a cylinder-plate assay, the essential comparisons are restricted to relationships between zone diameter measurements within plates, exclusive of the variation between plates in their preparation and subsequent handling. To conduct a turbidimetric assay so that the differences in observed turbidity will
reflect the differences in the antibiotic concentration requires both greater uniformity in the environment created for the tubes through closer thermostatic control of the incubator and the avoidance of systematic bias by use of a random placement of replicate tubes in separate tube racks, each rack containing one complete set of treatments. The essential comparisons are then restricted to relationships between the observed turbidities within racks.

NOTE-For some purposes, the practice is to design the assay so that a set of treatments consists of not fewer than three tubes for each sample and standard concentration, and each set is placed in a single rack.

Within these restrictions, the assay design recommended is a 1level assay with a standard curve. For this assay with a standard curve, prepare solutions of 5,6 , or more test dilutions, provided they include one corresponding to the reference concentration $\left(S_{3}\right)$, of the Standard and a solution of a single median test level of the Unknown as described under Preparation of the Standard and Preparation of the Sample. Consider an assay as preliminary if its computed potency with either design is less than $80 \%$ or more than $125 \%$ of that assumed in preparing the stock solution of the Unknown. In such a case, adjust its assumed potency accordingly and repeat the assay.

Microbial determinations of potency are subject to inter-assay as well as intra-assay variables, so that two or more independent assays are required for a reliable estimate of the potency of a given assay preparation or Unknown. Starting with separately prepared stock solutions and test dilutions of both the Standard and the Unknown, repeat the assay of a given Unknown on a different day. If the estimated potency of the second assay differs significantly, as indicated by the calculated standard error, from that of the first, conduct one or more additional assays. The combined result of a series of smaller, independent assays spread over a number of days is a more reliable estimate of potency than that from a single large assay with the same total number of plates or tubes.

## Cylinder-Plate Method

To prepare assay plates using Petri dishes, place 21 mL of Medium 2 in each of the required number of plates, and allow it to harden into a smooth base layer of uniform depth, except for Amphotericin B and Nystatin, where no separate base layer is used. For Erythromycin, Gentamicin, Neomycin B, Paromomycin, and Sisomicin, use Medium 11. For Bleomycin, use 10 mL of Medium 35. For Dihydrostreptomycin use Medium 5. For Vancomycin, use 10 mL of Medium 8. For Carbenicillin, Colistimethate Sodium, Colistin, and Polymyxin B, use Medium 9. For Netilmicin, use 20 mL of Medium 11. Add 4 mL of seed layer inoculum (see Preparation of Inoculum and Table 3), prepared as directed for the given antibiotic, except for Bleomycin (use 6 mL ), for Netilmicin (use 5 mL ), and for Nystatin and Amphotericin B (use 8 mL ), tilting the plate back and forth to spread the inoculum evenly over the surface, and allow it to harden. Drop 6 assay cylinders on the inoculated surface from a height of 12 mm , using a mechanical guide or other device to insure even spacing on a radius of 2.8 cm , and cover the plates to avoid contamination. After filling the 6 cylinders on each plate with dilutions of antibiotic containing the test levels specified below, incubate the plates at $32^{\circ}$ to $35^{\circ}$, or at the temperature specified below for the individual case, for 16 to 18 hours, remove the cylinders, and measure and record the diameter of each zone of growth inhibition to the nearest 0.1 mm . Incubate the plates at $29^{\circ}$ to $31^{\circ}$ for Amphotericin B and Nystatin. Incubate
at $34^{\circ}$ to $36^{\circ}$ for Novobiocin. Incubate at $36^{\circ}$ to $37.5^{\circ}$ for Carbenicillin, Colistimethate Sodium, Colistin, Dihydrostreptomycin, Gentamicin, Neomycin, Netilmicin, Paromomycin, Polymyxin B, Sisomicin, and Vancomycin.

For the 1-level assay with a standard curve, prepare dilutions representing 5 test levels of the Standard $\left(S_{1}\right.$ to $\left.S_{5}\right)$ and a single test level of the Unknown $U_{3}$ corresponding to $S_{3}$ of the standard curve, as defined under Preparation of the Standard and Preparation of the Sample. For deriving the standard curve, fill alternate cylinders on each of 3 plates with the median test dilution $\left(S_{3}\right)$ of the Standard and each of the remaining 9 cylinders with one of the other four dilutions of the Standard. Repeat the process for the three dilutions of the Standard. For each Unknown, fill alternate cylinders on each of 3 plates with the median test dilution of the Standard $\left(S_{3}\right)$, and the remaining 9 cylinders with the corresponding test dilution $\left(U_{3}\right)$ of the Unknown.

## Turbidimetric Method

On the day of the assay, prepare the necessary doses by dilution of stock solutions of the Standard and of each Unknown as defined under Preparation of the Standard and Preparation of the Sample. Add 1.0 mL of each dose, except for Gramicidin, Thiostrepton and Tylosin (use 0.10 mL ) to each of 3 prepared test tubes, and place the 3 replicate tubes in a position, selected at random, in a test tube rack or other carrier. Include similarly in each rack 1 or 2 control tubes containing 1 mL of the test diluent (see Table 1) but no antibiotic. Upon completion of the rack of test solutions (with Candicidin, within 30 minutes of the time when water is added to the methyl-sulfoxide

- dimethyl sulfoxide $_{\mathbf{m}_{1 \mathrm{~S}} \text { (USP28) }}$
stock solution), add 9.0 mL of inoculum to each tube in the rack in turn, and place the completed rack immediately in an incubator or a water bath maintained at $36^{\circ}$ to $37.5^{\circ}$, except for Candicidin (incubate at $27^{\circ}$ to $29^{\circ}$ ). Incubate the tubes for 4 to 5 hours, except for Capreomycin, Chloramphenicol, Cycloserine, Dihydrostreptomycin, Spectinomycin, Streptomycin, and Troleandomycin (incubate these for 3 to 4 hours), Tylosin (incubate for 3 to 5 hours), and Candicidin (incubate for 16 to 18 hours). After incubation add 0.5 mL of dilute formaldehyde to each tube, except for Tylosin (heat the rack in a water bath at $80^{\circ}$ to $90^{\circ}$ for 2 to 6 minutes or in a steam bath for 5 to 10 minutes, and bring to room temperature), taking one rack at a time, and read its transmittance or absorbance in a suitable spectrophotometer fitted with a $530-\mathrm{nm}$ or $580-\mathrm{nm}$ filter (see Spectrophotometer under Apparatus).

For the 1-level assay with a standard curve, prepare dilutions representing 5 test levels of the Standard $\left(S_{1}\right.$ to $\left.S_{5}\right)$ and a single test level $\left(U_{3}\right)$ of each of up to 20 Unknowns corresponding to $S_{3}$ of the Standard. Prepare also an extra $S_{3}$ as a test of growth. Add 1 mL of each test dilution, except for Gramicidin, Thiostrepton, and Tylosin (use 0.10 mL ) to 3 tubes and 1 mL of antibiotic-free diluent to 6 tubes as controls. Distribute one complete set, including 2 tubes of controls, to a tube rack, intermingling them at random. Add 9.0 mL of inoculum, except for Thiostrepton (use 10.0 mL of inoculum), incubate, add 0.5 mL of dilute formaldehyde, and complete the assay as directed above. Determine the exact duration of incubation by observation of growth in the reference concentration (median dose) of the dilutions of the Standard $\left(S_{3}\right)$.

## Chemical Tests and Assays

## LIMIT TESTS

## Briefing

〈231〉 Heavy Metals, USP 27 page 2204 and page 614 of PF $30(2)$ [Mar.-Apr. 2004]. It is proposed to revise Method II to include a Note regarding the inability of this method to recover mercury.
(PA6: K. Zaidi) RTS-41212-1

## Change to read:

## METHOD I

pH 3.5 Acetate Buffer-Dissolve 25.0 g of ammonium acetate in 25 mL of water, and add 38.0 mL of 6 N hydrochloric acid. Adjust, if necessary, with 6 N ammonium hydroxide or 6 N hydrochloric acid to a pH of 3.5 , dilute with water to 100 mL , and mix.

Standard Preparation-Into a $50-\mathrm{mL}$ color-comparison tube pipet 2 mL of Standard Lead Solution $(20 \mu \mathrm{~g}$ of Pb$)$, and dilute with water to 25 mL . Adjust
${ }^{\Delta}$ Using a pH meter or short-range pH indicator paper as ex-
ternal indicator, adjust
with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0 , using short range pH indientor paper as external indientor,
${ }^{\Delta}$ AUSP28
dilute with water to 40 mL , and mix.
Test Preparation-Into a $50-\mathrm{mL}$ color-comparison tube place 25 mL of the solution prepared for the test as directed in the individual monograph; or, using the designated volume of acid where specified in the individual monograph, dissolve and dilute with water to 25 mL the quantity, in g , of the substance to be tested, as calculated by the formula:

$$
2.0 /(1000 L)
$$

in which $L$ is the Heavy metals limit, in percentage. Adjust
$\Delta^{\Delta}$ as a percentage. Using a pH meter or short-range pH indicator paper as external indicator, adjust $_{\mathbf{\Delta U S P 2 8}}$
with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0 , using shert range pH indienter paper as external indi--ator,
${ }^{\Delta}$ AUSP28
dilute with water to 40 mL , and mix.
Monitor Preparation-Into a third $50-\mathrm{mL}$ color-comparison tube place 25 mL of a solution prepared as directed for Test Preparation, and add 2.0 mL of Standard Lead Solution. Adjust
${ }^{\boldsymbol{4}}$ Using a pH meter or short-range pH indicator paper as external indicator, adjust $\Delta U S P 28$
with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0 , twing shom range pH indientor paper as extemal indl eator,

4 USP28
dilute with water to 40 mL , and mix.
Procedure-To each of the three tubes containing the Standard Preparation, the Test Preparation, and the Monitor Preparation, add 2 mL of pH 3.5 Acetate Buffer, then add 1.2 mL of thioaceta-mide-glycerin base TS, dilute with water to 50 mL , mix, allow to stand for 2 minutes, and view downward over a white surface *: the color of the solution from the Test Preparation is not darker than that of the solution from the Standard Preparation, and intensity of the coler of the
${ }^{\Delta}$ the color of the solution from the $\boldsymbol{A}_{\triangle U S P 28}$
Monitor Preparation is equal to or greater
${ }^{\Delta}$ darker $_{\mathbf{A S P}}{ }^{\text {U }}$
than that of the
${ }^{\Delta_{\text {solution }}}$ from the ${ }_{\mathbf{\Delta U S P 2 8}}$
Standard Preparation. [NOTE-If the color of the Monitor Preparation is lighter than that of the Standard Preparation, use Method II instead of Method I for the substance being tested.]

## Change to read:

## METHOD II

- $_{\text {NOTE——This method does not recover mercu- }}$ ry.■1S (USP28)
pH 3.5 Acetate Buffer-Prepare as directed under Method I. Standard Preparation - Prepare as directer Meth $I$.
${ }^{\Delta}$ Pipet 4 mL of the Standard Lead Solution into a suitable test tube, and add 10 mL of 6 N hydrochloric acid. $\triangle$ USP28

[^98]Test Preparation-Use a quantity, in $g$, of the substance to be tested as calculated by the formula:

$$
\begin{gathered}
z .0 /(1000 L), \\
\mathbf{4}_{4.0 /(1000 L), \mathbf{\Delta} U S P 28}
\end{gathered}
$$

in which $L$ is the Heavy metals limit, im
$\mathbf{\Delta a s ~ a}_{\mathbf{n} U S P 28}$
percentage. Transfer the weighed quantity of the substance to a suitable crucible, add sufficient sulfuric acid to wet the substance, and carefully ignite at a low temperature until thoroughly charred. (The crucible may be loosely covered with a suitable lid during the charring.) Add to the carbonized mass 2 mL of nitric acid and 5 drops of sulfuric acid, and heat cautiously until white fumes no longer are evolved. Ignite, preferably in a muffle furnace, at $500^{\circ}$ to $600^{\circ}$, until the carbon is completely burned off
(no longer than 2 hours). If carbon remains, allow the residue to cool, add a few drops of sulfuric acid, evaporate, and ignite again. $\mathbf{\Delta U S P 2 8}$
Cool, add 4 mb
${ }^{\Delta} 5 \mathrm{~mL}_{\mathbf{\Delta U S P 2 8}}$
of 6 N hydrochloric acid, cover,

- and $_{\text {AUSP28 }}$
digest on a steam bath for 15 minntes, uncover, and slowly evaperate on a steam bath to dryness. Moisten the residue with 1 drop-of hydrechloric acid, add 10 mL of hot water, and digest for 2 min utes. Add 6 N ammenimm hydroxide drepwise, until the solution is just alkaline to litmus paper, dilute with water to 25 mL , and adjust with 1 Nacetic acid to apH between 3.0 and 4.0 , using shert range pH indicator paper as external indieator. Filter if neeessayy, rimse the crucible and the filter with 10 mL of water, combine the filtrate and rinsing in a 50 mL color comparison tube, dilute with water to 40 mL , and mix.
${ }^{\mathbf{4}} 10$ minutes. Cool, and quantitatively transfer the solution to a test tube. Rinse the crucible with a second $5-\mathrm{mL}$ portion of 6 N hydrochloric acid, and transfer the rinsing to the test tube.

Monitor Preparation—Pipet 4 mL of the Standard Lead
Solution into a crucible identical to that used for the Test Preparation and containing a quantity of the substance under test that is equal to $10 \%$ of the amount required for the Test Preparation. Evaporate on a steam bath to dryness. Ignite at the same time, in the same muffle furnace, and under the same conditions used for the Test Preparation. Cool, add 5 mL of 6 N hydrochloric acid, cover, and digest on a steam bath for 10 minutes. Cool, and quantitatively transfer
to a test tube. Rinse the crucible with a second $5-\mathrm{mL}$ portion of 6 N hydrochloric acid, and transfer the rinsing to the test tube. $\mathbf{\Delta U S P 2 8}$
Procedure- To
${ }^{\Delta}$ Adjust the solution in in $_{\triangle U P 28}$ each of the tubes containing the Standard Preparation,
$\Delta \Delta U S P 28$
the Test Preparation,
© and the Monitor Preparation with ammonium hydroxide, added cautiously and dropwise, to a pH of 9 . Cool, and adjust with glacial acetic acid, added dropwise, to a pH of 8 , and then add 0.5 mL in excess. Using a pH meter or shortrange pH indicator paper as external indicator, check the pH , and adjust, if necessary, with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0. Filter, if necessary, washing the filter with a few mL of water, into a 50 mL color-comparison tube, and then dilute with water to 40
mL. $\mathbf{A U S P 2 8}$

Add 2 mL of pH 3.5 Acetate Buffer, then add 1.2 mL of thioacet-amide-glycerin base TS, dilute with water to 50 mL , mix, allow to stand for 2 minutes, and view downward over a white surface : the color of the solution from the Test Preparation is not darker than that of the solution from the Standard Preparation,
$\Delta$ and the color of the solution from the Monitor Preparation is equal to or darker than that of the solution from the Standard Preparation. [NOTE-If the color of the solution from the Monitor Preparation is lighter than that of the solution from the Standard Preparation, proceed as directed for Method III for the substance being tested.] $]_{\text {USP28 }}$

## Change to read:

## METHOD III

pH 3.5 Acetate Buffer-Prepare as directed under Method $I$.
Standard Preparation-Transfer a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid to a clean, dry, $100-\mathrm{mL}$ Kjeldahl flask, and add a further volume of nitric acid equal to the incremental volume of nitric acid added to the Test Preparation. Heat the solution to the production of dense, white fumes, cool, cautiously add 10 mL of water and, if hydrogen peroxide was used in treating the Test Preparation, add a volume of 30 percent hydrogen peroxide equal to that used for the substance being tested, and boil gently to the production of dense, white fumes. Again cool, cautiously add 5 mL of water, mix, and boil gently to the production of dense, white fumes and to a volume of 2 to 3 mL . Cool, dilute cautiously
with a few mL of water, add 2.0 mL of Standard Lead Solution (20 $\mu \mathrm{g}$ of Pb ), and mix. Transfer to a $50-\mathrm{mL}$ color-comparison tube, rinse the flask with water, adding the rinsing to the tube until the volume is 25 mL , and mix.

## Test Preparation-

${ }^{\Delta}$ Unless otherwise indicated in the individual monograph, use a quantity, in $g$, of the substance to be tested as calculated by the formula:

$$
2.0 /(1000 L)
$$

in which $L$ is the Heavy metals limit, as a percentage. $\Delta$ USP28 If the substance is a solid-Transfer the
$\Delta_{\text {weighed }}^{\Delta U S P 28}$
quantity of the test substance specified in the individut menegraph

4 4 USP28
to a clean, dry, $100-\mathrm{mL}$ Kjeldahl flask. [NOTE-A $300-\mathrm{mL}$ flask may be used if the reaction foams excessively.] Clamp the flask at an angle of $45^{\circ}$, and add a sufficient quantity of a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid to moisten the substance thoroughly. Warm gently until the reaction commences, allow the reaction to subside, and add additional portions of the same acid mixture, heating after each addition, until a total of 18 mL of the acid mixture has been added. Increase the amount of heat, and boil gently until the solution darkens. Cool, add 2 mL of nitric acid, and heat again until the solution darkens. Continue the heating, followed by addition of nitric acid until no further darkening occurs, then heat strongly to the production of dense, white fumes. Cool, cautiously add 5 mL of water, boil gently to the production of dense, white fumes, and continue heating until the volume is reduced to a few mL . Cool, cautiously add 5 mL of water, and examine the color of the solution. If the color is yellow, cautiously add 1 mL of 30 percent hydrogen peroxide, and again evaporate to the production of dense, white fumes and a volume of 2 to 3 mL . If the solution is still yellow in color, repeat the addition of 5 mL of water and the peroxide treatment. Cool, dilute cautiously with a few mL of water, and rinse into a $50-\mathrm{mL}$ color-comparison tube, taking care that the combined volume does not exceed 25 mL .

If the substance is a liquid-Transfer the
$\Delta_{\text {weighed }}^{\Delta U S P 28}$
quantity of the test substance specified in the individut menegraph
$\Delta \Delta U S P 28$
to a clean, dry, $100-\mathrm{mL}$ Kjeldahl flask. [NOTE-A $300-\mathrm{mL}$ flask may be used if the reaction foams excessively.] Clamp the flask at an angle of $45^{\circ}$, and cautiously add a few mL of a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid. Warm gently until the reaction commences, allow the reaction to subside, and proceed as directed for If the substance is a solid, beginning with "add additional portions of the same acid mixture.'
${ }^{\Delta}$ Monitor Preparation-Proceed with the digestion using the same amount of sample and the same procedure as directed in the Test Preparation until the step "Cool, dilute cautiously with a few mL of water." Add 2.0 mL of

Lead Standard Solution (20 $\mu \mathrm{g}$ of lead), and mix. Transfer to a $50-\mathrm{mL}$ color comparison tube, rinse the flask with water, adding the rinsing to the tube until the volume is 25 mL , and mix. $\triangle$ USP28

Procedure-Treat the Test Preparation, the Standard Preparation
${ }^{\boldsymbol{4}}$ and the Monitor Preparation $\boldsymbol{\Delta U S P 2 8}$ as follows: Adjust
${ }^{\Delta}$ Using a pH meter or short-range pH indicator paper as external indicator, adjust $_{\mathbf{\Delta U S P 2 8}}$
the solution to a pH between 3.0 and 4.0 , using shert range pH in dienter paper as extemal indieator,
© $\mathbf{A U S P 2 8}$
with ammonium hydroxide (a dilute ammonia solution may be used, if desired, as the specified range is approached), dilute with water to 40 mL , and mix.

To each tube add 2 mL of pH 3.5 Acetate Buffer, then add 1.2 mL of thioacetamide-glycerin base TS, dilute with water to 50 mL , mix, allow to stand for 2 minutes, and view downward over a white surface ${ }^{*}$ : the color of the Test Preparation is not darker than that of the Standard Preparation,
$\Delta_{\text {and }}$ the color of the Monitor Preparation is equal to or darker than that of the Standard Preparation. $\mathbf{\Delta U S P 2 8}$

## OTHER TESTS AND ASSAYS

## Briefing

$\langle\mathbf{3 0 1}\rangle$ Acid-Neutralizing Capacity, USP 27 page 2209. On the basis of comments received, revisions are proposed to clarify the description of the magnetic stirring bar and the calculations presented under each procedure.
(PA4: E. Gonikberg) RTS-40959-1

## Change to read:

Magnetic Stirrer-Transfer 100 mL of water to a $250-\mathrm{mL}$ beaker containing a $40-\times 10-\mathrm{mm}$
$\boldsymbol{\bullet}^{(\text {or other suitable size })^{\square 1 S}}{ }_{\text {(USP28) }}$
magnetic stirring bar that is coated with solid perfluorocarbon and has a spin ring at its center. Adjust the power setting of the magnetic stirrer to produce a stirring rate of $300 \pm 30 \mathrm{rpm}$ when the stirring bar is centered in the beaker, as determined by a suitable optical tachometer.

## Change to read:

Procedure for Powders, Effervescent Solids, Suspensions and Other Liquids, Lozenges, Nonchewable Tablets, Chewable Tablets, and Capsules-Pipet 30.0 mL of 1.0 N hydrochloric acid VS into the Test Preparation while continuing to stir with the Magnetic Stirrer. [NOTE-Where the acid-neutralizing capacity of the specimen under test is greater than 25 mEq , use 60.0 mL of 1.0 N hydrochloric acid VS,

■and make the appropriate modifications in the calculation.] $\boldsymbol{m}_{1 S}$ (USP28)
Stir for 15 minutes, accurately timed, after the addition of the acid, begin to titrate immediately, and in a period not to exceed an additional 5 minutes, titrate the excess hydrochloric acid with 0.5 N sodium hydroxide VS to attain a stable (for 10 to 15 seconds) pH of 3.5. Calculate the number of mEq of acid consumed, and express the result in terms of mEq of acideensumed per of of the substance tested. Each mL of 1.0 N hydrochloric acid is equal to 1 mEq of acid concumed
-by the formula:

$$
\text { Total } \mathrm{mEq}=\left(30 \times N_{H C l}\right)-\left(V_{\mathrm{NaOH}} \times N_{\mathrm{NaOH}}\right)
$$

in which $N_{H C I}$ and $N_{N a O H}$ are the normalities of the hydrochloric acid VS and the sodium hydroxide VS, respectively; and $V_{\text {Nаон }}$ is the volume of sodium hydroxide VS used for titration. Express the result in terms of mEq of acid consumed per $g$ of the substance tested. $\quad$ IS (USP28)

## Change to read:

Procedure for Tablets That Are Required To Be ChewedPipet 30.0 mL of 1.0 N hydrochloric acid VS into the Test Preparation while continuing to stir with the Magnetic Stirrer for $10 \mathrm{~min}-$ utes, accurately timed, after the addition of the acid. Discontinue stirring briefly, and without delay remove any gum base from the beaker using a long needle. Promptly rinse the needle with 20 mL of water, collecting the washing in the beaker, and resume stirring for 5 minutes, accurately timed, then begin to titrate immediately, and in a period not to exceed an additional 5 minutes, titrate the excess hydrochloric acid with 0.5 N sodium hydroxide VS to attain a stable (for 10 to 15 seconds) pH of 3.5 . Calculate the number of
mEq of acid consumed by the Tablet tested Each mL of 1.0 N hy
drechloric acid is equal to 1 mEq of acid consumed.
-by the formula:

Total mEq $=\left(30 \times N_{\text {HCI }}\right)-\left(V_{\text {NaOH }} \times N_{\text {NaOH }}\right)$,
in which the terms are as defined above. $\quad$ 1S (USP28)

## Physical Tests and Determination

## Briefing

〈621〉Chromatography, USP 27 page 2272, page 3108 of the First Supplement, and page 618 of PF 30(2) [Mar.-Apr. 2004]. On the basis of comments received, it is proposed to revise the sections Interpretation of Chromatograms and Glossary of Symbols. The proposed changes are intended to update $U S P$ terminology to be consistent with that currently used in chromatography. It is proposed to expand the particle size range for L8 and L14 columns to accomodate columns used in new monographs proposed for inclusion in $U S P-N F$. It is also proposed to (1) delete the new entries for columns used in the monograph for Enoxaparin Sodium because Dowex IX8 and Dowex 50WX2 are now included under Reagent Specifications and (2) delete the columns used in the Enoxaparin Sodium Injection monograph because those columns are already classified as L46 columns. In addition, other editorial changes have been made.
(HDQ: M. Marques; PA2: H. Pappa) RTS-40760-1; 41080-1

## Change to read:

## INTRODUCTION

This chapter defines the terms and procedures used in chromatography and provides general information. Specific requirements for chromatographic ests and

## ${ }^{\text {a }}$ procedures for ${ }_{\Delta U S P 28}$

drug substances and dosage forms, including adsorbent and developing solvents, are given in the individual monographs.

Chromatography is defined as a procedure by which solutes are separated by a dynamic differential migration process in a system consisting of two or more phases, one of which moves continuously in a given direction and in which the individual substances
exhibit different mobilities by reason of differences in adsorption, partition, solubility, vapor pressure, molecular size, or ionic charge density. The individual substances thus ebtined
$\Delta_{\text {separated }}{ }_{\triangle U S P 28}$
can be identified or determined by analytical
© procedures. $\Delta$ USP28
The general chromatographic technique requires that a solute undergo distribution between two phases, one of them fixed (stationary phase), the other moving (mobile phase). It is the mobile phase that transfers the solute through the medium until it eventually emerges separated from other solutes that are eluted earlier or later. Generally, the solute is transported through the separation medium by means of a flowing stream of a liquid or a gaseous solvent known as the "eluant." The stationary phase may act through adsorption, as in the case of adsorbents such as activated alumina ; silice gel, and ion exehange resins,
$\Delta_{\text {and silica }}$ gel, $\mathbf{\Delta U S P 2 8}$
or it may act by dissolving the solute, thus partitioning the latter between the stationary and mobile phases. th the latter proeess, a tiquid coating held on an inert support serves as the stationary phase.
${ }^{\mathbf{\Delta}}$ In the latter process, a liquid coated onto an inert support, or chemically bonded onto silica gel, or directly onto the wall of a fused silica capillary, serves as the stationary phase. $\quad$ USP28
Partitioning is the predominant mechanism of separation in gas-liquid chromatography, paper chromatography, and forms of column chromatography
$\Delta_{\text {and thin-layer chromatography }}^{\mathbf{\Delta U S P 2 8}}$
designated as liquid-liquid ehrematography.
${ }^{\Delta}$ separation. $\Delta$ USP28
In practice, separations frequently result from a combination of adsorption and partitioning effects.
${ }^{\Delta}$ Other separation principles include ion exchange, ion pair formation, size exclusion, hydrophobic interaction, and
chiral recognition. $\Delta U S P 28$
The types of chromatography useful in qualitative and quantitative analysis that are employed in the $U S P$ tests and assays

are column, gas, paper, thin-layer,
© (including high-performance thin-layer chromatogra-
phy), $\Delta U S P 28$
and pressurized liquid chromatography (commonly called highpressure or high-performance liquid chromatography). Paper and thin-layer chromatography are ordinarily more useful for purposes of identification, because of their convenience and simplicity. Column chromatography offers a wider choice of stationary phases and is useful for the separation of individual compounds, in quantity, from mixtures. Both ehrematography and pressurized liquid chrematography require mere elaborate apparatus and usually provide high resolution methods that will identify and quantitate very small ameunts of material.
${ }^{\mathbf{4}}$ Modern high-performance thin-layer chromatography, gas chromatography, and pressurized liquid chromatography require more elaborate apparatus but usually provide high resolution and identify and quantitate very small amounts of material. $\triangle$ USP28

## Change to read:

Use of Reference Substances in Identity Tests-In paper and thin-layer chromatography, the ratio of the distance (this distance being measured to the point of maximum intensity of the spot
$\left.\Delta^{\text {or zone }}\right)_{\mathbf{\Delta S P 2 8}}$
traveled on the medium by a given compound to the distance traveled by the front of the mobile phase, from the point of application of the test substance, is designated as the $R_{F}$ value of the compound. The ratio between the distances traveled by a given compound and a reference substance is the $R_{R}$ value. $R_{F}$ values vary with the experimental conditions, and thus identification is best accomplished where an authentic specimen of the compound in question is used as a reference substance on the same chromatogram.

For this purpose, chromatograms are prepared by applying on the thin-layer adsorbent or on the paper in a straight line, parallel to the edge of the chromatographic plate or paper, solutions of the substance to be identified, the authentic specimen, and a mixture of nearly equal amounts of the substance to be identified and the authentic specimen. Each sample application contains approximately the same quantity by weight of material to be chromatographed. If the substance to be identified and the authentic specimen are identical, all chromatograms agree in color and $R_{F}$ value and the mixed chromatogram yields a single spot; i.e., $R_{R}$ is 1.0 .

## Change to read:

Location of Components-The spots
$\Delta^{\text {or }}$ zones $_{\Delta U S P 28}$
produced by paper or thin-layer chromatography may be located by the following: ( 1 ) direct inspection if the compounds are visible tader white or either shert wavelength $(254 \mathrm{~nm})$ or long wavelength ( 360 nm ) UV light, (2) inspection in white or UV light after treatment with reagents that will make the spets visible (reagents are most eonveniently applied with an atomizer), (3) use of a Gei ger Müller counter or attoradiographic teehniques in the case of the presence of radionctive substanees, of (4) evidence resulting from stimulation or inhibition of bacterial growth by the placing of removed portions of the adsorbent and substance on inoculated media.
© (1) direct inspection if the compounds are visible under white or either short-wavelength ( 254 nm , quenching of fluorescence of indicator) or long-wavelength ( 365 nm , self-fluorescence) UV light, (2) inspection in white or UV light after treatment (derivatization) with reagents that will make the substance visible (reagents are most conveniently applied by dipping the plate into the reagent solution or spraying such solution onto the plate with an atomizer),
(3) scanning the plate prior to or after derivatization at any desired wavelength (in absorption or fluorescence mode) using a scanning densitometer, (4) use of a Geiger-Müller counter or autoradiographic techniques in the case of the presence of radioactive substances, or (5) evidence resulting from biological activity (such as stimulation or inhibition of growth of microorganisms, bioluminescence, or biochemical reactions) by the placing of removed portions of the adsorbent and substance on inoculated media, or performing biochemical tests directly on the plate by covering the plate with, or dipping it into, a suspension of the biological test

## system. $\Delta$ USP28

In open-column chromatography, in pressurized liquid chromatography performed under conditions of constant flow rate, and in gas chromatography, the retention time, $t$, defined as the time elapsed between sample injection and appearance of the peak concentration of the eluted sample zone, may be used as a parameter of identification. Solutions of the substance to be identified or derivatives thereof, of the reference compound, and of a mixture of equal amounts of these two are chromatographed successively on the same column under the same chromatographic conditions. Only one peak should be observed for the mixture. The ratio of the retention times of the test substance, the reference compound, and a mixture of these, to the retention time of an internal standard is called the relative retention time $R_{R}$ and is also used frequently as a parameter of identification.
The deviations of $R_{R}, R_{F}$, or $t$ values measured for the test substance from the values obtained for the reference compound and mixture should not exceed the reliability estimates determined statistically from replicate assays of the reference compound.

Chromatographic identification by these methods under given conditions strongly indicates identity but does not constitute definitive identification. Coincidence of identity parameters under 3 to 6 different sets of chromatographic conditions (temperatures, column packings, adsorbents, eluants, developing solvents, various chemical derivatives, etc.) increases the probability that the test and reference substances are identical. However, many isomeric compounds cannot be separated. Specific and pertinent chemical, spectroscopic, or physicochemical identification of the eluted component combined with chromatographic identity is the most valid criterion of identification. For this purpose, the individual components separated by chromatography may be collected for further identification
$\Delta_{\text {or chato }}$ chromatographic separation may be combined with other analytical techniques. Some of those investigations (such as UV, IR, RAMAN, and MS) can also be made directly on the thin-layer chromatography plate. $\triangle$ USP28

## Change to read:

## THIN-LAYER CHROMATOGRAPHY

In thin-layer chromatography, the adsorbent is a relatively thin, uniform layer of dry, finely powdered material applied to a glass, plastic, or metal sheet or plate, glass plates being most commonly employed. The coated plate can be considered an "open chromatographic column" and the separations achieved may be based upon adsorption, partition, or a combination of both effects, depending on the particular type of stppert,
$\boldsymbol{\Delta}_{\text {stationary phase, }, \text { USP28 }}$
its preparation, and its use with different solvents. Thin-layer chromatography on ion-exchange films
$\Delta_{\text {layers }_{\triangle U S P 28}}$
can be used for the fractionation of polar compounds. Presumptive identification can be effected by observation of spots
$\Delta_{\text {or zones }}^{\triangle U S P 28}$
of identical $R_{F}$ value and about equal magnitude obtained, respectively, with an unknown and a reference sample chromatographed on the same plate. A visual comparison of the size of the
$\Delta^{\text {or intensity }}$ of the spots or zones $\mathbf{Z U S P 2 8}$
may serve for semiquantitative estimation. Quantitative measurements are possible by means of densitometry, fltwreseenee, and fluresene quenching;
© (absorbance or fluorescence measurements), $\mathbf{\Delta U S P 2 8}$ or the spots may be carefully removed from the plate, followed by elution with a suitable solvent and spectrophotometric measurement. For two-dimensional thin-layer chromatography, the chromatographed plate is turned at a right angle and again chromatographed, usually in another chamber equilibrated with a different solvent system.
Apparatus-Acceptable apparatus and materials for thin-layer chromatography consist of the following.

Flat glass plates of convenient size, ypieally $20 \mathrm{em} \times 20 \mathrm{~cm}^{+}$
An aligning trayor a flat surface upen whieh to align andrest the plates during the applieation of the adsorbent.

A storage rack to hold the prepared plates during drying and transpertation. The rack holding the plates sheuld be kept in a desiecator or be eapable of being sealed in order to proteet the plates from the envirenment after remeval frem the drying oven.

The adsorbent consists of fanely divided adsorbent materiats, formally $5 \mathrm{t}-40 \mathrm{~mm}$ in diameter, stitable for ehromatography. It ean be applied directly to the glass plate or can be bended to the plate by means of plaster of paris (hy drated caleium sulfate) [at a ratio of $5 \%$ to $15 \%$ or with stareh paste-or other binders. The for mer will net yield as hard a-surface as will the stareh, but it is net affected by strengly oxidizing spray reagents. The adsorbent may eentain fluereseing material to aid in the visualization of spets that abserb-ultravielet light.

A spreader, which, when moved over the glass plate, will apply a uniform layer of adsorbent of desired thickness over the entire surface of the plate.

Adeveloping ehamber that can aceommodateoneor more plates and can be properly clesed and sealed as described under Ascent ing Chramatography. The chamber is fitted with a plate suppert fack that supperts the plates, back to back, with the lid of the cham ber in place.

[^99]A template (generally made of plastic) to aid in placing the test spots at definite intervals, to mark distances as needed, and to aid in tabeling the plates.

A graduated mieropipe capable of delivering $10-\mu \mathrm{L}$ veltmes. Fotal volumes of test and standard solutions are specified in the individual menograph.

A reagent sprayer that willemit a fine spray and will net itself be attacked by the reagent.

An ultraviolet light source suitable for observations with short $(254 \mathrm{~nm})$ and long ( 360 nm ) UV wavelengths.
${ }^{\Delta} \mathrm{A}$ TLC or HPTLC plate. The chromatography is generally carried out using precoated plates or sheets (on glass, aluminum, or polyester support) of suitable size. It may be necessary to clean the plates prior to separation. This can be done by migration of, or immersion in, an appropriate solvent. The plates may also be impregnated by procedures such as development, immersion, or spraying. At the time of use, the plates may be activated, if necessary, by heating in an oven at $120^{\circ}$ for 20 minutes. The stationary phase of TLC plates has an average particle size of $10-15 \mu \mathrm{~m}$, and that of HPTLC plates an average particle size of $5 \mu \mathrm{~m}$. Alternatively flat glass plates of convenient size, typically 20 $\mathrm{cm} \times 20 \mathrm{~cm}$ can be coated as described under Preparation of Chromatographic Plates.

A suitable manual, semiautomatic, or automatic application device can be used to ensure proper positioning of the plate and proper transfer of the sample, with respect to volume and position, onto the plate. Alternatively, a template can be used to guide in manually placing the test spots at definite intervals, to mark distances as needed, and to aid in labeling the plates. For the proper application of the solutions, micropipets, microsyringes, or calibrated disposable capillaries are recommended.

For ascending development, a chromatographic chamber made of inert, transparent material and having the following specifications is used: a flat bottom or twin trough, a tightly fitted lid, and a size suitable for the plates. For horizontal development, the chamber is provided with a reservoir for the mobile phase, and it also contains a device for directing the mobile phase to the stationary phase.

Devices for transfer of reagents onto the plate by spraying, immersion, or exposure to vapor and devices to facilitate any necessary heating for visualization of the separated spots or zones.

A UV light source suitable for observations under short ( 254 nm ) and long ( 365 nm ) wavelength UV light.

A suitable device for documentation of the visualized chromatographic result.

Procedure-Apply the prescribed volume of the test solution and the standard solution in sufficiently small portions to obtain circular spots of 2 to 5 mm in diameter ( 1 to 2 mm on HPTLC plates) or bands of 10 to 20 mm by 1 to 2 mm ( 5 to 10 mm by 0.5 to 1 mm on HPTLC plates) at an appropriate distance from the lower edge-during chromatography the application position must be 3 mm (HPTLC) to 5 mm (TLC) above the level of the developing solvent-and from the sides of the plate. Apply the solutions on a line parallel to the lower edge of the plate with an interval of at least 10 mm ( 5 mm on HPTLC plates) between the centers of spots or 4 mm ( 2 mm on HPTLC plates) between the edges of bands, and allow to dry.

Ascending Development-Line at least one wall of the chromatographic chamber with filter paper. Pour into the chromatographic chamber a quantity of the mobile phase sufficient for the size of the chamber to give, after impregnation of the filter paper, a level of depth appropriate to the dimension of the plate used. For saturation of the chromatographic chamber, close the lid, and allow the system to equilibrate. Unless otherwise indicated, the chromatographic separation is performed in a saturated chamber.
Place the plate in the chamber, ensuring that the plate is as vertical as possible and that the spots or bands are above the surface of the mobile phase, and close the chamber. The stationary phase faces the inside of the chamber. Remove the plate when the mobile phase has moved over the prescribed
distance. Dry the plate, and visualize the chromatograms as prescribed. For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

Horizontal Development-Introduce a sufficient quantity of the developing solvent into the reservoir of the chamber using a syringe or pipet. Place the plate horizontally in the chamber, connect the mobile phase direction device according to the manufacturer's instructions, and close the chamber. If prescribed, develop the plate starting simultaneously at both ends. Remove the plate when the mobile phase has moved over the distance prescribed in the monograph. Dry the plate, and visualize the chromatograms as prescribed.

For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

Detection-Observe the dry plate first under short-wavelength UV light ( 254 nm ) and then under long-wavelength UV light ( 365 nm ) or as stated in the monograph. If further directed, spray, immerse, or expose the plate to vapors of the specified reagent, heat the plate when required, observe, and compare the test chromatogram with the standard chromatogram. Document the plate after each observation. Measure and record the distance of each spot or zone from the point of origin, and indicate for each spot or zone the wavelength under which it was observed. Determine the $R_{F}$ values for the principal spots or zones (see Glossary of Symbols).

Quantitative Measurement-Using appropriate instrumentation, substances separated by TLC and responding to ultraviolet-visible (UV-Vis) irradiation prior to or after derivatization can be determined directly on the plate. While moving the plate or the measuring device, the plate is examined by measuring the reflectance of the incident light. Similarly, fluorescence may be measured using an appropriate
optical system. Substances containing radionuclides can be quantified in three ways: (1) directly by moving the plate alongside a suitable counter or vice versa; (2) by cutting the plates into strips and measuring the radioactivity on each individual strip using a suitable counter; or (3) by scraping off the stationary phase, dissolving it in a suitable scintillation cocktail, and measuring the radioactivity using a liquid scintillation counter (see Radioactivity $\langle 821\rangle$ ).

The apparatus for direct quantitative measurement on the plate is a densitometer that is composed of a mechanical device to move the plate or the measuring device along the x axis and the $y$-axis, a recorder, a suitable integrator or a computer, and, for substances responding to UV-Vis irradiation, a photometer with a source of light, an optical device capable of generating monochromatic light, and a photo cell of adequate sensitivity, all of which are used for the measurement of reflectance. In the case where fluorescence is measured, a suitable filter is also required to prevent the light used for excitation from reaching the photo cell while permitting the emitted light or specific portions thereof to pass. The linearity range of the counting device must be verified.

For quantitative tests, it is necessary to apply to the plate not fewer than three standard solutions of the substance to be examined, the concentrations of which span the expected value in the test solution (e.g., $80 \%, 100 \%$, and $120 \%$ ). Derivatize with the prescribed reagent, if necessary, and record the reflectance or fluorescence in the chromatograms obtained. Use the measured results for the calculation of the amount of substance in the test solution.

Preparation of Chromatographic Plates-
Apparatus-
Flat glass plates of convenient size, typically $20 \mathrm{~cm} \times 20$ cm .

An aligning tray or a flat surface upon which to align and rest the plates during the application of the adsorbent.

A storage rack to hold the prepared plates during drying and transportation. The rack holding the plates should be kept in a desiccator or be capable of being sealed in order to protect the plates from the environment after removal from the drying oven.

The adsorbent consists of finely divided adsorbent materials, normally 5 to $40 \mu \mathrm{~m}$ in diameter, suitable for chromatography. It can be applied directly to the glass plate or can be bonded to the plate by means of plaster of Paris (calcium sulfate hemihydrate [at a ratio of $5 \%$ to $15 \%$ ]) or with starch paste or other binders. The plaster of Paris will not yield as hard a surface as will the starch, but it is not affected by strongly oxidizing spray reagents. The adsorbent may contain fluorescing material to aid in the visualization of spots that absorb UV light.

A spreader, which, when moved over the glass plate, will apply a uniform layer of adsorbent of desired thickness over the entire surface of the plate. $\triangle U S P 28$

Procedure-[NOTE-In this procedure, use purified water that is obtained by distillation.] Clean the
$\Delta_{\text {glass }}^{\triangle U S P 28}$
plates scrupulously, as by immersion in chremic acid cleansing mixtare,
«using an appropriate cleaning solution (see Cleaning Glass
Apparatus $\langle 1051\rangle$ ), $\mathbf{\Delta U S P 2 8}$
rinsing them with copious quantities of water until the water runs off the plates without leaving any visible water or oily spots, then dry. It is important that the plates be completely free from lint and dust when the adsorbent is applied.

Arrange the plate or plates on the aligning tray, place a $5-\times 20$ cm plate adjacent to the front edge of the first square plate and another $5-\times 20-\mathrm{cm}$ plate adjacent to the rear edge of the last square, and secure all of the plates so that they will not slip during the application of the adsorbent. Position the spreader on the end plate opposite the raised end of the aligning tray. Mix 1 part of adsorbent with 2 parts of water (or in the ratio suggested by the supplier) by shaking vigorously for 30 seconds in a glass-stoppered conical flask, and transfer the slurry to the spreader. Usually 30 g of adsorbent and 60 mL of water are sufficient for five $20-\times 20-\mathrm{cm}$ plates. Complete the application of adsorbents using plaster of Paris binder within 2 minutes of the addition of the water, because thereafter the mixture begins to harden. Draw the spreader smoothly over the plates toward the raised end of the aligning tray, and remove the spreader when it is on the end plate next to the raised end of the aligning tray. (Wash away all traces of adsorbent from the spreader
immediately after use.) Allow the plates to remain undisturbed for 5 minutes, then transfer the square plates, layer side up, to the storage rack, and dry at $105^{\circ}$ for 30 minutes. Preferably place the rack at an angle in the drying oven to prevent the condensation of moisture on the back sides of plates in the rack. When the plates are dry, allow them to cool to room temperature, and inspect the uniformity of the distribution and the texture of the adsorbent layer; transmitted light will show uniformity of distribution, and reflected light will show uniformity of texture. Store the satisfactory plates over silica gel in a suitable chamber.

Place fwo flter paper wieks, 18 cm in height and as wide as the length of the developing chamber, into the chamber, add about 100 mL of the solvent (sufficient to have depth of 5 to 10 mm at the bettom of the chamber), seal the cover to the top of the chamber, and allow the system to equilibrate; it is essential that the wieks become completely wet. Altematively, the chamber may be com pletely lined with filter paper. In either case, ascure that the filter paper dips int the solvent at the bettom of the chamber. Where rapor saturation of the chamber by these methods is undesirable, it is so indieated in the individual menegraph.

Apply the test selution and the standard solution, as direeted in the individual menograph, at peints about 1.5 cm apart and about 2 em from the lower edge of the plate (the lower edge is the first part over which the spreader moved in the upplication of the adsorbent layer), and allow to dry. Avoid physieal distubanee of the adsor bent during the spetting procedure (by the pipet or other applieator) er when handling the plates. The template will aid in determining the spot points and the $10-15 \mathrm{~cm}$ distanee through which the solvent fromt sheuld pass.

Place a mark 10 to 15 em abeve the spet peint. Arrange the plate en the supperting rack (test spets toward the bottom), and introduce the rack inte the developing chamber. Allow the solvent in the chamber to reach the lower edge of the adsorbent, but do not allow the spot peints to be immersed. Put the cover in place, and maintain the system until the solvent aseends to a peint 10 to 15 cm above the initial spots, this ustally requires about 15 minutes to 1 heur. Remeve the plate frem the develeping chamber, mark the solvent front, air dry the plates, and observe first under short wavelength UV light ( 254 nm ) and then under long wavelength UV light $(360 \mathrm{~nm})$. Measure and record the distance of each spot from the peint of origin, and indicate for each spet the wavelength under which it was observed. Determine the $R_{t}$ values for the principat spets (see Glessetfy of Sybels). If futher direeted, spray the spets with the reagent speeified, observe, and compare the test chromatogram with the standard chromatogram.

## Contintous Development Thin-Layer Chromatography

In contrast to conventional thin layer chrematography, whieh is earried out in a closed tank, the continuous development or contintous flow technique allows the upper end of the plate to project through a slot in the cover of the developing chamber. When the developing solvent reaches the slot, continteus evaporation oceurs, producing a steady flow of solvent over the plate. In conventional thin layer chromatography, spot migration cease when the solvent reaches the top of the plate, after which the spots simply enlarge by diffusion. In the continuous flow process, spot migration continues as long as the plate remains in the tank and the developing solvent is not exhatusted.

Pevelopment may be continted for several hours after the sol went reaches the top of the plate, to provide adequate migration of the spets. Usually spets of a standard solution, a test solution, and a mixture of equal amounts of test and standard solutions, are initially applied at a standard distance from the base of the plate. Identity of the standard and test substances is confirmed by their migrating equal distances from the origin and by the observation that the two substanees applied as a mixture show no tendency to separate.

A major advantage of contintous development thin layer chromatography stems from the greater solvent selectivity for solvents of low solvent strength. Solvent strength refers to the property of a developing solvent that eauses solutes to migrate, and it is strongly influeneed by the polarity of the solvent. Inereasing the solvent strength by adding a mere polar solvent causes the $R_{5}$ value to in erease. Solvent selectivity refers to the ability of a solvent system to produre different $R_{-}$- values for closely related-substances. In eonventional thin layer chromatography, a solvent system giving an $R_{f}$ value in the range of 0.3 to 0.7 , but with adequate selectivity to permit separation of the substanees being examined is usually selected. It is muth easier to find solvent systems producing adequate migration than to find these afferding adequate selectivity.

Solvent systems of lower strength generally exhibit higher selectivity, but are difficult to employ in conventional thin layer chromatography beeause they result in very little migration before the solvent reaches the top of the plate. Migration may be increased, however, by repented drying and redevelopment of the plate or, more conveniently, by providing means for eraporation of solvent at the top of the plate, which results in contintrous development. Two techniques are used: contintrous development and short bed eontinuous development thin layer chromatography.

An $R_{\mu}$ value cannot be measured in continurus development thin layer chromatography. Substances may be compared either by their migration distance over a fixed period of time or by com parisen with the migration of a standard substance applied to the plate.

## EONTINUOUS DEVELOPMENT

Apparatus. Aceeptable apparatus and materials for continteus development thin layer chromatography are the same as these de seribedunder conventional Thin Latyer Chromatography, exeeptas follows.

A developing chamber is used that consists of a rectangular tank, approximately $23 \mathrm{~cm} \times 23 \mathrm{~cm} \times 9 \mathrm{~cm}$, equipped with a glass solvent trough and a platform about 3.75 cm high to elevate the solvent trough above the base of the tank. The-chamber is fitted with a cover having a $21 \times 6 \mathrm{em}$ slat in the front edge.

Procedure Apply the standard solution, the test solution, and a mixture of equal amounts of the standard solution and the test solution to a line about 2 cm from the base of the plate. Place the plate in the elevated empty solvent trough with the adsorbent on the underside of the leaning plate. The adsorbent rests against a piecof hery (about 1 mm thick) ${ }^{2}$ filter paper measuring $20 \mathrm{~cm} *$ 3 cm , folded lengthwise and placed over the front edgeof the tank. Place the developing solvent in the trough; set the cover in place, and seal all openingsexeept where the adsorbent contacts the paper wiek. The plate extends about 1 cm beyond the top of the tank.

After the solvent reaches the top of the plate, allow development tocontinue for an appropriate time. Then remove and dry the plate, and detect the spots by suitable means.

## SHORT BED-CONTINUOUS DEVELOPMENT

A major advantage of the short bed teehnique derives from the fact that solvent velocity is inversely related to bed length. Since spet migration depends upen the tolamount of solvent passing over the plate, the short bed permits useful migration to be obtained in a reasmable time with solvent having very low solvent strength. Lower diffusion in solvents of low solvent strength produrees smaller and more dense spots, which enhanees both detect ability and diseemment of small differences in migration distance.

Apparatus Acceptable apparatus and materials for shert bed eontinneus development thin layer chrematography are the same as these described under conventional Thin Layer Chrematograt phy, except as follows.

A shallow de eloping ehamber ${ }^{3}$ approximately $22 \mathrm{~cm}-9-\mathrm{cm}$ $* 3 \mathrm{~cm}$, equipped with a cover plate and tight fitting polytef wings that enable the chamber to be sealed against the plate, is used. The inside bettom of the chamber contains ridges that suppert the plate and allow it to be inserted at different angles, thereby warying the length of the plate eontained within the tank.
Proeedure-Apply the standard solution, the test solution, and a mixture of equal parts of the standard solution and the test solution to a line about 2 cm from the base of the plate. Place the plate in the developing chamber (adsorbent side up), and add the devel eping solvent to the chamber. No paper wiek is employed. After the solvent reaches the top of the plate, allow development to con tince for an appropriate time. Then remove and dry the plate, and detect the spets by suritable means.
^USP28

## Change to read:

## INTERPRETATION OF CHROMATOGRAMS

Figure 1 represents a typical chromatographic separation of two substances, 1 and 2, where $t_{1}$ and $t_{2}$ are the respective retention times; and $h, h / 2$, and $W_{h 2}$ are the height, the half-height, and the width at half-height, respectively, for peak 1. $W_{1}$ and $W_{2}$ are the respective widths of peaks 1 and 2 at the baseline. Air peaks are a feature of gas chromatograms and correspond to the solvent front in liquid chromatography.

[^100][^101]

Fig. 1. Chromatographic separation of two substances

Chromatographic retention times are characteristic of the compounds they represent but are not unique. Coincidence of retention times of a test and a reference substance can be used as a feature in construction of an identity profile but is insufficient on its own to establish identity. Absolute retention times of a given compound vary from one chromatogram to the next. Comparisons are normally made in terms of relative retention, *,
${ }^{\mathbf{4}}$ r, $\mathbf{\Delta}$ USP 28
which is calculated by the equation:


$$
r=\frac{t_{2}-t_{a}}{t_{1}-t_{a}}
$$

where $t_{2}$ and $t_{1}$ are the retention times, measured from the point of injection, of the test and reference substances, respectively, determined under identical experimental conditions on the same column, and $t_{a}$ is the retention time of a nonretained substance, such as methane in the case of gas chromatography.

In this and the following expressions, the corresponding retention volumes or linear separations on the chromatogram, both of which are directly proportional to retention time, may be substituted in the equations. Where the value of $t_{a}$ is small, $\mathbb{R}_{p}$
$\mathrm{m}_{1}$ 1S (USP28)
may be estimated from the retention times measured from the point of injection $\left(t_{2} t_{+}\right)$.

[^102]The number of theoretical plates, $N$, is a measure of column efficiency. For Gaussian peaks, it is calculated by the equation:


$$
N=16\left(\frac{t}{w}\right)^{2}, \mathbf{m}_{1 \mathrm{~S}(U S P 28)}
$$

where $t$ is the retention time of the substance and $W$ is the width of the peak at its base, obtained by extrapolating the relatively straight sides of the peak to the baseline. $\mathbb{H}_{\mu \sim}$ is the peak width at hatf height, obtained directly by electronic integrators.
-11 (USP28)
The value of $N$ depends upon the substance being chromatographed as well as the operating conditions such as mobile phase or carrier gas flow rates and temperature, the quality of the packing, the uniformity of the packing within the column and, for capillary columns, the thickness of the stationary phase film, and the internal diameter and length of the column.

The separation of two components in a mixture, the resolution, $R$, is determined by the equation:

$$
R=\frac{2\left(t_{2}-t_{1}\right)}{W_{2}+W_{1}}
$$

in which $t_{2}$ and $t_{1}$ are the retention times of the two components, and $W_{2}$ and $W_{1}$ are the corresponding widths at the bases of the peaks obtained by extrapolating the relatively straight sides of the peaks to the baseline.

Where electronic integrators are used, it may be convenient to determine the resolution, $R$, by the equation:

$$
R=\frac{2\left(t_{2}-t_{1}\right)}{1.70\left(W_{1, h} / 2+\mathrm{W}_{2, h / 2}\right)}
$$

and to determine the number of theoretical plates, $N$, by the equation:

$$
N=5.54\left(t / W_{h / 2}\right)^{2}
$$

$\square_{\text {where }} W_{h / 2}$ is the peak width at half-height, obtained di-
rectly by electronic integrators

- 1 S (USP28)

However, in the event of dispute, only equations based on peak width at baseline are to be used.

Peak areas and peak heights are usually proportional to the quantity of compound eluting. These are commonly measured by electronic integrators but may be determined by more classical approaches. Peak areas are generally used but may be less accurate if peak interference occurs. For manual measurements, the chart should be run faster than usual, or a comparator should be used to measure the width at half-height and the width at the base of the peak, to minimize error in these measurements. For accurate quantitative work, the components to be measured should be separated from any interfering components. Peak tailing and fronting and the measurement of peaks on solvent tails are to be avoided.

Chromatographic purity tests for drug raw materials are sometimes based on the determination of peaks due to impurities, expressed as a percentage of the area due to the drug peak. It is preferable, however, to compare impurity peaks with those in the chromatogram of a standard at a similar concentration. The standard may be the drug itself at a level corresponding to, for example, $0.5 \%$ impurity, or in the case of toxic or signal impurities, a standard of the impurity itself.

## Change to read:

## SYSTEM SUITABILITY

System suitability tests are an integral part of gas and liquid chromatographic methods. They are used to verify that the resolution and reproducibility of the chromatographic system are adequate for the analysis to be done. The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such.

The resolution, $R$, [NOTE-All terms and symbols are defined in the Glossary of Symbols] is a function of column efficiency, $N$, and is specified to ensure that closely eluting compounds are resolved from each other, to establish the general resolving power of the system, and to ensure that internal standards are resolved from the drug. Column efficiency may be specified also as a system suitability requirement, especially if there is only one peak of interest in the chromatogram; however, it is a less reliable means to ensure resolution than direct measurement. Column efficiency is a measure of peak sharpness, which is important for the detection of trace components.

Replicate injections of a Standard preparation used in the assay or other standard solution are compared to ascertain whether requirements for precision are met. Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation, $S_{R}$, if the requirement is $2.0 \%$ or less; data from six replicate injections are used if the relative standard deviation requirement is more than $2.0 \%$.

The tailing factor, $T$, a measure of peak symmetry, is unity for perfectly symmetrical peaks and its value increases as tailing becomes more pronounced (see Fig. 2). In some cases, values less than unity may be observed. As peak asymmetry increases, integration, and hence precision, becomes less reliable.


Fig. 2. Asymmetrical chromatographic peak
These tests are performed by collecting data from replicate injections of standard or other solutions as specified in the individual monograph. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions (see Procedures under Tests and Assays in the General Notices). Adjustments of operating eonditions to meet system suit ability requirements may be necessary.
${ }^{\mathbf{\Delta}}$ If adjustments of operating conditions to meet system suitability requirements are necessary, each of the following is the maximum specification that can be considered, unless otherwise directed in the monograph. Adjustments are permitted only when Reference-Standards suitable standards (including Reference Standards) are available for all ant lytes compounds used in the suitability test and are used to show that the adjustments have improved the quality of the chromatography in meeting system suitability requirements. Adjustments to chromatographic systems performed in order to comply with system suitability requirements are not to be made to compensate for column failure or to circumvent replacing a deteriorated column. Multiple adjustments that may have a cumulative effect in the performance of the system are to be avoided.
pH of Mobile Phase (HPLC)-The pH of the aqueous buffer used in the preparation of the mobile phase can be adjusted to within $\pm 0.2 \pm 0.5$ units of the value or range specified.

Concentration of Salts in Buffer (HPLC)—The concentration of the salts used in the preparation of the aqueous buffer used in the mobile phase can be adjusted to within $\pm 10 \%$, provided the permitted pH variation (see above) is met.

Ratio of Components in Mobile Phase (HPLC)- The of the miner The following adjustment limits apply to minor components of the mobile phase (specified at 50\% or less). The amount(s) of these component(s) can be adjusted by $\pm 30 \%$ relative or $\pm 2 \%$ absolute (i.e., in relation to the total mobile phase), whichever is larger. However, the change in any component cannot exceed $\pm 10 \%$ absolute, nor can the final concentration of any component be reduced to zero. Adjustment can be made to one minor component in a ternary mixture. Examples of adjustments for binary and ternary mixtures are given below.

## Binary Mixtures-

SPECIFIED RATIO OF $50: 50$-Thirty percent of 50 is $15 \%$ absolute, but this exceeds the maximum permitted change of $\pm 10 \%$ absolute in either component. Therefore, the mobile phase ratio may be adjusted only within the range of $40: 60$ to $60: 40$.

SPECIFIED RATIO OF 95:5-Thirty percent of 5 is $1.5 \%$ absolute. However, because adjustments up to $\pm 2 \%$ absolute are allowed, the ratio may be adjusted within the range of $93: 7$ to $97: 3$.

SPECIFIED RATIO OF 2 :98-Thirty percent of 2 is $0.6 \%$ absolute. In this case an absolute adjustment of $\pm 2 \%$ is not allowed because it would reduce the amount of the first component to zero. Therefore the maximum allowed adjustment is within the range of $1.4: 98.6$ to $2.6: 97.4$.

Ternary Mixtures-
SPECIFIED RATIO OF 60:35:5-For the second component, 30\% of 35 is $10.5 \%$ absolute, which exceeds the maximum permitted change of $\pm 10 \%$ absolute in any component. Therefore the second component may be adjusted only within the range of $25 \%$ to $45 \%$ absolute. For the third component, $30 \%$ of 5 is $1.5 \%$ absolute. Since $\pm 2 \%$ absolute is permitted and provides more flexibility, the third component may be adjusted within the range of $3 \%$ to $7 \%$ absolute. In all cases, a sufficient quantity of the first component is used to give a total of $100 \%$. Therefore, mixture ranges of $50: 45: 5$ to $70: 25: 5$ or $58: 35: 7$ to $62: 35: 3$ would meet the requirement.

## Betectar Wavelength of UV-Visible Detector

(HPLC)—Deviations from the wavelengths specified in the method are not permitted. The procedure specified by the detector manufacturer, or another validated procedure, is to be used to verify that error in the detector wavelength is, at most, $\pm 3 \mathrm{~nm}$.

Column Length (GC, HPLC): can be adjusted by as much as $\pm 70 \% .-50 \%$ to $+100 \%$.

Column Inner Diameter (GC, HPLC): can be adjusted by as much as $\pm 25 \% 50 \% . \pm 25 \%$ for HPLC and $\pm 50 \%$ for GC.

Film Thickness (Capillary GC): can be adjusted by as much as $-50 \%$ to $100 \%$.

Particle Size (HPLC): can be reduced by as much as $50 \%$.

Particle Size (GC): going from a larger to a smaller or a smaller to a larger (if it is the same "Range Ratio", which is the diameter of the largest particle divided by the diameter of the smallest particle) particle size GC mesh support is acceptable, provided the chromatography meets the requirements of the system suitability.

Flow Rate (GC, HPLC): can be adjusted by as much as $\pm 50 \%$.

Injection Volume (GC, HPLC): can be reduced as far as is consistent with accepted precision and detection limits. It may be-inereased to as mueh as twiee the-volume-speeiffed, provided there are no adverse effects on factors such as baseline, peak shapes, resolution, linearity, and retention times.

Column Temperature (HPLC): can be adjusted by as much as $\pm 20^{\circ} . \pm 10^{\circ}$. Column thermostating is recommended to improve control and reproducibility of retention time.

Column Temperature (GC): can be adjusted by as much as $\pm 2 \%$, in terms of absolute temperature. $\pm 10 \%$.

Oven Temperature Program (GC)—Adjustment of temperatures is permitted as stated above. For the times specified for the temperature to be maintained or for the temperature to be changed from one value to another, an adjustment of up to $\pm 20 \%$ is permitted.

Gradient Elution (HPLC)—The configuration of the equipment employed may significantly alter the resolution, retention time, and relative retentions described in the method. Should this occur, it may be due to excess dwell time, which is the volume between the point at which the two eluants meet and the top of the column. UUSP $28^{\text {P }}$

Unless otherwise directed in the monograph, system suitability parameters are determined from the analyte peak.
To ascertain the effectiveness of the final operating system, it should be subjected to suitability testing. Replicate injections of the standard preparation required to demonstrate adequate system precision may be made before the injection of samples or may be
interspersed among sample injections. System suitability must be demonstrated throughout the run by injection of an appropriate control preparation at appropriate intervals.

The control preparation can be a standard preparation or a solution containing a known amount of analyte and any additional materials useful in the control of the analytical system, such as excipients or impurities. Whenever there is a significant change in equipment or in a critical reagent, suitability testing should be performed before the injection of samples. No sample analysis is acceptable unless the requirements of system suitability have been met. Sample analyses obtained while the system fails
${ }^{\Delta}$ system suitability ${ }_{\Delta U S P 28}$
requirements are unacceptable.

## Change to read:

## GLOSSARY OF SYMBOLS

To promote uniformity of interpretation, the following symbols and definitions are employed where applicable in presenting formulas in the individual monographs. [NOTE-Where the terms $W$ and $t$ both appear in the same equation they must be expressed in the same units.]
*
*
relativeretention,

$e_{R}, e_{b}, e_{H} \quad$ enneentrations-of Reference-Standard, inter mat standard, and analyte in a partieular solut tion.
$\epsilon_{4} \quad$ eoncentration ratio of analyte and internal standard in test solutionor $A$ sisey preparation,

$\epsilon_{s} \quad$ enneentration ratio-of Reference Standard and internal- standard in Standard solution,


$$
\begin{gathered}
f^{\text {1S (USP28) }} \begin{array}{l}
\begin{array}{l}
\text { distance from the peak maximum to the lead- } \\
\text { ing edge of the peak, the distance being mea- } \\
\text { sured at a point } 5 \% \text { of the peak height from } \\
\text { the baseline. } \\
\text { capacity factor, }
\end{array} \\
k^{\prime}=\frac{\text { amount of substance in stationary phase }}{\text { amount of substance in mobile phase }}
\end{array} \\
k^{\prime}=\frac{\text { time spent by substance in stationary phase }}{\text { time spent by substance in mobile phase }}=\frac{t}{t_{a}}-1 .
\end{gathered}
$$

$N$
number of theoretical plates in a chromatographic column,


$$
\mathbf{■}_{N=16}\left(\frac{t}{w}\right)^{2} \text { or } N=5.54\left(\frac{t}{W_{h / 2}}\right)^{2} \mathbf{\square 1 S}(U S P 28)
$$

tat quantities (weights) of Reference
Standard, internal- standard, and analyte in a particular solution.
quantity ratio of analyte and internal standard in test solution or Assay preparation,

quantity ratio of Reference Standard and internal-standard in Standard solution,

relative retention

$$
r=\frac{t_{2}-t_{a}}{t_{1}-t_{a}}
$$

peak response of an impurity obtained from a chromatogram peak response of the Internal Standard obtained from a chromatogram $\mathbf{1 S}_{1 S}$ (USP28) peak response of the Reference Standard obtained from a chromatogram. peak response of the analyte obtained from a chromatogram.
resolution between two chromatographic peaks,

$$
R=\frac{2\left(t_{2}-t_{1}\right)}{W_{1}+W_{2}}
$$

■ or $R=\frac{2\left(t_{2}-t_{1}\right)}{1.70\left(W_{1, h / 2}+W_{2, h / 2}\right)} \square_{1 \mathrm{~S}(\text { USP28) }}$
chromatographic retardation factor equal to the ratio of the distance from the origin to the center of a zone divided by the distance from the origin to the solvent front. relative retention

$$
R_{r}=\frac{\text { distance traveled by test substance }}{\text { distance traveled by standard }}
$$

relative retention time

$$
R_{R}=\frac{t_{2}}{t_{1}}
$$

relative retardation
$R_{\text {rel }}=\frac{\text { distance traveled by test substance }}{\text { distance traveled by standard }} \boldsymbol{\square}_{15}$ (USP28)
peak response ratio for a Standard preparation containing Reference Standard and internal standard,

$$
R_{S}=\frac{r_{s}}{r_{I}}
$$

peak response ratio for Assay preparation containing the analyte and internal standard,

$$
R_{U}=\frac{r_{U}}{r_{I}}
$$

$S_{R}(\%) \quad$ relative standard deviation in percentage,

$$
S_{R}(\%)=\frac{100}{\bar{X}}\left[\frac{\sum_{i=1}^{N}\left(X_{i}-\bar{X}\right)^{2}}{N-1}\right]^{1 / 2},
$$

where $X_{i}$ is an individual measurement in a set of $N$ measurements and $X$ is the arithmetic mean of the set. tailing factor,

$$
T=\frac{W_{0.05}}{2 f}
$$

$t$
$t_{a}$
W
$W_{h / 2}$
$W_{0.05}$
retention time measured from time of injection to time of elution of peak maximum. retention time of nonretarded component, air with thermal conductivity detection. width of peak measured by extrapolating the relatively straight sides to the baseline. width of peak at $5 \%$ height.

## Change to read:

## CHROMATOGRAPHIC REAGENTS

The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer. [NOTE-Particle sizes given in this listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category of packings or phases listed below, there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

## Packings

L1—Octadecyl silane chemically bonded to porous silica or ceramic micro-particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L2-Octadecyl silane chemically bonded to silica gel of a controlled surface porosity that has been bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L3-Porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.
L4-Silica gel of controlled surface porosity bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L5-Alumina of controlled surface porosity bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L6-Strong cation-exchange packing-sulfonated fluorocarbon polymer coated on a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L7-Octylsilane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L8-An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support,
-3 to $\mathbf{m}_{1 S}$ (USP28)
$10 \mu \mathrm{~m}$ in diameter.
L9- $10-\mu \mathrm{m}$ irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating.

L10-Nitrile groups chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L11-Phenyl groups chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L12-A strong anion-exchange packing made by chemically bonding a quaternary amine to a solid silica spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L13-Trimethylsilane chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L14-Silica gel $10 \mu \mathrm{~mm}$ in diameter
-1S (USP28)
having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating,
-5 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{1 \mathrm{~S}}$ (USP28)
L15-Hexylsilane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L16-Dimethylsilane chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.
L17-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form, 7 to $11 \mu \mathrm{~m}$ in diameter.

L18-Amino and cyano groups chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L19-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the calcium form, about $9 \mu \mathrm{~m}$ in diameter.
L20-Dihydroxypropane groups chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L21-A rigid, spherical styrene-divinylbenzene copolymer, 5 to $10 \mu \mathrm{~m}$ in diameter.

L22-A cation-exchange resin made of porous polystyrene gel with sulfonic acid groups, about $10 \mu \mathrm{~m}$ in size.

L23-An anion-exchange resin made of porous polymethacrylate or polyacrylate gel with quaternary ammonium groups, about $10 \mu \mathrm{~m}$ in size.
L24-A semi-rigid hydrophilic gel consisting of vinyl polymers with numerous hydroxyl groups on the matrix surface, 32 to $63 \mu \mathrm{~m}$ in diameter. ${ }^{5}$

L25-Packing having the capacity to separate compounds with a molecular weight range from 100-5000 (as determined by polyethylene oxide), applied to neutral, anionic, and cationic water-soluble polymers. A polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contained some residual carboxyl functional groups) was found suitable.

L26-Butyl silane chemically bonded to totally porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L27-Porous silica particles, 30 to $50 \mu \mathrm{~m}$ in diameter.
L28-A multifunctional support, which consists of a high purity, $100 \AA$, spherical silica substrate that has been bonded with anionic exchanger, amine functionality in addition to a conventional reversed phase C8 functionality.

L29-Gamma alumina, reverse-phase, low carbon percentage by weight, alumina-based polybutadiene spherical particles, $5 \mu \mathrm{~m}$ in diameter with a pore volume of $80 \AA$.

L30-Ethyl silane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L31-A strong anion-exchange resin-quaternary amine bonded on latex particles attached to a core of $8.5-\mu \mathrm{m}$ macroporous particles having a pore size of $2000 \AA$ and consisting of ethylvinylbenzene cross-linked with $55 \%$ divinylbenzene.

L32-A chiral ligand-exchange packing-L-proline copper complex covalently bonded to irregularly shaped silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

[^103]L33-Packing having the capacity to separate dextrans by molecular size over a range of 4000 to $500,000 \mathrm{Da}$. It is spherical, silica-based, and processed to provide pH stability. ${ }^{6}$

L34-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the lead form, about $9 \mu \mathrm{~m}$ in diameter.

L35-A zirconium-stabilized spherical silica packing with a hydrophilic (diol-type) molecular monolayer bonded phase having a pore size of $150 \AA$.

L36-A 3,5-dinitrobenzoyl derivative of L-phenylglycine covalently bonded to $5-\mu \mathrm{m}$ aminopropyl silica.

L37-Packing having the capacity to separate proteins by molecular size over a range of 2,000 to $40,000 \mathrm{Da}$. It is a polymethacrylate gel.

L38-A methacrylate-based size-exclusion packing for watersoluble samples.

L39-A hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin.

L40-Cellulose tris-3,5-dimethylphenylcarbamate coated porous silica particles, 5 to $20 \mu \mathrm{~m}$ in diameter.
L41-Immobilized $\alpha_{1}$-acid glycoprotein on spherical silica particles, $5 \mu \mathrm{~m}$ in diameter.

L42-Octylsilane and octadecylsilane groups chemically bonded to porous silica particles, $5 \mu \mathrm{~m}$ in diameter.

L43-Pentafluorophenyl groups chemically bonded to silica particles by a propyl spacer, ${ }^{1 S}$ (USP27) 5 to $10 \mu \mathrm{~m}$ in diameter.

L44-A multifunctional support, which consists of a high purity, $60 \AA$, spherical silica substrate that has been bonded with a cationic exchanger, sulfonic acid functionality in addition to a conventional reversed phase C8 functionality.

L45-Beta cyclodextrin bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L46-Polystyrene/divinylbenzene substrate agglomerated with quaternary amine functionalized latex beads,
-about ${ }_{\text {1S }}$ (USP28)
$10 \mu \mathrm{~m}$ in diameter.
L47-High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, $8 \mu \mathrm{~m}$ in diameter. ${ }^{7}$

L48-Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion-exchange microbeads, $15 \mu \mathrm{~m}$ in diameter.

L49-A reversed-phase packing made by coating a thin layer of polybutadiene onto spherical porous zirconia particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L50-Multifunction resin with reversed-phase retention and strong anion-exchange functionalities. The resin consists of ethylvinylbenzene, $55 \%$ cross-linked with divinylbenzene copolymer, 3 to $15 \mu \mathrm{~m}$ in diameter, and a surface area not less than $350 \mathrm{~m}^{2}$ per $g$. Substrate is coated with quaternary ammonium functionalized latex particles consisting of styrene cross-linked with divinylbenzene. ${ }^{9}$

[^104]L51-Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{10}$

L52-A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{11}$

L53-Weak cation-exchange resin consisting of ethylvinylbenzene, $55 \%$ cross-linked with divinylbenzene copolymer, 3 to 15 $\mu \mathrm{m}$ diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than $500 \mu \mathrm{Eq} /$ column. ${ }^{12}$

L54-A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 $\mu \mathrm{m}$ in diameter. ${ }^{13}$
${ }^{\wedge}$ L55-A strong cation-exchange resin made of porous silica coated with polybutadiene-maleic acid copolymer, about $5 \mu \mathrm{~m}$ in diameter. ${ }^{14} \mathbf{\Delta U S P 2 7}$
${ }^{\mathbf{\Delta}}$ L56-Propyl silane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{15} \mathbf{\Delta U S P 2 7}$
-L53 \#\# (Alendronic Acid Tablets, PRP-X100)—An an-ion-exchange resin consisting of a rigid, spherical styrenedivinylbenzene copolymer with trimethylammonium groups at a loading of about 2 mEq per $\mathrm{g}, 3$ to $20 \mu \mathrm{~m}$ in diameter. ${ }^{\text {a }}$ (USP27)
-L54 \#\# (Maltose, Aminex HPX-87N)—Strong cationexchange resin consisting of sulfonated cross-linked styr-ene-divinylbenzene copolymer in the sodium form, about
7 to $11 \mu \mathrm{~m}$ in diameter. ${ }^{\mathrm{b}}{ }^{2 S}$ (USP27)
${ }^{10}$ Available as Chiralpak AD from Chiral Technologies, Inc., 730
Springdale Prive, P.O. Box 564, Extm, PA 19341.
-(www.chiraltech.com).■1S (USP28)
${ }^{11}$ Available as TSK IC SW Cation from TosoHaas.
-Tosoh Biosep (www.tosohbiosep.com)..1s (USP28)
12 Available as IonPac CS14 distributed by Dionex Corperation -Corp.■1S (USP28)
(www.dionex.com).
${ }^{13}$ Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).
${ }^{14}$ Available as IC-Pak C M/D from Waters Corp. (www.waters. com).
${ }^{15}$ Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem)
${ }^{\text {a }}$ Available as PRP-X100 from Hamilton Company (www.hamiltoncompany.com).
${ }^{\text {b }}$ Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, \#125-0143) Group-Headquaters, Bio Rad La beratories, 2000 Alfred Nobel Dr., Hereules, California- 94547 (wnwdiseover.bio rad.com).
-(www.bio-rad.com).■1S (USP28)
-L57 \#\# (Nevirapine, Supelcosil ABZ)—Spherical, porous silica gel, 3 or $5 \mu \mathrm{~m}$ in diameter, the surface of which has been covalently modified with palmitamidopropyl groups and endcapped with acetamidopropyl groups to a ligand density of about $6 \mu$ moles per $\mathrm{m}^{2} .^{\mathrm{c}} \mathrm{m}^{2 \mathrm{~S}}$ (USP27)

■L58 \#\# (Albumin Human, Antithrombin III Human, TSKgel G3000 SW)—Packing having the capacity to separate proteins by molecular weight over the range of 10 to 500 kDa . It is spherical $(10 \mu \mathrm{~m})$, silica-based, and processed to provide hydrophilic characteristics and pH stability. ${ }^{\mathrm{d}}{ }^{2 S}$ (USP27)
-L64 \#\# (Lycopene, Lycopene Preparation, YMC 30)C30 silane bonded phase on a fully porous spherical silica, 3
to $15 \mu \mathrm{~m}$ in diameter. $\quad$ 2S (USP27)
-L\#\# (Clopidogrel Bisulfate, Ultron ES-OVM)-A chir-al-recognition protein, ovomucoid, chemically bonded to silica particles, about $5 \mu \mathrm{~m}$ in diameter, with a pore size of


[^105]
## Phases

G1-Dimethylpolysiloxane oil.
G2-Dimethylpolysiloxane gum.
G3-50\% Phenyl-50\% methylpolysiloxane.
G4-Diethylene glycol succinate polyester.
G5-3-Cyanopropylpolysiloxane.
G6-Trifluoropropylmethylpolysiloxane.
G7-50\% 3-Cyanopropyl-50\% phenylmethylsilicone.
G8-80\% Bis(3-cyanopropyl)-20\% 3-cyanopropylphenylpoly-
siloxane (percentages refer to molar substitution).
G9-Methylvinylpolysiloxane.
G10-Polyamide formed by reacting a $\mathrm{C}_{36}$ dicarboxylic acid with 1,3-di-4-piperidylpropane and piperidine in the respective mole ratios of $1.00: 0.90: 0.20$.
G11—Bis(2-ethylhexyl) sebacate polyester.
G12-Phenyldiethanolamine succinate polyester.
G13-Sorbitol.
G14-Polyethylene glycol (av. mol. wt. of 950 to 1050).
G15-Polyethylene glycol (av. mol. wt. of 3000 to 3700).
G16-Polyethylene glycol compound (av. mol. wt. about 15,000 ). A high molecular weight compound of polyethylene glycol with a diepoxide linker. Available commercially as Polyethylene Glycol Compound 20M, or as Carbowax 20M, from suppliers of chromatographic reagents.
G17-75\% Phenyl-25\% methylpolysiloxane.
G18-Polyalkylene glycol.
G19-25\% Phenyl-25\% cyanopropyl-50\% methylsilicone.
G20-Polyethylene glycol (av. mol. wt. of 380 to 420).
G21-Neopentyl glycol succinate.
G22-Bis(2-ethylhexyl) phthalate.
G23-Polyethylene glycol adipate.
G24-Diisodecyl phthalate.
G25-Polyethylene glycol compound TPA. A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with terephthalic acid. Available commercially as Carbowax 20M-TPA from suppliers of chromatographic reagents.

G26-25\% 2-Cyanoethyl-75\% methylpolysiloxane.
G27-5\% Phenyl-95\% methylpolysiloxane.
G28-25\% Phenyl-75\% methylpolysiloxane.
G29-3, $3^{\prime}$-Thiodipropionitrile.
G30-Tetraethylene glycol dimethyl ether.
G31-Nonylphenoxypoly(ethyleneoxy)ethanol (av. ethyleneoxy chain length is 30 ); Nonoxynol 30 .
G32-20\% Phenylmethyl-80\% dimethylpolysiloxane.
G33-20\% Carborane-80\% methylsilicone.
G34-Diethylene glycol succinate polyester stabilized with phosphoric acid.

G35-A high molecular weight compound of a polyethylene
glycol and a diepoxide that is esterified with nitroterephthalic acid.
G36-1\% Vinyl-5\% phenylmethylpolysiloxane.
G37-Polyimide.
G38-Phase G1 containing a small percentage of a tailing inhibitor. ${ }^{16}$

G39—Polyethylene glycol (av. mol. wt. about 1500).
G40-Ethylene glycol adipate.
G41-Phenylmethyldimethylsilicone ( $10 \%$ phenyl-substituted).
G42-35\% phenyl-65\% dimethylpolysiloxane (percentages re-
fer to molar substitution).
G43-6\% cyanopropylphenyl-94\% dimethylpolysiloxane (percentages refer to molar substitution).
G44-2\% low molecular weight petrolatum hydrocarbon grease and $1 \%$ solution of potassium hydroxide.

G45-Divinylbenzene-ethylene glycol-dimethylacrylate.

[^106]G46－14\％Cyanopropylphenyl－86\％methylpolysiloxane．
G47－Polyethylene glycol（av．mol．wt．of about 8000）．
G48－Highly polar，partially cross－linked cyanopolysiloxane．
G49－Proprietary derivatized phenyl－groups on a pelysiloxane backbone．
－G50 \＃\＃（Docosahexaenoic Acid）—Polyethylene glycol， cross－linked（av．mol．wt．of more than 20，000）．${ }^{\mathrm{e}}{ }^{-}$ － 2 S （USP27）

## Supports

NOTE－Unless otherwise specified，mesh sizes of 80 to 100 or， alternatively， 100 to 120 are intended．

S1A－Siliceous earth for gas chromatography has been flux－cal－ cined by mixing diatomite with $\mathrm{Na}_{2} \mathrm{CO}_{3}$ flux and calcining above $900^{\circ}$ ．The siliceous earth is acid－washed，then water－washed until neutral，but not base－washed．The siliceous earth may be silanized by treating with an agent such as dimethyldichlorosilane ${ }^{18}$ to mask surface silanol groups．

S1AB－The siliceous earth as described above is both acid－and base－washed．${ }^{18}$

S1C－A support prepared from crushed firebrick and calcined or burned with a clay binder above $900^{\circ}$ with subsequent acid－ wash．It may be silanized．

S1NS－The siliceous earth is untreated．
S2－Styrene－divinylbenzene copolymer having a nominal sur－ face area of less than $50 \mathrm{~m}^{2}$ per g and an average pore diameter of 0.3 to $0.4 \mu \mathrm{~m}$ ．

S3－Copolymer of ethylvinylbenzene and divinylbenzene hav－ ing a nominal surface area of 500 to $600 \mathrm{~m}^{2}$ per g and an average pore diameter of $0.0075 \mu \mathrm{~m}$ ．

S4－Styrene－divinylbenzene copolymer with aromatic－ O and－ N groups，having a nominal surface area of 400 to $600 \mathrm{~m}^{2}$ per g and an average pore diameter of $0.0076 \mu \mathrm{~m}$ ．

S5－40－to 60－mesh，high－molecular weight tetrafluorethylene polymer．

S6－Styrene－divinylbenzene copolymer having a nominal sur－ face area of 250 to $350 \mathrm{~m}^{2}$ per g and an average pore diameter of $0.0091 \mu \mathrm{~m}$ ．

S7－Graphitized carbon having a nominal surface area of $12 \mathrm{~m}^{2}$ per g．

S8－Copolymer of 4－vinyl－pyridine and styrene－divinylben－ zene．

S9－A porous polymer based on 2，6－diphenyl－p－phenylene oxide．

S10－A highly polar cross－linked copolymer of acrylonitrite and divinylbenzene．

S11－Graphitized carbon having a nominal surface area of 100 $\mathrm{m}^{2}$ per g modified with small amounts of petrolatum and polyethy－ lene glycol compound．${ }^{19}$

S12－Graphitized carbon having a nominal surface area of 100 $\mathrm{m}^{2}$ per g ．

[^107]
## BRIEFING

〈730〉 Inductively Coupled Plasma，page 1922 of $P F$ 28（6） ［Nov．－Dec．2002］．On the basis of comments received，it is pro－ posed to revise this new general chapter under the new title＂Plas－ ma Spectrochemistry．＂This new chapter provides information supporting the use of a high－temperature source for subsequent ele－ mental analysis by atomic emission spectroscopy or by mass spec－ trometry．These techniques are used in the determination of multiple elements either sequentially or simultaneously，which can yield good general－purpose results for drug and excipient sub－ stances and dietary supplements．The incorporation of this pro－ posed new chapter will increase the assurance of quality of compendial articles by encouraging the use of this powerful analy－ tical technology for determination of inorganic impurities．USP＇s working group on Plasma Spectrochemistry arranged a roundtable discussion session at the 2004 Winter Conference on Plasma Spec－ trochemistry（January 2－10，2004，Ft．Lauderdale，Florida）and re－ ceived much input from the conference attendees．Currently there are no monographs in $U S P-N F$ using this technique．Plasma spec－ trochemistry could have a great impact on the testing of inorganic elements in the pharmaceutical industry in the future．
（PA6：K．Zaidi）RTS—39609－1；39751－01；39756－01；39778－ 01；39802－01；40718－1

## Add the following：

## $\langle 730\rangle$ INDUCTIVELYCOUPLED PLASMA PLASMA SPECTROCHEMISTRY

## INTRODUCTION

This chapter provides general information and defines the terms and procedures used in element determinations by int duetively coupled plasma（ICP），either with detection by atemic emissions spectroseopy（ICP AES）or with detection by mass spectrometry（ICP MS）．Specific requirements for tests and assays of drug substances，nutritional supplements， and their correspending dosage forms are indieated within the－individutal menegraphs．

他 is a very high－temperature excitation souree that des－ olvates，vaporizes，atomizes，excites，andionizes atoms．ICP is used to excite analyte atoms for subsequent detection by atomic emission spectroseopy or to ionize atoms for detec
tion by mass spectremetry. Similar to the sample atomization required for flame and graphite farnace atomic abserption spectremetry, in ICP teehniques the sample is converted into an aeresel, which is then excited by the plasma-for subsequent detection. Single element detection and narrow linear ranges limit flame and graphite furnace atomic absorption spectrometers, although these are relatively inex pensive and adequately sensitive for some elements and analyses. ICP techniques can provide good general purpese procedures that may detect multiple-elements sequentially or simultaneously over an extended linear range and with greater sensitivity.

## APPARATUS

The compenents that make the ICP excitation souree include the sample nebulizer, plasma-suppert gas, the plasma toreh, and a magnetic freld produced from a radio fre quency generator. A peristaltic pump-continuously introduces sample solutions into the nebulizer where a sample aeresel is formed and carried into the excitation source by a stream of plasma-suppert gas. Argen is ypically used as the plasma suppert gas and may contain other modifiers. The plasma toreh consists of a series of concentric quartz tubes through which flows the sample aerosel/suppert gas mixture in the inner tube and through which flows an additional stream of support gas in the outer tube to cool the torch assembly. A radio frequency (RF) generator coil surrounds the toreh and produces an oseillating magnetic field which, in turn, sets up an oseillating eurrent in the ions and electrons of the suppert gas. In the induction coil of the RF generater, the energy transfer between the coil and the suppert gas creates a self-sustaining plasma. Collisions of the ions and electrons of the-stepport gas ionize and excite the analyte atoms in the high temperature plasma. The plasma

Operates at temperatures generally around $6,000-10,000 \mathrm{~K}$, such that essentially all covalent bends and analyte analyte interactions have been eliminated.

The uniform introduction of a sample solution containing the analyte atoms inte the nebulizer is critical to stable-sys-tem-operation and reproducible peak response. Peristaltic pumps that deliver a constant flow are crucial since the mag nittde of the peak respense is propertional to the amount of sample introduced inte the plasma per unit time. Sample-sefations may be assayed directly after appropriate dilution. Solid samples may require dissolution and predigestion with acombination of mineral acids and oxidants before analysis. Sample digestion and ignition proeedures similar to that deseribed for Arsenic $\langle 211\rangle$, Heary Metals $\langle 231\rangle$, and Residue On Ignition $\langle 284\rangle$ may be appropriate to clean up the sample matrix and for the removal of organic material. The sample preparation for analysis is then obtained from a quantitative dilution of the sample residue.

Alternative methods for introduction of selid or liquid samples into the plasma can be achieved by additional teehniques ineluding but not limited to laser ablation, graphite furnace, hydride generation, mierowave induction, and spark excitation. Eltents from-ion chrematographs and similar liquid chrematographic techniques can also be used to introduce a sample solution into the nebulizer.

## SAMPLE PREPARATHON

Appropriate sample preparation-is of vital impertance to the analysis procedure using ICP AES and ICP MS techniques. The introduction of various mineral acids for sample digestion and/or solution preparation may have signifieant impact on the analysis of the sample preparation. Depending en the detection mode and/or equipment configuration, sample adducts with these various acids or their deemposition products produced within the plasma may inerease the com-
plexity of the resulting emission and mass spectra. The in terference of various species of $S \Theta_{*}$ and their isotopes with Zn- determination by ICP MS as well as other interferences involving hydrochloric and phosphoric acids are well known. The impact of some potential interferences can be eliminated by appropriate optimization of operational parameters including support gas flow, sample flow, plasma temperature, RF power, extraction lens voltage, ete. The presence of high coneentrations of some-mineral acids in a sample preparation may also catuse an inerease in solution viscosity versus that of the standard preparation resulting in a decrease in the peak respenses due to decreased selution flow into the nebulizer. The use of an internal standard in the form of an additional element in each of the standard and sample preparations would be recommended under such eonditions for an aceurate determination of the peak respense ratio.

Sample solutions of atomic elements may be assayed directly after appropriate dilution. Solid organic samples re-quire-dissolution and/or predigestion with a combination Of mineral acids and oxidants, which may inelude hydregen peroxide, nitric acid, perchloric acid, hydrochloric acid, or sulfuric acid. Subsequent ignition may also be needed to remove carbenaceous material andelean up the-sample matrix prior to analysis to achieve-suitable-sensitivity. However, due to the volatility of some metals at high temperature, the ignition temperattre should not exceed $600^{\circ}$ and is ypieally performed at $500^{\circ} 550^{\circ}$ unless-speciffed in the indivi dual menegraph.

## DETECTHO TECHNYQUES

## ICPAtomic Emission-Spectroseopy

Atemic emission spectreseopy (AES, also called-Optient Emission-Spectroscopy or OES) is a-specialized branch-of spectroscopy shating many of the attributes with other spectroscopic measurements listed in the general chapter Spec trophetmetry and Light Scattering $\langle 851\rangle$. AES uses the quantitative measurement of the wavelength and intensity of the optical emission frem excited atoms to determine the identity of an analyte atom and its concentration. Upen excitation, an atom emits an array of different frequenciesof tight that is characteristic of the distinet energy transitions allowed for that element (See Table 1 for a list of primary and-some alternative analysis wavelengths for the most eommen elements analyzed by ICP AES. The-signifieant figures given for the wavelengths are to allow identifiention. The instrument vender may specify mere-signifieant figures in their operational procedures for a given emission line). The intensity of light emitted is generally propertional to the analyte concentration. It may be necessary to correct for the background signal from the plasmaemission or from matrix interference. Due to variations in atomization eff eieney, detector respense, and background signalcorrection, single peint standards are often not sutitable for quantitative analysis. As a result, sample concentration measurements are usually determined from a working curve ofknown standards in the concentration range of interest.

Since there are distinet transitions between atomic energy levels, emission lines have narrow bandwidths. All atems in a sample are-excited simultaneously, however, so samples eontaining multiple elements can lead to spectral overlap. Spectral separation of multiple emissions requires a high-resolution spectrometer. If there is evidence of spectral inter
ference, selection of an alternate wavelength may be justifred. Mathematical modeling to subtract the interfering sig fal as a background correction may also be performed.

An instrument that observes these emission lines in a-se quential manner can offer beth complete wavelength coverage and good resolution. However, when performing multielement analyses and seamning across the entire spectrum, the speed of analysis is reduced. Other instruments can si-
fattaneously detect the individutemission lines frem each atom by using a pelychromator with multiple detectors or solid state pixel detectors on a-single-chip. This ability to simultaneously detect multiple elements is a major advantage of AES compared to atomic absorption-spectroseopy but may have the disadvantage of incomplete wavelength eoverage.

Table 1. Primary and Some Alternative Analysis-Wavelengths for ICP AES

| Element | Primary wavelength, nm | Alternative wavelengths, nm |
| :---: | :---: | :---: |
| Altminmm, At | 308.2 | 396.2, 237.3, 167.0 |
| Antimeny, Sb | 206.8 | 217.6, 231.1, 252.9 |
| Arsenic, As | 189.0 | 193.7 |
| Barimm, Ba | 493.4 | 455.4 |
| Bismmth, Bi | 223.4 | 190.2 |
| Boron, B | 249.7 | 249.7 |
| Cadmium, Cd | 214.4 | 226.5, 228.8 |
| Galcium, Ca | 317.9 | 396.8, 393.4, 422.7, 315.9 |
| Cerimm, Ce | 413.8 | 413.4, 418.7, 393.4 |
| Cesium, Cs | 452.7 | 459.3, 455.5 |
| Chromium, Cr | 283.6 | 284.3, 267.7, 205.6 |
| Gobalt, Ce | 228.6 | 238.9 |
| Copper, Cut | 324.8 | 224.7, 327.4, 213.6 |
| Hen, Fe | 238.2 | 239.6, 259.9, 302.1 |
| Lead, Pb | 220.4 | 217.0, 261.4, 283.3 |
| Lithimm, Li | 670.8 | 610.4, 413.3, 460.3 |
| Magnesitm, Mg | 279.1 | 280.3, 285.2, 279.6 |
| Manganese, Ma | 257.6 | 259.4, 279.5 |
| Mereury, Hg | 253.7 | 404.7, 435.8,194.2 |
| Molybdentm, Me | 202.0 | 203.8, 204.6, 281.6 |
| Nickel, Ni | 221.6 | $232.0,341.5,231.6$ |
| Palladium, Pd | 340.5 | $363.5,324.3,248.9$ |
| Phesphors, $P$ | 213.6 | 214.9, 178.2,177.4 |
| Petassitm, $K$ | 766.5 | 404.7 |
| Selenitm, Se | 196.0 | 204.0 |

Table 1. Primary and-Some Alternative Analysis Wavelengths for ICP AES (Continted)

| Element | Primary wavelength, nm | Alternative wavelengths, nm |
| :---: | :---: | :---: |
| Silver, Ag | 328.4 | 338.3, 243.8,224.9 |
| Sodium, Na | 330.2 | 589.6, 589.0, 288.4 |
| Fin, Sn | +89.9 | $235.5,284.0,242.2$ |
| Titanimm, Ti | 334.9 | 336.4 |
| Vanadium, $V$ | 292.4 | 309.3, 310.2, 311.4 |
| Yittritm, Y | 371.0 | 324.2, 360.1 |
| Zine, Zn | 243.9 | 202.5, 206.2, 334.5 |

ICP AES detectors view the plasma either radially (sideen viewing) or axially (end-on viewing). Axial viewing of the plasma provides an-inereased and more-sensitive signal respense, however, in seme situations where background or sample interference is signifieant at the wavelength of inter est, radial viewing may yield mere reliable results. Because of the wide range of elemental concentration in some reat World samples and becatuse of complex matrix problems, there are many cases where the axial and radial configura tion for the plasma may not give equivalent results. Further sample dilution or changes in other operational conditions may be neeessary. Methods validated using an instrument with a radial configuration may not be completely transfer able to an instrument with an axial conflguration, and vice versa. Some ICP AES instruments have combined the axial and radial conflgurations into a single wnit. With such an int strument, the user has the ability to optimize the appropriate ennfiguration for the sample ype and/or suppression of petential interference. The viewing configuration of the plasma can be-interehanged using system-centrelled mirrers without the added expense of a separate instrument.

## ICP-Mass-Spectrometry

The utilization of mass spectremetry (MS) for the detection of atomic elements in conjunction with-ionization by ICP (ICP MS) shares many of the attributes listed in the general chapter Mass Spectrometry $\langle 736\rangle$.ICP MS is analegous to other sample introduction/detectiontechniques sueh as GC MS and LC MS. Gas phase ions are generated from the analyte atoms by the plasma. The analyte ions are then extracted frem the plasma and inte the mass spectremeter through sampling and skimmer cones. The mass spectrometer separates the ions in a magnetic freld by the difference in mass to charge (mte) ratio of the ionized atoms. Since all relatively stable atomic isotopes have atomic masses less than 240 , a mass spectremeter with sufficient resolution within this mass range is required. See Table 2 for a list of the primary and some alternative analysis isotopes for the most commen elements analyzed by ICP MS. The ion rese tetion power, $R$, of a mass-spectrometer is defined by the formula

$$
R=m / \Delta m,
$$

where $m$ is the ion mass of interest and $\Delta m$ is the difference in mass between resolvable peaks in a mass-spectrum.

Depending on the equipment configuration, sample ad duets with diluent acids or their decomposition products, oxides, and multiply charged element ions (see-Glossaty of Terms and Symbols) produced within the plasma may inerease the complexity of the resulting mass spectra. Interfer ences can be minimized by appropriate optimization of eperational parameters including suppert gas flow, sample flow, plasma temperature, RF power, extraction lens vol tage, ete., or through a background correction. The signift eance of the petential interference for the massion of interest may be evaluated from the nattral isetope ratio of the given element versus the observed isotope ratio for the
sample-element, as long as the sample has not originated from an enriched source. The evaluation of the isotope ratios may be used to determine appropriat background correc tion.

ICP-MS is generally mere-sensitive than ICP AES. The ability of a mass-spectrometer to menitor a single ion of a specific mass/charge ratio (SIM mode) is a major advantage of ICP MS when assaying for very low analyte concentra tiens or when elimination of matrix interference is required. Analyte can-often be detected at the parts per trillion (ppt) level utilizing ICP MS.

Table 2. Primary and Some Alternative Analysis Isotopes for ICP MS

| Element | Primary isotope, mle | Alternative isotope, mhe |
| :---: | :---: | :---: |
| Altmintm, Al | 27 | - |
| Antimeny, Sb | 124 | 123 |
| Arsenic, As | 75 | - |
| Barium, Ba | 137 | 138,135 |
| Bismath, Bi | 209 | - |
| Boren, B | 4 | 10 |
| Cadmitum, Cd | 44 | 44 |
| Galcium, Ca | 44 | 43 |
| Cerium, Ce | 140 | - |
| Cesitm, Cs | 133 | - |
| Chromitam, Cr | 53 | 52 |
| Cobalt, 6 | 59 | - |
| Copper, Ct | 65 | - |
| Hen, Fe | 56 | 57 |
| Lead, Pb | 208 | - |
| Lithium, Li | 7 | - |
| Magnesitm, Mg | 25 | 26,24 |
| Manganese, Ma | 55 | - |
| Meremry, Hg | 202 | 200, 199 |
| Molybdenmm, Me | 95 | 98 |
| Nickel, Ni | $6 \theta$ | 62 |

Table 2. Primary and-Some Alternative-Analysis Isotopes for ICP-MS (Continted)

| Element | Primary isotope, mle | Alternative isotope, mhe |
| :---: | :---: | :---: |
| Palladium, Pd | 105 | - |
| Phesphorts, $P$ | 34 | - |
| Potassitm, $K$ | 39 | - |
| Selenium, Se | 82 | 77 |
| Silver, Ag | 107 | 109 |
| Soditmm, Na | 23 | - |
| Sulfur, S | 34 | 33 |
| Fin, Sn | 48 | 119,117 |
| Fitanium, 7 | 47 | 49 |
| Vanadium, V | 54 | - |
| Yittritm, $Y$ | 89 | - |
| Zine, Zn | 66 | 68,64 |

## CALßRATHON AND-SYSTEM SUHABHHY

The wavelength aceuracy for $A$ AES detection or mass aceuracy for MS detection must be in accordance with the applicable operating procedures. The ICP instrument must be standardized for quantifieation at each use. System-suitabil ity tests are an integral part of all-user-standardized test methods and are used to verify that the aceuracy and reproducibility of the system are adequate for the analysis of sam ples to be performed. Evaluations of the system's suitability include reproducibility of repliente measurements of a-sin gle solution introduction, linearity of a standard curve, and stability of peak respense-over the analysis run time. The fests are based on the concept that the equipment, electrenies, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as a whele.

Standard solutions of element ions-should be aceurately prepared frem standard materials and titrated as apprepriate, or purehased commereially and used as received if the re perted titer is traceable to standardization against a primaty standard. Replieate readings of a-single-introduction of a standard preparation used in the assay or other standard se letion are compared to ascertain whether requirements-for precision are met.

Suitable linearity should be demenstrated throughout the range of test measurements to be performed. For quantita tive analyses, an appropriate blank solution and at least three standard preparations that bracket the expected range of the sample concentrations should be assayed and detector respense plotted as a function of analyte concentration. Regression analysis of this plot should be used to evaluate the linearity of detector respense in addition to consisteney ef solution introduction. A correlation coefficient not less than- 0.995 , or as indicated in the individual monograph, must be demenstrated for the working standard eurve. For
timit tests, an appropriate blank solution and singlestandard selution may be sufficient. To demenstrate the stability of the system over the analysis time-since initial standardization, a solution used in the initial standard curve must be reassayed as a cheek standard after the last test preparation in the-sample-set. The difference in peak respense-of the eheck standard from the initial value must not be more than $5 \%$, or as indieated in the individual menegraph. For assays where tight control of reproducibility is required, the use of an-internal-standard in the-standard preparations and test preparations may be necessary.

When utilizing mass spectrometric detection, additional system suitability is required to demenstrate that the flow of plasma support gas and ionization energies are appropri ate. Proper flow of plasma-support gas is necessary to achieve a residence time of the analyte within the plasmat such that dissociation of all atomic species has oceurred prior to detection. Proper ionization energies are necessary to achieve sufficient atomic ionization but to prevent multi-ply-chargedions. A control solution containing ceritm may be introduced to determine an acceptable flow rate of plas ma suppert gas. The flow rate is adjusted to achieve a resi dence time of the evium analyte within the plasma such that the ratio of CeO to Ce is less than $3.0 \%$. An appropriateenfrolsolation containing baritum ions may be introduced to determine acceptable ionization energy such that the ratio of $\mathrm{Ba}^{-+}+0 \mathrm{Ba}^{+}$is less than 3.0\%\%

The specification of definitive parameters in a menograph does net preclude the use of other suitable operating eonditions (see Procedures under Tests and Assays in the General Notices). Adjustments of operating conditions to meet sys-tem-suitability requirements may be neeessary. Unless Otherwise noted, system suitability parameters are measured from the analyte peak.

Replicate introductions of the standard preparation re quired to demonstrate system performance may be made be fore the introduction of samples or may be-interspersed among sample introductions. System suitability must be demonstrated throughout the run by introduction of an appropriate contrel preparation at appropriate-intervals. The eentrel preparation can be a standard preparation or a selution containing a known amount of analyte and any additional materiats useful in the control of the analyticat system. Whenever there is a signifieant change in equipment Or in a critieal reagent, suitability testing should be per formed before the introduction of additional samples. Ne sample analysis is aceeptable unless the requirements-of system suitability have been met. Sample analyses obtained while the-system faits-such requirements are invalid.

## PROCEDURE

Follow the procedure as directed in the individual menegraph for the detection mode and instrument parameters. Pue to slight differences in mantafacturer equipment eonfig urations, suggested vender default conditions including but net limited to plasma-suppert gas flow rate, auxiliary gas flow rate, RF Power, and sample flow rate for the ype-of analyses should be used and then adjusted to achieve the requirements of system suitability as specified in the menegraph and in this general chapter. Data collected from a single-sample introduction are treated as a single result. Data from wor three sequential readings from a single solution introduction of the apprepriate-standard or sample prepara-tions-should be averaged as a single result. Sample coneentrations are caleulated versus the working standard eurve generated by plotting the detector respense versus the coneentration of the analyte in the standard preparations.

Standard Addition Methed A usefultechnique for seme samples is the standard addition technique, in whieh a known concentration of the analyte element is added to the sample. When the detector response is plotted against the concentration of the added analyte element, and a linear regression line drawn through the data peints, the coneentration of analyte in the sample is the absolute value of theen tension of the regression line at the point where it crosses the eoncentration axis. This technique may prove to be useful in samples that show interferences from other elements that are present.

## GHOSSARY OF TERMS ANP-SYMBOLS

Axial viewing A configuration of the plasma for AES where the plasma is directed toward the-spectremeter optic path, alsocalled end-on viewing.
m The ion mass of interest.
Am The difference in mass between resolvable peaks in a-mass-spectrum.

Multiply-charged ions Atoms that, when-subjected to high ionization energies, can form doubly or triply charged ions ( $\mathrm{X}^{-- \text {-r }} \mathrm{X}^{-}$, ete.) steh that when detected by MS, the apparent mass will be $1 / 2$ or $\frac{1}{3}$ that of the atomic mass.

## Plasmatoreh A series of concentric quartz tubes-in

which the sample aeresel/suppert gas mixture flows threugh the inner tube; acooling gas flows through the outer tube to eool the toreh assembly.

Radial viewing A cenflguration of the plasma for AES where the plasma is directed orthogenal to the spectrometer eptic path, alse called side on viewing.
$R$ The resolution of a mass spectrometer defined by

## $R=m / \Delta m$.

Sample nebulizer. Used to form a consistent sample aerosol that mixes with the plasma support gas.

Sequential A type of detector configuration for AES where-discrete-emission lines are observed by seanning aeress the spectral range using a menechremator.

Simaltaneats A typeof detector configuration for AES where all selected emission lines are observed at the same time using a polychromator, offering inereased analysis speed for multi-element samples.

Suppert gas A gas stream, generally Ar, whieh carries the analyte inte the plasma.

User-standardization A correlation between a known analyte concentration and the corresponding detector respense for the system, determined at the time of sample ana lysis and used to determine the concentration of an analyte in a sample-solution.

Plasma-based instrumental techniques that are useful for pharmaceutical analyses fall into two major categories: those based on inductively coupled plasma, and those where a plasma is generated on the surface of the sample. Inductively coupled plasma (ICP) is a high-temperature excitation source that desolvates, vaporizes, atomizes, excites, and ionizes atoms. The excited analyte ions and atoms are subsequently detected by any of a variety of plasma-based spectrochemical means, including inductively coupled plas-ma-atomic emission spectroscopy (ICP-AES), also known as inductively coupled plasma-optical emission spectroscopy (ICP-OES) and inductively coupled plasma-mass spectrometry (ICP-MS). ICP-AES and ICP-MS may be used for either single- or multi-element analysis and provide good general-purpose procedures for either sequential or simultaneous analyses over an extended linear range with good sensitivity.

An emerging technique in plasma spectrochemistry is la-ser-induced breakdown spectroscopy (LIBS). In LIBS, a solid, liquid, or gas sample is heated directly by a pulsed laser,
and brought to a transient high-energy plasma state where the sample components are reduced to atoms, molecular fragments, and larger clusters. Emissions from the atoms and ions in the sample are collected typically using fiber optics and measured using an array detector such as a chargecoupled device (CCD). LIBS can be used for qualitative analysis or against a working standard curve for quantitative analysis. While LIBS is not currently in wide use by the pharmaceutical industry, LIBS is suited for at-line or on-line measurements in a production setting as well as in the laboratory. Because of its potential, it should be considered a viable technique for plasma spectrochemistry in the pharmaceutical laboratory. However, because LIBS is still an emerging technique, details will not be further discussed in this general chapter.

## SAMPLE PREPARATION

Sample preparation is critical to the success of plasmabased analysis, and it is the first step in performing any analysis via ICP-AES or ICP-MS. Plasma-based techniques are heavily dependent on sample transport into the plasma, and because ICP-AES and ICP-MS share the same sample introduction system, the means by which samples are prepared may be applicable to either technique. The most conventional means by which samples are introduced into the plasma is via solution nebulization. If solution nebulization is employed, solid samples must be dissolved in order to be presented into the plasma for analysis. Samples may be dissolved in any appropriate solvent. There is a strong preference for the use of aqueous or dilute nitric acid solutions, due to minimal interferences with these solvents, when compared to other solvent choices. Hydrogen peroxide, hydrochloric acid, sulfuric acid, perchloric acid, combinations of acids, or various concentrations of acids may all be used to dissolve the sample for analysis. Dilute hydrofluoric acid
may also be used, but great care must be taken to ensure the safety of the analyst, as well as to protect the equipment when using this acid. Additionally, alternative means of dissolving the sample may be employed. These include, but are not limited to, the use of dilute bases, straight or diluted organic solvents, combinations of acids or bases, or combinations of organic solvents.

When analyzing samples that are presented to the plasma via solution nebulization, it is important to consider the potential interferences that may arise from the solvent used. In all cases, when samples are to be analyzed using ICP-MS, use an appropriate internal standard. In cases where sample viscosity differs from the standard viscosity, matrix matching or an appropriate internal standard should also be used for ICP-AES analysis. In either event, the selection of an appropriate internal standard should consider the analyte in question, ionization energy, wavelengths or masses, and the nature of the sample matrix.

Where a sample is not found to be soluble in any acceptable solvent, a variety of digestion techniques may be employed. These include hot-plate digestion, or microwave assisted digestions, including open-vessel and closed-vessel digestions. The decision regarding the type of digestion technique to use is dependent on the nature of the sample being digested, as well as on the analytes of interest. Because some metals are volatile (e.g., mercury and selenium), open-vessel or hot-plate digestions are not appropriate for all analytes.

Use acids, bases, and hydrogen peroxide of ultra-high purity. Deionized water must be at least 18 megohm. Check diluents for interferences prior to their use in an analysis. Because it is not always possible to obtain organic solvents that are free of metals, use organic solvents of the highest quality possible with regard to metals contaminants.

## SAMPLE INTRODUCTION

There are two ways to introduce the sample into the nebulizer: using a peristaltic pump or by self-aspiration. The peristaltic pump is used to ensure that the flow rate of sample and standard solution to the nebulizer is the same irrespective of sample viscosity. In some cases, self-aspiration can be used, where a peristaltic pump is not required.

A wide variety of nebulizer types is available, including pneumatic (concentric and cross-flow), grid, and ultrasonic nebulizers. Micronebulizers, high efficiency nebulizers, direct injection high-efficiency nebulizers, and flow-injection nebulizers are also available. The selection of the nebulizer for a given analysis should consider the sample matrix, analyte, and sensitivity desired. Some nebulizers are better suited for use with solutions containing a high concentration of dissolved solids, while others are better-suited for use with organic solutions.

Once a sample leaves the nebulizer, it enters the spray chamber, which is designed to permit only the smallest droplets of sample into the plasma. The spray chamber functions to remove the larger sample droplets generated during the nebulization process, and as a result, typically only $1 \%$ to $2 \%$ of the sample aerosol reaches the ICP. As with nebulizers, there is more than one type of spray chamber available for use with ICP-AES or ICP-MS. Examples include the Scott double-pass spray chamber, as well as cyclonic spray chambers of various configurations. The spray chamber must be compatible with the sample and solvent and must equilibrate and washout in as short a time as possible. When selecting a spray chamber, the nature of the sample matrix, the desired sensitivity, and the analyte should be considered.

In addition to solution nebulization, it is possible to perform analyses using solid samples via laser ablation (LA). In such instances, the sample directly enters the torch. LA-ICP
and LA-ICP-MS are better-suited for qualitative analyses of pharmaceutical compounds, due to the difficulty in obtaining appropriate standards. Nonetheless, quantitative analyses may be performed if it can be demonstrated that the standards used are adequate. This must be demonstrated through appropriate method validation.

## STANDARD PREPARATION

Single- or multi-element standard solutions, whose concentrations are traceable to primary reference standards, such as those of the National Institute of Standards and Technology (NIST), may be purchased for use in the preparation of working standard solutions. Alternatively, standard solutions of elements may be accurately prepared from standard materials and their concentration determined independently, as appropriate. Where possible, standards, blanks, and sample solutions should be matrix matched to minimize matrix interference. In cases where matrix matching is not possible, an appropriate internal standard or the method of standard additions should be used for ICPAES. Standards and blank solutions to be used for ICPMS analysis should always contain an appropriate internal standard. In either event, the selection of an appropriate internal standard should consider the analyte in question, their ionization energies, their wavelengths or masses, and the nature of the sample matrix.

## ICP

The components that make up the ICP excitation source include the argon gas supply, torch, radio frequency (RF) induction coil, and RF generator. Argon gas is typically used in ICP, although other gases may also be used, depending on the instrumentation available. The use of gases other than argon is not common practice. The plasma torch consists of three concentric quartz tubes designated the inner, the in-
termediate, and the outer tube. The nebulizer gas flow helps to create a fine aerosol of the sample solution, and the sample is then carried through the inner tube of the torch and into the plasma. The intermediate tube carries the auxiliary gas. The auxiliary gas flow helps to lift the plasma off of the inner and intermediate tubes to prevent melting and the deposition of carbon and salts on the inner tube. The outer tube carries the plasma or coolant gas, which is used to form and sustain the plasma. The tangential flow of the coolant gas through the torch constricts the plasma and prevents the ICP from expanding to fill the outer tube, preventing the torch from melting. An RF induction coil, also called the load coil, surrounds the torch and produces an oscillating magnetic field which, in turn, sets up an oscillating current in the ions and electrons of the argon. In the load coil of the RF generator, the energy transfer between the coil and the argon creates a self-sustaining plasma. Collisions of the ions and electrons of the argon ionize and excite the analyte atoms in the high-temperature plasma. The plasma operates at temperatures of 6,000 to $10,000 \mathrm{~K}$, such that essentially all covalent bonds and analyte-to-analyte interactions have been eliminated.

## ICP-AES

An inductively coupled plasma may utilize either an optical or a mass spectral detection system. In the former case, ICP-AES, analyte detection is dependent on the emission wavelength of the analyte in question. Due to differences in technology, a wide variety of ICP-AES systems are available, each with different capabilities, as well as different advantages and disadvantages. Simultaneous systems are capable of analyzing multiple elements at the same time, thereby shortening analysis time. Sequential systems move from one wavelength to the next to perform analyses, and usually provide a larger number of analytical lines to choose
from. Charge-coupled devices and charge injection devices, with detectors on a chip, make it possible to combine the advantages of both simultaneous and sequential systems, providing the rapid analysis of the simultaneous units with a wider selection of analytical lines as found with sequential units.

In addition, the ICP can be oriented in either axial or radial (also called lateral) configurations. The torch is positioned horizontally in axial plasmas, and the sample is viewed "end on"; while it is positioned vertically in radial plasmas, and the sample is viewed from the side. Axial viewing of the plasma can provide a more sensitive signal response; however, in some situations where background or sample interference is significant at the wavelength of interest, radial viewing may yield more reliable results. Because of the wide range of elemental concentrations in some real world samples and because of complex matrix problems, there are many cases where radial is better than axial or visa versa. Methods validated using an instrument with a radial configuration may not be completely transferable to an instrument with an axial configuration, and vice versa.

Additionally, dual-view instrument systems are available, making it possible for the analyst to take advantage of either torch configuration. The selection of torch configuration is dependent on the sample matrix, analyte in question, analytical wavelength used, cost of instrumentation, required sensitivity, and type of instrumentation available in a given laboratory.

Regardless of torch configuration or detector technology, ICP-AES is a technique which provides a quantitative measurement of the optical emission from excited atoms or ions at specific wavelengths. These measurements are then used to determine the analyte concentration in a given sample. Upon excitation, an atom emits an array of different frequencies of light that is characteristic of the distinct energy
transition allowed for that element. The intensity of the light is generally proportional to the analyte concentration. It is necessary to correct for the background signal from the plasma. Sample concentration measurements are usually determined from a working curve of known standards in the concentration range of interest. It is, however, also possible to perform a single-point calibration under certain circumstances, such as with limit tests.

Since there are distinct transitions between atomic energy levels, emission lines have narrow bandwidths. Spectral separation of multiple emission lines requires a high-resolution spectrometer. The decision regarding which spectral line to measure should include an evaluation of potential spectral interferences. All atoms in a sample are excited simultaneously, however, so samples containing multiple elements can lead to spectral overlap. Spectral interference can also be caused by background emission from the sample or plasma. Modern ICP's usually have background correction available and a number of background correction techniques may be applied. Simple background correction typically involves measuring the background emission intensity at some point away from the main peak and subtracting this value from the total signal being measured. Mathematical modeling to subtract the interfering signal as a background correction may also be performed.

The selection of the analytical line is critical to the success of an analysis, regardless of torch configuration or detector type. Though some wavelengths are most often considered to be the primary analytical wavelengths, because there can be a tremendous variety of sample matrices, the selection of the analytical wavelength must be considered in the context of the sample matrix, the composition of the sample itself, the type of instrument being used, and the sensitivity required. Analysts might first choose to start with the wavelengths recommended by the manufac-
turer of their particular instrument and select alternate wavelengths based on manufacturer recommendations or published wavelength tables.

Forward power, gas flow rates, and torch position may all be optimized to provide the best signal. When organic solvents are used, it is often necessary to use a higher forward power setting than would be used for aqueous solutions, as well as a reduction in the nebulizer gas flow. When using organic solvents, it may also be necessary to bleed small amounts of oxygen into the torch to prevent carbon buildup in the torch.

## Calibration

The wavelength accuracy for ICP-AES detection must comply with the manufacturer's applicable operating procedures. The instrument must be standardized for quantification at time of use. Due to the inherent differences between the types of instruments available, there is no general "system suitability" procedure that may be employed. Tests recommended by the instrument manufacturer for a given ICP-AES instrument should be followed. These may include, but are not limited to, use of a multi-element wavelength calibration using a reference solution, internal mercury ( Hg ) calibration, and peak search. Perform system checks in accordance with the manufacturer's recommendations.

Because ICP-AES is a technique that is generally considered to be linear over a range of $10^{6}$ to $10^{8}$ orders of magnitude, it is not always necessary to continually demonstrate linearity by the use of a standard curve. It is possible to calibrate with a blank and a single standard once a method has been developed and is in routine use. For new methods, it is advisable that suitable linearity be demonstrated throughout the range of test measurements to be performed. An appropriate blank solution and standards that bracket the expected
range of the sample concentrations should be assayed and the detector response plotted as a function of analyte concentration. However, it may not always be possible to analyze a bracketing standard when an analysis is performed at or near the detection limit. This is acceptable. The number and concentration of standard solutions used should be based on the analyte in question, the desired sensitivity, and the sample matrix. Use regression analysis of the standard plot to evaluate the linearity of detector response, and individual monographs may require criteria for the residual error of the regression line. Optimally, a correlation coefficient of not less than 0.99 , or as indicated in the individual monograph, should be demonstrated for the working standard curve. Here, too, however, the nature of the sample matrix, the analyte(s), the desired sensitivity, and the type of instrumentation available may dictate a poorer correlation coefficient than 0.99 . The analyst should use caution when proceeding with such an analysis, and should use additional working standards.

To demonstrate the stability of the system over the analysis time since initial standardization, a solution used in the initial standard curve must be reassayed as a check standard at appropriate intervals throughout the analysis of the sample set. Appropriate intervals may be as deemed adequate by the analyst, based on the analysis being performed. The reassayed standard should agree with its theoretical value to within $\pm 10 \%$ for single-element analyses when analytical wavelengths are between 200 and 500 nm , or concentrations are $>1 \mu \mathrm{~g}$ per mL . The reassayed standard should agree with its theoretical value to within $\pm 20 \%$ for multi-element analyses, when analytical wavelengths are $<200 \mathrm{~nm}$ or $>500 \mathrm{~nm}$, or at concentrations $<1 \mu \mathrm{~g}$ per mL . In cases where an individual monograph provides different guidance regarding the reassayed check standard, the requirements of the monograph take precedence.

## Procedure

Follow the procedure as directed in the individual monograph for the instrumental parameters. Due to differences in manufacturers' equipment configurations, the manufacturer's suggested default conditions may be used and modified as needed. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions, and adjustments of operating conditions may be necessary. Alternate conditions must be supported by suitable validation data, and the conditions in the monograph will take precedence for official purposes. Data collected from a single sample introduction are treated as a single result. This result may be the average of data collected from replicate sequential readings from a single solution introduction of the appropriate standard or sample preparations. Sample concentrations are calculated versus the working standard curve generated by plotting the detector response versus the concentration of the analyte in the standard preparations. This calculation is normally performed by the instrument.

The method of standard additions or internal standards may be employed for situations where matrix interferences would result in an inaccurate analyte determination. The method of standard additions involves adding a known concentration of the analyte element to the sample at several concentration levels. The instrument response is plotted against the concentration of the added analyte element, and a linear regression line is drawn through the data points. The absolute value of the $x$-intercept multiplied by any dilution factor is the concentration of the analyte in the sample.

## ICP-MS

When an inductively coupled plasma utilizes a mass spectral detection system, the technique is referred to as inductively coupled plasma-mass spectrometry (ICP-MS). In
this technique, analyte detection is dependent on the masses of the various elemental components of a sample. ICP-MS is an elemental technique, whereby, due to the heat intensity of the plasma source, a sample is, theoretically, reduced to its ionic components. As is the case with ICP-AES, due to differences in technology, a wide variety of ICP-MS instrumentation systems are available.

The systems most commonly in use are quadrupole-based systems. Gaining in interest is time-of-flight ICP-MS. Although still not in widespread use, this approach may see greater use in the future. Additionally, high-resolution instruments are also available.

Regardless of instrument design or configuration, ICPMS is a technique that provides a quantitative measurement of the components of the sample. Ions are generated from the analyte atoms by the plasma. The analyte ions are then extracted from the plasma using the sampling cone. The skimmer cone, located behind the sampling cone "skims" the ions as they emerge from the sampling cone, where they are then passed into the mass spectrometer. The mass spectrometer separates the ions in a magnetic field according to their mass-to-charge ( $\mathrm{m} / \mathrm{z}$ ) ratios. The ICP-MS has a mass range up to 240 atomic mass units (amu). Depending on the equipment configuration, sample adducts with diluents or their decomposition products, oxides, and multiply-charged element ions produced within the plasma may increase the complexity of the resulting mass spectra. Interferences can be minimized by appropriate optimization of operational parameters, including gas flow (nebulizer, plasma, and auxiliary gas flow rates), sample flow, RF power, extraction lens voltage, etc., or through the use of collision or reaction cells, or cool plasma operation, if available on a given instrument. Unless a laboratory is generating or examining isotopes that are not naturally occurring, a list of naturally occurring isotopes will provide the analyst with acceptable isotopes for
analytical purposes. Additionally, tables of commonly found interferences and polyatomic isobaric interferences and correction factors may be used.

ICP-MS is generally more sensitive than ICP-AES. The ability of a mass spectrometer to monitor a single ion of a specific mass/charge ratio is a major advantage of ICP-MS for determination of very low analyte concentrations or when elimination of matrix inferences is required. Analytes can often be detected at the parts per trillion (ppt) level using ICP-MS.

The selection of the analytical mass to use is critical to the success of an analysis, regardless of instrument design. Though some masses are often considered to be the primary analytical masses, because there can be a tremendous variety of sample matrices, the recommendation of a specific mass for a given element is not possible. Selection of an analytical mass is always considered in the context of the sample matrix, the type of instrument being used, and the sensitivity required. Analysts might first choose to start with masses recommended by the manufacturer of their particular instrument and select alternate masses based on manufacturer's recommendations or published tables of naturally occurring isotopes.

Optimization of an ICP-MS method is also highly dependent on the plasma parameters and means of sample introduction. Forward power, gas flow rates, and torch position may all be optimized to provide the best signal. When organic solvents are used, it is often necessary to use a higher forward power setting than would be used for aqueous solutions and to reduce the nebulizer flow rate. Additionally, when using organic solvents, it may be necessary to titrate small amounts of oxygen into the auxiliary gas to prevent carbon build-up in the torch. The use of a platinum-tipped sampling or skimmer cone may also be required to reduce cone degradation with some organic solvents.

## Calibration

The mass spectral accuracy for ICP-MS detection must be in accordance with the applicable operating procedures. The instrument must be standardized for quantification at time of use. Due to the inherent differences between the types of instruments available, there is no general "system suitability" procedure that may be employed. Analysts should refer to the tests recommended by the instrument manufacturer for a given ICP-MS instrument. These may include, but are not limited to, tuning on a reference mass or masses, peak search, and mass calibration. Perform system checks recommended by the instrument manufacturer.

Because ICP-MS is a technique that is generally considered to be linear over a range of $10^{6}$ to $10^{8}$ orders of magnitude, it is not always necessary to continually demonstrate linearity by the use of a standard curve. It is common practice to calibrate with a blank and a single standard, once a method has been developed and is in routine use. For new methods, it is advisable that suitable linearity be demonstrated through the range of test measurements to be performed. An appropriate blank solution and standards that bracket the expected range of the sample concentrations should be assayed and the detector response plotted as a function of analyte concentration. The number and concentration of standard solutions used should be based on the analyte in question, the desired sensitivity, and the sample matrix and should be left to the discretion of the analyst. Optimally, a correlation coefficient of not less than 0.99 , or as indicated in the individual monograph, should be demonstrated for the working standard curve. Here, too, however, the nature of the sample matrix, the analyte, the desired sensitivity, and the type of instrumentation available may dictate a poorer correlation coefficient than 0.99 . The analyst should use caution when proceeding with such an analysis and should use additional working standards.

To demonstrate the stability of the system over the analysis time since initial standardization, a solution used in the initial standard curve must be reassayed as a check standard at appropriate intervals through the analysis of the sample set. Appropriate intervals may be established as after every fifth or tenth sample, or as deemed adequate by the analyst, based on the analysis being performed. The reassayed standard should agree with its theoretical value to within $\pm 10 \%$ for single-element analyses when analytical masses are free of interferences and when concentrations are $>1 \mathrm{ng}$ per mL . The reassayed standard should agree with its theoretical value to within $\pm 20 \%$ for multi-elemental analyses, or when concentrations are $<1 \mathrm{ng}$ per mL . In cases where an individual monograph provides different guidance regarding the reassayed check standard, the requirements of the monograph take precedence.

## Procedure

Follow the procedure as directed in the individual monograph for the detection mode and instrument parameters. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions, and adjustments of operating conditions may be necessary. Alternate conditions must be supported by suitable validation data, and the conditions in the monograph will take precedence for official purposes. Due to differences in manufacturers' equipment configurations, the analyst may wish to begin with the manufacturer's suggested default conditions and modify them as needed. Data collected from a single sample introduction are treated as a single result. Data collected from replicate sequential readings from a single solution introduction of the appropriate standard or sample preparations should be averaged as a single result. Sample concentrations are calculated versus the working standard curve generated by plotting the detector
response versus the concentration of the analyte in the standard preparations. With modern instruments, this calculation is normally performed by the instrument. Data collected from two or three sequential readings from a single solution introduction of the appropriate standard or sample preparations is averaged as a single result. Sample concentrations are calculated versus the working standard curve generated by plotting the detector response versus the concentration of the analyte in the standard preparations. With modern instruments, this calculation is performed by the instrument.

The method of standard additions may be employed for situations where matrix interferences would result in an inaccurate analyte determination. This method involves adding a known concentration of the analyte element to the sample at several concentration levels. The instrument response is plotted against the concentration of the added analyte element and a linear regression line is drawn through the data points. The absolute value of the $x$-intercept multiplied by any dilution factor is the concentration of the analyte in the sample.

## GLOSSARY

AUXILIARY GAS: The auxiliary gas is used to "lift" the plasma off of the surface of the torch, thereby preventing melting of the intermediate tube and the formation of carbon and salt deposits on the inner tube.

AXIAL VIEWING: A configuration of the plasma for AES where the plasma is directed toward the spectrometer optical path, also called "end-on."

COLLISION CELL: A design feature on ICP-MS instruments. Collision cells are used to eliminate or minimize interferences from argon and facilitate the analysis of elements that might be affected by those interferences.

COOLANT OR PLASMA GAS: The coolant gas is the main gas supply for the plasma.

COOL PLASMA: Plasma conditions used for ICP-MS that result in a plasma that is cooler than normally used for an analysis. This is achieved by using a lower forward power setting and is used to help minimize isotopic interferences caused by argon.

FORWARD POWER: The number of watts used to ignite and sustain the plasma during an analysis. Forward power requirements may vary, depending on sample matrix and analyte.
INTERNAL STANDARD: An element in an analysis added to or present in the same concentration in blanks, standards, and samples to act as an intensity reference for the analysis. An internal standard may be used for ICP-AES work and should always be used for quantitative ICP-MS analyses.

Lateral viewing: See also Radial viewing.
$m$ : The ion mass of interest.
mULTIPLY-CHARGED IONS: Atoms that, when subjected to high-ionization energies, can form doubly or triply charged ions $\left(\mathrm{X}^{++}\right.$or $\mathrm{X}^{+++}$, etc.) such that when detected by MS, the apparent mass will be $1 / 2$ or $\frac{1}{3}$ that of the atomic mass.

NEBULIZER: Used to form a consistent sample aerosol that mixes with the argon gas.
NEBULIZER GAS: One of three regions of argon gas flow in a torch. The nebulizer gas is used to help create a fine mist of the sample when using solution nebulization. This fine mist is then directed through the center tube of the torch and into the plasma.
plasma gas: See also Coolant gas.
RADIAL VIEWING: A configuration of the plasma for AES where the plasma is directed orthogonal to the spectrometer optic path, also called "side-on viewing." See also Lateral viewing.

REACTION CELL: Similar to collision cell. Designed to reduce or eliminate interferences.
SAMPLING CONE: A metal cone (usually nickel, aluminum, or platinum-tipped) with a small opening, through which ionized sample flows after leaving the plasma.

SEQUENTIAL: A type of detector configuration for AES where discrete emission lines are observed by scanning across the spectral range using a monochromator. SIMULTANEOUS: A type of detector configuration for AES where all selected emission lines are observed at the same time, using a polychromator, offering increased analysis speed for multi-element samples.

SKIMMER CONE: A metal cone, with an opening that is smaller than that of the sampling cone, through which ionized sample flows after leaving the sampling cone and prior to entering the vacuum region of an ICP-MS.

STANDARD ADDITIONS: A method used to determine the actual analyte concentration in a sample when viscosity effects may cause erroneous results.

TORCH: A series of three concentric quartz tubes in which the ICP is formed.

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## GENERAL CHAPTERS

## General Information

## Briefing

$\langle 1265\rangle$ Written Prescription Drug Information-Guidelines, page 1224 of $P F 29(4)$ [July-Aug. 2003]. It is proposed to revise this general information chapter to include criteria from the "Keystone Action Plan" and related references to provide consistency with other regulatory requirements. Additional editorial revisions have been made to clarify the text.
(PSD: C. Okeke) RTS-39753-1

## Add the following:

## <1265 $\rangle$ WRITTEN PRESCRIPTION DRUG INFORMATION—GUIDELINES

The purpose of these guidelines-comprising format, content, and accessibility of prescription drug leaflets-is to help ensure that leaflets are useful. In this context, "useful" means that recipients receive, understand, and are motivated to apply written information about their medicines to achieve maximum benefit and minimize harm. Dispensers, prescribers, health-care providers who counsel patients about their medicines, and the patients themselves are intended to be the primary beneficiaries for these guidelines.

## CRITERIA

## (from the Keystone Action Plan ${ }^{1}$ )

Written prescription medicine information should be based on the following criteria:

1. Scientifically accurate,
2. Unbiased in content and tone,
3. Sufficiently specific and comprehensive,
4. Presented in an understandable and legible format that is readily comprehensible to consumers,
5. Timely and up-to-date, and
6. Useful.

## FORMAT GUIDELINES

1. Group all information from the same category, using brief, clear titles and bullets or subheadings as needed. Avoid symbols and subheadings not directly connected to the information they mark.
2. Be consistent in the placement and labeling of categories of information in all leaflets.
3. Provide information at the sixth-grade reading level or below, if possible (never above eighth-grade level). Do not exclude information to achieve a lower reading level.
4. Use simple, common, accurate terms (for example, use "noise in the ears", not "tinnitus").

[^108]5. Use direct language that avoids words with opposite meanings (for example, use "decrease blood pressure", not "increase low blood pressure effect").
6. Provide reasons for instructions (for example, "take with food to avoid upset stomach").
7. Emphasize the most important information. Clearly distinguish warnings from instructions or from other text that may be misinterpreted as warnings.
8. Accompany each pictogram, if used, with corresponding text placed close to the pictogram. Use the simplest pictograms possible. For pictograms intended to prompt patients to ask questions or inform health-care providers, add text such as "Tell Doctor" or "Ask Pharmacist".
9. Make text readable by using 12-point or larger type, both uppercase and lowercase letters, an easy-to-read font (for example, a sams serif font), and adequate space between lines and paragraphs. To call attention to important information, use a larger, boldface type.
10. Evaluate format by performing tests of readability, comprehension, memory, problem solving, and behavioral efficacy and intention, using representative samples of the target population.

## CONTENT GUIDELINES

1. Provide enough detail to facilitate correct use, achieve maximum benefit, and minimize harm, including a statement that identifies activities (such as driving or sunbathing) that the patient should avoid.
2. Write text that is unbiased in content and tone and scientifically accurate. The uses described should be consistent with FDA-approved labeling or otherwise permitted by FDA, or should appear in federally recog-
nized drug compendia. Distinguish unlabeled from labeled use. For labeled use, state the date on which-it was approved.
3. For drugs sold under a brand name, provide both brand and generic names and include a pronunciation guide for each.
4. Describe the drug and its dosage form. Include indications and contraindications, specific directions for use, what to do if a dose is missed, and what to do in the event of an overdose or poisoning.
5. Do not use abbreviations.
6. Indicate the intended type of benefit (for example, "cure", "prevention", "to help relieve symptoms"). Indicate how-and how soon-the patient should recognize the benefit and what to do if none is observed.
7. Give a balanced evaluation of risks and benefits.
8. List side effects, in order of severity, withestimated frequency and action to be taken if one or more oceur such as "serious," "most common," and other similar type groupings. It may not be appropriate to provide sufficient detail for the patient to be able to monitor serious or frequently eceuring common side effects. If ne-side effects are known, say-so. Provide guidance to consult the doctor or pharmacist, and indicate that all the side effects are not listed.
9. List drug drug, drug food, drug lab-test, and drug disease interations. If no such interactions are known, say so. If appropriate, include botanieats, dietary supplements, and over the-counter medieines, as well as other preseription medieines. If known, inelude estimated severity of interactions(mild, moderate, or severe). one-or most impertant interactions, as deseribed earlier. sufficiently specific and comprehensive information
that includes the provision of all important risk information. Patients should be advised to be sure to inform the provider about all the medicines they are taking.
10. Indicate the potential for therapeutic duplication if the drug is available under multiple names or over-thecounter, or if the active ingredient is contained in other products.
11. If known, include a statement concerning the safety of use in the presence of other conditions and during pregnancy or breast-feeding. Direct affected patients to discuss their condition with health-care providers. If the safety of use during pregnancy or breast-feeding has not been established, say so.
12. State whether safety and efficacy have been established in pediatric, geriatric, and other special populations. and, if so, for what Patients should be encouraged to discuss with their health-care provider any recommendations for dosage adjustment.
13. Illustrate information with diagrams when appropriate. Label the diagram components (for example, device parts) if they are not obvious. The words on the label should be prominently placed thereon with such conspicuousness and in such terms as to render them likely to be read and understood by the ordinary individual under customary conditions of purchase and use.
14. Include the following:
a. a warning to keep out of the reach of young
ehildren
b. a statement about the impertance of adhering
to-dosing instructions
e. a. A statement that the product is to be used only by the person for whom it was prescribed, \&. b. Storage information,
e. c. A completeness disclaimer advising the patient to discuss this issue with the health-care provider,
f. a direction to check the expiration or beyonduse date
15. The publisher of the leaflet and the date the leaflet was developed or revised,
h. e. Sources of in-depth information and answers to questions, and f. f. Other relevant general statements.
16. The patient should be advised about risks of developing dependence on, or tolerance to, the medications.

## ACCESSIBILITY GUIDELINES

1. Write text that is relevant to the intended use of the drug.
2. Design the leaflets to be easy to recognize, consistent in format, and easy to store and retrieve.
3. Supplement the leaflets with oral counseling of patients, including children, the elderly, and caregivers.
4. Include a statement asking the patient to reread the leaflet.
5. Distribute the leaflets with all prescription medicines to consumers (namely, persons independently responsible for any aspect of medicine use or for giving medicines to others).
6. Produce leaflets in Spanish, as win English; English, or other languages; and establish criteria for producing them in other languages and for special populations (for example, children, visually handicapped, etc.). [NOTE-Ideally, prescription drug information leaflets would be customized for the patient's condition and for other relevant information (for example, gender, age, or physical limitations), and would be
available in the patient's primary language. Currently, such customization is neither feasible nor practical, but it remains a goal. $]_{\square 1 S}$ (USP28)

## REAGENTS, INDICATORS, AND SOLUTIONS Reagent Specifications

## BRIEFING

Ammonium Pyrrolidinedithiocarbamate. This new reagent is used in the preparation of the Standard solutions and the Test solution in the test for Limit of lead under the proposed new monograph for Galactose, published in PF 30(2) [Mar.-Apr. 2004].
(HDQ: M. Marques) RTS-40995-1

## Add the following:

-Ammonium Pyrrolidinedithiocarbamate (1-pyrrolidinecarbodithioic acid, ammonium salt), $\mathrm{C}_{5} \mathrm{H}_{12} \mathrm{~N}_{2} \mathrm{~S}_{2}$ 164.29 [5108-96-3]—Use a suitable grade. 1 (USP28)

## BRIEFING

Anion-exchange Resin, Styrene-Divinylbenzene. This new reagent is used in the test for Molar ratio of sulfate to carboxylate under Enoxaparin Sodium, which appeared in PF 29(6) [Nov.Dec. 2003].
(HDQ: M. Marques) RTS-41081-1

## Add the following:

-Anion-exchange Resin, Styrene-DivinylbenzeneStrongly basic, cross-linked resin containing quaternary ammonium groups and about $8 \%$ of divinylbenzene. It is available in the chloride form in the 50 - to 100 -, 100 - to 200-, and 200- to 400-mesh sizes. It can be converted to the hydroxide form by regeneration with a sodium hydroxide solution (5 in 100). Insoluble in water, in methanol, and in acetonitrile. Suitable for use in column chromatography.
[NOTE-A suitable resin is "Dowex 1 X 8 ", produced by Dow Chemical Co. (www.dow.com) and available through Sigma-Aldrich (www.sigma-aldrich.com).] $]_{\text {■S (USP28) }}$

## BRIEFING

Cation-Exchange Resin, Styrene Divinylbenzene USP 27 page 2674. It is proposed to revise the particle size ranges for this reagent used in the test for Molar ratio of sulfate to carboxylate under Enoxaparin Sodium, which appeared in PF 29(6) [Nov.Dec. 2003]. Minor editorial style changes have also been made.
(HDQ: M. Marques) RTS-41081-2

## Change to read:

Cation-Exchange Resin, Styrene-Divinylbenzene-A strongly acidic, cross-linked sulfonated resin containing about $2 \%$ of divinylbenzene. It consists of white to light tan colored beads which may be relatively free flowing.

- 1 (USP28)

It is available in the hydrogen form in the 25 , 50, 45 and 80 to 270 mesh sizes.
-50- to 100 -, 100 - to 200 -, and 200- to $400-$ mesh sizes.■1S (USP28)
It can be regenerated to the hydrogen form by treating with a hydrochloric acid solution (5 in 100). For satisfactory regeneration, a contact time of at least 30 minutes is required after which it must be washed free of excess acid. It is insoluble in water, methanol, and acetonitrile. Suitable for use in column chromatography.

Moisture content of fully regenerated and expanded resinTransfer 10 to 12 mL of the resin (as received) to a flask, and convert it completely to the hydrogen form by stirring with 150 mL of hydrochloric acid solution ( 5 in 100) for not less than 30 minutes. Decant the acid, and wash the resin in the same manner with water until the wash water is neutral to litmus ( pH 3.5 ).

Transfer 5 to 7 mL of the regenerated resin to a glass filtering crucible, and remove only the excess surface water by very careful suction filtration. Transfer the conditioned resin to a tared weighing bottle, and weigh. Dry in a vacuum oven at a pressure of 50 mm of mercury at $100^{\circ}$ to $105^{\circ}$ for 16 hours. Transfer from the vacuum oven to a desiccator, cool to room temperature, and weigh again. The loss in weight is between $75 \%$ and $83 \%$.

Total wet volume capacity-Transfer 3 to 5 mL of the regenerated, undried (See Moisture content above) resin to a $5-\mathrm{mL}$ graduated cylinder, and fill it with water. Remove any air bubbles from the resin bed with a stainless steel wire, and settle the resin to its minimum volume by tapping the graduated cylinder. Record the volume of the resin.

Transfer the resin to a $400-\mathrm{mL}$ beaker. Add about 5 g of sodium chloride, and titrate, stirring well, with 0.1 N sodium hydroxide to the blue end-point of bromothymol blue ( pH 7.0 ).

$$
(\text { net } \mathrm{mL} \mathrm{NaOH} \times N) /(\mathrm{mL} \text { of resin })=\mathrm{mEq} / \mathrm{mL}
$$

The total wet volume capacity of the resin is more than 0.6 mEq per mL .

Wet screen analysis-The purpose of this test is to properly identify the mesh size of the resin. To obtain an accurate screen analysis would require special apparatus and technique.

Add 150 mL of resin to 200 mL of water in an appropriate bottle, and allow it to stand at least 4 hours to completely swell the resin.

Transfer by means of a graduated cylinder 100 mL of settled and completely swollen resin to the top screen of a series of the designated U. S. Standard $20.3-\mathrm{cm}$ brass screens. Thoroughly wash the resin on each screen with a stream of water until the resin is completely classified, collecting the wash water in a suitable container. Wash the beads remaining on the respective screens back into the $100-\mathrm{mL}$ graduate, and record the volume of settled resin on each screen. At least $70 \%$ of the resin will be within the specific mesh size.

- [NOTE—A suitable resin is "Dowex 50WX2" produced by Dow Chemical Co. (www.dow.com) and also available through Sigma-Aldrich (www.sigma-aldrich. com).] $]_{\text {1S (USP28) }}$


## Briefing

Citric Acid, USP 27 page 2677. It is proposed to cross-reference this reagent to the USP monograph for Citric Acid Monohydrate.
(HDQ: M. Marques) RTS-41083-2

## Change to read:

Citric Acid—Use the menehydrate form of Citrie Aeid
$\square_{\text {Citric Acid Monohydrate }}{ }_{\text {1S (USP28) }}$
(USP monograph).

## Briefing

Citric Acid, Anhydrous, USP 27 page 2677. It is proposed to cross-reference this reagent to the USP monograph for Anhydrous Citric Acid.
(HDQ: M. Marques) RTS-41083-1

## Change to read:

Citric Acid, Anhydrous- $\mathrm{G}_{6} \mathrm{H}_{8} \Theta_{7}-\mathbf{1 9 2 . 1 2}$ Use-ACS reagent srade-Citric Acid, Anhydreus.
-Use Anhydrous Citric Acid (USP monograph).■1S (USP28)

## Briefing

p-Chlorophenol, USP 27 page 2676; 4-Chlorophenol, USP 27 page 2677. It is proposed to delete the entry for $p$-Chlorophenol because of its redundancy and to revise the entry for 4-Chlorophenol to reflect the specifications of products currently available on the market.
(HDQ: M. Marques) RTS-41153-1

## Delete the following:

 erystalline selid, having a characteristic oder. Sparingly soluble in water, very soluble-in aeetone, in benzene, in ether, and in methanel.
Assay Transfer about 200 me, aceurately weighed, to a 100 mL beaker, add 25 mL of water, swinl to dissolve, and cantiously add, dreprise, sufficient sodium hydrexide solution to ensure eधmplete selution of the specimen. Transfer the-selution to a glass stoppered, 500 mL flask, using water to rinse the beaker, and dilute with water to about 100 mL . Add 25.0 mL of 0.1 Npe fascium bromide bromate VS and 10 mL of hydrechleric acid, im mediately insent the stopper in the flask, and swirl vigorously for 2 t-3 minutes. Remove the-stopper, quiekly ade 5 mL of petassitm iodide selution ( 1 in 5), taking care to avoid loss of bromine, im mediately insert the-stopper in the flask, and shake theroughly for about 1 minute. Remove the-stopper, rinse-it and the neek of the flask with water, and then titrate with 0.1 N sodium thiosulfate VS , adding 3 mL of starch TS as the endpeint is appreached. Each mL of 0.1 N petassium bremide bromate consumed is equivalent to 6.43 ma of $\mathrm{C}_{6} \mathrm{H}_{5} \Theta \mathrm{Cl}$. Not less than $99 \%$ is fount.

Melting range $\langle 744\rangle$ - between $42^{\circ}$ and $44^{\circ}$.
Boiling range (Reagent test) Not less than-90\% distils between $218.5^{\circ}$ and $221.5^{\circ} \mathrm{M}$ 1S (USP28)

## Change to read:

Dimethyl Sulfoxide-See Methyl Sulfoxide.
-(Methyl Sulfoxide), $\left(\mathrm{CH}_{3}\right)_{2} \mathrm{SO}-78.13-U s e ~ A C S ~ r e a g e n t ~$ grade methyl sulfoxide. 1 (USP28)

## Briefing

Hexane, Solvent, USP 27 page 2688. It is proposed to update the information regarding this reagent to reflect the product currently available on the market.
(HDQ: M. Marques) RTS-41114-2

## Change to read:

Hexane, Solvent (Petrolen Benzin; Petrotenn Ether)
-(Petroleum Benzin; Petroleum Ether, Ligroin) 1 (USP28)

- Clear, volatile liquid, having an ethereal or faint, petroleum-like odor. Practically insoluble in water; soluble in absolute alcohol. Miscible with ether, with chloroform, with benzene, and with most fixed and volatile oils.
Caution-It is dangerously flammable. Keep it away from flames and store in tight containers in a cool place.
Appertar Pour 100 mL , previendy well mixed in its original container, into 100 mL color compaisen tube, and eompare vith standard, in similar tube, containing 2 mb of platimme cobalt TS in similar wolume: the liequids are equally elear and free from suspended matter or sediment and when viewed aeress the eolumns by transmitted light, the test specimen is not darker in eolor than the standard.

Odor Its oder is not disagreeable or suggestive of mereaptans or thiophene.
Pistilling range (Rengent test) Distil $100 \mathrm{~mL}:$ none distils be low $30^{\circ}$ and not less than $100^{\circ}$ distils between $30^{\circ}$ and $60^{\circ}$.

Residte en evaporation- Evaporate $150 \mathrm{~mL}(100 \mathrm{~g})$ on a stemm bath, and dry at $105^{\circ}$ for 30 minutes: the residue weighs not more than $1 \mathrm{mg}(0.091 \%)$.

Acidity Shake 10 mL with 5 mL of water for 2 minttes, and allow the layers to separate: the water layer does not tarn blue lit mens red within 15 -seeonds.

Heary oils and fats Gradually pour 10 mL ont the center of a elean filter paper: there is no disagreeable odor and no greasy stain risible on the paper after it has stood for 30 minutes.

■Use ACS reagent grade Petroleum Ether.■1S (USP28)

## Briefing

Hexane, Solvent, Chromatographic, USP 27 page 2689. It is proposed to update the information regarding this reagent to reflect the product currently available on the market.
(HDQ: M. Marques) RTS-41113-1

## Change to read:

Hexane, Solvent, Chromatographic-It eomplies with the speeifications for Hexane, Solvent, and meets the requirements of the following additional test.

Speetral purity Measure in a 1 em cell at 300 nm, with a sui-table-spectrophemeter, against air as the blank: its absorbance is net mere than 0.08 .

- Use ACS HPLC reagent grade.■1S (USP28)


## Briefing

Hexanes (suitable for use in UV spectrophotometry), USP 27 page 2689 . It is proposed to update the information regarding this reagent to reflect the product currently available on the market.
(HDQ: M. Marques) RTS-41114-1

## Change to read:

Hexanes (suitable for use in UV spectrophotometry); usually a mixture of several isomers of hexane $\left(\mathrm{C}_{6} \mathrm{H}_{14}\right)$, predominantly $n$ hexane, and methylcyclopentane $\left(\mathrm{C}_{6} \mathrm{H}_{12}\right)$-Use ACS
$\boldsymbol{■}_{\text {spectrophotometric }}{ }_{\text {■1S (USP28) }}$
reagent grade.

## BRIEFING

Isovaleric Acid. This new reagent is used to prepare the Internal standard solution in the test for Acetyl and butyryl content under Cellaburate (Cellulose Acetate Butyrate), appearing on page 597 of PF 30(2) [Mar.-Apr. 2004].
(HDQ: M. Marques) RTS-41117-1

## Add the following:

-Isovaleric Acid (3-Methylbutanoic Acid, Isovalerianic Acid, Isopropylacetic Acid), $\mathrm{C}_{5} \mathrm{H}_{10} \mathrm{O}_{2}-\mathbf{1 0 2 . 1 3}$ [503-74-2]
—Use a suitable grade.■1S (USP28)

## Briefing

Methoxyphenylacetic Acid. This new reagent is used in Identification test $B$ under Sodium Caprylate, which appears elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-40974-1

## Add the following:

-Methoxyphenylacetic Acid ( $\alpha$-Methoxyphenylacetic Acid), $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{O}_{3}-\mathbf{1 6 6 . 2}$ [1701-77-5]—Use a suitable grade.■1S (USP28)

## Briefing

Methyl Iodide, USP 27 page 2695. It is proposed to specify that ferric ammonium sulfate TS is to be used in the Assay for this reagent.
(HDQ: M. Marques) RTS-41083-3

## Change to read:

Methyl Iodide, $\mathrm{CH}_{3} \mathrm{I}-141.94$ - Colorless, heavy, transparent liquid. Slightly soluble in water. Miscible with alcohol, with ether, and with solvent hexane. Turns brown on exposure to light as a result of liberation of iodine.

Assay-Add 1 mL to a $100-\mathrm{mL}$ volumetric flask tared with 10 mL of alcohol. Weigh again, add alcohol to volume, and mix. Pipet 20 mL into a glass-stoppered flask, and add 50.0 mL of 0.1 N silver nitrate VS and 2 mL of nitric acid. Insert the stopper immediately, shake frequently during 2 hours, and allow to stand in the dark overnight. Shake again during 2 hours, then add 50 mL of water and 3 mL of ferric ammonium sulfate
-TS, $\quad$ 1S (USP28)
and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS. Each mL of 0.1 N silver nitrate is equivalent to 14.19 mg of $\mathrm{CH}_{3} \mathrm{I}$ : not less than $98.5 \%$ is found.

Boiling range (Reagent test)-Distill 50 mL into a chilled, partly closed receiver: not less than 48 mL distills between $41.5^{\circ}$ and $43^{\circ}$.

Density: between 2.270 and 2.285 .
Residue on evaporation-Evaporate $4 \mathrm{~mL}(10 \mathrm{~g})$ on a steam bath, and dry the residue at $105^{\circ}$ for 1 hour: the residue weighs not more than $1 \mathrm{mg}(0.01 \%)$.

Acidity-Shake 3 mL with 5 mL of water for 30 seconds, and immediately draw off the lower layer: the aqueous layer is neutral to litmus, and when 1 mL of silver nitrate TS is added, it shows not more than a slight opalescence.

## BRIEFING

Methyl Sulfoxide, USP 27 page 2696. Because the use of the name "dimethyl sulfoxide" for methyl sulfoxide is being standardized throughout the $U S P-N F$, it is proposed to cross-reference the reagent methyl sulfoxide to dimethyl sulfoxide.
(HDQ: M. Marques) RTS-41082-8

## Change to read:

Methyl Sulfoxide (Pimethyl Sulfoxide), $\left(\mathrm{CH}_{2}\right)_{2} \mathrm{SO} \quad 78.13-$ Use ACS reagent grade.

- —See Dimethyl Sulfoxide.■1S (USP28)


## Briefing

Nonionic Wetting Agent. It is proposed to add this new reagent, which is used in the monographs for Ringer's Injection, Sodium Acetate Injection, and Chlorophyllin Copper Complex Sodium.
(HDQ: M. Marques) RTS-40997-1

## Add the following:

-Nonionic Wetting Agent-Use a suitable amphoteric surfactant.
[NOTE-A suitable grade is commercially available as Triton X-100 or Octoxynol 9.] $]_{\text {1S (USP28) }}$

## Briefing

Sodium 1-Heptanesulfonate, USP 27 page 2710 and page 315 of PF 30(1) [Jan.-Feb. 2004]; Sodium 1-Hexanesulfonate, USP 27 page 2710 and page 315 of $P F 30$ (1) [Jan. - Feb. 2004]. It is proposed to correct the previously proposed synonyms of these two reagents.
(HDQ: M. Marques) RTS-40980-1

## Change to read:

Sodium 1-Heptanesulfonate (1-Hexald),
-(1-Heptanesulfonic acid sodium salt) $\mathbf{1 S}_{1 \mathrm{~S}}$ (USP28) $\mathrm{C}_{7} \mathrm{H}_{15} \mathrm{NaO}_{3} \mathrm{~S}-\mathbf{2 0 2 . 2 5}$ - Use a suitable grade.

## Briefing

Sodium 1-Hexanesulfonate, USP 27 page 2710 and page 315 of PF 30(1) [Jan.-Feb. 2004]-See briefing under Sodium 1-Heptanesulfonate.
(HDQ: M. Marques) RTS-40980-1

## Change to read:

Sodium 1-Hexanesulfonate, (1-Pentic
 $\mathrm{C}_{6} \mathrm{H}_{13} \mathrm{NaO}_{3} \mathrm{~S}-\mathbf{1 8 8 . 2 2}$-Use a suitable grade.

## Briefing

Tropic Acid. This new reagent is used to prepare the System suitability preparation in the Assays under Hyoscyamine Sulfate Elixir and Hyoscyamine Sulfate Tablets, which appear elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-40539-5

## Add the following:

-Tropic Acid, $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{O}_{3}-\mathbf{1 6 6 . 1 8}$ [529-64-6]—Use a sui-
table grade.■1S (USP28)

## Volumetric Solutions

## Briefing

Lead Perchlorate, Tenth-Molar ( 0.1 M ). This new reagent is used in the test for Content of sulfate under Indinavir Sulfate, which appears elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-41029-1

## Add the following:

■Lead Perchlorate, Tenth-Molar (0.1 M)

$\mathrm{Pb}\left(\mathrm{ClO}_{4}\right)_{2} \cdot 3 \mathrm{H}_{2} \mathrm{O}, 460.15$
46.01 g in 1000 mL

Dissolve 46 g of lead perchlorate in water, and dilute with water to 1000.0 mL . Accurately weigh about 150 mg of sodium sulfate, previously dried at $105^{\circ}$ for 4 hours, and dissolve in 50 mL of water. Add 50 mL of a mixture of water and formaldehyde (1:1), and stir for about 1 minute. Determine the end point potentiometrically using a lead ion selective electrode. Perform a blank determination, and make any necessary corrections. Each 14.204 mg of sodium sulfate is equivalent to 1 mL of 0.1 M lead perchlorate. $\boldsymbol{m}_{1 S}$ (USP28)

## REFERENCE TABLES

## BRIEFING

Container Specifications for Capsules and Tablets, USP 27 page 2741, page 3166 of the First Supplement, and page 648 of PF 30(2) [Mar.-Apr. 2004].
(HDQ) RTS—37249-3; 39849-2; 40185-2

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the Packaging and storage requirements set forth in the individual monographs. It lists the capsules and tablets that are, or will be, official in the United States Pharmacopeia and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

| Container Specifications for Capsules and Tablets |  | Monograph Title | Container Specification |  |
| :---: | :---: | :---: | :---: | :---: |
| Monograph Title | Container Specification | Add the following: |  |  |
| Change to read: |  | ${ }^{\text {^ Gabapentin Capsules }}$ | $\mathrm{W}_{\mathbf{\wedge U S P 2 8}}$ |  |
| Acepromazine Maleate Tablets |  | Add the following: |  |  |
| Change to read: |  | ${ }^{\text {© }}$ Ginkgo Capsules | $\mathrm{T}, \mathrm{LR}_{\mathbf{\Delta} U S P 28}$ |  |
| Acetaminophen, Aspirin, and Caffeine Tablets | ${ }^{-1} \mathrm{~T}_{1 S}$ (USP27) | Add the following: |  |  |
| Change to read: <br> Acetazolamide Tablets | $\mathrm{m}_{\mathrm{T}}$ 1S (USP27) | ${ }^{\wedge}$ Ginkgo Tablets | $\mathrm{T}, \mathrm{LR}_{\mathbf{\Delta} U S P 28}$ |  |
| Add the following: |  | Change to read: <br> Asian Ginseng Capsules | T,LR |  |
| ${ }^{\wedge}$ Alendronate Sodium Tablets | $\mathrm{T}_{\mathbf{\Delta} U S P 28}$ |  | ${ }^{\text {A }}$ USP28 |  |
| Add the following: |  | Add the following: |  |  |
| ${ }^{\mathbf{4}}$ Benazepril Tablets | $\mathrm{W}_{\mathbf{\wedge} \text { USP28 }}$ | ${ }^{\text {A }}$ Indinavir Sulfate Capsules | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |  |
| Add the following: |  | Add the following: |  |  |
| ■Bisoprolol Fumarate Tablets | $\mathrm{T}, \mathrm{LR}_{\mathbf{■ 1 S ~}_{\text {(USP27) }}}$ | ${ }^{\mathbf{\Delta}}$ Irbesartan Tablets | $\mathrm{W}_{\mathbf{\Delta U S P 2 8}}$ |  |
| Add the following: |  | Add the following: |  |  |
| ■Bisoprolol Fumarate and Hydro- |  | ${ }^{\mathbf{4}}$ Irbesartan and Hydrochlorothiazide |  |  |
| chlorothiazide Tablets | $\mathrm{WT}_{\text {■1S (USP27) }}$ | Tablets | $\mathrm{W}_{\wedge U S P 28}$ |  |
| Add the following: |  | Add the following: |  |  |
| ${ }^{\text {© }}$ Cefaclor Tablets | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ | ${ }^{\text {4 }}$ Isosorbide Mononitrate Tablets | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |  |
| Add the following: |  | Add the following: |  |  |
| ${ }^{\text {© }}$ Clarithromycin Tablets, Extended- |  | ${ }^{\Delta}$ Isosorbide Mononitrate Tablets, |  |  |
| Release | $\mathrm{W}_{\mathbf{\wedge} \text { USP28 }}$ | Extended-Release | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |  |
| Add the following: |  | Add the following: |  | F |
| ${ }^{\text {® }}$ Black Cohosh Tablets | $\mathrm{T}, \mathrm{LR}_{\mathbf{\Delta} U S P 28}$ | ${ }^{\mathbf{4}}$ Isradipine Capsules | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |  |
| Add the following: |  | Add the following: |  | $\stackrel{3}{0}$ |
| ${ }^{\text {a }}$ Desogestrel and Ethinyl Estradiol |  | ■Loratadine Tablets | $\mathrm{T}_{\text {■1S (USP27) }}$ | $\stackrel{0}{3}$ |
| Tablets | $\mathrm{W}_{\mathbf{\Delta U S P 2 8}}$ | Add the following: |  |  |
| Add the following: |  | ${ }^{\boldsymbol{\Delta}}$ Metformin Hydrochloride Tablets | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |  |
| ${ }^{\text {A }}$ Fluoxetine Capsules, Delayed- |  | Add the following: |  |  |
| Release | $\mathrm{T}_{\mathbf{\wedge U S P 2 8}}$ | ■Metolazone Tablets | T, LR $\mathbf{■}_{\text {2S }}$ (USP27) |  |


| Monograph Title | Container Specification | Monograph Title | Container Specification |
| :---: | :---: | :---: | :---: |
| Add the following: |  | Add the following: |  |
| ${ }^{\text {A }}$ Misoprostol Tablets | $\mathrm{T}_{\mathbf{\triangle U S P 2 8}}$ | ${ }^{\text {® }}$ Valsartan Capsules | $\mathrm{T}, \mathrm{LR}_{\mathbf{4} U S P 28}$ |
| Add the following: |  |  |  |
| ■ Naratriptan Tablets | $\mathrm{T}_{\text {■1S (USP27) }}$ | Add the following: <br> ${ }^{\Delta}$ Valsartan and Hydrochlorothiazide |  |
| Add the following: |  | Tablets | $\mathrm{W}_{\mathbf{\Delta U S P 2 8}}$ |
| ${ }^{\text {s }}$ Norgestimate and Ethinyl Estradiol |  |  |  |
| Tablets | $\mathrm{W}_{\wedge U S P 28}$ |  |  |
| Add the following: |  |  |  |
| ${ }^{\wedge}$ Oxaprozin Tablets | T, LR $\mathbf{\Delta u S S P 2 8}$ | Briefing |  |

## Add the following:

■Paroxetine Tablets
$\mathrm{W}_{\text {■2S (USP27) }}$

## Add the following:

■ Pygeum Capsules

Add the following:
${ }^{\Delta}$ Quinapril Tablets
$\mathrm{W}_{\mathbf{\Delta} U S P 28}$

Change to read:
-Rimantadine Hydrochloride

Tablets

## Add the following:

■Stavudine Capsules
Add the following:
-Tolcapone Tablets

Add the following:
${ }^{\boldsymbol{4}}$ Valerian Capsules

$$
\mathrm{T}, \mathrm{LR}_{\boldsymbol{\square} 1 \mathrm{~S}(U S P 27)}
$$

$\mathrm{T}_{\text {■1S (USP28) }}$$\mathrm{T}, \mathrm{LR}_{\mathbf{\Delta} U S P 28}$

Add the following:
${ }^{\Delta}$ Valsartan Capsules
$\mathrm{T}, \mathrm{LR}_{\mathbf{\Delta} U S P 28}$

## Add the following:

${ }^{\Delta}$ Valsartan and Hydrochlorothiazide
Tablets

## Briefing

Description and Relative Solubility of USP and NF Articles, USP 27 page 2747, page 3166 of the First Supplement, page 5310 of PF 23(6) [Nov.-Dec. 1997], page 7017 of PF 24(5) [Sept.-Oct. 1998], page 8282 of $P F 25(3)$ [May-June 1999], page 8589 of $P F$ 25(4) [July-Aug. 1999], page 8917 of $P F$ 25(5) [Sept.-Oct. 1999], page 9254 of $P F$ 25(6) [Nov.-Dec. 1999], page 837 of $P F$ 26(3) [May-June 2000], page 1135 of $P F$ 26(4) [July-Aug. 2000], page 1385 of $P F$ 26(5) [Sept.-Oct. 2000], page 1907 of $P F$ 27(1) [Jan.Feb. 2001], page 2281 of PF 27(2) [Mar.-Apr. 2001], page 2839 of $P F$ 27(4) [July-Aug. 2001], page 3374 of $P F$ 27(6) [Nov.-Dec. 2001], page 554 of $P F 28(2)$ [Mar.-Apr. 2002], page 1236 of $P F$ 28(4) [July-Aug. 2002], page 1542 of $P F 28(5)$ [Sept.-Oct. 2002], page 1953 of PF 28(6) [Nov.-Dec. 2002], page 266 of PF 29(1) [Jan.-Feb. 2003], page 509 of $P F$ 29(2) [Mar.-Apr. 2003], page 812 of $P F$ 29(3) [May-June 2003], page 1262 of $P F$ 29(4) [July-Aug. 2003], page 1684 of $P F 29(5)$ [Sept.-Oct. 2003], page 2057 of PF 29(6) [Nov.-Dec. 2003], page 317 of PF 30(1) [Jan.Feb. 2004]; and page 650 of $P F 30(2)$ [Mar.-Apr. 2004].
(HDQ) RTS-39849-4; 39860-1; 40185-1; 40241-1; 409081; 40947-1; 40951-1; 40973-1; 41011-1

## Change to read:

Glyceryl Monostearate: White, wax like selid or as white, wax like-beads-or flakes.
-White to yellowish wax-like solid; or white to yellowish wax-like beads, flakes, or powder. 1 (USP28)
Slight, agreeable, fatty odor and taste. Is affected by light. Dissolves in hot organic solvents such as alcohol, minerals or fixed oils, benzene, ether, and acetone. Insoluble in water, but it may be dispersed in hot water with the aid of a small amount of soap or other suitable surface-active agent. NF category: Emulsifying and/or solubilizing agent.

## Change to read:

## Malathion: Yellow deep brown liquid,

- Clear, colorless, or slightly yellowish liquid, ${ }^{1 S}$ (USP28) having a characteristic odor. Congeals at about $2.9^{\circ}$. Slightly soluble in water. Miscible with alcohols, with esters, with ketones, with ethers, with aromatic and alkylated aromatic hydrocarbons, and with vegetable oils.


## Add the following:

-Maltol: A white, crystalline powder having a characteristic caramel-butterscotch odor, suggestive of a fruity-strawberry aroma in dilute solution. One gram dissolves in about 82 mL of water, in 21 mL of alcohol, in 80 mL of glycerin, and in 28 mL of propylene glycol. NF category: Flavors and perfumes.■1S (USP28)

## Add the following:

-Mirtazapine: White to creamy white, crystalline powder. Freely soluble in methanol and in toluene; soluble in ethyl ether; sparingly soluble in $n$-hexane; practically insoluble in water. 1 IS (USP28)

## Add the following:

-Palmitic Acid: Hard, white, or faintly yellow, somewhat glossy crystalline solid, or white or yellowish white powder. It has a slight characteristic odor and taste. Soluble in alcohol, in ether, and in chloroform; practically insoluble in

## Add the following:

-Phenylephrine Bitartrate: White or almost white powder or colorless crystals. Freely soluble in water. 1 (USP28)

## Add the following:

-Sodium Caprylate: A white, crystalline powder. Very soluble or freely soluble in water; freely soluble in acetic acid; sparingly soluble in alcohol; practically insoluble in acetone.m (USP28)

## Add the following:

-Stavudine: White to off-white crystalline powder. Soluble in water, in dimethylacetamide, and in dimethyl sulfoxide; sparingly soluble in methanol, in ethanol, and in acetonitrile; slightly soluble in dichloromethane; insoluble in hexane. 1 (USP28)

## Add the following:

-Tolcapone: Yellow, fine powder or fine powder with lumps. Freely soluble in acetone and in tetrahydrofuran; soluble in methanol and in ethyl acetate; sparingly soluble in chloroform and in dichloromethane; insoluble in water and in $n$-hexane. $\quad$ 1S (USP28)

Items from Earlier Numbers of PF that Have Not Yet Appeared in a Supplement, and are Therefore Candidates for Subsequent Supplements.

## GENERAL NOTICES AND REQUIREMENTS

Significant Figures and Tolerances-See PF Vol. 30 No. 2, page 424.

General Chapters-See PF Vol. 30 No. 2, page 424.
Tests and Assays-See PF Vol. 30 No. 2, page 425.
Preservation, Packaging, Storage, and Labeling-See PF Vol. 30 No. 2, page 428.

## USP MONOGRAPHS

Acepromazine Maleate-See PF Vol. 29 No. 6, page 1832.
Acetaminophen Oral Solution-See PF Vol. 30 No. 1, page 40.
Acetaminophen Oral Suspension-See PF Vol. 30 No. 1, page 40.
Acetaminophen and Aspirin Tablets-See PF Vol. 30 No. 1, page 41.

Capsules Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 43.
Oral Powder Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 44.
Oral Solution Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 44.
Tablets Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine-See PF Vol. 30 No. 1, page 42.
Tablets Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 44.
Acetaminophen and Codeine Phosphate Capsules-See PF Vol. 30 No. 1, page 45.
Acetaminophen and Codeine Phosphate Oral Solution-See PF Vol. 30 No. 1, page 46.
Acetaminophen and Codeine Phosphate Oral Suspension-See PF Vol. 30 No. 1, page 46.
Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solu-tion-See PF Vol. 30 No. 1, page 46.
Acetaminophen and Diphenhydramine Citrate Tablets-See PF Vol. 30 No. 1, page 47.
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets-See PF Vol. 30 No. 1, page 47.
Acetaminophen and Pseudoephedrine Hydrochloride TabletsSee PF Vol. 30 No. 1, page 48.
Acetazolamide-See PF Vol. 27 No. 3, page 2500.
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Acetazolamide Tablets-See PF Vol. 27 No. 3, page 2501.
Glacial Acetic Acid-See PF Vol. 27 No. 3, page 2501.
Acetic Acid Irrigation-See PF Vol. 27 No. 3, page 2501.
Acetic Acid Otic Solution-See PF Vol. 27 No. 3, page 2501.
Acetohexamide Tablets-See PF Vol. 27 No. 3, page 2501.
Acetohydroxamic Acid Tablets-See PF Vol. 30 No. 1, page 49.
Acyclovir-See PF Vol. 30 No. 2, page 431.
Acyclovir Capsules-See PF Vol. 30 No. 2, page 432.
Acyclovir for Injection-See PF Vol. 30 No. 2, page 433.
Acyclovir Ointment-See PF Vol. 30 No. 2, page 434.
Acyclovir Oral Suspension-See PF Vol. 30 No. 2, page 435.
Acyclovir Tablets-See PF Vol. 30 No. 2, page 436.
Adenosine-See PF Vol. 29 No. 6, page 1834.
Medical Air-See PF Vol. 28 No. 4, page 1065.
Albendazole Oral Suspension-See PF Vol. 29 No. 4, page 991.
Albumin Human-See PF Vol. 29 No. 4, page 992.
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Albuterol Sulfate-See PF Vol. 27 No. 3, page 2506.

Albuterol Tablets-See PF Vol. 30 No. 1, page 50.
Alendronate Sodium-See PF Vol. 30 No. 2, page 437.
Alendronate Sodium Tablets-See PF Vol. 28 No. 3, page 740.
Alendronic Acid Tablets-See PF Vol. 30 No. 2, page 440.
Alfentanil Hydrochloride-See PF Vol. 29 No. 6, page 1834.
Allopurinol-See PF Vol. 28 No. 5, page 1386.
Alprazolam Tablets-See PF Vol. 30 No. 1, page 51.
Alprostadil-See PF Vol. 29 No. 5, page 1412.
Alteplase-See PF Vol. 29 No. 6, page 1835.
Altretamine-See PF Vol. 27 No. 3, page 2514.
Altretamine Capsules-See PF Vol. 27 No. 3, page 2514.
Potassium Alum-See PF Vol. 27 No. 3, page 2515.
Alumina and Magnesia Oral Suspension-See PF Vol. 27 No. 3, page 2515.
Alumina and Magnesia Tablets-See PF Vol. 27 No. 3, page 2515.
Alumina, Magnesia, and Calcium Carbonate Oral SuspensionSee PF Vol. 27 No. 6, page 3241.
Alumina, Magnesia, and Calcium Carbonate Tablets-See PF Vol. 29 No. 6, page 1835.
Alumina, Magnesia, and Calcium Carbonate Chewable TabletsSee PF Vol. 29 No. 6, page 1836.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Ta-blets-See PF Vol. 29 No. 6, page 1837.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets-See PF Vol. 29 No. 6, page 1837.
Alumina, Magnesia, and Simethicone Tablets-See PF Vol. 29 No. 6 , page 1841.
Alumina, Magnesia, and Simethicone Chewable Tablets-See PF Vol. 29 No. 6, page 1842.
Amantadine Hydrochloride Capsules-See PF Vol. 30 No. 1, page 51.

Amifostine-See PF Vol. 30 No. 1, page 52.
Aminocaproic Acid-See PF Vol. 29 No. 5, page 1414.
Aminopentamide Sulfate-See PF Vol. 29 No. 6, page 1844.
Aminophylline-See PF Vol. 29 No. 5, page 1414.
Aminosalicylate Sodium Tablets-See PF Vol. 30 No. 1, page 53.
Amitriptyline Hydrochloride-See PF Vol. 29 No. 6, page 1844.
Ammonium Chloride-See PF Vol. 29 No. 5, page 1415.
Ferric Ammonium Citrate for Oral Solution-See PF Vol. 29 No. 6 , page 1845 .
Ammonium Molybdate-See PF Vol. 29 No. 5, page 1416.
Amobarbital Sodium-See PF Vol. 29 No. 6, page 1845.
Amoxicillin Tablets-See PF Vol. 29 No. 1, page 48.
Amoxicillin and Clavulanate Potassium for Oral Suspension-See PF Vol. 30 No. 1, page 53.
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Amphetamine Sulfate-See PF Vol. 30 No. 2, page 443.
Amphetamine Sulfate Tablets-See PF Vol. 30 No. 1, page 54.
Amphotericin B Lotion-See PF Vol. 30 No. 2, page 444.
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Ampicillin-See PF Vol. 28 No. 6, page 1766.
Ampicillin Capsules-See PF Vol. 30 No. 1, page 55.
Ampicillin Tablets-See PF Vol. 30 No. 1, page 56.
Anecortave Acetate-See PF Vol. 30 No. 2, page 445.
Anecortave Acetate Injectable Suspension-See PF Vol. 30 No. 2, page 447.
Anileridine-See PF Vol. 29 No. 6, page 1846.
Antithrombin III Human-See PF Vol. 30 No. 1, page 56.
Arginine Hydrochloride-See PF Vol. 30 No. 2, page 449.
Ascorbic Acid Tablets-See PF Vol. 30 No. 1, page 60.
L-Asparagine-See PF Vol. 29 No. 3, page 687.
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules-See PF Vol. 30 No. 1, page 60.
Atenolol-See PF Vol. 29 No. 5, page 1416.
Atenolol Tablets-See PF Vol. 29 No. 1, page 49.
Atovaquone Oral Suspension-See PF Vol. 30 No. 2, page 449.
Atracurium Besylate-See PF Vol. 29 No. 6, page 1846.
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Atropine Sulfate-See PF Vol. 29 No. 6, page 1847.
Aurothioglucose-See PF Vol. 29 No. 6, page 1847.
Azaperone-See PF Vol. 29 No. 6, page 1847.
Azithromycin-See PF Vol. 30 No. 2, page 450.
Azithromycin Capsules-See PF Vol. 27 No. 6, page 3394.
Aztreonam-See PF Vol. 30 No. 1, page 61.
Baclofen-See PF Vol. 29 No. 6, page 1848.
Baclofen Tablets-See PF Vol. 30 No. 1, page 61.
BCG Live-See PF Vol. 30 No. 2, page 452.
Benazepril Hydrochloride-See PF Vol. 29 No. 5, page 1422.
Benazepril Hydrochloride Tablets-See PF Vol. 29 No. 3, page 606.

Benzoyl Peroxide Gel-See PF Vol. 30 No. 2, page 455.
Benzoyl Peroxide Lotion-See PF Vol. 30 No. 2, page 456.
Benzoyl Peroxide Topical Emulsion-See PF Vol. 30 No. 2, page 456.

Benztropine Mesylate-See PF Vol. 29 No. 6, page 1848.
Benzyl Benzoate Lotion-See PF Vol. 30 No. 2, page 457.
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Betahistine Hydrochloride-See PF Vol. 29 No. 4, page 1008.
Betamethasone-See PF Vol. 29 No. 5, page 1427.
Betamethasone Oral Solution-See PF Vol. 30 No. 2, page 460.
Betamethasone Syrup-See PF Vol. 30 No. 2, page 460.
Betamethasone Tablets-See PF Vol. 30 No. 1, page 62.
Betamethasone Acetate-See PF Vol. 29 No. 5, page 1427.
Betamethasone Benzoate-See PF Vol. 29 No. 5, page 1427.
Betamethasone Benzoate Gel-See PF Vol. 29 No. 5, page 1428.
Betamethasone Dipropionate-See PF Vol. 29 No. 5, page 1428.
Betamethasone Dipropionate Cream-See PF Vol. 29 No. 5, page 1429.

Betamethasone Dipropionate Lotion-See PF Vol. 30 No. 2, page 458.

Betamethasone Dipropionate Ointment—See PF Vol. 29 No. 5, page 1430.
Betamethasone Dipropionate Topical Aerosol—See PF Vol. 29 No. 5, page 1428.
Betamethasone Dipropionate Topical Emulsion-See PF Vol. 30 No. 2, page 459.
Betamethasone Valerate Lotion-See PF Vol. 30 No. 2, page 461.
Betamethasone Valerate Topical Emulsion-See PF Vol. 30 No. 2, page 461.
Bethanechol Chloride-See PF Vol. 29 No. 6, page 1848.
Bethanechol Chloride Tablets-See PF Vol. 29 No. 1, page 54.
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers-See PF Vol. 30 No. 1, page 63.
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions-See PF Vol. 30 No. 1, page 66.
Biperiden-See PF Vol. 29 No. 6, page 1851.
Bismuth Subsalicylate Oral Suspension-See PF Vol. 28 No. 2, page 627 .
Bismuth Subsalicylate Tablets-See PF Vol. 28 No. 5, page 1603.
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Bretylium Tosylate-See PF Vol. 29 No. 5, page 1431.
Bromodiphenhydramine Hydrochloride and Codeine Phosphate Syrup-See PF Vol. 27 No. 5, page 2980.
Brompheniramine Maleate-See PF Vol. 29 No. 5, page 1431.
Brompheniramine Maleate and Pseudoephedrine Sulfate Oral So-lution-See PF Vol. 30 No. 1, page 79.
Brompheniramine Maleate and Pseudoephedrine Sulfate SyrupSee PF Vol. 30 No. 1, page 80.
Bumetanide-See PF Vol. 29 No. 5, page 1432.
Bupivacaine Hydrochloride-See PF Vol. 29 No. 5, page 1432.
Butalbital, Acetaminophen, and Caffeine Tablets-See PF Vol. 30 No. 1, page 80.
Butorphanol Tartrate-See PF Vol. 29 No. 6, page 1851.
Caffeine-See PF Vol. 29 No. 6, page 1852.
Caffeine Injection-See PF Vol. 30 No. 2, page 462.

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Phenolated Calamine Topical Suspension-See PF Vol. 30 No. 2, page 467.
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Calcitriol Injection-See PF Vol. 29 No. 5, page 1434.
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| Azithromycin-Preview (Assay) | 27 | 6 | 3393 |
| Barium Sulfate Paste-Title | 25 | 4 | 8479 |
| Dihydroergotamine Mesylate Nasal Solution (new)_Preview | 25 | 6 | 9078 |
| Helium-Identification, Assay | 28 | 4 | 1121 |
| Hydrocodone Bitartrate-USP Reference standards | 28 | 1 | 63 |
| Indinavir Sulfate (new) | 27 | 2 | 2165 |
| Indinavir Sulfate Capsules (new)-Preview | 26 | 6 | 1641 |
| Molindone Hydrochloride Tablets-Preview (Dissolution) | 24 | 1 | 5460 |
| Nitrogen-Assay | 28 | 4 | 1219 |
| Nitrogen 97 Percent-Assay | 28 | 4 | 1220 |
| Nitrous Oxide-Identification, Assay | 28 | 4 | 1169 |
| $\dagger$ Oxybutynin Chloride-Related compounds | 29 | 3 | 642 |
| Potassium Chloride-Packaging and storage | 29 | 4 | 1064 |
| $\dagger$ Potassium Chloride Extended-Release Capsules-Labeling, Dissolution, Drug release | 22 | 6 | 3043 |
| Propofol (new)-Bacterial endotoxins | 28 | 6 | 1854 |
| Talc (entire submission) | 29 | 1 | 157 |
| Unithiol (new)-Preview | 25 | 2 | 7752 |
| Dietary Supplements Monographs |  |  |  |
| Powdered Hawthorn Leaf with Flower-Packaging and storage | 26 | 5 | 1362 |
| Kava (new) | 28 | 1 | 100 |
| Powdered Kava (new) | 28 | 1 | 104 |
| Powdered Kava Extract (new) | 28 | 3 | 815 |
| Native Kava Extract (new) | 28 | 3 | 817 |
| Kava Capsules (new) | 28 | 3 | 818 |
| Kava Tablets (new) | 28 | 3 | 820 |
| USP General Test Chapters |  |  |  |
| <1) Injections-Labels and Labeling | 28 | 6 | 1910 |
| <11) USP Reference Standards |  |  |  |
| USP Indinavir RS | 27 | 2 | 2268 |
| USP Kawain RS | 26 | 3 | 793 |
| USP Powdered Kava Extract RS | 26 | 3 | 793 |
| <231) Heavy Metals-Harmonization | 28 | 5 | 1570 |
| <621) Chromatography-System Suitability | 26 | 5 | 1370 |
| USP General Information Chapters |  |  |  |
| <1141〉 Packaging, Storage, and Distribution of Pharmacopeial Articles (new) | 26 | 2 | 493 |
| <1151 Pharmaceutical Dosage Forms-Stability | 26 | 2 | 499 |
| 1172 Photostability Testing (new)-Preview | 26 | 2 | 384 |
| 1175 Preformulation Guidelines (new)-Preview | 26 | 6 | 1672 |
| <1191) Stability Considerations in Dispensing Practice- | 26 | 5 | 1378 |
| Introduction, Stability Studies in Manufacturing, Responsibility of the Pharmacist, Labile Preparations |  |  |  |
| Reagents, Indicators, and Solutions |  |  |  |
| Bromobimane (added) | 25 | 2 | 7804 |
| $\dagger$ Cesium Chloride (added) | 29 | 6 | 2054 |
| Potassium Permanganate, Tenth-Normal (0.1 N)-Erratum | 29 | 1 | 266 |

Proposed Revisions and New Text Previously Presented in PF but Now Canceled (Canceled proposals may be republished at any time in a future number of Pharmacopeial Forum.) [PF 30(1)-PF 30(6)] (continued)

| Title and Proposal | PFVolume, Issue, and Page Numbers of Canceled Proposals <br> Vol. <br> Reference Tables <br> No. | Page(s) |
| :--- | :---: | :--- |
| Container Specifications |  |  |
| Kava Capsules | 26 | 3 |
| Kava Tablets | 26 | 3 |

$\dagger$ New cancellations in 30(3).

Proposed Revisions and New Text Previously Presented in PF but Now Canceled
(Canceled proposals may be republished at any time in a future number of Pharmacopeial Forum.)

$$
[P F 30(1)-P F 30(6)]
$$

| Title and Proposal | PF Volume, Issue, and Page Numbers of Canceled Proposals |  |  |
| :---: | :---: | :---: | :---: |
|  | Vol. | No. | Page(s) |
| USP Monographs |  |  |  |
| Acetohexamide-Packaging and storage | 27 | 3 | 2501 |
| Adenine-Packaging and storage | 27 | 3 | 2504 |
| Alcohol-Packaging and storage | 27 | 3 | 2507 |
| Dehydrated Alcohol—Packaging and storage | 27 | 3 | 2507 |
| Allopurinol-Packaging and storage | 28 | 5 | 1386 |
| Allyl Isothiocyanate-Packaging and storage | 27 | 3 | 2509 |
| Azithromycin-Preview (Assay) | 27 | 6 | 3393 |
| Barium Sulfate Paste-Title | 25 | 4 | 8479 |
| Dihydroergotamine Mesylate Nasal Solution (new)_Preview | 25 | 6 | 9078 |
| Helium-Identification, Assay | 28 | 4 | 1121 |
| Hydrocodone Bitartrate-USP Reference standards | 28 | 1 | 63 |
| Indinavir Sulfate (new) | 27 | 2 | 2165 |
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| $\dagger$ Oxybutynin Chloride-Related compounds | 29 | 3 | 642 |
| Potassium Chloride-Packaging and storage | 29 | 4 | 1064 |
| $\dagger$ Potassium Chloride Extended-Release Capsules-Labeling, Dissolution, Drug release | 22 | 6 | 3043 |
| Propofol (new)-Bacterial endotoxins | 28 | 6 | 1854 |
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| Powdered Hawthorn Leaf with Flower-Packaging and storage | 26 | 5 | 1362 |
| Kava (new) | 28 | 1 | 100 |
| Powdered Kava (new) | 28 | 1 | 104 |
| Powdered Kava Extract (new) | 28 | 3 | 815 |
| Native Kava Extract (new) | 28 | 3 | 817 |
| Kava Capsules (new) | 28 | 3 | 818 |
| Kava Tablets (new) | 28 | 3 | 820 |
| USP General Test Chapters |  |  |  |
| <1) Injections-Labels and Labeling | 28 | 6 | 1910 |
| <11) USP Reference Standards |  |  |  |
| USP Indinavir RS | 27 | 2 | 2268 |
| USP Kawain RS | 26 | 3 | 793 |
| USP Powdered Kava Extract RS | 26 | 3 | 793 |
| <231) Heavy Metals-Harmonization | 28 | 5 | 1570 |
| <621) Chromatography-System Suitability | 26 | 5 | 1370 |
| USP General Information Chapters |  |  |  |
| <1141〉 Packaging, Storage, and Distribution of Pharmacopeial Articles (new) | 26 | 2 | 493 |
| <1151 Pharmaceutical Dosage Forms-Stability | 26 | 2 | 499 |
| 1172 Photostability Testing (new)-Preview | 26 | 2 | 384 |
| 1175 Preformulation Guidelines (new)-Preview | 26 | 6 | 1672 |
| <1191) Stability Considerations in Dispensing Practice- | 26 | 5 | 1378 |
| Introduction, Stability Studies in Manufacturing, Responsibility of the Pharmacist, Labile Preparations |  |  |  |
| Reagents, Indicators, and Solutions |  |  |  |
| Bromobimane (added) | 25 | 2 | 7804 |
| $\dagger$ Cesium Chloride (added) | 29 | 6 | 2054 |
| Potassium Permanganate, Tenth-Normal (0.1 N)-Erratum | 29 | 1 | 266 |

Proposed Revisions and New Text Previously Presented in PF but Now Canceled (Canceled proposals may be republished at any time in a future number of Pharmacopeial Forum.) [PF 30(1)-PF 30(6)] (continued)

| Title and Proposal | PFVolume, Issue, and Page Numbers of Canceled Proposals <br> Vol. <br> Reference Tables <br> No. | Page(s) |
| :--- | :---: | :--- |
| Container Specifications |  |  |
| Kava Capsules | 26 | 3 |
| Kava Tablets | 26 | 3 |

$\dagger$ New cancellations in 30(3).

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$$

## HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps (Stages).

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In $P F$, this stage appears as OFFICIAL INQUIRY STAGE 4 in the Harmonization section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

## Stage 5: Consensus

## A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

## B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.

## PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the Staff Directory to find the contact information).

Briefings Each Preview is preceded by a Briefing in the following format:

## Briefing

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being used, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see How To Use PF), the name of the scientific staff liaison who handled this item, and the USP tracking correspondence number, as shown in the example below:
(PA5: K. Russo) RTS—55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.
PHARMACOPEIAL PREVIEWS ..... 1069
DIETARY SUPPLEMENTS-MONOGRAPHS ..... 1071
Cat's Claw [new] ..... 1071
Powdered Cat's Claw [new] ..... 1075
Powdered Cat's Claw Extract [new] ..... 1075
Cat's Claw Capsules [new] ..... 1077
Cat's Claw Tablets [new] ..... 1078

## DIETARY SUPPLEMENTS— MONOGRAPHS

(DSB: G. Giancaspro) RTS—33274-1

## Add the following:

## Cat's Claw

» Cat's Claw consists of the inner bark of the stems of Uncaria tomentosa (Willd.) DC (Fam. Rubiaceae). It contains not less than 0.3 percent

[^109]
#### Abstract

\section*{BRIEFING}

Cat's Claw; Powdered Cat's Claw; Powdered Cat's Claw Extract; Cat's Claw Capsules; Cat's Claw Tablets. Because there are no existing USP monographs for these articles, the following new monographs are being previewed. There are two species of South American Uncaria known as Cat's Claw: $U$. tomentosa and U. guianensis. Also, the bark from both the root and the stem is commercially used, but due to conservational issues the bark from the stem is recommended for commercial exploitation. In addition, there are two chemotypes described in the literature: the pentacyclic alkaloid type and the tetracyclic alkaloid type. (See Keplinger K., et al. Uncaria tomentosa (Willd.) DC. Ethnomedicinal use and new pharmacological, toxicological and botanical results. J Ethnopharmacol. 1998, 64(1), 23-34.) This monograph refers to the stem bark from U. tomentosa, with predominance of the pentacyclic alkaloid chemotype. The microscopic description of the bark is based on the following articles: Lindorf, H. Reconocimiento al microscopio de la corteza y el polvo farmacéutico de las "uñas de gato" (Uncaria guianensis y Uncaria tomentosa). Uncaria 2001: 85-91 (I Reunión Internacional del género Uncaria "uña de gato," Iquitos, Peru); and Gattuso M., et al. Morphoanatomical studies of Uncaria tomentosa and Uncaria guianensis bark and leaves. Phytomedicine, Vol. 11, 2004 (in Press). ${ }^{*}$ The procedure for determination of content of pentacyclic alkaloids was based on the following article: Ganzera M., et. al. Improved method for the determination of oxindole alkaloids in Uncaria tomentosa by high performance liquid chromatography. Planta Med. 2001, 67, 447-450. Data for the HPLC procedure were obtained using a Luna C18 brand column containing packing L1. Typical retention times are $9.5,12.0,14.0,19.7,20.0$, and 26.8 minutes for speciophylline, uncarine F , mitraphylline, isomitraphylline, pteropodine, and isopetropodine, respectively.


of pentacyclic oxindole alkaloids, calculated on the dried basis, as the sum of speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine.

Packaging and storage-Preserve in tight, light-resistant containers, and store at room temperature.

Labeling-The label states the Latin binomial and, following the official name, the parts of the plant contained in the article.

USP Reference standards $\langle 11\rangle$ —USP Isopteropodine $R S$. USP Powdered Cat's Claw Extract RS.

Botanic characteristics-[NOTE-The pharmacopeial article is constituted only by the stem inner bark of $U$. tomentosa (Willd.) DC. Descriptions of other parts of the plant are given to aid in the collection of the right species. Compliance should be determined using the entire monograph and not only the botanical description.]

Macroscopic-Cat's Claw is a woody vine with a main stem up to 20 cm in diameter and 30 m long. The branches are obtusely quadrangular and generally puberulous. Stipules in the buds are densely tomentose in the upper side (difference with $U$. guianensis in which the stipules are glabrous) with the hairs, often with curved tips, meshed together and with the longer hairs of the leaf helping to connect the pair of stipules along the margins, but split when older (difference with $U$. guianensis in which the stipules separate early in the bud development). Thorns are straight to sickle-shaped, not spirally twisted (difference with $U$. guianensis), very pungent and woody, from 8 to 20 mm long and 3 to 6 mm wide. When recently cut, the color of the inner bark can be whitish gray, yellowish brown, or dark red, with longitudinal fissures and persistent rhytidome. The internal part has a slightly dusty fibrous and laminar texture
with a characteristic ferruginous dust and an extremely astringent taste. The terminal branches have a quadrangular section and yellowish green internal medulla.
Microscopic-The periderm with cork (phellem) is constituted by 6 to 8 rows of cells having walls evenly thickened, a compressed phellogen [NOTE-The periderm and phellogen should be absent in the pharmacopeial article], and a phelloderm with 1 to 7 rows of sclereids. The secondary cortex with concentric rings of fibers are separated by rings of parenchyma; rings of fibers are frequently interrupted by radial rows of parenchyma cells (predominately 1 cell broad) or narrow medullary rays (few cells broad), forming rectangular bundles of fibers in a regular network; in longitudinal view the fibers appear with numerous conspicuous pits; calcium oxalate microcrystals (sand-like) are abundant in the parenchyma, but usually absent as large polyhedral crystals or in the form of styloids with bifurcated endings, the latter forms typically present in the parenchyma of $U$. guianensis; a brown substance is dispersed in parenchyma cells; starch is abundant, granules are solitary (circular in outline, up to $10 \mu \mathrm{~m}$ in diameter) or compound (2 to 3 components up to $15 \mu \mathrm{~m}$ in diameter).

## Identification-

A: Thin Layer Chromatographic Identification Test〈201〉—

Test solution-Transfer about 1 g of the powdered Cat's Claw to a screw-capped centrifuge tube. Add 10 mL of methanol, and sonicate for 5 minutes, shaking occasionally. Heat the mixture in a water bath at $60^{\circ}$ for 15 minutes, cool, and filter. Apply $20 \mu \mathrm{~L}$ to the plate in bands that are 1 cm in length.

Standard solution-Transfer about 100 mg of USP Powdered Cat's Claw Extract RS to a screw-capped centrifuge tube. Add 10 mL of methanol, and sonicate for 5 minutes,
shaking occasionally. Heat in a water bath at $60^{\circ}$ for 15 min utes, cool, and filter. Apply $20 \mu \mathrm{~L}$ to the plate in bands that are 1 cm in length.

Developing solvent system-Prepare a solution of ethyl acetate and hexane ( $95: 5$ ).

Spray reagent $A$-Dissolve 0.85 g of basic bismuth nitrate in 10 mL of glacial acetic acid and 40 mL of water by heating. Filter if necessary (Solution A). Dissolve 8 g of potassium iodide in 30 mL of water (Solution B). Mix Solution A and Solution B (1:1) to obtain a stock solution. Dilute 1 mL of the stock solution with 2 mL of glacial acetic acid and 10 mL of water.

Spray reagent B-Use a $10 \%$ solution of sodium nitrite in water.

Procedure-Develop the chromatogram to a length of not less than 12 cm , and dry the plate in a current of air. Examine the plates under short UV light: the chromatogram obtained from the Test solution shows quenching zones that correspond in $R_{F}$ value to those for speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine in the chromatogram obtained from the Standard solution. Other quenching zones of varying intensities may be observed in the chromatogram obtained from the Test solution.

Spray the plate with Spray reagent $A$ followed by Spray reagent $B$, and examine the plate under daylight: the chromatogram obtained from the Test solution shows orangebrown zones that correspond in color and $R_{F}$ value to those for speciophylline, pteropodine, and isopteropodine in the chromatogram obtained from the Standard solution. Other colored zones of varying intensities may be observed in the chromatogram obtained from the Test solution.
B: The chromatogram of the Test solution exhibits peaks for speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine at retention
times that correspond to those in the chromatogram of Standard solution 1, as obtained in the test for Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindoles.

Microbial limits $\langle 2021\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total aerobic microbial count does not exceed $10^{5}$ per g , the total combined molds and yeasts count does not exceed $10^{3}$ per g , and the enterobacterial count is not more than $10^{3}$ per g.

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 2 hours: it loses not more than $7.0 \%$.

Foreign organic matter $\langle 561\rangle$ : not more than $2.0 \%$.
Total ash $\langle 561\rangle$ : not more than $8.0 \%$.
Acid-insoluble ash $\langle 561\rangle$ : not more than $2.0 \%$.
Pesticide residues $\langle 561\rangle$ : meets the requirements.
Heavy metals, Method III $\langle 231\rangle$ : not more than $20 \mu \mathrm{~g}$ per $g$.

Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindoles-

Solution A-Prepare a filtered and degassed 10 mM pH 7.0 phosphate buffer by mixing 6 mL of 1 N sodium hydroxide, 10 mL of 1 M monobasic potassium phosphate, and sufficient water to make 1000 mL , and adjusting to a pH of $7.0 \pm 0.1$ by adding more of either solution.

Solution B-Use filtered and degassed acetonitrile.
Solution C-Prepare a filtered and degassed solution of methanol and glacial acetic acid (99:1).

Mobile phase-Use variable mixtures of Solution A, Solution B, and Solution C as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution 1-Dissolve an accurately weighed quantity of USP Powdered Cat's Claw Extract RS in methanol, shaking for 1 minute. Dilute with methanol to obtain a solution having a known concentration of about 0.5 mg of the labeled amount of total oxindole alkaloids per mL. Pass through a filter having a $0.45-\mu \mathrm{m}$ or finer porosity.

Standard solution 2-Dissolve an accurately weighed quantity of USP Isopteropodine RS in methanol. Dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL . Pass through a nylon filter having a 0.45 $\mu \mathrm{m}$ or finer porosity.

Test solution-Accurately weigh approximately 750 mg of ground Cat's Claw, and place in a $10-\mathrm{mL}$ centrifuge tube. Sonicate with 2.5 mL of methanol for 10 minutes. Centrifuge, and transfer this solution to a $10-\mathrm{mL}$ volumetric flask. Repeat the above extraction three additional times combining the extracts in the $10-\mathrm{mL}$ volumetric flask, and dilute with methanol to volume. Transfer about 3 mL of the solution to a test tube containing 300 mg of polyamide powder, and shake for 1 minute. Pass through a nylon filter having a $0.45-\mu \mathrm{m}$ or finer porosity, discarding the first part of the filtrate.
Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a $245-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ column that contains endpacked $3-\mu \mathrm{m}$ packing L1. The flow rate is about 0.75 mL per minute. The chromatograph is programmed as follows.

| Time | Solution $A$ | Solution $B$ | Solution $C$ |  |
| :---: | :---: | :---: | :---: | :--- |
| $($ minutes $)$ | $(\%)$ | $(\%)$ | $(\%)$ | Elution |
| $0-17$ | 65 | 35 | 0 | isocratic |
| $17-22$ | $65 \rightarrow 50$ | $35 \rightarrow 50$ | 0 | linear gradient |
| $22-28$ | 50 | 50 | 0 | isocratic |
| $28-29$ | $50 \rightarrow 0$ | $50 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| $29-34$ | 0 | 0 | 100 | isocratic |
| $34-39$ | $0 \rightarrow 65$ | $0 \rightarrow 35$ | $100 \rightarrow 0$ | linear gradient |
| $39-49$ | 65 | 35 | 0 | equilibration |

Inject into the chromatograph Standard solution 1, and record the peak responses as directed for Procedure: the chromatograms obtained are similar to the Reference Chromatogram provided with the USP Powdered Cat's Claw Extract RS; the tailing factor for isopteropodine is not more than 2.0 ; and the relative standard deviation for replicate injections of Standard solution 1 is not more than 2.0\%.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of Standard solution 1, Standard solution 2, and the Test solution into the chromatograph, record the chromatograms, and measure the areas of the analyte peaks. Identify the retention times of the peaks corresponding to speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine by comparison of the chromatogram of Standard solution 1 with that obtained from the Reference Chromatogram. Separately calculate the percentages of speciophylline, uncarine F, mitraphylline, isomitraphylline, rhynchophyllin, isorhynchophyllin, pteropodine, and isopteropodine in the portion of Cat's Claw taken by the formula:
in which $C$ is the concentration, in mg per mL , of USP Isopteropodine RS in Standard solution 2; $W$ is the weight, in g , of Cat's Claw taken to prepare the Test solution; $r_{U}$ is the peak response for each relevant alkaloid obtained from the Test solution; and $r_{s}$ is the peak response for isopteropodine obtained from Standard solution 2. Calculate the content of pentacyclic oxindole alkaloids by adding the percentages of speciophylline, uncarine F , mitraphylline, isomitraphylline, pteropodine, and isopteropodine. Calculate the content of tetracyclic oxindole alkaloids by adding the individual percentages of rhynchophyllin and isorhynchophyllin: not more than 0.05 percent of tetracyclic oxindole alkaloids is found.

## $\langle 11\rangle$ USP Reference Standards <br> Add the following:

## USP Isopteropodine RS.

Add the following:

## USP Powdered Cat's Claw Extract RS.

$$
(C / W)\left(r_{U} / r_{s}\right),
$$

Briefing

Powdered Cat's Claw-See briefing under Cat's Claw.
(DSB: G. Giancaspro) RTS—33274-4

## Add the following:

## Powdered Cat's Claw

» Powdered Cat's Claw is Cat's Claw reduced to a powder or very fine powder. It contains not less than 0.3 percent of pentacyclic oxindole alkaloids, calculated on the dried basis, as the sum of speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine.

Packaging and storage-Preserve in tight, light-resistant containers, and store at room temperature.

Labeling-The label states the Latin binomial and, following the official name, the part of the plant from which the article was derived.

USP Reference standards $\langle 11\rangle$ —USP Isopteropodine RS. USP Powdered Cat's Claw Extract RS.

Botanic characteristics-Presence of fragments of cork and suberized cells, with cell walls evenly thickened. Presence of phelloderm sclereids. Fragments of fibers crossed by vascular rays are darkened due to the presence of sandlike calcium oxalate microcrystals. Solitary or two- to threecompound starch grains up to $15 \mu \mathrm{~m}$ in diameter. Absence of styloids, typically present in U. guianensis.

Other requirements-It meets the requirements of the tests for Identification, Microbial limits, Loss on drying, Total ash, Acid-insoluble ash, Pesticide residues, Heavy metals, and Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids under Cat's Claw.

## Briefing

Powdered Cat's Claw Extract-See briefing under Cat's Claw. (DSB: G. Giancaspro) RTS-33274-5

## Add the following:

## Powdered Cat's Claw Extract

» Powdered Cat's Claw Extract is prepared from Cat's Claw by extraction with hydroalcoholic mixtures or other suitable solvents. The ratio of plant material to extract is between $4: 1$ and $6: 1$. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of pentacyclic oxindole alkaloids, calculated on the dried basis, as the sum of speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine. It may contain suitable added substances.

Packaging and storage-Preserve in tight, light-resistant containers, and store at room temperature.

Labeling-The label states the Latin binomial and, following the official name, the part of the plant from which the article was prepared. The label also indicates the content of pentacyclic oxindole alkaloids, the extracting solvent or solvent mixture used for preparation, and the ratio of the starting crude plant material to Powdered Extract. It meets the requirements for Labeling under Botanical Extracts $\langle 565\rangle$.

USP Reference standards $\langle 11\rangle$ —USP Isopteropodine RS. USP Powdered Cat's Claw Extract RS.

## Identification-

A: Thin Layer Chromatographic Identification Test $\langle 201\rangle$ -
Standard solution, Developing solvent system, Spray reagent $A$, Spray reagent $B$, and Procedure-Proceed as directed for Thin-Layer Chromatographic Identification Test〈201〉 under Cat's Claw.

Test solution-Shake a quantity of Powdered Extract, equivalent to 25 mg of the labeled amount of pentacyclic oxindole alkaloids, in 20 mL of methanol. Allow to stand for 15 minutes before use.

B: The chromatogram of the Test solution exhibits peaks for speciophylline, uncarine $F$, mitraphylline, isomitraphylline, pteropodine, and isopteropodine at retention times that correspond to those in the chromatogram of Standard solution 1, as obtained in the test for Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids. The sum of the peak area for the tetracyclic oxindole alkaloids rhynchophylline and isorhynchophylline is less than $25 \%$ of the total area detected for pentacyclic oxindole alkaloids.

Microbial limits $\langle 2021\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total aerobic microbial count does not exceed $10^{4}$ per g , the total combined molds and yeasts count does not exceed $10^{3}$ per g , and the enterobacterial count is not more than $10^{3}$ per $g$.

Loss on drying $\langle 731\rangle$ —Dry 1 g at $105^{\circ}$ for 2 hours: it loses not more than $10.0 \%$ of its weight.

Heavy metals, Method II $\langle 231\rangle$ : not more than $10 \mu \mathrm{~g}$ per g.

Organic volatile impurities, Method $V I\langle 467\rangle$ : meets the requirements.

## Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindoles-

Solution A, Solution B, Solution C, Mobile phase, Standard solution 1, Standard solution 2, and Chromatographic system-Proceed as directed in the test for Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindoles under Cat's Claw.

Test solution-Transfer an accurately weighed quantity of Powdered Extract, equivalent to about 5 mg of the labeled content of pentacyclic oxindole alkaloids, to a $10-\mathrm{mL}$ centrifuge tube. Add 2.5 mL of methanol, and sonicate for 10 minutes. Centrifuge, and transfer the supernatant to a $10-\mathrm{mL}$ volumetric flask. Repeat the above extraction three additional times combining the extracts in the $10-\mathrm{mL}$ volumetric flask, and dilute with methanol to volume. Transfer about 3 mL of the solution to a test tube containing 300 mg of polyamide powder, and shake for 1 minute. Pass through a nylon filter having a $0.45-\mu \mathrm{m}$ or finer porosity, discarding the first part of the filtrate. Centrifuge, or pass through a filter having a $0.45-\mu \mathrm{m}$ or finer porosity.

Procedure-Proceed as directed in the test for Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids under Cat's Claw. Separately calculate the percentage of each relevant alkaloid in the portion of Powdered Extract taken by the formula:

$$
(C / W)\left(r_{U} / r_{S}\right)
$$

in which $W$ is the weight, in g , of Powdered Extract taken to prepare the Test solution; and the other terms are as defined therein. Calculate the percentage of pentacyclic oxindole alkaloids in the Powdered Extract taken by adding the individual percentages of speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine. Calculate the percentage of tetracyclic oxindole alkaloids in the Powdered Extract taken by adding the individual percentages of rhynchophylline and isorhynchophylline: not more than $25 \%$ of the labeled amount of pentacyclic oxindole alkaloids is found.

Other requirements-It meets the requirements for Residual Solvents and Pesticide Residues under Botanical Extracts $\langle 565\rangle$.

## Briefing

Cat's Claw Capsules-See briefing under Cat's Claw.
(DSB: G. Giancaspro) RTS—33274-2

## Add the following:

## Cat's Claw Capsules

» Cat's Claw Capsules contain Powdered Cat's Claw Extract. Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Powdered Extract, calculated as pentacyclic oxindole alkaloids.

Packaging and storage-Preserve in tight, light-resistant containers, and store at room temperature.

Labeling-The label states the Latin binomial and, following the official name, the article from which the Capsules were prepared. If prepared with Extract, the label also indicates the quantity, in mg, of Extract per Capsule and the content, in mg , of pentacyclic oxindole alkaloids per 100 mg of Powdered Extract.

USP Reference standards $\langle 11\rangle$ —USP Isopteropodine $R S$. USP Powdered Cat's Claw Extract RS.

Identification-The chromatogram of the Test solution exhibits peaks for speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine at retention times that correspond to those in the chromatogram of Standard solution 1, as obtained in the test for Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids. The content of tetracyclic oxindole alkaloids, calculated as the sum of rhynchophylline and isrhynchophylline, is not more than $25 \%$ of the labeled amount of pentacyclic oxindole alkaloids.

Microbial limits $\langle 2021\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total aerobic microbial count does not exceed
$10^{4}$ per g , the total combined molds and yeasts count does not exceed $10^{3}$ per g , and the enterobacterial count is not more than $10^{3}$ per $g$.

Disintegration $\langle 2040\rangle$ : meet the requirements for disintegration of botanical dosage forms.

Weight variation $\langle 2091\rangle$ : meet the requirements.
Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids-
Solution A, Solution B, Solution C, Mobile phase, Standard solution 1, Standard solution 2, and Chromatographic system-Proceed as directed in the test for Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids under Cat's Claw.

Test solution-Weigh accurately the contents of not fewer than 20 Capsules, and pulverize, using a mortar and pestle. Transfer an accurately weighed quantity of the powder, equivalent to 20 mg of the labeled amount of pentacyclic oxindole alkaloids, to a $50-\mathrm{mL}$ centrifuge tube. Sonicate with 10 mL of methanol for 10 minutes. Centrifuge, and transfer this solution to a $50-\mathrm{mL}$ volumetric flask. Repeat the above extraction three additional times combining the extracts in the $50-\mathrm{mL}$ volumetric flask, and dilute with methanol to volume. Transfer about 3 mL of the solution to a test tube containing 300 mg of polyamide powder, and shake for 1 minute. Pass through a nylon filter having a $0.45-\mu \mathrm{m}$ or finer porosity, discarding the first part of the filtrate.

Procedure-Proceed as directed in the test for Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids under Cat's Claw. Calculate the content of each relevant alkaloid, in mg, in the portion of Capsules taken by the formula:

$$
50 C\left(r_{U} / r_{s}\right)
$$

in which the terms are as defined therein. Calculate the content of total pentacyclic oxindole alkaloids by adding the individual contents of speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine. Calculate the content of tetracyclic oxindole alkaloids by adding the individual contents of rhynchophylline and isorhynchophylline: not more than $25 \%$ of the labeled amount of pentacyclic oxindole alkaloids is found.

## Container Specifications for Capsules and Tablets

## Add the following:

Cat's Claw Capsules
T, LR

BRIEFING

Cat's Claw Tablets-See briefing under Cat's Claw.
(DSB: G. Giancaspro) RTS-33274-3

## Add the following:

## Cat's Claw Tablets

» Cat's Claw Tablets contain Powdered Cat's Claw Extract. Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Powdered Extract, calculated as pentacyclic oxindole alkaloids.

Packaging and storage-Preserve in tight, light-resistant containers, and store at room temperature.

Labeling-The label states the Latin binomial and, following the official name, the article from which Tablets were prepared. The label also indicates the quantity, in mg, of Powdered Extract per Tablet. Label Tablets to indicate the content, in mg, of pentacyclic oxindole alkaloids per 100 mg of Powdered Extract.

USP Reference standards $\langle 11\rangle$ —USP Isopteropodine RS. USP Powdered Cat's Claw Extract RS.

Identification-The chromatogram of the Test solution exhibits peaks for speciophylline, uncarine F , mitraphylline, isomitraphylline, pteropodine, and isopteropodine at retention times that correspond to those in the chromatogram of Standard solution 1, as obtained in the test for Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids. The content of tetracyclic oxindole alkaloids, calculated as the sum of rhynchophylline and isrhynchophylline, is not more than $25 \%$ of the labeled amount of pentacyclic oxindole alkaloids.

Microbial limits $\langle 2021\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total aerobic microbial count does not exceed $10^{4}$ per g , the total combined molds and yeasts count does not exceed $10^{3}$ per g , and the enterobacterial count is not more than $10^{3}$ per $g$.

Disintegration $\langle 2040\rangle$ : meet the requirements for disintegration of botanical dosage forms.

Weight variation $\langle 2091\rangle$ : meet the requirements.

## Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids-

Solution A, Solution B, Solution C, Mobile phase, Standard solution 1, Standard solution 2, and Chromatographic system-Proceed as directed in the test for Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids under Cat's Claw.

Test solution-Weigh accurately not fewer than 20 Tablets, and pulverize, using a mortar and pestle. Transfer an accurately weighed quantity of the powder, equivalent to 20 mg of the labeled amount of pentacyclic oxindole alkaloids, to a $50-\mathrm{mL}$ centrifuge tube. Sonicate with 10 mL of methanol for 10 minutes. Centrifuge, and transfer this solution to a $50-\mathrm{mL}$ volumetric flask. Repeat the above extraction three additional times combining the extracts in the $50-\mathrm{mL}$ volumetric flask, and dilute with methanol to volume. Transfer about 3 mL of the solution to a test tube containing 300 mg of polyamide powder, and shake for 1 minute. Pass through a nylon filter having a $0.45-\mu \mathrm{m}$ or finer porosity, discarding the first part of the filtrate.

Procedure-Proceed as directed in the test for Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids under Cat's Claw. Calculate the content of each relevant alkaloid, in mg , in the portion of Tablets taken by the formula:

$$
50 C\left(r_{U} / r_{s}\right),
$$

in which the terms are as defined therein. Calculate the content of total pentacyclic oxindole alkaloids by adding the individual contents of speciophylline, uncarine F , mitraphylline, isomitraphylline, pteropodine, and isopteropodine.

Calculate the content of tetracyclic oxindole alkaloids by adding the individual contents of rhynchophylline and isorhynchophylline: not more than $25 \%$ of the labeled amount of pentacyclic oxindole alkaloids is found.

Container Specifications for Capsules and Tablets
Add the following:
Cat's Claw Tablets T, LR

## STIMULI TO THE REVISION PROCESS

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- reports or statements of authoritative committees
- original research reports
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# Pepsin and Pancreatin Performance in the Dissolution of Crosslinked Gelatin Capsules from pH 1 to 8 

Jean Gallery, *ian-Hwa Han, and Chiramel Abraham


#### Abstract

The authors conducted a systematic study of the use of pepsin and pancreatin in dissolution of crosslinked gelatin capsules in order to understand the digestive performance ability of the enzymes across the pH range from 1 to 8 . The work presented here includes a description of the experimental design and controls, followed by actual dissolution profiles obtained with pepsin from pH 1 to 6.8 and pancreatin from pH 4 to 8 . The results generally agree with published activity curves for the enzymes and bring into question the appropriateness of the recommended pancreatin level set forth in USP $\langle 711\rangle$.


## INTRODUCTION

Since the publication of the two-tier dissolution testing stimuli article in 1998 (1) and its subsequent adoption in USP $\langle 711\rangle$, there has been discussion in industry about the enzyme and activity recommendations based on the pH of the medium. Much of this discussion has been anecdotal, but published proteolytic activity curves for pepsin ( 1 , 2) and pancreatin (trypsin and chymotrypsin components) $(1,2)$ confirm that peak pepsin activity occurs around pH 2 and peak pancreatin activity appears around pH 8 . Unfortunately, the proteolytic activity of these enzymes in the pH range of 5-6 is significantly less than the peak activity.

The intention of this study was to characterize the proteolytic activity of pepsin and pancreatin through actual dissolution testing on crosslinked capsules across the pH range in which a dissolution laboratory typically operates.

Table 1. Experimental plan

|  | Pepsin |  |  |  | Pancreatin |  |  |  |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Enzyme | No | Yes | No | Yes | No | Yes | No | Yes |
| pH | Control |  | Crosslinked |  | Control |  | Crosslinked |  |
| 1 | X | X | X | X |  |  |  |  |
| 4 | X | X | X | X | X | X | X | X |
| 6 | X | X | X | X | X | X | X | X |
| 6.8 | X | X | X | X | X | X | X | X |
| 8 |  |  |  |  | X | X | X | X |

Dissolution was performed in medium containing aqueous hydrochloric acid or phosphate buffers to achieve the specified pH . The enzymes were added at the level recommended in USP $\langle 711\rangle$. That is, pepsin was added to the medium at not more than 750,000 units per liter, and pancreatin

[^110]
## EXPERIMENTAL DESIGN AND CONTROLS

## Experimental Design

Tier 1 and Tier 2 (Tier $1+$ enzyme) dissolution profiles of crosslinked gelatin capsules across the pH range of 1 to 8 have been collected according to the experimental plan outlined in Table 1. Dissolution profiles of six capsules were collected at each test condition. Each profile presented graphically in this article represents a mean of 6 capsules tested. Crosslinking of substrate capsules was achieved by treatment with formaldehyde vapor. The control capsules were untreated.
was added at not more than 1750 units of proteolytic activity per liter. Enzymes were freshly purchased from Sigma-Aldrich, and the labeled activities (from certificates of analysis) were used to determine the amount of enzyme to weigh for the media preparations to provide the maximum allowed activity levels. Each medium was prepared immediately before use to minimize potential autolysis and subsequent activity loss over time.

## Substrate Capsules

The substrate capsules chosen for this study have a dissolution profile that is independent of pH across the range studied ( $\mathrm{pH} 1-8$ ). The chosen substrate capsules are soft gelatin capsules with a hydrophilic liquid fill (development product at Abbott Laboratories). The dissolution profiles in Figure 1 show that dissolution is rapid, and opening of the gelatin shell dictates the release profile. Capsule opening is faster at lower pH , but this is to be expected well below the isoelectric point ( pI ) of the gelatin.


Fig.1. Substrate capsule dissolution profiles (untreated, Tier 1).
In addition, the untreated substrate capsule dissolution profiles are not affected by the addition of pepsin or pancreatin, as shown in Figure 2.


Fig. 2. Substrate capsule dissolution profiles (untreated, Tier 2).

## Induced Crosslinking

The goal of the induced crosslinking was to prepare capsules that would not meet $Q=80 \%$ in 30 minutes under Tier 1 conditions but would meet the requirement under Tier 2 conditions (with enzyme). Crosslinking was induced by treatment with formaldehyde vapor in a manner similar to a process previously published (6). The capsules were placed on a tray inside a vacuum desiccator, and approximately $5 \mu \mathrm{~L}$ of formaldehyde was added to a separate dish inside the chamber. A vacuum was pulled briefly to increase
the vapor pressure of the formaldehyde, and the flask was left closed for a length of time for the crosslinking reaction to occur.
Residual formaldehyde vapor will remain in the gelatin shell and further crosslink the capsules after they are removed from the reaction chamber. For this reason, it was decided to standardize the exposure time so that capsules could be prepared immediately before testing in the different media. Figure 3 depicts the exposure selection process. The profiles were generated in 0.1 N HCl medium with pepsin at $\sim 750,000$ units per liter.



Fig. 3. Aldehyde exposure study ( 0.1 N HCl Tier 1, Tier 2 with pepsin).

A 2-hour exposure time was insufficient to cause a Tier 1 failure. However, crosslinking induced by overnight exposure ( 15.5 hours) was too severe for pepsin to overcome at the USP activity level. A 4-hour exposure provided the desired failure and allowed complete recovery with the digestive enzyme. This aldehyde exposure time was used to crosslink capsules for the study outlined in Table 1 above. The Tier 1 and Tier 2 capsules for each test condition were prepared and tested on the same day for direct comparability. Figure 4 demonstrates the reproducibility of the 4-hour crosslinking process for each experiment in Table 1.


Fig. 4. Tier 1 capsule profiles after 4 hours of aldehyde exposure
Figure 4 does show some variability in the degree of crosslinking, which is to be expected. However, with the exception of the pH 1 curve, all other profiles show approximately $60 \%$ or less released at 30 minutes. Although the higher solubility of gelatin at pH 1 again is apparent, the profile does not meet $Q$ of $80 \%$ at 30 minutes. There is no trend among the pH 4 to pH 8 Tier 1 profiles. One can observe variability at the same pH on different days.

## Results and Discussion

The Tier 1 and Tier 2 dissolution profiles of crosslinked capsules were carried out as described in Table 1. The profiles obtained with pepsin are presented in Figure 5, and the profiles obtained with pancreatin are presented in Figure 6.

The data in Figure 5 confirm the wide pH range of published pepsin activity (2). The enzyme easily overcomes the crosslinking at pH 4 , where the profile is equivalent to the uncrosslinked profile presented in Figure 1. The Tier 2 release in pH 1 is slightly reduced at 20 minutes compared to the uncrosslinked profile; however the $Q$ value of $80 \%$ is easily met at 30 minutes. This agrees with the published activity curve (2) that shows a somewhat lower activity at pH 1 than at pH 4 . It is clear that pepsin begins to suffer activity loss at pH 6 . The chosen $Q$ is met at 30 minutes, but the release at 20 minutes is only $\sim 40 \%$. This indicates a delay in capsule shell opening that could lead to a failure at 30 minutes for products that are not immediately solubilized. Pepsin is unable to overcome the crosslinking at pH 6.8 , where the activity of the enzyme is greatly reduced.
The pancreatin data in Figure 6 are more surprising. The lack of response at pH 4 is expected based on the published activity curves $(4,5)$. However, the reduced ability to overcome crosslinking from pH 6 to 8 was not expected. The pancreatin activity at pH 8 was barely sufficient to bring the 30 -minute release value above $80 \%$, which is shown in part by the large standard deviation obtained ( $87 \pm$ $14 \%$ ). The Tier 2 profile at pH 6.8 is somewhat better than at pH 8 insofar as all 6 capsules achieve complete release in 30 minutes. The activity at pH 6 is not sufficient to allow the $Q$ of $80 \%$ to be met at 30 minutes; however it is very close (79\%).
Pancreatin was not able to bring the profiles back to the uncrosslinked appearance at any of the pH values studied. Delayed capsule shell opening was observed at each pH . Considering these capsules were crosslinked to the same extent as those in the pepsin portion of the study, it appears that the pancreatin level allowed in General Chapter $\langle 711\rangle$ is set too low. This statement is supported by a confirmation of the labeled activity of the lot of pancreatin used in the study. The value determined by the monograph test was $98 \%$ of the labeled amount of proteolytic activity from the vendor certificate of analysis.


Fig. 5. Demonstration of pepsin activity: Tier 1 and Tier 2 dissolution profiles of crosslinked capsules from pH 1 to 6.8 .


Fig. 6. Demonstration of pancreatin activity: Tier 1 and Tier 2 dissolution profiles of crosslinked capsules from pH 4 to 8 .

Further studies were performed to find the level of pancreatin that would bring the Tier 2 profiles back to the same appearance as the uncrosslinked capsule profile. Figure 7 shows the profiles obtained at pH 8 (expected peak activity) using the USP recommended pancreatin level of $\sim 1750$ activity units/L, along with profiles obtained with $2 \times, 3 \times$, and $5 \times$ levels of pancreatin.


Fig. 7. Dissolution profiles at pH 8 with multiple levels of pancreatin.

The profiles in Figure 7 indicate that a three-fold increase in pancreatin is required to bring the profile back to an uncrosslinked appearance. There is improvement at the twofold level; however the standard deviation is nearly $20 \%$ at the 20 -minute time point. At the $3 \times$ level, the standard deviation at 20 minutes is $\sim 2 \%$.

## CONCLUSION

The data presented in this study confirm that pepsin has a wide pH range of useful digestion activity in the dissolution of crosslinked capsules. The pH range of pancreatin activity also agrees with published values. However, the level allowed for dissolution testing according to USP General Chapter $\langle 711\rangle$ is insufficient when compared to the response of pepsin on the same capsules. It has been determined that a
three-fold increase in pancreatin is required to achieve the same level of digestion of crosslinked gelatin in the dissolution bath when compared to pepsin. The original study published by the Gelatin Capsule Working Group (1) showed that this level of pepsin was biologically relevant, but a rigorous study was not performed to match the activity of the enzymes. Now that this systematic study has been performed, USP is encouraged to consider formally revising the recommended level of pancreatin proteolytic activity in General Chapter $\langle 711\rangle$ on Dissolution.

Significant delay in capsule shell opening can be very detrimental to products that are not immediately solubilized. If the contents require a certain time to dissolve after the shell is breached, then the profile could be delayed enough to cause unnecessary failure. Because many products require time to dissolve the drug inside of the capsule, matching the pancreatin level to the biorelevant pepsin level will remove an unnecessary burden for industry.

## REFERENCES

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# Significant Digits and Rounding 

L. Torbeck


#### Abstract

This stimuli article on significant digits and rounding has been prepared in response to a need identified by the USP Biostatistics Expert Committee (BST). The clarification embodied in this text is intended as a preliminary presentation and is envisioned as part of a larger guidance on the reporting of measurement results. This is meant to be the initial presentation of material that may ultimately be included as a new general information chapter. The author is a member of BST and has received input on the content of this article from other committee members. Readers are invited to submit comments, suggested additions, changes, and revisions to the author.


## INTRODUCTION

In response to a need identified by the Biostatistics Expert Committee, this stimuli article on significant digits and rounding has been developed as part of a larger effort addressing the reporting of measurement results. This suggested approach is to be applied to all data collection activities and to all results generated by analytical laboratory testing or other means. Examples are provided.

The article clarifies and establishes standard practices for the following activities:

- reporting raw results;
- calculating intermediate results;
- using tabled values and spreadsheets;
- calculating analytical determinations;
- documenting reportable results; and
- defining procedures for rounding and determining the number of significant digits.
This approach also is recommended for application in other areas, such as manufacturing, where procedures may not currently exist. In some cases, this method may be superceded by specific standard operating procedures or monographs.

The procedures given here do not address analytical accuracy, precision, uncertainty estimates, or the statistical treatment of the results. The capability of an analytical method to provide sufficient accuracy and precision should be addressed during method development.

## RESPONSIBLE PARTIES

Within each testing setting, individual analysts, technicians, supervisors, group leaders, and reviewers are responsible for performing calculations, documenting, reviewing, and reporting results in accordance with the information given here. Supervisors and managers are further responsible for training and complying with this proposed procedure. The Information Technology department (or equivalent),

[^111]in conjunction with analysts or users, is responsible for recommending computer software that is not incompatible with this procedure.
The quality assurance department, quality control unit, or equivalent is responsible for resolving issues not specifically covered by this method or issues that conflict with software or external standards.

## USEFUL DEFINITIONS

The definitions that follow are not universal; rather, these definitions are for application in this suggested approach and related documents. The goal is to promote uniformity in the application of this suggested procedure.
Results may be numerical using the digits $0-9$, or they may be nonnumerical and may include words, colors, letters, and other nonnumerical symbols as the output of the instrument or the analytical method. Results may be as simple as a measurement with a ruler or as complex as NIR spectra. When recording numerical results, use a decimal point to separate any decimal fraction. If a value is less than one, a zero will precede the decimal point.
Raw results are the results or values displayed, printed, or manually recorded from a test method or an instrument. They may be the signal or instrument responses from the analyte or analytical property of interest that are captured, measured, and recorded manually, stored, displayed, or printed as a result of an analytical method or procedure. Examples include an absorbance value from a spectrophotometer or a peak area time slice from a chromatography data system. Note that in many instances the raw data accessible to the analyst will have fewer significant digits than the raw data used internally by the data-processing algorithms within the instrument or system. For this reason small discrepancies may arise when one compares internally generated intermediate results or analytical determinations with those calculated externally. Recognizing this is particularly important in validating software and/or verifying results generated during an audit.

Intermediate results are results or values derived from raw results to be used to calculate an analytical determination or a reportable result. For example, an intermediate result might be the average of a number of spectroscopic readings or the combination of individual peak areas from a set of samples or sample aliquots.

Analytical determinations are the results of the analytical measurement processes as described by the method and recorded in the laboratory notebook. They are calculated from predetermined documented combinations of raw results, metadata, tabled values, constants, and/or intermediate results. An analytical determination must contain no fewer significant digits than required by the specification criteria.

A reportable result is the end result or value of the complete measurement method and calculation procedure as documented in the official analytical procedure. It is derived from a predetermined number of analytical determinations that reflect the performance of the analytical method. It must be rounded to the same number of digits as in the specification criteria. If during development the specification criteria have not been defined, the reportable result should be rounded to the number of digits determined by a scientific consideration of the method precision and equipment characteristics. The reportable result is the official value reported out of the laboratory. Only the reportable result can be compared to the specification criteria. This comparison determines whether a sample is out of specification. It is possible to have more than one defined reportable result for the same set of raw results, intermediate results, or analytical determinations. Each is completely and independently defined and treated separately. For example, see Chapter $\langle 905\rangle$ Uniformity of Dosage Units.

Significant digits are the digits of a numerical result not including the zeros needed to locate the decimal point or the trailing zeros that function only as placeholders. Alternatively, they include those digits of a number beginning with the leftmost digit that is not zero and ending with the rightmost digit that is not zero or is a zero that is considered exact and not just a placeholder. The use of scientific notation with the correct number of significant digits is strongly recommended to avoid confusion. Counted numbers have an infinite number of significant digits. The word significant is used here as a synonym for meaningful and does not imply or relate to practical or statistical significance. See examples below.

Rounding a result approximates the true result to the appropriate number of significant digits according to the rounding rules. Double rounding within a single calculation to the final desired number of significant digits is never done. See examples below.

A specification is a document containing references to measurement and analytical test procedures and appropriate acceptance or rejection criteria that are numerical limits, ranges, nonnumerical results, or other criteria for the tests described.

Manual Recording occurs when results are calculated or documented by hand.

## PROCEDURES

## Reporting Raw Results

When raw results are not manually recorded before intermediate calculations are done, then all available digits are used. However, if raw results are manually recorded before intermediate calculations are done, then record the raw results with at least two more additional digits than are required by the specification criteria.

## Calculating Intermediate Results

If intermediate results are not manually recorded before analytical determinations are found, then all available digits are used and carried through the calculations. If intermediate results are manually recorded before the analytical determination is calculated, then the intermediate results are recorded with at least the number of digits in the raw results.
It is preferable to record standard deviations to no less than the same number of digits to the right of the decimal as the values from which they are based, maintaining two or more significant digits in these values.

## Calculating Analytical Determinations

Analytical determinations are calculated using intermediate results and tabled values. They are then rounded and recorded to a predetermined number of digits consistent with the calculations performed. This must be at least equal to the specification criteria if such criteria exist.
If there are fewer significant digits in the analytical determination than called for by the specification criteria, a valid determination cannot be made. In this case, the laboratory manager should be consulted for corrective action. (Unrounded analytical determinations are considered intermediate results.) This may also result in more significant digits than in the specification criteria. It is desirable to preserve this information for future investigations and analysis.

## Using Tabled Values and Spreadsheets

Tabled values from published scientific works or statistical tables are used with the number of significant digits as shown. Trailing zeros are considered significant. If the value is found while using a hand calculator or spreadsheet, then all the digits available are used.
For ease of use, linear interpolation can be used to find values between tabled values and used with the same number of digits as shown in the tabled values.

Published tables should be referenced. When there is a choice, $U S P-N F$, other compendia, publications from recognized standards-setting organizations, or government documents should be used and referenced.
Spreadsheets must not use the option of "precision as displayed" for any calculations.

## Rounding

Rounding is done by the five and up method. Unrounded analytical determinations are considered intermediate results. Rounding is only done once in calculating a reportable value from a data set, and it is always performed as the last step of calculation.

## Documenting Reportable Results

Reportable results are expressed by rounding the analytical determinations to the number of places that is in agreement with the specification criteria, if such criteria exist. This rounding is done before the comparison to the specification criteria.

A reportable result is the result used for official reports outside of the area generating the result. It is also the result used for any statistical calculations and/or analysis outside the area generating the result.

If specification criteria do not exist, the reportable result is documented to the number of digits in the analytical determination. Criteria in specifications are significant to the last digit shown. Reportable results are compared to the specification criteria, and a conclusion is made. An analytical determination may be used for more than one purpose. For example, LOD may be an element in determining another reportable value (perhaps a raw material assay) and also become a reportable value itself. For the raw material, all available significant digits are preserved and used to calculate the raw material assay. For LOD, the analytical determination would be rounded to agree with the LOD specification criteria and then reported.

Reportable results, by definition, cannot be averaged together in order to make quality assurance decisions affecting the acceptance or rejection of product. If, after the disposition of the product has been decided and documented and a single result is needed for a shipping Certificate of Analysis, then reportable results may be averaged and recorded for the Certificate of Analysis only.

## Documenting Digits

Note that the limits or values in specification criteria are fixed numbers and cannot be rounded off.

When one is rounding a sample size calculation, it is conservative and preferred to round any fraction up to the next whole number.

When one is rounding degrees of freedom (df), it is conservative and preferred to round any fraction down to the next whole number.

When rounding $p$ values, round to three digits to the right of the decimal.

Digits for $\ln (x)$ or $\log (x)$ are significant through the $n$-th place after the decimal point when $x$ has $n$ significant digits (ASTM E29).

The number of significant digits of $\epsilon^{x}$ or $10^{x}$ is equal to the place of the last significant digit in $x$ after the decimal (ASTM E29).

When changing units, keep the same number of significant digits, as in this example: $361 \mathrm{~mm}=36.1 \mathrm{~cm}=$ 0.361 m .

Positive values are rounded in the positive direction and negative values are rounded in the negative direction. For example, -1.689 if rounded to three significant digits is -1.69 , or -0.05 if rounded to one significant digit is -0.1 .
Some tests may give negative results. If, when appropriately rounded, the result is zero, the negative sign can be dropped. Optionally, the laboratory manager may elect to record $\pm$ zeros for trending and monitoring purposes.
For data such as percent recovery that are centered around 100, the calculated results will be treated, for significant digits purposes, as being at or above 100 . Values below 100 will carry as many digits to the right of the decimal as the values above 100 . Generically, this applies to data centered on a power of 10 .
Optionally, and for reporting of results, when there are six or more digits to the left of the decimal point, group the digits in threes and separate with commas. Optionally, when there are six or more digits to the right of the decimal point, group the digits in threes and separate by spaces. This is for convenience of reporting and not for analysis.

## Examples

## Rounding to Significant Digits

If a numerical result is determined to be 100.2 , its true value lies somewhere between $100.150 \quad 000 \rightarrow \infty$ and $100.249999 \rightarrow \infty$, given the rounding rule below.

| Examples of Significant Digits |  |  |
| :---: | :---: | :--- |
| Number | Significant <br> Digits | Notes |
| 102.4 | 4 |  |
| 102.44 | 5 |  |
| 0.00108 | 3 |  |
| 0.0010800 | 5 | The trailing zeros are not |
| $3.5 \times 10^{3}$ | 2 |  |
| $3.55 \times 10^{3}$ | 3 |  |
| $2800 \pm 50$ | 2,3 , or 4 | The trailing zeros may be <br> placeholders. |
| $0.060 \pm 0.005$ | 2 | The trailing zero is not a <br> placeholder. |
| $10 \pm 5$ | 1 or 2 |  |
| 38 counted | infinite |  |

Counted numbers, references standards, official targets, and standard conversions are assumed to have an infinite number of significant digits. For example, 38 as a count is considered to be $38.0000000 \rightarrow \infty$. Similarly, $60 \mathrm{mg} / \mathrm{mL}$ as a label claim is assumed to have an infinite number of significant digits. And $1 \mathrm{oz}=437.5$ grains exactly. For the ratio of two counted numbers, $100 / 3000=0.0333333 \rightarrow \infty$; report as many digits as needed for further calculations.

Fundamental constants and irrational numbers such as $\mathrm{e}=$ $2.718281 \ldots, \pi=3.141592 \ldots, \sqrt{ } 2=1.414213 \ldots$, and fractions such as $1 / 6=0.6666666 \ldots$ are used with sufficient digits to accommodate the other values in the calculation and should not be the limit on the number of significant digits in the result.

## Employing the Five and Up Rounding Rule

For the number to be rounded, identify one digit to the right of the last place that is in the specification criteria (lim$\mathrm{it})$. If this digit is four or less, it is dropped and the preceding digit is unchanged. If it is five or greater, it is dropped and the preceding digit is increased by one.

| Criteria | Calculation | Result |
| :---: | :---: | :---: |
| 95.0 to 105.0 | 97.47 | 97.5 |
|  | 97.44 | 97.4 |
|  | 97.45 | 97.5 |

Double rounding within a single calculation to the final desired number of significant digits is never permitted. Example:

| Calculation | First round | Second round |  |
| :---: | :---: | :--- | :--- |
| 100.345 | 100.35 | 100.4 | Incorrect |
| 100.345 | 100.3 |  | Correct |

Rounding up for a sample size calculation:

| Calculation | Result |
| :---: | :---: |
| 13.1 | 14 |
| 13.5 | 14 |
| 13.9 | 14 |

Rounding down for degrees of freedom (df) in a calculation:

| Calculation | Result |
| :---: | :---: |
| 13.1 | 13 |
| 13.5 | 13 |
| 13.9 | 13 |

Rounding $r$ from a calculation: Specification criteria: $r \geq 0.999$ :

| Calculation | Result |
| :---: | :--- |
| 0.99949 | 0.999 |
| 0.99950 | $1.000[0.99950]$ |
| 0.99988 | $1.000[0.99988]$ |

Report the analytical determination in brackets if the reportable result is $1.000 ; r$ is Pearson's correlation coefficient. Same rule for $r^{2}$, the coefficient of determination.

Rounding $p$ values to three digits to the right of the decimal:

| Calculation | Result |
| :---: | :---: |
| 0.0494 | 0.049 |
| 0.0495 | 0.050 |

Rounding for logarithms:

| Initial | Calculation | Result |
| :---: | :---: | :---: |
| $\ln (4.62)$ | 1.5303947 | 1.530 |

The result is to three places after the decimal because the number 4.62 has three significant digits.

Rounding for exponentials:

| Initial | Calculation | Result |
| :---: | :---: | :---: |
| $10^{2.875}$ | 749.8942 | 750 |

The result is to three significant digits because the value 2.875 has three digits to the right of the decimal.

The rounding rule can be generalized. Following are definitions by examples:

- Rounded to the nearest $0.01,16.385$ is 16.39 .
- Rounded to the nearest $0.1,13.95$ is 14.0.
- Rounded to the nearest $0.2,61.1$ is 61.2 .
- Rounded to the nearest $0.5,8.61$ is 8.5 .
- Rounded to the nearest $10 \mathrm{~s}, 8035$ is 8040 with the last zero a placeholder.
- Rounded to the nearest 50,8035 is 8050 with the last two zeros as placeholders.
Nonnumeric lists of acceptable categories are an analogy to rounding numeric results. For example, color categories could be defined as: white, off-white, light yellow, yellow, dark yellow. Only these categories would be used to report the results.


## Manually Recording Raw Results

As an example, a peak height is given as 8343.9867543. It is known to have only six significant digits. The analyst wishes to record a value in the laboratory notebook for ease of future calculations that contain more digits than six but fewer than the full number. It is appropriate to delete digits beyond the significant digits to, for example, 8343.9868. Optionally, all digits would be recorded and used.

The output of a digital meter is given as 0.956734576 3, but it is known that the instrument has only six significant digits. The value 0.95673458 could be manually recorded after deleting digits beyond the eighth place to the right of the decimal.

## Calculations

## UV Example:

Raw data as absorbances

| Standard Ab | 0.99021 |
| :--- | :---: |
| Sample Ab1 | 0.92672 |
| Sample Ab2 | 0.91594 |
| Standard Weight | 65.310 mg |


| Formula | $\mathrm{mg} / \mathrm{mL}=$ Sample $\mathrm{Ab} /$ Standard $\mathrm{Ab} \cdot$ Standard Wt mg |
| :--- | :--- |
| Sample 1 | $\mathrm{mg} / \mathrm{mL}=0.92672 / 0.99021 \cdot 65.310=61.12247220$ |
| Sample 2 | $\mathrm{mg} / \mathrm{mL}=0.91594 / 0.99021 \cdot 65.310=60.41146969$ |

The intermediate results are significant to at least five digits. However, if the results are to be manually recorded for further calculations, extra digits should be recorded.

Because 65.310 has five significant digits, and carrying two extra digits, the intermediate results can be reduced to seven digits as $61.12247 \mathrm{mg} / \mathrm{mL}$ and $60.41147 \mathrm{mg} / \mathrm{mL}$.

The analytical determination is the average of the intermediate results of the two samples: (61.12247 + 60.41147 ) $/ 2=60.766$ 97. This result, when rounded to five significant digits, is $60.767 \mathrm{mg} / \mathrm{mL}$.

The label claim is $60 \mathrm{mg} / \mathrm{mL}$. The $\%$ label claim $=$ $(60.767 \mathrm{mg} / \mathrm{mL}) /(60 \mathrm{mg} / \mathrm{mL})=101.27833$, which, when rounded to five significant digits, is $101.28 \%$. This is the analytical determination that is recorded in the laboratory notebook. (Note that the label claim of $60 \mathrm{mg} / \mathrm{mL}$ is assumed to have an infinite number of significant digits.)

The specification criterion is $98.0 \%$ to $102.0 \%$. A reportable value at or above 100 must be reported with four significant digits. Values below 100 are reported with the same number of digits to right of the decimal as the values at or above 100. In this example, the reportable value is $101.3 \%$ (noting that 101.27833 was rounded, not the analytical determination of 101.28 to avoid double rounding). Now compared to the criteria, the result passes.
Averages and standard deviations:
$\%$
100.8
100.1
99.9
101.0
99.6
99.5

|  | On the <br> Calculator | Analytical Determination |
| :--- | :--- | :---: |
| Average: | 100.15 | $100.2 \%$ |
| Std Dev: | 0.622093241 <br> (not calculated because the Std Dev is already <br> \%RSD <br>  <br> in \%) |  |
| Count | 6 |  |

Because there is no specification criterion, the reportable value is the analytical determination.

## Residue on Ignition Test:

Specification criterion: not more than (NMT) $0.1 \%$
Calculator display is 0.045881 from the calculation of the raw data.
This intermediate result could be recorded for further calculation by dropping two digits as 0.0458 (herein assuming two significant digits.)
The reportable result is found by rounding to agreement with the criteria as $0.0 \%$. The result passes.

## Comparison to Criteria

Criteria and limits, when shown numerically, are significant to the last digit shown. Upper and lower limits are inclusive. For example, limits of $95.0 \%$ to $105 \% .0$ include the values $95.0 \%$ and $105.0 \%$, so that values of 95.0 or $105.0 \%$ are a passing result.

Criteria and limits are assumed to allow for variability in raw materials, analytical testing, compounding, manufacturing, and for increases and decreases due to product instability. The reportable results as defined must meet the criteria as written. Additional compensation, guard bands, or adjustments for sources of variation are not permitted.

Analytical determinations with fewer significant digits or fewer digits to the right of the decimal than the criteria are inconclusive and may not be used to determine compliance with the specification criteria. The laboratory manager must resolve such issues, but the following summary table offers examples for guidance.

Table 1. Summary examples

| Compendial Requirement | Analytical <br> Determination | Reportable Value | Decision |
| :--- | :---: | :---: | :--- |
| Assay Limit $\leq 0.1 \%$ | $0.04 \%$ |  |  |
| Assay Limit $\leq 0.10 \%$ | $0.04 \%$ | $0.0 \%$ | Conforms |
| Assay Limit $\leq 0.10 \%$ | $0.1051 \%$ | $0.04 \%$ | Conforms |
| Assay Limit $\leq 0.10 \%$ | None detected | Invalid, not a number | Does not conform |
| Assay Limit $\leq 0.20 \%$ | $0.1 \%$ | Does not conform |  |
|  |  | Invalid, too few significant | Does not conform |
| Assay Limit $\leq 0.1 \%$ | $-0.02 \%$ | $0.0 \%$ |  |
| Assay Limit $\leq 0.5 \%$ | $-0.05 \%$ | $-0.1 \%$ | Conforms |
| Assay Limit $\geq 98.0 \%$ | $97.96 \%$ | $98.0 \%$ | Does not conform |
| Assay Limit $\geq 98.0 \%$ | $97.94 \%$ | $97.9 \%$ | Conforms |
| Assay Limit $\geq 98.0 \%$ | $97.95 \%$ | $98.0 \%$ | Does not conform |
| Limit Test $\leq 3 \mathrm{ppm}$ | 3.5 ppm | 4 ppm | Conforms |
| Limit Test $\leq 3 \mathrm{ppm}$ | 3.4 ppm | 3 ppm | Does not conform |
| Limit Test $\leq 3 \mathrm{ppm}$ | 2.8 ppm | 3 ppm | Conforms |
| NMT $2 \%$ | $1.971 \%$ | $2 \%$ | Conforms |
| NMT $2 \%$ | $2.499 \%$ | $2 \%$ | Conforms |
| NMT $2 \%$ | $2.500 \%$ | $3 \%$ | Conforms |
| $98.0 \%-102.0 \%$ | $97.950 \%$ | $98.0 \%$ | Does not conform |
| $98.0 \%-102.0 \%$ | $102.049 \%$ | $102.0 \%$ | Conforms |
| $98 \%-102 \%$ | $97.500 \%$ | $98 \%$ | Conforms |
| $98 \%-102 \%$ | $102.499 \%$ | $102 \%$ | Conforms |
| $r \geq 0.999$ | $r=0.99949$ | $r=0.999$ | Conforms |
| $r \geq 0.999$ | $r=0.99950$ | $r=1.000$ | Conforms |
|  |  | $[0.9950]$ | Conforms |
| $r \geq 0.999$ | $r=0.99849$ | 0.998 |  |
| Powder is white | Off-white | Clear | Off-white |

## SUMMARY

Readers are invited to submit comments, proposed additions, changes, and revisions. References and examples for substantive changes are strongly suggested.

## ACKNOWLEDGMENTS

Thanks to the members of the USP Biostatistics Expert Committee for their assistance and substantial feedback. Thanks also to Russell Nelson, Dr. Chris Burgess, John Elvig, and Dr. Robert Kieffer for reading the article and for their valuable comments.


## NOMENCLATURE

This section includes supplements to the latest edition of the USP Dictionary of USAN and International Drug Names that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

## USP Dictionary of USAN and International Drug Names 2004 USP DICTIONARY SUPPLEMENT 1

IMPORTANT-Save this Supplement. This and all supplements appearing in $P F$ are needed to keep the 2004 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2004) edition will be included in the next complete edition of the Dictionary.

## New United States Adopted Names (USAN)

The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of $P F$ for other new USAN to supplement the Dictionary main volume.

Ciluprevir [2004] (si loo pre' veer). $\mathrm{C}_{40} \mathrm{H}_{50} \mathrm{~N}_{6} \mathrm{O}_{8}$ S. 774.93. (1) Cyclopropa $[e]$ pyrrolo $[1,2-a][1,4]$ diazacyclopentadecine$14 \mathrm{a}(5 H)$-carboxylic acid, 6-[[(cyclopentyloxy)carbonyl]ami-no]-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydro-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]-4-thiazolyl]-4-qui-nolinyl]oxy]-5,16-dioxo-, ( $2 R, 6 S, 12 Z, 13 \mathrm{a} S, 14 \mathrm{a} R, 16 \mathrm{aS})-;$ (2) (2R,6S,12Z,13aS,14aR,16aS)-6-[[(Cyclopentyloxy)carbony-1]amino]-2-[[7-methoxy-2-[2-[(1-methylethyl)amino]thiazol4 -yl]quinolin- 4 -yl]oxy] -5,16-dioxo- 1,2,3,6,7,8,9,10,11,13a, 14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2a] $[1,4]$ diazacyclopentadecine-14a(5H)-carboxylic acid. CAS-300832-84-2. Treatment of Hepatitis C infection. (Boehringer Ingelheim GmbH, Germany) $\triangleleft B I L N 2061$ ZW

Dextofisopam [2004] (dex toe fis' oh pam). $\mathrm{C}_{22} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O}_{4}$. 382.45 . (1) 5H-2,3-Benzodiazepine, 1-(3,4-dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-, (5R)-; (2) (+)-(5R)-1-(3,4-Dimethoxyphenyl)-5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3benzodiazepine. CAS-82059-50-5. Treatment of irritable bowel syndrome, Crohn's disease; anti-anxiety, anti-stress. (Novasep) $\diamond R$-tofisopam

Ecopladib [2004] (ek oh pla' dib). $\mathrm{C}_{39} \mathrm{H}_{33} \mathrm{Cl}_{3} \mathrm{~N}_{2} \mathrm{O}_{5} \mathrm{~S}$. 748.11. (1) Benzoic acid, 4-[2-[5-chloro-2-[2-[[[(3,4-dichlorophenyl)-methyl]sulfonyl]amino]ethyl]-1-(diphenylmethyl)-1 H -indol-3-yl]ethoxy]-; (2) 4-[2-[5-Chloro-2-[2-[[(3,4-dichloroben-zyl)sulfonyl]amino]ethyl]-1-(diphenylmethyl)-1 H -indol-3yl]ethoxy]benzoic acid. CAS-381683-92-7. Treatment of pain and symptomatic management of arthritis. (Wyeth) $\triangleleft P L A-$ 725

Maropitant Citrate [2004] (mar oh pit' ant). $\mathrm{C}_{32} \mathrm{H}_{40} \mathrm{~N}_{2} \mathrm{O}$.$\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7} . \mathrm{H}_{2} \mathrm{O} .678 .81$. (1) 1-Azabicyclo[2.2.2]octan-3-amine, N -[[5-(1,1-dimethylethyl)-2-methoxyphenyl]methyl]-2-(di-phenylmethyl)-, ( $2 S, 3 S$ )-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1), monohydrate; (2) $(2 S, 3 S)-N-[5-(1,1-$ Dimethylethyl)-2-methoxybenzyl]-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-amine 2-hydroxy-1,2,3-propanetricarboxylate (1:1), monohydrate. CAS-359875-09-5. Antiemetic. (Pfizer) $\diamond C J-11,972$

Micafungin Sodium [2004] (mi ka fun' gin). $\mathrm{C}_{56} \mathrm{H}_{70} \mathrm{~N}_{9} \mathrm{NaO}_{23} \mathrm{~S}$. 1292.30. [Micafungin is INN.] (1) Pneumocandin A0, 1$\left[(4 R, 5 R)-4,5-\right.$ dihydroxy- $N^{2}$-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hy-droxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt; (2) $5-[(1 S, 2 S)-2-[(2 R, 6 S, 9 S, 11 R, 12 R, 14 \mathrm{a} S, 15 S, 16 S, 20 S, 23-$ $S, 25 \mathrm{a} S)$-20-[(1R)-3-Amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tetrahydroxy-6-[(1R)-1-hydroxyethyl]-16-methyl-

5,8,14,19,22,25-hexaoxo-9-[[4-[5-[4-(pentyloxy)phenyl]i-soxazol-3-yl]benzoyl]amino]tetracosahydro-1 H -dipyrrolo $\left[2,1-c: 2^{\prime}, 1^{\prime}-l\right][1,4,7,10,13,16]$ hexaazacyclohenicosin-23-yl]-1,2-dihydroxyethyl]-2-hydroxyphenyl sodium sulfate. CAS-208538-73-2; CAS-235114-32-6 [micafungin]. Treatment of Aspergillus and Candida fungal infections. Mycamine (Fujisawa) $\diamond F K 463$

Netoglitazone [2004] (net oh glit' a zone). $\mathrm{C}_{21} \mathrm{H}_{16} \mathrm{FNO}_{3} \mathrm{~S} .381 .42$. (1) 2,4-Thiazolidinedione, 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]-; (2) (5RS)-5-[[6-[(2-Fluorobenzy-1)oxy]-2-naphthyl]methyl]thiazolidine-2,4-dione.CAS-161600-01-7. INN. Antidiabetic; orally-administered insulin action enhancer to lower the plasma glucose in patients with non-insulin dependent diabetes mellitus (type 2). (Mitsubishi) $\checkmark M C C$ 555; RWJ-241947


Pelitrexol [2004] (pel' i trex ol). $\mathrm{C}_{20} \mathrm{H}_{25} \mathrm{~N}_{5} \mathrm{O}_{6} \mathrm{~S}$. 463.51. (1) LGlutamic acid, $N$-[[5-[2-[(6S)-2-amino-1,4,5,6,7,8-hexahy-dro-4-oxopyrido[ $2,3-d]$ pyrimidin-6-yl]ethyl]-4-methyl-2-thienyl]carbonyl]-; (2) (2S)-2-[[[5-[2-[(6S)-2-Amino-4-oxo-1,4,5,6,7,8-hexahydropyrido[2,3- $d$ ]pyrimidin-6-yl]ethyl]-4-methylthiophen-2-yl]carbonyl]amino]pentanedioic acid. CAS-446022-33-9. Antineoplastic (glycinamide ribonucleotide formyltransferase (GARFT) inhibitor). (Agouron) $\checkmark$ - $A$ G2037

Psyllium Hemicellulose [2004] (sil' i yum). Hemicellulose. CAS-9034-32-6. Laxation and cholesterol lowering. (Procter \& Gamble)

Ramelteon [2004] (ram el' tee on). $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{NO}_{2}$. 259.35. (1) Propanamide, $N$-[2-[(8S)-1,6,7,8-tetrahydro- 2 H -indeno[5,4-b]fu-ran-8-yl]ethyl $]-;(2)(-)-N-[2-([(8 S)-1,6,7,8-T e t r a h y d r o-2 H-$ indeno[5,4-b]furan-8-yl]ethyl]propanamide. CAS-196597-26-9. Treatment of sleep disorders. (Takeda) $\diamond T A K-375$

Tanaproget [2004] (tan a pro' jet). $\mathrm{C}_{16} \mathrm{H}_{15} \mathrm{~N}_{3} \mathrm{OS}$ 297.38. (1) 1 H -Pyrrole-2-carbonitrile, 5-(1,4-dihydro-4,4-dimethyl-2-thioxo-2H-3,1-benzoxazin-6-yl)-1-methyl-; (2) 5-(4,4-Dimethyl-2-
thioxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1-methyl-1 H -pyrrole-2-carbonitrile. CAS-304853-42-7. Oral contraception; nonsteroidal ligand for the progesterone receptor. (Wyeth) $\diamond N S P-989$

Teduglutide [2004] (te due' gloo tide). $\mathrm{C}_{164} \mathrm{H}_{252} \mathrm{~N}_{44} \mathrm{O}_{55} \mathrm{~S} .3752 .00$. (1) ALX 0600 (2-glycine-1-33-glucagon-like peptide II (human) ); (2) [2-Glycine]-1-33-glucagon-like peptide II (hu-
man). CAS-287714-30-1. Treatment of intestinal diseases characterized by chemical or surgical damage of the intestinal epithelium such as Short Bowel Syndrome (SBS) or damage to the intestinal epithelium due to disease (glucagonlike peptide-2 (GLP-2) analog). (NPS) $\diamond A L X 0600$

## Suggested United States Adopted Names

The United States Adopted Names (USAN) program is the specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs while the drugs are still in the investigational stages. The American Medical Association (AMA), the American Pharmaceutical Association (APhA), and the United States Pharmacopeial Convention (USPC) jointly sponsor the USAN program with representation from the FDA.

Each U.S. Adopted Name is chosen with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official United States Pharmacopeia or National Formulary. A measure of the prestige and recognition of the value of the USAN program can be found in the following regulations published by the Commissioner of Food and Drugs and the Secretary of Health and Human Services in the Federal Register of February 1988.

All who are concerned with the prescription, dispensing, use, sale or manufacture of drugs may, in the absence of the designation of an official name by the FDA, rely on the current compendial name or the U.S. Adopted Name (USAN) listed in this volume as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act.
A formal procedure ${ }^{1}$ is followed by the USAN Council in selecting an established name for a drug. The USAN Council Secretary is also an ex officio member of the International Nonproprietary Names (INN) Committee. USAN Guiding Principles are concordant with World Health Organization (WHO) principles, and all

| Suggested USAN | Category |
| :--- | :--- |
| Abacumab | Treatment of anthrax infection |
| Abbacumab |  |
| Agobacumab |  |
| Aribacumab |  |
| Raxibacumab |  |
| Abelacoxib | Treatment of pain, inflamma- |
| Gavacoxib | tion, and fever |
| Mavacoxib |  |
| Xavacoxib | Prevention of chronic solid or- |
| Zavacoxib | inflammatory, antioxidant, anti- |
| Abubucol | cholesterol-lowering properties |
| Abucolide |  |
| Elsibucol |  |
| Lebucolimus |  |
| Libobucol |  |
| Lidabucol | Treatment of psoriasis (vitamin |
| Lobucolide | Desibucol analog) |
| Acalcidiol |  |
| Acalcisecodiol |  |
| Becocalcidiol |  |
| Nobicalcidiol | Secocalcidiol |

[^112]

| Suggested USAN | Category | Suggested USAN | Category |
| :---: | :---: | :---: | :---: |
| Avanafil | Treatment of erectile dysfunc- | Cimtuzumab Ozogamicin | Treatment of cancer |
| Tyanafil | tion | Cintuzumab Ozogamicin |  |
| Vatanafil |  | Cituzumab Ozogamicin |  |
| Vitanafil |  | Inotuzumab Ozogamicin |  |
| Xyanafil |  | Intuzumab Ozogamicin |  |
|  |  | Tamatuzumab Ozogamicin |  |
| Batabulin | Treatment of various advanced refractory cancers (binds to $\beta$ tubulin) | Cinacalcet | Treatment of hyperparathyroidism and related disorders, such as hypercalcemia |
| Becotecarin | Antineoplastic |  |  |
| Bectcarin |  | Closafupermin | Treatment of immune thrombo- |
| Effectecarin |  | Karyopermin | cytopenic purpura |
| Eftecarin |  | Megapermin |  |
| Nebetecarin |  | Rocafupermin |  |
| Neotecarin |  | Tegafupermin |  |
|  |  | Tegafuplermin |  |
| Belocitabine | Treatment of HIV-1 and HIV-2infection |  |  |
| Revacitabine |  | Contafocon A | Hydrophobic contact lens material |
| Revcitavir |  | Disilfocon A |  |
| Tesacitabine |  | Disilofocon A |  |
| Tesrevir |  | Roflufocon A |  |
|  |  | Roflusifocon A |  |
| Bendamustine Hydrochloride | Treatment of hematologic cancer with initial focus on nonHodgkin's lymphoma | Contafocon B Roflufocon B | Hydrophobic contact lens material |
| Bisatrizole | Topical sunscreen active ingredient for OTC use | Contafocon C | Hydrophobic contact lens material |
| Bisoctrizole |  | Roflufocon C |  |
| Bistriazole |  |  |  |
| Bitrisorb |  | Contafocon D | Hydrophobic contact lens material |
| Microtriazol |  | Roflufocon D |  |
| Mirometrizole |  |  |  |
|  |  |  | Contafocon E | Hydrophobic contact lens material |
| Caremtorib | Antineoplastic; cytostatic | Roflufocon E |  |  |
| Carolistat |  |  |  |  |
| Casorolimus |  | Corstat Hydrochloride | Treatment of T-cell malignancies such as acute lymphoblastic leukemia ( $A L L$ ) and cutaneous T-cell lymphoma (CTCL) |  |
| Emtorolimus |  | Forodesine Hydrochloride |  |  |
| Macitorstat |  | Polastat Hydrochloride |  |  |
| Macrociclistat |  | Senistat Hydrochloride |  |  |
| Mactinistat |  | Zenstat Hydrochloride |  |  |
| Mactorolimus |  |  |  |  |
| Saticrolimus |  | Cortecorelin Acetate (human) | Treatment of symptoms associated with pertumoral edema in brain tumor patients |  |
| Sirolimus Bidproate |  | Cortecorelin Human Acetate |  |  |
| Temsirolimus |  | Corticorelin Acetate <br> Corticorelin Human Acetate |  |  |
| Carperitide | Treatment of decompensated congestive heart failure | Cresatumomab Sudotox | Cytotoxic agent to treat cancer |  |
|  |  | Luratumomab Sudotox |  |  |
| Carvedilol Phosphate | Treatment of congestive heart failure, left ventricular dysfunction following myocardial infarction, and management of hypertension | Luratumomab 38-Sudotox |  |  |
|  |  | Mesotumomab Sudotox |  |  |
|  |  | Nesotumomab Sitotox |  |  |
|  |  | Cribavirin | Antiviral; (pro-drug of ribavirin USP-1974) |  |
|  |  | Locarabine |  |  |
| Cefamersan Hydrochloride | Broad-spectrum parenteral antibiotic | Patarabine |  |  |
| Cefametsan Hydrochloride |  | Paribavirin |  |  |
| Cefazom Hydrochloride |  | Pribavirin |  |  |
| Cefazome Hydrochloride |  | Viramidine |  |  |
| Cefazomethine Hydrochloride |  |  |  |  |
| Cefazometine Hydrochloride |  | Deferamin | Treatment of patients with |  |
| Cefozom Hydrochloride |  | Deferatrimine | chronic iron overload who re- |  |
| Cefozome Hydrochloride |  | Deferitrin | quire iron chelation therapy |  |
|  |  | Deferitrine |  |  |
| Chlorsalbutrozate Sodium | Oral absorption promoter | Triferamin |  |  |
| Closalbuzate Sodium <br> Salchlorbutrozate Sodium <br> Salclobuzate Sodium |  | Deferasirox | Treatment of iron overload |  |


| Suggested USAN | Category | Suggested USAN | Category |
| :---: | :---: | :---: | :---: |
| Dekincept Sudotox | Antineoplastic | Ladostigil Tartrate | Treatment of Alzheimer's dis- |
| Litredekincept Sudotox |  |  | ease |
| Trekincept Sudotox |  |  |  |
| Trezdekincept Sudotox |  | Liopixen | Treatment of rheumatoid arthritis |
| Trezikincept Sudotox |  | Melopixen |  |
| Trezileukin 38Q-Sudotox |  | Mentaberel |  |
|  |  | Peliberel |  |
| Dinamostat | Anticancer; hematopoietic | Pelopixen |  |
| Dynamostat | stimulant | Penapixen |  |
| Falamostat |  |  |  |  |
| Oramostat |  | Liritrexate | Treatment of patients with malignancies |
| Talamostat |  | Panatrexate |  |
| Toramostat |  | Piritrexate |  |
| Valamostat |  | Pralatrexate |  |
|  |  | Travitrexate |  |
| Enoxaparin Sodium | Antithrombotic intended for use in the treatment of deep vein thrombosis; prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, and treatment of deep vein thrombosis |  |  |
|  |  | Pagibaximab | Prevention of staphylococcal sepsis in premature infants |
|  |  | Pediabacximab |  |
|  |  | Pilabaximab |  |
|  |  | Podobaximab |  |
|  |  | Panglitazar | Treatment of type 2 diabetes mellitus, mixed dyslipidemia, atherosclerosis and metabolic syndrome |
|  |  | Peliglitazar |  |
|  |  | Periglitazar |  |
| Eriforan | Treatment of sepsis | Puliglitazar |  |
| Eriquaran |  |  |  |
| Eritolforan |  | Probucol Hemisuccinate | Prevention of restenosis following PCI and the progression of atherosclerosis (antiproliferative; antioxidant with choles-terol-lowering properties) |
| Eritolimod |  | Resibucol |  |
| Ipoforan |  | Succinbucol |  |
| Lipoforan |  | Succinobucol |  |
|  |  | Succinprobucol |  |
| Etemucret | Treatment of dry eye (stimulates glycoprotein secretion) | Sucinbucol |  |
| Idroxicotrent |  | Tebucolide |  |
| Ferric Ferrocyanide | Antidote indicated for the treatment of patients with known or suspected internal contamination with radioactive cesium and/or radioactive or nonradioactive thallium to increase their rates of elimination | Procarogammadex <br> Pronagammadex <br> Sugammadex Sodium <br> Sunagammadex Sodium | Reversal agent for neuromuscular blocking agent |
| Ferric Hexacyanoferrate (II) |  |  |  |
| Ferric Hexacyanoferrate III |  |  |  |
| Insoluble Prussian Blue |  |  |  |
| Prussian Blue | and/or radioactive or nonradioactive thallium to increase their rates of elimination |  |  |
| Prussian Blue Insoluble |  | Ranofovir Mesylate Remofovir Mesylate | Antiviral |
| Gamoglitazar |  | Telithromycin | Antimicrobial agent |
| Gamoglitazil <br> mellitus |  |  |  |
| Soliglitazar |  | Tesaglitazar | Treatment of type 2 diabetes mellitus and insulin resistance syndrome |
| Soliglitazil |  |  |  |
| Soliglitia |  |  |  |  |
| SoliglitianSoliglixian |  |  |  |
|  |  |  |  | Treatment of tumors |
| Inkinesib Mesylate |  | Antineoplastic (kinesin inhibitor) | Yttrium Y90 EpratuzumabDOTA | A chelating agent used to conjugate radioisotope to monoclonal antibody in radioimmunotherapy (RAIT) for non-Hodgkin's B-Cell lymphoma |
| Iskinesib Mesylate |  |  |  |  |
| Ispinesib Mesylate | Yttrium Y90 Epratuzumab |  |  |  |
| Kispinesib Mesylate | Dotetate |  |  |  |
| Tokinesib Mesylate | Yttrium Y90 Epratuzumab |  |  |  |
| Tominesib Mesylate | Dotetran |  |  |  |
| Intadotin | Treatment of patients with advanced refractory neoplasms | Yttrium Y90 Epratuzumab Itraterate |  |  |
| Sintadotin |  | Yttrium Y90 Epratuzumab |  |  |
| Synthadotin |  | Itrateric |  |  |
| Tasidotin |  | Yttrium Y90 Epratuzumab Itratertan |  |  |
|  |  | Yttrium Y90 Epratuzumab Itraxetan |  |  |

## Suggested International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO). INNs for substances originating within the United States are applied for through the USAN Council. INN and USAN Guiding Principles are concordant, which assures that, with very few exceptions, INNs and USANs are identical.

Under its charter, the WHO is empowered simply to recommend specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as proposals ("Proposed International Nonproprietary Names"). A period of four months from the date of publication in WHO Drug Information is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event
that no objection is received, the WHO proceeds with listing and publishing the names so devised as recommendations ("Recommended International Nonproprietary Names'"), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

The names for the drugs that are categorized in the following list are under consideration for the selection of new Proposed International Nonproprietary Names. The name(s) being considered for each drug substance, and the applicable category, are separated by double spacing from the name(s) and category for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Suggested INN | Category |
| :---: | :---: |
| Benzacetylib | Treatment of solid and hemato- |
| Benzadacib | logic malignancies; inhibition |
| Carbadeacetylib | of histone deacetylase and consecutive hyperacetylation of histones |
| Caniglitazar | Treatment of type 2 diabetes and insulin resistance syndrome |
| Mesacanelion |  |
| Mesacanilir |  |
| Mesaglitazar |  |
| Mesircanelion |  |
| Mesirglitazar |  |
| Tesaglitazar |  |
| Ceftobasidril | Broad spectrum antibiotic active on multiresistant gram positive pathogens |
| Ceftobasitol |  |
| Ceftrobipirol |  |
| Ceftrotapirol |  |
| Ceftobasidril Daloxate | Broad spectrum antibiotic active on multiresistant gram positive pathogens |
| Ceftobasitol Daloxate |  |
| Ceftrobipirol Daloxate |  |
| Ceftrotapirol Daloxate |  |
| Cenadacad | Treatment of asthma and rhinitis |
| Linadacad |  |
| Seladacad |  |
| Valadacad |  |
| Vonadacad |  |
| Zaladacad |  |
| Cimabzumab | Immunotherapeutic agent to inhibit growth and spread of tumors of epithelial cell origin |
| Cimazumab |  |
| Cimzumab |  |
| Cinacalcet | Treatment of hyperthyroidism and related disorders, such as hypercalcemia |
| Cincalcept |  |
| Clopinotan | Neuroprotective effect against inschemic neuronal damage |
| Cloxazetan |  |
| Piclotan |  |


| Suggested INN | Category |
| :--- | :--- |
| Covitinib <br> Prolifinib <br> Selinib | Treatment of cancer |
| Dadenafil |  |
| Eudenafil |  |
| Kodanafil |  |
| Delamcimod Acetate <br> Delmitide Acetate | Treatment of erectile dysfunc- <br> tion; PDE 5 inhibitor |
| Defentasiderex <br> Defenterazirex <br> Defenterazoben <br> Deferasirox <br> Deferazirex | Treatment of chemotherapy-in- <br> duced diarrhea |
| Epoetin Lambda <br> Epoetin Sigma <br> Epoetin Theta | Treatment of iron overload |
| Flourocine | Antianemic |
| Flourocyanine | Fluorescence dye for use as a <br> Tribocine |
| Fluaquinimod | optical tomography |
| Fluquinimod |  |$\quad$| Anticancer; immunomodulat- |
| :--- |
| ing agent |


| Suggested INN | Category |
| :---: | :---: |
| Lactofertide Alfa | Anti-infective; anti-inflammatory, antineoplastic |
| Talactoferrin Alfa |  |
| Teractoferrin Alfa |  |
| Linaprazan | Potassium-competitive acid blocker |
| Lioprazan |  |
| Taraprazan |  |
| Luratumomab 38-Sudotox | Cytotoxic agent to treat cancer |
| Luratumomab Sudotox-38 |  |
| Mesotumomab Sudotox |  |
| Navaglitazar | Treatment of type 2 diabetes and associated cardiovascular indications |
| Naveglitazar |  |
| Naviglitazar |  |
| Neloglitazar |  |
| Procarogammadex | Reversal agent for neuromuscular blocking agents |
| Pronagammadex |  |
| Sugammadex |  |
| Sunagammadex |  |
| Succinbucol | Prevention of restinosis following PCI and the progression of atherosclerosis (antiproliferative; antioxidant with choles-terol-lowering properties) |
| Succinobucol |  |
| Succinprobucol |  |
| Talaglumetad Hydrochloride | Treatment of anxiety and stress disorders [metabotropic glutamate (mGlu) agonist $]$ |
| Trezileukin Sudotox-38Q | Treatment of malignant glioma |
| Trezileukin 38Q-Sudotox |  |
| Vatalanib | Antineoplastic |

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## USP CATALOG

## New Items at a Glance

See what's new in USP Reference Standards. For your convenient and quick reference, here's a list of Reference Standards released by USP over the past year.

This list is continuously updated with the newest Reference Standards released within the past 12 months.

| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1012939 | Allantoin (200 mg) | F0C169 | \$156 |
| 1048619 | Benazepril Hydrochloride ( 125 mg ) | F0C250 | \$156 |
| 1048620 | Benazepril Related Compound A ( 15 mg ) | F0C252 | \$487 |
| 1048630 | Benazepril Related Compound B ( 15 mg ) | F0C256 | \$487 |
| 1048641 | $\begin{aligned} & \text { Benazepril Related Compound C } \\ & (50 \mathrm{mg}) \end{aligned}$ | F0C425 | \$487 |
| 1071439 | Positive Bioreaction (3 strips; $10 \mathrm{~cm} \times 1$ cm ) | F0D014 | \$325 |
| 1098118 | Cefpiramide ( 300 mg ) | F0C203 | \$156 |
| 1105009 | Powdered Chaste Tree Extract (1.5 g) | F0C406 | \$520 |
| 1111001 | Chlorhexidine ( 200 mg ) | F0C306 | \$156 |
| 1111103 | Chlorhexidine Acetate ( 500 mg ) | F0C281 | \$156 |
| 1111307 | Chlorhexidine Related Compounds $(50 \mathrm{mg})$ | F0D017 | \$487 |
| 1115545 | Chlorogenic Acid ( 50 mg ) | F0C420 | \$156 |
| 1133547 | Choline Chloride ( 200 mg ) | F0C058 | \$156 |
| 1140247 | Clomipramine Hydrochloride ( 200 mg ) | F0C075 | \$156 |
| 1140349 | Clonazepam Related Compound C $(25 \mathrm{mg})$ | F0C340 | \$487 |
| 1140393 | Clonidine ( 200 mg ) | F0C401 | \$156 |
| 1140418 | Clonidine Related Compound A ( 25 mg ) | F0C373 | \$487 |
| 1140429 | Clonidine Related Compound B ( 25 mg ) | F0C403 | \$487 |
| 1148500 | Copovidone ( 100 mg ) | F0C194 | \$156 |
| 1152701 | Cyclandelate ( 200 mg ) | F0C384 | \$156 |
| 1171900 | Desflurane ( 0.5 mL ) | F0C187 | \$156 |
| 1171910 | Desflurane Related Compound A (0.1 mL ) | F0C031 | \$487 |
| 1179708 | Dextran 40 ( 50 mg ) | F0C247 | \$156 |
| 1179741 | Dextran 70 ( 50 mg ) | F0C260 | \$156 |
| 1224959 | Dolasetron Mesylate ( 200 mg ) | F0C319 | \$156 |
| 1224960 | Dolasetron Mesylate Related Compound A ( 25 mg ) | F0C321 | \$487 |
| 1225419 | Doxazosin Mesylate ( 200 mg ) | F0C079 | \$156 |
| 1231728 | Powdered Echinacea Purpurea Extract $(1 \mathrm{~g})$ | F0D018 | \$520 |
| 1231706 | Powdered Echinacea Angustifolia Extract (1 g) | F0D019 | \$520 |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | \$520 |
| 1272204 | Fludarabine Phosphate ( 300 mg ) | F0C374 | \$156 |
| 1273808 | Flumazenil ( 200 mg ) | F0C305 | \$780 |
| 1279837 | Fluoxetine Related Compound C $(15 \mathrm{mg})$ | F0C352 | \$487 |
| 1286060 | Formononetin ( 50 mg ) | F0C196 | \$520 |
| 1287675 | Gadoversetamide ( 200 mg ) | F0C172 | \$156 |
| 1287686 | Gadoversetamide Related Compound A ( 200 mg ) | F0C173 | \$487 |
| 1288306 | Ganciclovir (200 mg) | F0C287 | \$364 |
| 1288317 | Ganciclovir Related Compound A ( 15 mg ) | F0C288 | \$624 |
| 1294207 | Glucosamine Hydrochloride (200 mg) | F0C363 | \$156 |


| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1305507 | 2E, 4E-Hexadienoic Acid Isobutylamide ( 25 mg ) | F0C353 | \$540 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) | F0C214 | \$513 |
| 1349014 | Isoflurane Related Compound A (0.1 mL ) | F0C232 | \$487 |
| 1349025 | Isoflurane Related Compound B (0.1 mL ) | F0C233 | \$487 |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 | \$260 |
| 1355753 | Kawain (200 mg) | F0C160 | \$208 |
| 1356836 | Lamivudine ( 200 mg ) | F0C361 | \$156 |
| 1370270 | Loratadine ( 200 mg ) | F0C414 | \$260 |
| 1378012 | Medroxyprogesterone Acetate Related Compound A ( 25 mg ) | F0C427 | \$500 |
| 1392454 | Meropenem ( 300 mg ) | F0C201 | \$182 |
| 1396309 | Metformin Hydrochloride ( 200 mg ) | F0C209 | \$182 |
| 1396310 | Metformin Related Compound A ( 50 mg ) | F0C210 | \$487 |
| 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution CII ( 0.5 mL ) | F0C368 | \$560 |
| 1441232 | Metoprolol Related Compound A ( 20 mg ) | F0C343 | \$520 |
| 1441243 | Metoprolol Related Compound B ( 50 mg ) | F0C377 | \$520 |
| 1441254 | $\begin{aligned} & \text { Metoprolol Related Compound C } \\ & (20 \mathrm{mg}) \end{aligned}$ | F0C344 | \$520 |
| 1441265 | Metoprolol Related Compound D ( 50 mg ) | F0C378 | \$520 |
| 1441298 | Metoprolol Succinate ( 200 mg ) | F0C415 | \$156 |
| 1445211 | Mitoxantrone System Suitability Mixture ( 0.3 mg ) | F0D010 | \$500 |
| 1457469 | Naratriptan Hydrochloride ( 125 mg ) | F0C360 | \$208 |
| 1478582 | Ondansetron Hydrochloride ( 300 mg ) | F0C222 | \$208 |
| 1478593 | Ondansetron Related Compound A $(50 \mathrm{mg})$ | F0C191 | \$487 |
| 1478618 | Ondansetron Related Compound C $(50 \mathrm{mg})$ | F0C251 | \$487 |
| 1478629 | Ondansetron Related Compound D ( 50 mg ) | F0C226 | \$487 |
| 1483301 | Oxfendazole ( 200 mg ) | F0C128 | \$156 |
| 1491332 | Paclitaxel ( 200 mg ) | F0C180 | \$1,508 |
| 1491343 | Paclitaxel Related Compound A ( 20 mg ) | F0C179 | \$754 |
| 1491354 | Paclitaxel Related Compound B ( 20 mg ) | F0C181 | \$754 |
| 1500251 | $\begin{aligned} & \text { Paroxetine Related Compound D } \\ & (15 \mathrm{mg}) \end{aligned}$ | F0C228 | \$487 |
| 1535020 | Phenytoin Related Compound B ( 50 mg ) | F0C157 | \$487 |
| 1596807 | Quinine Hydrochloride Dihydrate (1 g) | F0C108 | \$156 |
| 1599500 | Powdered Red Clover Extract (500 mg) | F0C188 | \$260 |
| 1601102 | Residual Solvent Mixture - Class 1 ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C407 | \$156 |
| 1601146 | Residual Solvent Class 1 - Benzene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C408 | \$156 |
| 1601168 | Residual Solvent Class 1 - Carbon Tetrachloride ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C409 | \$156 |
| 1601180 | Residual Solvent Class 1-1,2Dichloroethane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C412 | \$156 |

New Items at a Glance (Continued)

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :--- | :--- | :--- | :--- |
| 1601204 | Residual Solvent Class 1 - 1,1- <br> Dichloroethene (1.2 mL/ampule; <br> a ampules) | F0C411 | $\$ 156$ |
| 1601226 | Residual Solvent Class 1-1,1,1- <br> Trichloroethane (1.2 mL/ampule; <br> 3 ampules) | F0C410 | $\$ 156$ |
| 1604508 | Rimantadine Hydrochloride (300 mg) | F0C266 | $\$ 156$ |
| 1610090 | Scopoletin (20 mg) | F0C329 | $\$ 156$ |
| 1612540 | Sevoflurane (1 mL) | F0C219 | $\$ 156$ |
| 1612550 | Sevoflurane Related Compound A (0.2 <br> mL) | F0C261 | $\$ 487$ |
| 1617408 | Sotalol Hydrochloride (300 mg) | F0C234 | $\$ 182$ |
| 1617419 | Sotalol Related Compound A (50 mg) | F0C235 | $\$ 487$ |
| 1617420 | Sotalol Related Compound B (50 mg) | F0C236 | $\$ 487$ |
| 1617430 | Sotalol Related Compound C (50 mg) | F0C237 | $\$ 487$ |
| 1621507 | Stearoyl Polyoxyglycerides (100 mg) | F0C286 | $\$ 156$ |
| 1642154 | Sumatriptan (50 mg) | F0C220 | $\$ 208$ |
| 1642201 | Sumatriptan Succinate (200 mg) | F0C231 | $\$ 208$ |
| 1642212 | Sumatriptan Succinate Related <br> Compound A (15 mg) | F0C221 | $\$ 624$ |
| 1642223 | Sumatriptan Succinate Related <br> Compound C (50 mg) | F0C230 | $\$ 624$ |


| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :--- | :--- | :--- | :--- |
| 1643452 | Terazosin Hydrochloride (200 mg) | F0C244 | $\$ 156$ |
| 1643463 | Terazosin Related Compound A <br> $(50 \mathrm{mg})$ | F0C245 | $\$ 487$ |
| 1643474 | Terazosin Related Compound B <br> $(50 \mathrm{mg})$ | F0C218 | $\$ 487$ |
| 1643485 | Terazosin Related Compound C <br> $(25 \mathrm{mg})$ | F0C257 | $\$ 487$ |
| 1667290 | Tiamulin Fumarate (250 mg) | F0C327 | $\$ 156$ |
| 1667337 | Tiamulin Related Compound A <br> $(50 \mathrm{mg})$ | F0C328 | $\$ 494$ |
| 1708762 | Valsartan (350 mg) | F0C147 | $\$ 156$ |
| 1708773 | Valsartan Related Compound A <br> $(20 \mathrm{mg})$ | F0C215 | $\$ 624$ |
| 1708795 | Valsartan Related Compound C <br> $(10 \mathrm{mg})$ | F0C208 | $\$ 624$ |
| 1711155 | Vecuronium Bromide (60 mg) | F0C367 | $\$ 156$ |
| 1711461 | Verteporfin (200 mg) | F0C166 | $\$ 156$ |
| 1714506 | Vinorelbine Tartrate (200 mg) | F0C243 | $\$ 156$ |
| 1714528 | Vinorelbine Related Compound A <br> $(25 \mathrm{mg})$ | F0C242 | $\$ 487$ |

## USING AND ORDERING USP REFERENCE STANDARDS

## Official Reference Standards

USP Reference Standards are required for use in pharmacopeial assays and tests in the official standards publication, the United States Pharmacopeia-National Formulary (USP-NF). USP Reference Standards help to ensure compliance with the official, FDA-enforceable quality requirements in the $U S P-N F$. The Reference Standards also lend themselves to many other applications, including measurements required to attain accurate and reproducible results in modern chromatographic and spectrophotometric methods.

## Rigorous Testing and Quality Control

USP Reference Standards are selected for their high purity, critical characteristics, and suitability for the intended purpose. Unless a USP Reference Standard label states a specific potency or content, the USP Reference Standard is taken as being $100 \%$ pure for the USP purposes for which it is provided.

Heterogeneous substances, of natural origin, are also designated "Reference Standards" where needed. Usually these are the counterparts of international standards.

USP Reference Standards are established through a process of rigorous testing, evaluation, and quality control. They are independently tested in three or more laboratories-USP, FDA, and academic and industrial laboratories throughout the United States. The Reference Standards are released under the authority of USP's Board of Trustees, on the recommendation of the USP Reference Standards Expert Committee, which approves selection and suitability of each lot.

## Reference Standards Categories

USP offers more than 1,540 Reference Standards for pharmaceuticals, excipients, and dietary supplements. On pages 13-52 of this catalog, you'll find a full list of available USP and NF Reference Standards, with information updated through Dec. 2003. The list includes:

- Reference Standards required by the current official edition of $U S P-N F$.
- Reference Standards not required in the current $U S P-N F$, but for which sufficient demand remains.
- Reference Standards specified in the current edition of the Food Chemicals Codex (FCC).
- Authentic Substances (AS)—highly purified samples of chemicals, including substances of abuse, required by analytical, clinical, pharmaceutical, and research laboratories.

The distribution of controlled substances is subject to the regulations and licensing provisions of the Drug Enforcement Administration (DEA) of the U.S. Department of Justice.

USP also collaborates with the World Health Organization in its program to provide international biological standards and chemical reference materials for antibiotics, biologicals, and chemotherapeutic agents. Some USP Reference Standards are standardized in terms of the corresponding international standards.

## Proper Use of USP Reference Standards

USP Reference Standards are provided primarily for quality control use in conducting the pharmacopeial assays and tests described in the $U S P-N F$. Neither Reference Standards nor Authentic Substances are intended for use as drugs, dietary supplements, or medical devices.

To serve its intended purpose, each USP Reference Standard must be properly stored, handled, and used. Users of USP Reference Standards should refer to General Chapter $\langle 11\rangle$ in the $U S P-N F$ :

## Listing and directions in USP-NF

- Refer to the list of revisions, additions, and deletions of individual USP Reference Standards in USP 27-NF 22. Individual $U S P$ or $N F$ monographs specify the USP Reference Standard(s) required for assay and test procedures. The USP 27-NF 22 General Test Chapter $\langle 11\rangle$ USP Reference Standards provides additional information and instructions for proper use and storage. Note that if specific instructions for use appearing on the label of a USP Reference Standard differ from the instructions in Chapter $\langle 11\rangle$, the instructions on the label take precedence.
- Consult the cumulative updates to Reference Standards information provided in USP-NF Supplements and also in $U S P-N F$ Interim Revision Announcements, which are published in USP's bimonthly journal, Pharmacopeial Forum.


## Suitability for use

- The user must ascertain that the Reference Standards they are using are an official lot.
- The user must determine the suitability of Reference Standards for applications and uses not in the $U S P-N F$.


## USING AND ORDERING USP REFERENCE STANDARDS

## Storing

- Ensure that the USP Reference Standards are stored in their original stoppered containers, according to any special label directions, away from heat and humidity, and protected from light.


## Weighing

- Ensure that Reference Standard substances are accurately weighed-taking due account of relatively large errors potentially associated with weighing small masses-where it is directed that a standard solution or a standard preparation be prepared for a quantitative determination. See USP 27-NF 22 General Chapters $\langle 41\rangle$ Weights and Balances and $\langle 31\rangle$ Volumetric Apparatus, and USP-NF General Notices, for information regarding appropriate use of USP Reference Standards.


## Drying

- Use a clean and dry vessel, and not the original container, as the drying vessel where a USP Reference Standard is required to be dried before use.
- Make sure not to dry a specimen repeatedly at temperatures above 25 degrees.
- Follow any special drying requirements specified on the Reference Standards label or in specific sections of USP or NF monographs (note that any specific instructions on the label or in the monograph supersede the usual instructions in Procedures under Tests and Assays in USP-NF General Notices).
- Follow Method I under $U S P-N F$ General Chapter $\langle 921\rangle$ Water Determination where the titrimetric determination of water is required at the time a Reference Standard is to be used.
Instrumental or microanalytical methods are acceptable for this purpose. When using typical amounts, users must titrate about 50 mg of the Reference Standard with a fourfold dilution of the reagent.


## ORDERING USP REFERENCE STANDARDS

## Four convenient ways to order

1. Phone: Call USP with your requirements: (800) 227-8772 from the U.S. or Canada and (301) 881-0666 from other countries. Please note that DEA controlled substances cannot be placed over the phone.

Hours of operation:
Monday-Friday
8:30AM-5:00PM

Fax: Fax your orders to (301) 816-8148.
Online: Order through the World Wide Web at http://store.usp.org. Please note that DEA controlled substances cannot be ordered online.
Mail: Send all mail orders to:
USP
Customer Service Department
12601 Twinbrook Parkway
Rockville, MD 20852, USA

## Important Order/Policy Information

For fax and mail orders, please use the order form at the back of this catalog. Official purchase orders on company letterhead may also be used to order USP Reference Standards. The purchase orders must have billing and shipping addresses and should include the catalog number, the name of the official Reference Standard, and the number of units ordered. Lot numbers need not be specified on written purchase orders as USP only ships current official lots. Confirmation orders may be sent and must clearly be designated as such. The USP does not assume responsibility for duplication of orders not clearly marked as confirmation orders.

## Pricing

USP Reference Standards must be ordered in whole units. Please note that one unit may include several individual containers.

Reference Standards unit prices included in the product listings from pages 13-52 of this catalog are effective until December 31, 2004. Please note that prices and package sizes are subject to change without notice.

## No Returns or Exchanges

USP Reference Standards may not be returned or exchanged for refund.

## Quantity Discounts

A 5\% discount is allowed for 5-24 units of any one Reference Standard in a single order, and a $10 \%$ discount for 25 or more units of any one Reference Standard in a single order. These discounts are subject to change without notice.

## Shipping

- Reference Standards orders can only be shipped to a street address and not to P.O. boxes.


## USING AND ORDERING USP REFERENCE STANDARDS

- Orders to the U.S. and Ontario, Canada are shipped via air courier of USP's choice at a charge of $\$ 11$ or via air courier of the customer's choice at an additional $\$ 25$ charge.
- Non-controlled substance orders to Canadian provinces other than Ontario are shipped via air courier of USP's choice at a charge of U.S. $\$ 70$. Carriers of the customer's choice incur an additional $\$ 25$ charge.
- Non-controlled substance orders to be shipped outside the U.S. and Canada are accepted directly by USP only when customs forms related to export are not required. They are shipped via air courier of USP's choice at a charge of U.S. $\$ 70$. Carriers of the customer's choice incur an additional $\$ 25$ charge.
- Shipping in cold pack can be done at customer request for an extra charge of $\$ 25$.
- Controlled substance orders to anywhere outside the U.S. are shipped via air courier of USP's choice with a charge of U.S. $\$ 220$.
- An additional shipping charge may be assessed for dangerous goods shipments.
- An additional shipping charge of $\$ 75$ will be assessed for rush/ same-day shipments.
- Customers may provide their shipping account numbers to have shipping charged directly.


## Payment

- Full payment in advance, in U.S. dollars, is required for all U.S. orders unless open account status has been granted by USP's Finance Department. To apply for open account status, an application can be requested by calling (301) 816-8177.
- Full payment in advance, in U.S. dollars, is required for all non-U.S. orders.
- Payment may be made by check, money orders, credit cards (VISA, MasterCard, American Express), and electronic wire transfer (please call (301) 816-8177 to get bank information for wire transfers). The customer is responsible for any bank fees and must include it in the payment. The customer is also responsible for any other fees such as customs duties, taxes, or tariffs.


## List Chemicals

The following Reference Standards are "List Chemicals": Dihydroergotamine Mesylate
*Ephedrine Sulfate
Ergonovine Maleate

[^113]Ergotamine Tartrate<br>Methylergonovine Maleate<br>Phenylpropanolamine Bitartrate<br>Phenylpropanolamine HCl<br>Pseudoephedrine HCl<br>Pseudoephedrine Sulfate

An organization in the United States seeking to purchase a List Chemical Reference Standard for resale to another customer must have a DEA registration (either a controlled substance or List Chemical registration). If an organization in the United States is purchasing the List Chemical Reference Standard for its own analytical use, it must provide USP with a letter on company letterhead describing the reason for the purchase.

## CONTROLLED DRUG SUBSTANCE ORDER

## DEA Requirements (U.S. Orders)

For all orders for controlled drug substances-regulated by the U.S. Drug Enforcement Administration (DEA)-to be shipped within the U.S., a copy of the customer's current DEA Registration Certificate must be on file with USP. To order Schedule I and II standards, customers must submit, with their order forms or purchase orders, a DEA Form 222-C, properly completed. In addition, customers ordering DEA Schedules III and IV must provide appropriate DEA registration numbers for those schedules on their order forms or purchase orders.

## DEA Requirements (International Orders)

For all international controlled drug substance orders, please contact Julie Smith at (301) 816-8164 or foreigncontrols@ usp.org.

All orders for controlled drug substances-regulated by the U.S. Drug Enforcement Administration (DEA)-to be shipped outside the U.S. must be accompanied by:

1. Full payment.
2. An import permit (in English or with an English translation attached) valid at least 6 months from the date of its receipt by USP Customer Service.
3. A statement of non-reexport and use for medical or scientific purposes (in English or with an English translation attached).
4. Purchase Order or Price Quote given by USP.

## USING AND ORDERING USP REFERENCE STANDARDS

On receiving the order, USP takes 2-3 business days to:

- Review all documents to make sure they are adequate and appropriate.
- Complete and legally approve the required DEA forms.
- Forward the forms to the DEA office to obtain the necessary Export Permits.

USP cannot ship items without an Export Permit. While it typically takes 6-10 weeks to get the permit from the DEA, USP has no control over the time in which permits are issued. On receiving the Export Permit, USP completes processing of the order in 1-3 days and ships out the materials through its freight forwarder.

Controlled substances (CI, CII, CIII, CIV, CV) and List Chemicals shipped to an international address, including Canada, add $\$ 25$ per unit.

For controlled substance orders to be shipped to Mexico, in addition to the DEA processing period, an additional week is required to obtain a certificate from the Mexican Embassy, authorizing the shipment to enter the country. Customers will pay an additional $\$ 114$ to cover the fee charged by the Mexican Embassy per import permit.

## Back Orders

USP will ship a back-ordered item if that item becomes available within 30 days of the date the order is placed if there is a valid open P.O. or payment for the item. If the order is more than 30 days old when the item becomes available, the customer will receive a Notice of Availability (NOA), indicating that the item is available. Such items will be shipped only after USP receives written authorization by the customer. The order will be canceled if the Reference Standard does not become available within six months of the original order. NOAs not replied to within 45 days of generation will be cancelled, and the customer account will be credited appropriately.

Customers may send confirmation orders for back-ordered Reference Standards that subsequently become available. They must clearly designate the confirmation orders as such-USP is not responsible for duplication of orders not clearly designated.

## HOW TO READ PRODUCT LISTINGS

Column 1 (Catalog Number): Catalog number currently assigned to each Reference Standard and Authentic Substance. Please include this number in your orders.

Column 2 (Description): Product description as designated in $U S P-N F$, the product label, and / or the Drug Enforcement Administration Control Schedule, as applicable. The quantity of material per container follows the name in parentheses (all materials are in single containers unless otherwise specified).

Column 3 (Current Lot): Current lot designation of each official item being distributed as of the date of this catalog. If the current lot is blank, the item is not in distribution.

Column 4 (Change Code): Codes that identify any change in USP Reference Standards status or information since the Jan./Feb. 2004, official Catalog. Code interpretations are as follows:

| Change <br> Code | Interpretation |
| :---: | :--- |
| 1 | New Reference Standard |
| 2 | New lot |
| 3 | Change in package size or description |
| 4 | Correction of typographical error |
| 5 | New catalog number-use for all orders |
| 6 | Previous lot no longer official; only <br> current lot to be used |
| 7 | Valid use date of previous lot extended <br> Change in catalog number and / or name, <br> 8 |
| 9 | see cross-reference section <br> Discontinued |

Column 5 (Previous Lot/Valid Use Date): Identifies lots no longer being distributed. The indicated month and in parenthesis indicates the date (last day of the month) through which that lot was valid as an official USP Reference Standard. (e.g. "F-1 (06/ 00 )" means lot F-1 is no longer being distributed, but was considered official through June 30, 2000.)

Column 6 (CAS Number)*: Chemical Abstracts Service number, when available, for USP Reference Standards and Authentic Substances. In case of mixtures, typically, the CAS number of the analyte of interest is listed.

Column 7 (Price) lists the price of the reference standard.

[^114]
## New Lots in Distribution

| Cat. <br> No. | Description | Curr. <br> Lot. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \hline \text { CAS } \\ \text { No. } \\ \hline \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1048641 | Benazepril Related Compound C (50 mg) ((3S)-3-[[(1S)-1-carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1H-1-benazepine]-1-acetic acid) | F0C425 | 1 |  | [86541-78-8] | \$487 |
| 1071439 | Positive Bioreaction (3 strips; $10 \mathrm{~cm} \times 1 \mathrm{~cm}$ ) | F0D014 | 1 |  | n/f | \$325 |
| 1105009 | Powdered Chaste Tree Extract (1.5 g) | F0C406 | 1 |  | [91722-47-3] | \$520 |
| 1111307 | Chlorhexidine Related Compounds ( 50 mg ) | F0D017 | 1 |  | n/f | \$487 |
| 1115545 | Chlorogenic Acid ( 50 mg ) | F0C420 | 1 |  | [327-97-9] | \$156 |
| 1140429 | Clonidine Related Compound B (25 mg) (2-[(E)-2,6-Dichlorophenylimi-no]-1-(1-\{2-[(E)-2,6-dichlorophenylimino]-imidazolidin-1-yl\}-ethyl)-imidazolidine) | F0C403 | 1 |  | n/f | \$487 |
| 1231728 | Powdered Echinacea Purpurea Extract (1 g) | F0D018 | 1 |  | [90028-20-9] | \$520 |
| 1231706 | Powdered Echinacea Angustifolia Extract (1 g) | F0D019 | 1 |  | [84696-11-7] | \$520 |
| 1305507 | 2E, 4E-Hexadienoic Acid Isobutylamide ( 25 mg ) | F0C353 | 1 |  | [82240-09-3] | \$540 |
| 1378012 | Medroxyprogesterone Acetate Related Compound A (25 mg) (4,5-betaDihydromedroxyprogesterone acetate) | F0C427 | 1 |  | n/f | \$500 |
| 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution CII ( 0.5 mL ) | F0C368 | 1 |  | n/f | \$560 |
| 1441298 | Metoprolol Succinate (200 mg) | F0C415 | 1 |  | [98418-47-4] | \$156 |
| 1445211 | Mitoxantrone System Suitability Mixture ( 0.3 mg ) | F0D010 | 1 |  | n/f | \$500 |
| 1457469 | Naratriptan Hydrochloride ( 125 mg ) | F0C360 | 1 |  | [143388-64-1] | \$208 |
| 1601102 | Residual Solvent Mixture - Class 1 ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C407 | 1 |  | n/f | \$156 |
| 1601146 | Residual Solvent Class 1 - Benzene ( $1.2 \mathrm{~mL} / \mathrm{ampule;} 3$ ampules) | F0C408 | 1 |  | n/f | \$156 |
| 1601168 | Residual Solvent Class 1 - Carbon Tetrachloride ( $1.2 \mathrm{~mL} / \mathrm{ampule}$; 3 ampules) | F0C409 | 1 |  | n/f | \$156 |
| 1601180 | Residual Solvent Class 1-1,2-Dichloroethane ( $1.2 \mathrm{~mL} /$ ampule; 3 am pules) | F0C412 | 1 |  | n/f | \$156 |
| 1601204 | Residual Solvent Class 1-1,1-Dichloroethene (1.2 mL/ampule; 3 ampules) | F0C411 | 1 |  | n/f | \$156 |
| 1601226 | Residual Solvent Class 1-1,1,1-Trichloroethane ( $1.2 \mathrm{~mL} / \mathrm{ampul}$; 3 ampules) | F0C410 | 1 |  | n/f | \$156 |
| 1708762 | Valsartan ( 350 mg ) | F0C147 | 1 |  | [137862-53-4] | \$156 |
| 1012123 | Adenosine ( 200 mg ) | G0C295 | 2 | $\begin{aligned} & \text { F1B058 (01/05) } \\ & \text { F (04/03) } \end{aligned}$ | [58-61-7] | \$156 |
| 1013002 | Allopurinol (250 mg) | J0C186 | 2 | $\begin{array}{\|l} \hline 1-1(01 / 05) \\ 1(07 / 02) \\ \hline \end{array}$ | [315-30-0] | \$156 |
| 1032007 | Amphotericin B (125 mg) | J3C246 | 2 | $\begin{array}{\|l\|l} \hline \mathrm{J}-2(01 / 05) \\ \mathrm{J}-1 & (07 / 02) \\ \hline \end{array}$ | [1397-89-3] | \$124 |
| 1044403 | Atenolol ( 200 mg ) | H1C320 | 2 | $\begin{array}{\|l\|} \hline \text { H }(01 / 05) \\ \text { G }(08 / 01) \\ \hline \end{array}$ | [29122-68-7] | \$156 |
| 1054000 | Benzocaine ( 500 mg ) | J0C130 | 2 | I (12/04) | [94-09-7] | \$156 |
| 1097104 | Cefadroxil ( 125 mg ) | 11B319 | 2 | $\begin{array}{\|l\|} \hline I(01 / 05) \\ H(04 / 99) \\ \hline \end{array}$ | [66592-87-8] | \$124 |
| 1097909 | Cefotaxime Sodium (250 mg) | J0C189 | 2 | I (11/04) | [64485-93-4] | \$124 |
| 1129007 | Chlortetracycline Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | KOC185 | 2 | $\begin{array}{\|l\|} \hline J-1(12 / 04) \\ \mathrm{J}(02 / 02) \\ \hline \end{array}$ | [64-72-2] | \$156 |
| 1134335 | Ciprofloxacin Hydrochloride ( 400 mg ) | 10 C 265 | 2 | $\begin{array}{\|l} \hline \text { H }(02 / 05) \\ \text { G }(04 / 00) \\ \hline \end{array}$ | [86393-32-0] | \$156 |
| 1134426 | Clavulanate Lithium (200 mg) | 11C270 | 2 | $\begin{aligned} & \text { I (02/05) } \\ & \mathrm{H}(09 / 02) \\ & \hline \end{aligned}$ | n/f | \$156 |
| 1141002 | Clotrimazole (200 mg) | K0C282 | 2 | $\begin{array}{\|l\|} \hline J(02 / 05) \\ I(05 / 99) \\ \hline \end{array}$ | [23593-75-1] | \$124 |
| 1157002 | Cyclophosphamide ( 500 mg ) | J1B200 | 2 | J (02/05) | [6055-19-2] | \$124 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

New Lots in Distribution

| Cat. <br> No. | Description | $\begin{aligned} & \text { Curr. } \\ & \text { Lot. } \end{aligned}$ | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \hline \text { CAS } \\ \text { No. } \\ \hline \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1162330 | Dacarbazine Related Compound B (50 mg) (2-azahypoxanthine) | G0C325 | 2,3 | $\begin{array}{\|l\|} \hline \text { F-1 (03/05) } \\ \text { F (12/01) } \\ \hline \end{array}$ | [63907-29-9] | \$600 |
| 1229001 | Droperidol (250 mg) | $10 \mathrm{C029}$ | 2 | $\begin{array}{\|l\|} \hline \mathrm{H}-1(01 / 05) \\ \mathrm{H}(04 / 99) \\ \hline \end{array}$ | [548-73-2] | \$156 |
| 1235274 | Enalaprilat (300 mg) | J0C268 | 2 | $\begin{array}{\|l\|l\|} \hline \text { I (11/04) } \\ \text { H (03/01) } \\ \text { G (08/99) } \\ \hline \end{array}$ | [84680-54-6] | \$124 |
| 1260001 | Ethinyl Estradiol (150 mg) | Q0C162 | 2 | $\begin{array}{\|l\|} \hline \text { P1B193 (11/04) } \\ \text { POB052 (01/04) } \\ \text { P (03/03) } \\ \text { O (08/99) } \\ \hline \end{array}$ | [57-63-6] | \$156 |
| 1270800 | Flecainide Acetate (200 mg) | F2A022 | 2 | $\begin{array}{\|l\|} \hline \text { F-1 (02/05) } \\ \text { F (06/03) } \\ \hline \end{array}$ | [54143-56-5] | \$156 |
| 1278302 | Fluoroquinolonic Acid (50 mg) | H0C140 | 2 | $\begin{array}{\|l\|} \hline \text { G (01/05) } \\ \text { F-1 (12/99) } \end{array}$ | [86393-33-1] | \$487 |
| 1279804 | Fluoxetine Hydrochloride (200 mg) | F2C132 | 2 | $\begin{array}{\|l} \hline \text { F-1 (02/05) } \\ \text { F (11/99) } \\ \hline \end{array}$ | [59333-67-4] | \$156 |
| 1285002 | Flurazepam Hydrochloride CIV (200 mg) | J0C365 | 2 | I (09/03) | [1172-18-5] | \$207 |
| 1285851 | Flutamide (200 mg) | H0B278 | 2 | $\begin{array}{\|l\|l\|} \hline \text { G (11/04) } \\ \text { F-1 }(06 / 00) \\ \hline \end{array}$ | [13311-84-7] | \$156 |
| 1289003 | Gentamicin Sulfate (200 mg) | L0C279 | 2 | $\begin{array}{\|l\|l} \hline \mathrm{K}(12 / 04) \\ \mathrm{J}-1(04 / 00) \\ \hline \end{array}$ | [1405-41-0] | \$156 |
| 1310008 | Homatropine Hydrobromide (200 mg) | H2C049 | 2 | $\begin{array}{\|l\|} \hline \text { H-1(02/05) } \\ \text { H (08/02) } \\ \hline \end{array}$ | [51-56-9] | \$156 |
| 1315001 | Hydrocodone Bitartrate CII (250 mg) | K0C217 | 2 | $\begin{array}{\|l\|} \hline \text { JOAO26 (01/05) } \\ \text { I-1 (12/02) } \\ \text { I (07/02) } \\ \text { H-2 (11/99) } \\ \hline \end{array}$ | [34195-34-1] | \$207 |
| 1323000 | Hydromorphone Hydrochloride CII (50 mg) | J0C372 | 2 | $\begin{array}{\|l} \hline \text { I (01/05) } \\ H-2(03 / 01) \\ \hline \end{array}$ | [71-68-1] | \$207 |
| 1335009 | Hyoscyamine Sulfate (125 mg) | H0C193 | 2 | $\begin{array}{\|l\|} \hline \text { G2A007 (09/04) } \\ \text { G-1 (08/02) } \\ \text { G (10/99) } \\ \hline \end{array}$ | [6835-16-1] | \$124 |
| 1337809 | Imipenem Monohydrate (100 mg) | G1C296 | 2 | $\begin{array}{\|l\|} \hline G(01 / 05) \\ F(01 / 01) \\ \hline \end{array}$ | [74431-23-5] | \$156 |
| 1350400 | Isopropyl Myristate ( 500 mg ) | I1C183 | 2 | $1(01 / 05)$ | [110-27-0] | \$156 |
| 1356676 | Anhydrous Lactose ( 100 mg ) | G1C004 | 2 | $\begin{array}{\|l\|} \hline \text { G }(12 / 04) \\ \text { F }(06 / 01) \\ \hline \end{array}$ | [63-42-3] | \$156 |
| 1368609 | Lisinopril (300 mg) | 11C045 | 2 | $\begin{aligned} & \mathrm{I}(11 / 04) \\ & \mathrm{H}(09 / 01) \\ & \mathrm{G}(10 / 99) \end{aligned}$ | [83915-83-7] | \$156 |
| 1379300 | Melphalan Hydrochloride (100 mg) | H0B296 | 2,3 | G (01/05) | [3223-07-2] | \$156 |
| 1409604 | Methenamine Mandelate ( 200 mg ) | G0C304 | 2 | $\begin{array}{\|l\|l\|} \hline \text { F-2 (01/05) } \\ \text { F-1 (11/00) } \\ \hline \end{array}$ | [587-23-5] | \$156 |
| 1410002 | Methicillin Sodium (500 mg) | J0C333 | 2 | $\begin{array}{\|l\|} \hline \text { I1B186 (11/04) } \\ \text { I (03/03) } \\ \text { H (03/00) } \\ \hline \end{array}$ | [7246-14-2] | \$156 |
| 1421009 | Methscopolamine Bromide (200 mg) | G1D004 | 2 | G (02/05) | [155-41-9] | \$156 |
| 1448901 | Mupirocin ( 50 mg ) | F2C158 | 2 | $\begin{array}{\|l} \hline \text { F-1 (12/04) } \\ \text { F (03/02) } \\ \hline \end{array}$ | [12650-69-0] | \$156 |
| 1460500 | Netilmicin Sulfate (500 mg) | 10 C 388 | 2 | $\begin{array}{\|l} \mathrm{H}(01 / 05) \\ \mathrm{G}(05 / 02) \\ \hline \end{array}$ | [56391-57-2] | \$156 |
| 1461003 | Niacin (200 mg) | H2C121 | 2 | $\mathrm{H}-1$ (01/05) | [59-67-6] | \$156 |
| 1483505 | Oxprenolol Hydrochloride (200 mg) | IOC344 | 2 | H (02/05) | [6452-73-9] | \$156 |

[^115]
## New Lots in Distribution

| Cat. No. | Description | Curr. <br> Lot. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1486004 | Oxymetazoline Hydrochloride ( 200 mg ) | J0C206 | 2 | I (03/05) | [2315-02-8] | \$156 |
| 1491004 | Oxytetracycline (200 mg) | J0C084 | 2 | I-1 (10/04) | [6153-64-6] | \$156 |
| 1500218 | Paroxetine Hydrochloride ( 350 mg ) | G0D003 | 2,3 | F0B288 (09/04) | [110429-35-1] | \$156 |
| 1505007 | Pentazocine CIV (500 mg) | I0C418 | 2 | $\begin{array}{\|l\|} \hline \text { H ( } 01 / 05 \text { ) } \\ \text { G-1 }(11 / 00) \\ \hline \end{array}$ | [359-83-1] | \$207 |
| 1515000 | Phenazopyridine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H0C426 | 2 | G-4 (12/04) | [136-40-3] | \$156 |
| 1554705 | Prazosin Hydrochloride ( 500 mg ) | H0B254 | 2 | $\begin{aligned} & \text { G-1 (02/05) } \\ & \text { G (02/01) } \end{aligned}$ | [19237-84-4] | \$156 |
| 1576005 | Propranolol Hydrochloride (200 mg) | 10 C 170 | 2 | $\begin{array}{\|l\|l\|} \hline \mathrm{H}-1(12 / 04) \\ \mathrm{H}(09 / 01) \\ \hline \end{array}$ | [318-98-9] | \$156 |
| 1586009 | Pyridostigmine Bromide ( 200 mg ) | I0C324 | 2 | H (01/05) | [101-26-8] | \$156 |
| 1613509 | Sodium Ascorbate (200 mg) | G2C067 | 2 | G-1 (03/05) | [134-03-2] | \$156 |
| 1618003 | Spectinomycin Hydrochloride (200 mg) | G0C310 | 2 | F-2 (01/05) | [22189-32-8] | \$156 |
| 1637008 | Sulfinpyrazone (200 mg) | H0C416 | 2 | G (03/05) | [57-96-5] | \$156 |
| 1651009 | Tetracycline Hydrochloride ( 200 mg ) | LOC216 | 2 | K (12/04) | [64-75-5] | \$156 |
| 1671006 | Tolnaftate (200 mg) | J0C405 | 2 | 1 (02/05) | [2398-96-1] | \$156 |
| 1675007 | Triacetin (1 g) | H0C413 | 2 | $\begin{array}{\|l} \hline \text { G-1 }(02 / 05) \\ \text { G }(06 / 01) \\ \hline \end{array}$ | [102-76-1] | \$156 |
| 1680608 | Tributyl Citrate ( 500 mg ) | G0C227 | 2 | F (01/05) | [77-94-1] | \$156 |
| 1710006 | Vanillin (200 mg) | J0A021 | 2 | $\begin{array}{\|l} \hline \text { I (03/05) } \\ \text { H (04/99) } \\ \hline \end{array}$ | [121-33-5] | \$156 |
| 1720407 | Xylazine ( 200 mg ) | F1C001 | 2 | F (02/05) | [7361-61-7] | \$156 |

## USP Reference Standards and Authentic Substances

| Cat. <br> No. | Description | Curr. <br> Lot. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1000601 | Acebutolol Hydrochloride (125 mg) | F-1 |  |  | [34381-68-5] | \$156 |
| 1001003 | Acenocoumarol (200 mg) | F |  |  | [152-72-7] | \$156 |
| 1001502 | Acepromazine Maleate ( 250 mg ) | F-2 |  | F-1 (05/02) | [3598-37-6] | \$156 |
| 1002505 | Acesulfame Potassium ( 200 mg ) | F0C136 |  |  | [55589-62-3] | \$260 |
| 1003009 | Acetaminophen ( 400 mg ) | J-1 |  | $\begin{array}{\|l\|} \hline \text { J (05/02) } \\ \text { I (05/99) } \\ \hline \end{array}$ | [103-90-2] | \$124 |
| 1004001 | Acetanilide Melting Point Standard (500 mg) (Approximately 114 degrees) | M0A029 |  | $\begin{array}{\|l\|} \hline \mathrm{L}(06 / 04) \\ \mathrm{K}(02 / 00) \\ \hline \end{array}$ | [103-84-4] | \$75 |
| 1005004 | Acetazolamide (2 g) | J |  |  | [59-66-5] | \$156 |
| 1006007 | Acetohexamide ( 250 mg ) | H |  | G-1 (06/99) | [968-81-0] | \$156 |
| 1006506 | Acetohydroxamic Acid ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  | F (03/03) | [546-88-3] | \$156 |
| 1007000 | Acetophenazine Maleate ( 200 mg ) | F-1 |  |  | [5714-00-1] | \$156 |
| 1008002 | alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane ( 125 mg ) | G-3 |  |  | n/f | \$487 |
| 1008501 | Acetylcholine Chloride (200 mg) | G |  |  | [60-31-1] | \$156 |
| 1009005 | Acetylcysteine (200 mg) | H1B169 |  | H (01/04) | [616-91-1] | \$156 |
| 1009901 | Acetyltributyl Citrate ( 500 mg ) | G0C120 |  | F (05/04) | [77-90-7] | \$156 |
| 1009923 | Acetyltriethyl Citrate ( 500 mg ) | F-1 |  | F (05/02) | [77-89-4] | \$156 |
| 1012065 | Acyclovir (300 mg) | J0C149 |  | I (06/04) | [59277-89-3] | \$197 |
| 1012101 | Adenine ( 200 mg ) | G-1 |  | G (06/00) | [73-24-5] | \$156 |
| 1012123 | Adenosine ( 200 mg ) | G0C295 | 2 | $\begin{array}{\|l\|} \hline \text { F1B058 (01/05) } \\ \text { F (04/03) } \\ \hline \end{array}$ | [58-61-7] | \$156 |
| 1012145 | Agigenin (25 mg) | F |  |  | n/f | \$156 |
| 1012509 | L-Alanine ( 200 mg ) | F-2 |  | F-1 (04/01) | [56-41-7] | \$156 |
| 1012553 | Albendazole (200 mg) | G |  | F-1 (01/00) | [54965-21-8] | \$156 |
| 1012600 | Albuterol ( 200 mg ) | 1 |  | H (12/00) | [18559-94-9] | \$156 |
| 1012633 | Albuterol Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | J |  | $1(04 / 00)$ | [51022-70-9] | \$156 |
| 1012757 | Alclometasone Dipropionate ( $300 \mathrm{mg} \mathrm{)}$ | H |  | G (01/00) | [66734-13-2] | \$156 |
| 1012780 | Alendronate Sodium (200 mg) | F0B315 |  |  | [121268-17-5] | \$156 |
| 1012906 | Alfentanil Hydrochloride CII ( 500 mg ) | F0B016 |  |  | [70879-28-6] | \$207 |
| 1012939 | Allantoin (200 mg) | F0C169 |  |  | [97-59-6] | \$156 |
| 1012950 | Alliin (25 mg) | F |  |  | [556-27-4] | \$1,525 |
| 1013002 | Allopurinol (250 mg) | J0C186 | 2 | $\begin{array}{\|l\|} \hline I-1(01 / 05) \\ I(07 / 02) \\ \hline \end{array}$ | [315-30-0] | \$156 |
| 1013024 | Allopurinol Related Compound A ( 50 mg ) (3-Amino-4-carboxamidopyrazole Hemisulfate) | G |  | $\begin{array}{\|l\|l\|} \hline \text { F-3 }(05 / 02) \\ \text { F-2 }(04 / 99) \\ \hline \end{array}$ | n/f | \$487 |
| 1013057 | S-Allyl-L-Cysteine ( 25 mg ) | F |  |  | n/f | \$487 |
| 1014005 | Alphaprodine Hydrochloride CII ( $250 \mathrm{mg} \mathrm{)}$ | F |  |  | [561-78-4] | \$207 |
| 1015008 | Alprazolam CIV (200 mg) | H |  |  | [28981-97-7] | \$207 |
| 1016000 | Alprostadil ( 25 mg ) | H |  |  | [745-65-3] | \$1,525 |
| 1017105 | Altretamine ( 500 mg ) | F |  |  | [645-05-6] | \$156 |
| 1017502 | Dried Aluminum Hydroxide Gel ( $200 \mathrm{mg} \mathrm{)}$ | F2B120 |  | F-1 (01/04) | [21645-51-2] | \$156 |
| 1018505 | Amantadine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G (04/01) | [665-66-7] | \$156 |
| 1019202 | Amcinonide ( 200 mg ) | G0B260 |  | F-1 (03/04) | [51022-69-6] | \$156 |
| 1019417 | Amifostine Disulfide ( 25 mg ) | F0C152 |  |  | [112901-68-5] | \$487 |
| 1019508 | Amikacin (200 mg) | 1 |  | H (08/00) | [37517-28-5] | \$156 |
| 1019701 | Amiloride Hydrochloride ( 500 mg ) | H |  |  | [17440-83-4] | \$156 |
| 1019756 | Aminobenzoate Potassium (200 mg) | F-1 |  | F (06/01) | [138-84-1] | \$156 |
| 1019767 | Aminobenzoate Sodium (200 mg) | F |  |  | [55-06-6] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1019803 | Aminobenzoic Acid (200 mg) (p-aminobenzoic acid) | H1C083 |  | $\begin{array}{\|l} \hline H(10 / 04) \\ G(10 / 00) \\ \hline \end{array}$ | [150-13-0] | \$156 |
| 1020008 | Aminobutanol ( 500 mg ) | G-1 |  | G (06/99) | [13054-87-0] | \$389 |
| 1021000 | Aminocaproic Acid (200 mg) | F-4 |  |  | [60-32-2] | \$156 |
| 1021703 | N -(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methylene)-amino]-glycine ( 25 mg ) | F-1 |  |  | n/f | \$487 |
| 1022808 | 2-Amino-5-chlorobenzophenone ( 25 mg ) | I |  | H-1 (01/03) | [719-59-5] | \$487 |
| 1025205 | Aminoglutethimide (200 mg) | F |  |  | [125-84-8] | \$156 |
| 1025307 | m -Aminoglutethimide ( 100 mg ) | G |  | F (05/01) | n/f | \$487 |
| 1025351 | Aminohippuric Acid ( 200 mg ) | F-1 |  |  | [61-78-9] | \$156 |
| 1025806 | 2-[3-Amino-5-(n-methylacetamido)-2,4,6-triiodobenzamido]-2-deoxy-dglucose ( 25 mg ) | F |  |  | n/f | \$487 |
| 1025908 | Aminopentamide Sulfate (200 mg) | F0B273 |  |  | [60-46-8] | \$156 |
| 1026004 | m-Aminophenol ( $300 \mathrm{mg} \mathrm{)}$ | F |  |  | [591-27-5] | \$487 |
| 1026401 | Aminosalicylic Acid (125 mg) | F-1 |  | F (03/99) | [65-49-6] | \$124 |
| 1026605 | 3 -Amino-2,4,6-triiodobenzoic Acid ( 50 mg ) | G |  |  | [3119-15-1] | \$487 |
| 1027007 | 5-Amino-2,4,6-triiodo-N-methylisophthalamic Acid ( 50 mg ) | F-1 |  |  | [2280-89-9] | \$487 |
| 1028000 | Amitraz (200 mg) | FOC042 |  |  | [33089-61-1] | \$156 |
| 1029002 | Amitriptyline Hydrochloride (200 mg) | J0A004 |  | $1(03 / 03)$ | [549-18-8] | \$156 |
| 1029909 | Ammonio Methacrylate Copolymer Type A (100 mg) | F-1 |  | F (06/01) | [33434-24-1] | \$156 |
| 1029910 | Ammonio Methacrylate Copolymer Type B (100 mg) | F-1 |  | F (05/00) | [33434-24-1] | \$156 |
| 1029953 | Ammonium Chloride (200 mg) | F0C134 |  |  | [12125-02-9] | \$156 |
| 1030001 | Amobarbital CII (200 mg) | F-2 |  |  | [57-43-2] | \$207 |
| 1031004 | Amodiaquine Hydrochloride ( 500 mg ) | H0B238 |  | G-1 (04/03) | [6398-98-7] | \$156 |
| 1031401 | Amoxapine ( 200 mg ) | G |  | F-1 (04/02) | [14028-44-5] | \$156 |
| 1031503 | Amoxicillin (200 mg) | J0C043 |  | $1(07 / 04)$ | [61336-70-7] | \$156 |
| 1032007 | Amphotericin B (125 mg) | J3C246 | 2 | $\begin{array}{\|l\|} \hline \mathrm{J}-2(01 / 05) \\ \mathrm{J}-1(07 / 02) \\ \hline \end{array}$ | [1397-89-3] | \$124 |
| 1033000 | Ampicillin (200 mg) | J-1 |  | $J(12 / 01)$ | [69-53-4] | \$156 |
| 1033203 | Ampicillin Sodium ( 125 mg ) | G-1 |  | G (10/99) | [69-52-3] | \$124 |
| 1033407 | Ampicillin Trihydrate (200 mg) | G |  |  | [7177-48-2] | \$156 |
| 1034002 | Amprolium ( 200 mg ) | F-1 |  | F (04/02) | [121-25-5] | \$156 |
| 1034308 | Amrinone ( 500 mg ) | G |  |  | [60719-84-8] | \$156 |
| 1034320 | Amrinone Related Compound A (100 mg) (5-carboxamide[3,4'-bipyr-idin]-6(1H)-one) | F |  |  | [62749-46-6] | \$487 |
| 1034341 | Amrinone Related Compound B (100 mg) (N-(1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-yl)-2-hydroxypropanamide) | F-1 |  | F (03/00) | n/f | \$487 |
| 1034363 | Amrinone Related Compound C (50 mg) (1,6-dihydro-6-0xo-(3,4'-bipyridine)-5-carbonitrile) | F-1 |  | F (05/00) | n/f | \$487 |
| 1036008 | Anileridine Hydrochloride CII ( $250 \mathrm{mg} \mathrm{)}$ | F |  |  | [126-12-5] | \$207 |
| 1036507 | 3 -Anilino-2-(3,4,5-trimethoxybenzyl) acrylonitrile ( 25 mg ) | G-1 |  |  | [30078-48-9] | \$487 |
| 1038003 | Antazoline Phosphate (200 mg) | H |  | G-1 (04/02) | [154-68-7] | \$156 |
| 1039006 | Anthralin (200 mg) | IOB221 |  | H (11/02) | [1143-38-0] | \$156 |
| 1040005 | Antipyrine (200 mg) | G |  | F-4 (09/01) | [60-80-0] | \$156 |
| 1040708 | Apigenin-7-glucoside ( 30 mg ) | F |  |  | n/f | \$487 |
| 1041008 | Apomorphine Hydrochloride ( 250 mg ) | H |  | G (01/03) | [41372-20-7] | \$162 |
| 1041609 | Apraclonidine Hydrochloride ( 100 mg ) | H0B112 |  | G (06/03) | [73218-79-8] | \$479 |
| 1042000 | Aprobarbital CIII (200 mg) (AS) | F-1 |  |  | [77-02-1] | \$207 |
| 1042500 | L-Arginine (200 mg) | G-1 |  | G (09/00) | [74-79-3] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1042601 | Arginine Hydrochloride ( 125 mg ) | G0B060 |  | F-1 (05/03) | [1119-34-2] | \$124 |
| 1042703 | Arsanilic Acid (25 mg) | F |  |  | [98-50-0] | \$156 |
| 1043003 | Ascorbic Acid (1 g) (Vitamin C) | Q0B012 |  | P (04/03) | [50-81-7] | \$156 |
| 1043706 | Aspartame ( 200 mg ) | H1B125 |  | H (05/03) | [22839-47-0] | \$156 |
| 1043750 | Aspartame Acesulfame (200 mg) | F0C137 |  |  | [106372-55-8] | \$156 |
| 1043728 | Aspartame Related Compound A (75 mg) (5-Benzyl-3,6-dioxo-2piperazineacetic Acid) | H |  | G-1 (10/99) | [5262-10-2] | \$487 |
| 1043819 | Aspartic Acid (100 mg) | F0B087 |  |  | [6899-03-2] | \$156 |
| 1044006 | Aspirin ( 500 mg ) | H |  | G-1 (11/02) | [50-78-2] | \$156 |
| 1044301 | Astemizole ( 200 mg ) | F |  |  | [68844-77-9] | \$156 |
| 1044403 | Atenolol ( 200 mg ) | H1C320 | 2 | $\begin{array}{\|l} \hline \text { H }(01 / 05) \\ \text { G }(08 / 01) \\ \hline \end{array}$ | [29122-68-7] | \$156 |
| 1044651 | Atovaquone ( 200 mg ) | FOB190 |  |  | [95233-18-4] | \$156 |
| 1044662 | Atovaquone Related Compound A ( 25 mg ) (cis-2-[4-(4-chlorophenyl)-cyclohexyl]-3-hydroxy-1,4-naphthoquinone) | FOB188 |  |  | n/f | \$487 |
| 1044800 | Atracurium Besylate ( $100 \mathrm{mg} \mathrm{)}$ | F0B143 |  |  | [64228-81-5] | \$156 |
| 1045009 | Atropine Sulfate ( 500 mg ) | M0B098 |  | L-2 (04/03) <br> L-1 (06/02) <br> L (10/00) | [5908-99-6] | \$156 |
| 1045337 | Avobenzone ( 500 mg ) | G0B280 |  | F (09/03) | [70356-09-1] | \$156 |
| 1045508 | Aurothioglucose ( 100 mg ) | H0B224 |  | $\begin{aligned} & \mathrm{G}(10 / 03) \\ & \mathrm{F}(12 / 01) \\ & \hline \end{aligned}$ | [12192-57-3] | \$156 |
| 1045600 | Azaerythromycin A (100 mg) | G |  | $\begin{array}{\|l\|l\|} \hline \text { F-1 (02/02) } \\ \text { F (02/99) } \\ \hline \end{array}$ | [76801-85-9] | \$156 |
| 1045756 | Azaperone (200 mg) | F |  |  | [1649-18-9] | \$156 |
| 1045803 | Azatadine Maleate (200 mg) | G0B300 |  | $\begin{array}{\|l\|} \hline \text { F-1 (04/04) } \\ \text { F (06/00) } \\ \hline \end{array}$ | [3978-86-7] | \$156 |
| 1046001 | Azathioprine (200 mg) | H |  | G-1 (02/00) | [446-86-6] | \$156 |
| 1046056 | Azithromycin (100 mg) | H0C212 |  | $\begin{aligned} & \text { G (11/04) } \\ & F(06 / 00) \\ & \hline \end{aligned}$ | [117772-70-0] | \$156 |
| 1046103 | Azlocillin Sodium (200 mg) | F |  |  | [37091-65-9] | \$156 |
| 1046147 | Azo-aminoglutethimide ( 100 mg ) | F |  |  | n/f | \$487 |
| 1046205 | Aztreonam ( 200 mg ) | G0C077 |  | F-1 (03/04) | [78110-38-0] | \$156 |
| 1046307 | Aztreonam E-Isomer ( 50 mg ) | F |  |  | n/f | \$156 |
| 1046409 | Open Ring Aztreonam ( 50 mg ) |  |  | F (12/04) | [87500-74-1] | \$156 |
| 1047300 | Bacampicillin Hydrochloride ( 200 mg ) | G0B053 |  | F (11/02) | [37661-08-8] | \$156 |
| 1047503 | Bacitracin (1 g) (Susceptibility disk standard) | G1C254 |  | G (07/04) | [1405-87-4] | \$156 |
| 1048007 | Bacitracin Zinc (200 mg) | N0A024 |  | $\begin{array}{\|l} \mathrm{M}-1(11 / 02) \\ \mathrm{M}(02 / 00) \\ \hline \end{array}$ | [1405-89-6] | \$156 |
| 1048200 | Baclofen ( 500 mg ) | 1 |  |  | [1134-47-0] | \$156 |
| 1048222 | Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone) | H1C289 |  | H (11/04) | n/f | \$389 |
| 1048506 | Beclomethasone Dipropionate (200 mg) | K |  | $J(12 / 00)$ | [5534-09-8] | \$156 |
| 1048619 | Benazepril Hydrochloride ( 125 mg ) | F0C250 |  |  | [86541-74-4] | \$156 |
| 1048620 | Benazepril Related Compound A (15 mg) ((3R)-3-[[(1R)-1-(ethoxycar-bonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benaza-pine-1-acetic acid, monohydrochloride) | F0C252 |  |  | n/f | \$487 |
| 1048630 | Benazepril Related Compound B ( 15 mg ) ( $(3 \mathrm{~S})-3-[[(1 \mathrm{R})$-1-(ethoxycar-bonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benaza-pine-1-acetic acid, monohydrochloride) | F0C256 |  |  | n/f | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1048641 | Benazepril Related Compound C (50 mg) ((3S)-3-[[(1S)-1-carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1H-1-benazepine]-1acetic acid) | F0C425 | 1 |  | [86541-78-8] | \$487 |
| 1049000 | Bendroflumethiazide (200 mg) | G-1 |  |  | [73-48-3] | \$156 |
| 1050009 | Benoxinate Hydrochloride ( 200 mg ) | F-2 |  | F-1 (10/99) | [5987-82-6] | \$124 |
| 1051001 | Benzalkonium Chloride ( 5 mL of approx. 10\% aqueous solution) | K0B151 |  | $J(06 / 03)$ | [8001-54-5] | \$156 |
| 1054000 | Benzocaine ( 500 mg ) | J0C130 | 2 | I (12/04) | [94-09-7] | \$156 |
| 1055002 | Benzoic Acid ( 300 mg ) | F6B173 |  | $\begin{aligned} & \text { F-5 }(03 / 04) \\ & \text { F-4 (07/01) } \\ & \hline \end{aligned}$ | [65-85-0] | \$156 |
| 1056005 | Benzonatate (1 g) | IOB003 |  | H (01/03) | [104-31-4] | \$156 |
| 1056504 | 1,4-Benzoquinone (200 mg) | G1B145 |  | $\begin{array}{\|l\|l} \hline \text { G (01/04) } \\ \text { F-1 (11/01) } \\ F(09 / 00) \\ \hline \end{array}$ | [106-51-4] | \$156 |
| 1057507 | Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide) | H0B069 |  | G-4 (03/03) | [121-30-2] | \$487 |
| 1059003 | Benzphetamine Hydrochloride CIII (200 mg) (AS) | F-1 |  |  | [5411-22-3] | \$207 |
| 1060002 | Benzthiazide (200 mg) | F |  |  | [91-33-8] | \$156 |
| 1061005 | Benztropine Mesylate (200 mg) | 10 C 038 |  | H (09/04) | [132-17-2] | \$156 |
| 1061901 | Benzyl Alcohol ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | G0B306 |  | FOB106 (10/03) | [100-51-6] | \$156 |
| 1062008 | Benzyl Benzoate (5 g) | J0C060 |  | I (05/04) | [120-51-4] | \$156 |
| 1064003 | 1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride ( 25 mg ) | F-1 |  |  | n/f | \$487 |
| 1065006 | Bephenium Hydroxynaphthoate ( 500 mg ) | F |  |  | [3818-50-6] | \$156 |
| 1065618 | Betahistine Hydrochloride ( 200 mg ) | F0C105 |  |  | [5579-84-0] | \$156 |
| 1065709 | Betaine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  | F (11/02) | [590-46-5] | \$156 |
| 1066009 | Betamethasone (200 mg) | K2C204 |  | $\begin{array}{\|l\|} \hline \text { K-1 (10/04) } \\ \text { K (11/02) } \\ \hline \end{array}$ | [378-44-9] | \$156 |
| 1067001 | Betamethasone Acetate ( 500 mg ) | J0B079 |  | I (08/03) | [987-24-6] | \$156 |
| 1067307 | Betamethasone Benzoate ( 200 mg ) | F-1 |  |  | [22298-29-9] | \$156 |
| 1067704 | Betamethasone Dipropionate (125 mg) | K0C229 |  | $\begin{array}{\|l\|} \hline J \text { (04/04) } \\ I(03 / 99) \\ \hline \end{array}$ | [5593-20-4] | \$124 |
| 1068004 | Betamethasone Sodium Phosphate (500 mg) | J0B043 |  | $\begin{array}{\|l} \text { I-1 (02/03) } \\ \text { I (01/01) } \\ \hline \end{array}$ | [151-73-5] | \$156 |
| 1069007 | Betamethasone Valerate (200 mg) | $J$ |  | I (05/00) | [2152-44-5] | \$156 |
| 1069903 | Betaxolol Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G |  | F-1 (06/00) | [63659-19-8] | \$156 |
| 1070006 | Betazole Hydrochloride (200 mg) | H |  |  | [138-92-1] | \$156 |
| 1071009 | Bethanechol Chloride (200 mg) | G |  | F-3 (07/01) | [590-63-6] | \$156 |
| 1071304 | Bile Salts (10 g) | 10C003 |  | $\begin{aligned} & \mathrm{H}-1(05 / 04) \\ & \mathrm{H}(05 / 99) \end{aligned}$ | [145-42-6] | \$124 |
| 1071439 | Positive Bioreaction (3 strips; $10 \mathrm{~cm} \times 1 \mathrm{~cm}$ ) | F0D014 | 1 |  | n/f | \$325 |
| 1071508 | Biotin (200 mg) | H1B019 |  | H (04/03) | [58-85-5] | \$156 |
| 1072001 | Biperiden ( 200 mg ) | F2B080 |  | F-1 (02/04) | [514-65-8] | \$156 |
| 1073004 | Biperiden Hydrochloride (200 mg) | F-3 |  | F-2 (06/99) | [1235-82-1] | \$156 |
| 1074007 | Bisacodyl (125 mg) | 11B162 |  | $\begin{array}{\|l} \mathrm{I}(01 / 04) \\ \mathrm{H}-1(02 / 99) \\ \hline \end{array}$ | [603-50-9] | \$124 |
| 1074700 | 2,5-Bis(D-arabino-1,2,3,4-tetrahydroxybutyl)pyrazine ( 25 mg ) | F |  |  | n/f | \$487 |
| 1075203 | Bis(2-ethylhexyl)maleate ( 250 mg ) | F-2 |  | F-1 (01/01) | [142-16-5] | \$487 |
| 1075509 | p-Bis(di-n-propyl)carbamylbenzenesulfonamide ( 50 mg ) | F |  |  | n/f | \$487 |
| 1075531 | Bismuth Citrate ( 100 mg ) | F |  |  | [813-93-4] | \$156 |
| 1075553 | Bismuth Subsalicylate ( 100 mg ) | F |  |  | [14882-18-9] | \$156 |
| 1075757 | Bisoprolol Fumarate ( $200 \mathrm{mg} \mathrm{)}$ | F0B038 |  |  | [104344-23-2] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1076002 | 4,4'-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone ( 25 mg ) |  |  | G (05/03) | n/f | \$487 |
| 1076308 | Bleomycin Sulfate ( 15 mg ) | J0B213 |  | I (01/04) | [9041-93-4] | \$307 |
| 1076352 | Bretylium Tosylate (200 mg) | F-1 |  |  | [61-75-6] | \$156 |
| 1076363 | Brinzolamide (200 mg) | F0C034 |  |  | [138890-62-7] | \$156 |
| 1076374 | Brinzolamide Related Compound A (50 mg) ((S)-(-)-4-ethylamino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide) | F0C033 |  |  | n/f | \$487 |
| 1076385 | Brinzolamide Related Compound B (50 mg) ((R)-4-amino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide ethanedioate) | F0C035 |  |  | n/f | \$487 |
| 1076501 | Bromocriptine Mesylate ( 150 mg ) | I1C197 |  | I (09/04) | [22260-51-1] | \$156 |
| 1077005 | Bromodiphenhydramine Hydrochloride (200 mg) | F-1 |  |  | [1808-12-4] | \$156 |
| 1077708 | 8 -Bromotheophylline ( 400 mg ) | G |  | F (07/02) | [10381-75-6] | \$156 |
| 1078008 | Brompheniramine Maleate (125 mg) | 11A036 |  | $\begin{aligned} & \hline \text { I (01/03) } \\ & \text { H-1 (04/99) } \\ & \hline \end{aligned}$ | [980-71-2] | \$124 |
| 1078303 | Bumetanide (250 mg) | 10 C 111 |  | $\begin{aligned} & \text { HOBO30 (05/04) } \\ & \text { G (03/03) } \\ & \hline \end{aligned}$ | [28395-03-1] | \$156 |
| 1078325 | Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5sulfamoylbenzoic Acid) | F-2 |  | F-1 (05/00) | n/f | \$487 |
| 1078336 | Bumetanide Related Compound B (25 mg) (3-Nitro-4-phenoxy-5sulfamoylbenzoic Acid) | F-2 |  | F-1 (01/03) | [28328-53-2] | \$487 |
| 1078507 | Bupivacaine Hydrochloride (1 g) | H |  | $\begin{array}{ll} \hline \text { G-2 }(03 / 03) \\ \text { G-1 } & (08 / 02) \\ \hline \end{array}$ | [14252-80-3] | \$156 |
| 1078700 | Buprenorphine Hydrochloride CIII ( 50 mg ) | F-1 |  | F (02/99) | [53152-21-9] | \$207 |
| 1078711 | Buprenorphine Related Compound A ( 50 mg ) (21-[3-(1-propenyl)]-7-alpha-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14tetrahydrooripavine) | F1C076 |  | F (04/04) | n/f | \$487 |
| 1078733 | Bupropion Hydrochloride ( 200 mg ) | F0C123 |  |  | [31677-93-7] | \$208 |
| 1078802 | Buspirone Hydrochloride (200 mg) | G |  |  | [33386-08-2] | \$156 |
| 1079000 | Butabarbital CIII (200 mg) | H0C007 |  | G (03/04) | [125-40-6] | \$207 |
| 1080000 | Butacaine Sulfate (600 mg) | F |  |  | [149-15-5] | \$156 |
| 1081002 | Butalbital CIII (200 mg) | H0C054 |  | $\begin{array}{\|l\|} \hline \text { G2B077 (07/04) } \\ \text { G-2 (06/03) } \\ \text { G (05/02) } \\ \hline \end{array}$ | [77-26-9] | \$207 |
| 1081501 | Butamben (200 mg) | F |  |  | [94-25-7] | \$156 |
| 1082300 | Butoconazole Nitrate ( $200 \mathrm{mg} \mathrm{)}$ | F1B097 |  | F (03/03) | [64872-77-1] | \$156 |
| 1082504 | Butorphanol Tarrrate CIV (500 mg) | J |  | I (06/00) | [58786-99-5] | \$207 |
| 1082800 | Monotertiary-butyl-p-benzoquinone (100 mg) (FCC) | F |  |  | [3602-55-9] | \$156 |
| 1082901 | Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate ( 25 mg ) | F-1 |  |  | n/f | \$487 |
| 1083008 | 2-tert-Butyl-4-hydroxyanisole ( 200 mg ) | L0C028 |  | K (09/03) | [88-32-4] | \$156 |
| 1083100 | 3-tert-Butyl-4-hydroxyanisole ( $200 \mathrm{mg} \mathrm{)}$ | J |  | I-1 (09/01) | [121-00-6] | \$156 |
| 1084000 | Butylparaben (200 mg) | 10C139 |  | $\begin{aligned} & \mathrm{H}-1(03 / 04) \\ & \mathrm{H}(09 / 01) \\ & \hline \end{aligned}$ | [94-26-8] | \$156 |
| 1085003 | Caffeine ( 200 mg ) | J |  | I (06/02) | [58-08-2] | \$156 |
| 1086006 | Caffeine Melting Point Standard (1 g) (Approximately 236 degrees) | JOB204 |  | I (03/04) | [58-08-2] | \$92 |
| 1086108 | Calcifediol ( 75 mg ) | G |  |  | [63283-36-3] | \$156 |
| 1086356 | Calcium Ascorbate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  | F (08/01) | [5743-28-2] | \$156 |
| 1086800 | Calcium Gluceptate ( 200 mg ) | F-1 |  | F (09/00) | [29039-00-7] | \$156 |
| 1086902 | Calcium Lactobionate ( $200 \mathrm{mg} \mathrm{)}$ | G0B138 |  | $\begin{array}{\|l\|} \hline \text { F-1 (01/04) } \\ \text { F (11/01) } \\ \hline \end{array}$ | [110638-68-1] | \$156 |
| 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) | N-1 |  | N (06/00) | [137-08-6] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1087202 | Calcium Saccharate ( 200 mg ) | F |  |  | [5793-89-5] | \$156 |
| 1088001 | Candicidin ( 200 mg ) | F |  |  | [1403-17-4] | \$156 |
| 1089004 | Cannabidiol Cl (25 mg) (AS) | F-2 |  |  | [13956-29-1] | \$207 |
| 1090003 | Cannabinol CI (25 mg) (AS) |  |  | F-2 (05/02) | [521-35-7] | \$207 |
| 1091006 | Capreomycin Sulfate (200 mg) | G |  | F (06/01) | [1405-37-4] | \$156 |
| 1091108 | Capsaicin (100 mg) | G-1 |  | $\begin{array}{\|l\|} \hline \text { G (03/02) } \\ \text { F-1 (06/00) } \\ \text { F (03/99) } \\ \hline \end{array}$ | [404-86-4] | \$156 |
| 1091200 | Captopril (200 mg) | H |  |  | [62571-86-2] | \$156 |
| 1091221 | Captopril Disulfide ( 100 mg ) | G1B066 |  | G (01/04) | [64806-05-9] | \$487 |
| 1092009 | Carbachol (200 mg) | G |  |  | [51-83-2] | \$156 |
| 1093001 | Carbamazepine ( 100 mg ) | $J$ |  | I-1 (02/00) | [298-46-4] | \$156 |
| 1093205 | Carbarsone ( 200 mg ) | F |  |  | [121-59-5] | \$156 |
| 1093500 | Carbenicillin Indanyl Sodium ( 300 mg ) | G |  |  | [26605-69-6] | \$156 |
| 1094004 | Carbenicillin Monosodium Monohydrate ( 200 mg ) | G-2 |  |  | n/f | \$156 |
| 1095506 | Carbidopa ( 400 mg ) | 1 |  | H (10/99) | [38821-49-7] | \$156 |
| 1095517 | Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa) | H0B121 |  | G (04/03) | n/f | \$487 |
| 1096000 | Carbinoxamine Maleate ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G-1 (11/02) | [3505-38-2] | \$156 |
| 1096407 | Carboplatin ( 100 mg ) | H0C240 |  | $\begin{array}{\|l\|} \hline G(07 / 04) \\ F(03 / 00) \\ \hline \end{array}$ | [41575-94-4] | \$159 |
| 1096509 | Carboprost Tromethamine (25 mg) | F-1 |  | F (02/01) | [58551-69-2] | \$487 |
| 1096600 | Carisoprodol (1 g) | G |  | F-2 (05/02) | [78-44-4] | \$156 |
| 1096757 | Carteolol Hydrochloride (200 mg) | F-1 |  | F (11/00) | [51781-21-6] | \$156 |
| 1096804 | Cathinone Hydrochloride $\mathbf{C l}(50 \mathrm{mg})$ (alpha-Aminopropiophenone Hydrochloride) | I |  |  | [76333-53-4] | \$560 |
| 1096906 | Cefaclor ( 400 mg ) | H |  |  | [70356-03-5] | \$156 |
| 1096917 | Cefaclor, Delta-3-Isomer ( 30 mg ) | G |  | F-1 (02/00) | n/f | \$156 |
| 1097104 | Cefadroxil ( 125 mg ) | 11B319 | 2 | $\begin{aligned} & \text { I (01/05) } \\ & \mathrm{H}(04 / 99) \end{aligned}$ | [66592-87-8] | \$124 |
| 1097308 | Cefamandole Lithium (200 mg) | H |  |  | n/f | \$156 |
| 1097400 | Cefamandole Nafate ( 200 mg ) | H |  |  | [42540-40-9] | \$156 |
| 1097501 | Cefamandole Sodium ( 250 mg ) | F |  |  | [30034-03-8] | \$156 |
| 1097603 | Cefazolin ( 400 mg ) | K |  | $J(06 / 00)$ | [25953-19-9] | \$156 |
| 1097636 | Cefepime Hydrochloride ( 500 mg ) | F0C063 |  |  | [123171-59-5] | \$156 |
| 1097647 | Cefepime Hydrochloride System Suitability ( 25 mg ) | F0C095 |  |  | n/f | \$156 |
| 1097658 | Cefixime ( 500 mg ) | F |  |  | [79350-37-1] | \$156 |
| 1097771 | Cefmenoxime Hydrochloride ( 350 mg ) | F |  |  | [75738-58-8] | \$156 |
| 1097782 | Cefmetazole (200 mg) | F-1 |  | F (04/02) | [56796-20-4] | \$156 |
| 1097750 | Cefonicid Sodium (1 g) | G |  |  | [61270-78-8] | \$156 |
| 1097705 | Cefoperazone Dihydrate (200 mg) | H |  | G (12/99) | [62893-19-0] | \$156 |
| 1097807 | Ceforanide ( 200 mg ) | F-1 |  | F (07/00) | [60925-61-3] | \$156 |
| 1097909 | Cefotaxime Sodium ( 250 mg ) | J0C189 | 2 | I (11/04) | [64485-93-4] | \$124 |
| 1097975 | Cefotetan ( 500 mg ) | H0C175 |  | $\begin{array}{\|l\|} \hline G(07 / 04) \\ F(09 / 00) \\ \hline \end{array}$ | [69712-56-7] | \$156 |
| 1098005 | Cefotiam Hydrochloride ( 325 mg ) | G0B050 |  | F (01/03) | [66309-69-1] | \$156 |
| 1098107 | Cefoxitin ( 500 mg ) | 1 |  | H (05/00) | [35607-66-0] | \$156 |
| 1098118 | Cefpiramide ( 300 mg ) | F0C203 |  |  | [70797-11-4] | \$156 |
| 1098049 | Cefprozil E-Isomer ( 50 mg ) | F2C284 |  | $\begin{array}{\|l\|} \hline \text { F-1 (10/04) } \\ \text { F (05/01) } \\ \hline \end{array}$ | [121123-17-9] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1098050 | Cefprozil Z-Isomer (200 mg) | G0C037 |  | F (12/03) | [121123-17-9] | \$156 |
| 1098129 | Ceftazidime, Delta-3-Isomer ( 25 mg ) | G |  | F (03/00) | n/f | \$208 |
| 1098130 | Ceftazidime Pentahydrate ( 300 mg ) | H |  | G (12/99) | [78439-06-2] | \$156 |
| 1098173 | Ceftizoxime (200 mg) | H |  |  | [68401-81-0] | \$156 |
| 1098184 | Ceftriaxone Sodium ( 350 mg ) | G0B264 |  | F (08/03) | [104376-79-6] | \$156 |
| 1098195 | Ceftriaxone Sodium E-Isomer ( 25 mg ) | 10C190 |  | H (07/04) G (08/01) F-1 (02/00) | n/f | \$208 |
| 1098209 | Cefuroxime Sodium ( 200 mg ) | H |  | G-1 (05/00) | [56238-63-2] | \$156 |
| 1098220 | Cefuroxime Axetil ( 500 mg ) | G |  | F-1 (05/02) | [64544-07-6] | \$156 |
| 1098231 | Cefuroxime Axetil Delta-3-Isomers ( 35 mg ) | H0B160 |  | G (03/03) | n/f | \$156 |
| 1098300 | Cellulose Acetate ( 125 mg ) | F-1 |  | F (11/99) | [9004-35-7] | \$124 |
| 1098355 | Cellulose Acetate Phthalate ( 125 mg ) | F-1 |  | F (03/99) | [9004-38-0] | \$124 |
| 1098708 | Cephaeline Hydrobromide ( 200 mg ) | G-1 |  |  | n/f | \$487 |
| 1099008 | Cephalexin ( 250 mg ) | I-2 |  | I-1 (03/00) | [23325-78-2] | \$156 |
| 1102000 | Cephalothin Sodium (200 mg) | I |  |  | [58-71-9] | \$156 |
| 1102408 | Cephapirin Benzathine ( 100 mg ) | F |  |  | [97468-37-6] | \$156 |
| 1102500 | Cephapirin Sodium ( 200 mg ) | I-1 |  | 1 (07/02) | [24356-60-3] | \$156 |
| 1102805 | Cephradine ( 200 mg ) | J |  | $1(04 / 00)$ | [58456-86-3] | \$156 |
| 1103003 | Cetyl Alcohol ( 100 mg ) | 1 |  | H (03/99) | [36653-82-4] | \$156 |
| 1103105 | Cetyl Palmitate ( 50 mg ) | F0B241 |  |  | [540-10-3] | \$156 |
| 1104006 | Cetylpyridinium Chloride ( 500 mg ) | I |  | $\begin{aligned} & \text { H-1 (06/01) } \\ & \text { H (08/99) } \\ & \hline \end{aligned}$ | [6004-24-6] | \$156 |
| 1105009 | Powdered Chaste Tree Extract (1.5 g) | F0C406 | 1 |  | [91722-47-3] | \$520 |
| 1106001 | Chlorambucil ( 125 mg ) | G |  | F-1 (02/99) | [305-03-3] | \$124 |
| 1107004 | Chloramphenicol (200 mg) | N1C074 |  | $\begin{array}{\|l\|} \hline N(10 / 04) \\ M(03 / 00) \\ \hline \end{array}$ | [56-75-7] | \$156 |
| 1107300 | Chloramphenicol Palmitate (200 mg) | G-1 |  |  | [530-43-8] | \$156 |
| 1107401 | Chloramphenicol Palmitate Nonpolymorph A (200 mg) | F-1 |  |  | [530-43-8] | \$487 |
| 1107503 | Chloramphenicol Palmitate Polymorph A (200 mg) | G |  | F (08/99) | [530-43-8] | \$487 |
| 1109000 | Chlordiazepoxide CIV (200 mg) | IOB063 |  | H-1 (03/03) | [58-25-3] | \$207 |
| 1110009 | Chlordiazepoxide Hydrochloride CIV ( 200 mg ) | G-4 |  |  | [438-41-5] | \$207 |
| 1110020 | Chlordiazepoxide Related Compound A ( 25 mg ) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide) | G |  |  | [963-39-3] | \$487 |
| 1111001 | Chlorhexidine ( 200 mg ) | F0C306 |  |  | [55-56-1] | \$156 |
| 1111103 | Chlorhexidine Acetate ( 500 mg ) | F0C281 |  |  | [56-95-1] | \$156 |
| 1111307 | Chlorhexidine Related Compounds ( 50 mg ) | F0D017 | 1 |  | n/f | \$487 |
| 1112503 | Chlorobutanol (200 mg) | G |  | F-3 (12/01) | [6001-64-5] | \$156 |
| 1115545 | Chlorogenic Acid ( 50 mg ) | FOC420 | 1 |  | [327-97-9] | \$156 |
| 1115556 | beta-Chlorogenin ( 20 mg ) | F |  |  | n/f | \$156 |
| 1117008 | Chloroprocaine Hydrochloride (200 mg) | G0B285 |  | $\begin{aligned} & \hline \text { F-3 (01/04) } \\ & \text { F-2 (03/99) } \\ & \hline \end{aligned}$ | [3858-89-7] | \$156 |
| 1118000 | Chloroquine Phosphate ( 500 mg ) | 1 |  | H (10/99) | [50-63-5] | \$156 |
| 1121005 | Chlorothiazide ( 200 mg ) | H0B161 |  | G (04/03) | [58-94-6] | \$156 |
| 1122008 | Chlorotrianisene (1 g) | F |  |  | [569-57-3] | \$156 |
| 1122700 | Chloroxylenol ( 125 mg ) | F2C259 |  | $\begin{aligned} & \hline \text { F-1 (07/04) } \\ & \text { F (10/99) } \\ & \hline \end{aligned}$ | [88-04-0] | \$124 |
| 1122722 | Chloroxylenol Related Compound A (25 mg) (2-chloro-3,5-dimethylphenol) | G0C275 |  | F-1 (07/04) | [5538-41-0] | \$487 |
| 1123000 | Chlorpheniramine Maleate (125 mg) | м0B020 |  | L-1 (06/03) | [113-92-8] | \$124 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1123102 | Chlorpheniramine Maleate Extended-Release Tablets (Drug Release Calibrator, Single Unit) ( 60 Tablets) | G0B259 |  | F (06/03) | [113-92-8] | \$156 |
| 1124003 | Chlorphenoxamine Hydrochloride (200 mg) | F-1 |  |  | [562-09-4] | \$156 |
| 1125006 | Chlorpromazine Hydrochloride ( 200 mg ) | J |  | I (04/99) | [69-09-0] | \$156 |
| 1126009 | Chlorpropamide (200 mg) | H |  |  | [94-20-2] | \$156 |
| 1127001 | Chlorprothixene (200 mg) | F-1 |  |  | [113-59-7] | \$156 |
| 1129007 | Chlortetracycline Hydrochloride ( 200 mg ) | K0C185 | 2 | $\begin{array}{\|l} \mathrm{J}-1(12 / 04) \\ \mathrm{J}(02 / 02) \\ \hline \end{array}$ | [64-72-2] | \$156 |
| 1130006 | Chlorthalidone (200 mg) | 10 C 255 |  | $\begin{array}{\|l\|l\|l\|l\|l\|} \hline \text { H-1 (11/04) } \\ \text { H (07/99) } \\ \hline \end{array}$ | [77-36-1] | \$156 |
| 1119309 | Chlorthalidone Related Compound A (25 mg) (4'-Chloro-3'-sulfamoyl-2benzophenone Carboxylic Acid) | G0C376 |  | F-3 (07/04) | n/f | \$487 |
| 1130505 | Chlorzoxazone ( 500 mg ) | I |  | H (07/01) | [95-25-0] | \$156 |
| 1130527 | Chlorzoxazone Related Compound A (50 mg) (2-Amino-4-chlorophenol) | G-1 |  | G (11/00) | [95-85-2] | \$487 |
| 1131009 | Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3) | M0B157 |  | $\begin{array}{\|l\|} \hline L(10 / 03) \\ K \\ \hline \end{array}$ | [67-97-0] | \$159 |
| 1131803 | Delta-4,6-cholestadienol ( 30 mg ) | F |  |  | [14214-69-8] | \$156 |
| 1132001 | Cholesteryl Caprylate (200 mg) | F |  |  | [1182-42-9] | \$156 |
| 1133004 | Cholestyramine Resin ( 500 mg ) | 1 |  |  | [11041-12-6] | \$124 |
| 1133503 | Cholic Acid (2 g) (AS) | F3B159 |  | F-2 (01/03) | [81-25-4] | \$156 |
| 1133536 | Choline Bitartrate ( $200 \mathrm{mg} \mathrm{)}$ | F0C057 |  |  | [87-67-2] | \$156 |
| 1133547 | Choline Chloride ( 200 mg ) | F0C058 |  |  | [67-48-1] | \$156 |
| 1133570 | Chondroitin Sulfate Sodium ( 300 mg ) | F0B256 |  |  | [39455-18-0] | \$156 |
| 1133638 | Chromium Picolinate ( 100 mg ) | F |  |  | [14639-25-9] | \$156 |
| 1134007 | Chymotrypsin ( 300 mg ) | 1 |  | H (06/01) | [9004-07-3] | \$156 |
| 1134030 | Ciclopirox Olamine ( 125 mg ) | H0C207 |  | G (05/03) | [41621-49-2] | \$124 |
| 1134051 | Cilastatin Ammonium Salt ( 100 mg ) | F-1 |  | F (07/00) | n/f | \$156 |
| 1134062 | Cimetidine (200 mg) | I1C081 |  | I (05/04) | [51481-61-9] | \$156 |
| 1134073 | Cimetidine Hydrochloride ( 200 mg ) | F |  |  | [70059-30-2] | \$156 |
| 1134109 | Cinoxacin (200 mg) | F |  |  | [28657-80-9] | \$156 |
| 1134313 | Ciprofloxacin ( 125 mg ) | G-1 |  | G (05/01) | [85721-33-1] | \$124 |
| 1134324 | Ciprofloxacin Ethylenediamine Analog (25 mg) | J0A030 |  | $\begin{array}{\|l\|} \hline \text { I (01/03) } \\ \text { H-1 (02/99) } \\ \hline \end{array}$ | n/f | \$208 |
| 1134335 | Ciprofloxacin Hydrochloride ( 400 mg ) | $10 C 265$ | 2 | $\begin{array}{\|l\|} \hline \mathrm{H}(02 / 05) \\ \mathrm{G}(04 / 00) \\ \hline \end{array}$ | [86393-32-0] | \$156 |
| 1134357 | Cisplatin (100 mg) | H |  | G (03/01) | [15663-27-1] | \$156 |
| 1134368 | Citric Acid (200 mg) | F1B092 |  | $\begin{array}{\|l\|} \hline \text { F-1 (01/04) } \\ \text { F (07/02) } \\ \hline \end{array}$ | [77-92-9] | \$156 |
| 1134379 | Clarithromycin (75 mg) | F4B183 |  | $\begin{array}{\|l\|l\|} \hline \text { F-3 }(01 / 04) \\ \text { F-2 } & (09 / 01) \\ \hline \end{array}$ | [81103-11-9] | \$156 |
| 1134380 | Clarithromycin Related Compound A (50 mg) (6,11-di-O-methylerythromycin A) | G |  | F (04/01) | n/f | \$208 |
| 1134404 | Clavam-2-carboxylate Potassium (1 Pellet) | H0C089 |  | $\begin{aligned} & \text { GOB225 (12/03) } \\ & \text { F (10/03) } \end{aligned}$ | n/f | \$487 |
| 1134426 | Clavulanate Lithium ( 200 mg ) | I1C270 | 2 | $\begin{array}{\|l\|l\|} \hline I(02 / 05) \\ H \\ \hline \end{array}$ | n/f | \$156 |
| 1134506 | Clemastine Fumarate (250 mg) | 1 |  | H (10/00) | [14976-57-9] | \$156 |
| 1135000 | Clidinium Bromide ( 2 g ) | G |  |  | [3485-62-9] | \$156 |
| 1135021 | Clidinium Bromide Related Compound A ( 250 mg ) (3-Hydroxy-1methylquinuclindinium Bromide) | I |  |  | [76201-95-1] | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1136002 | Clindamycin Hydrochloride (200 mg) | G4A017 |  | $\begin{aligned} & \text { G-3 (07/03) } \\ & \text { G-2 (05/99) } \\ & \hline \end{aligned}$ | [58207-19-5] | \$428 |
| 1137005 | Clindamycin Palmitate Hydrochloride (200 mg) | F-2 |  |  | [25507-04-4] | \$428 |
| 1138008 | Clindamycin Phosphate (125 mg) | IOC165 |  | $\begin{array}{ll} \hline \mathrm{H}-3(04 / 04) \\ \mathrm{H}-2(07 / 03) \\ \mathrm{H}-1(02 / 99) \\ \hline \end{array}$ | [24729-96-2] | \$214 |
| 1138201 | Clioquinol ( 500 mg ) | M |  | L-1 (01/03) | [130-26-7] | \$156 |
| 1138405 | Clobetasol Propionate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  | F (10/01) | [25122-46-7] | \$156 |
| 1138427 | Clobetasol Propionate Related Compound A ( 50 mg ) (9-alpha-fluoro-11-beta-hydroxy-16-beta-methyl-3-oxo-androsta-1,4-diene-17(R)-spiro-2'-[4'-chloro-5'-ethylfuran-3'(2'H)-one]) | F-1 |  | F (01/03) | n/f | \$208 |
| 1138507 | Clocortolone Pivalate (200 mg) | G |  |  | [34097-16-0] | \$156 |
| 1138904 | Clofazimine ( 200 mg ) | F |  |  | [2030-63-9] | \$156 |
| 1139000 | Clofibrate (1 g) | 1 |  | H (04/01) | [637-07-0] | \$156 |
| 1140000 | Clomiphene Citrate ( 500 mg ) | H |  | G-1 (10/99) | [50-41-9] | \$156 |
| 1140101 | Clomiphene Related Compound A (100 mg) ((E,Z)-2-[4-(1,2-dipheny-lethenyl)phenoxy]-N,N-diethylethanamine Hydrochloride) | F1B206 |  | F (09/03) | n/f | \$208 |
| 1140247 | Clomipramine Hydrochloride ( 200 mg ) | F0C075 |  |  | [17321-77-6] | \$156 |
| 1140305 | Clonazepam CIV (200 mg) | G1B175 |  | $\begin{array}{\|l\|} \hline \text { G (01/04) } \\ \text { F-2 (01/00) } \\ \hline \end{array}$ | [1622-61-3] | \$207 |
| 1140327 | Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophe-nyl)-6-nitrocarbostyril) | G2B110 |  | $\begin{aligned} & \text { G-1 (01/04) } \\ & \text { G (02/99) } \\ & \hline \end{aligned}$ | n/f | \$487 |
| 1140338 | Clonazepam Related Compound B ( 25 mg ) (2-Amino-2'-chloro-5nitrobenzophenone) | H |  | G (04/01) | [2011-66-7] | \$487 |
| 1140349 | Clonazepam Related Compound C (25 mg) (2-Bromo-2'-(2-chloroben-zoyl)-4'-nitroacetanilide) | F0C340 |  |  | n/f | \$487 |
| 1140393 | Clonidine ( 200 mg ) | F0C401 |  |  | [4205-90-7] | \$156 |
| 1140407 | Clonidine Hydrochloride (200 mg) | G |  |  | [4205-91-8] | \$156 |
| 1140418 | Clonidine Related Compound A ( 25 mg ) (Acetylclonidine) | F0C373 |  |  | [54707-71-0] | \$487 |
| 1140429 | Clonidine Related Compound B ( 25 mg ) (2-[(E)-2,6-Dichlorophenylimi-no]-1-(1-\{2-[(E)-2,6-dichlorophenylimino]-imidazolidin-1-yl\}-ethyl)-imidazolidine) | F0C403 | 1 |  | n/f | \$487 |
| 1140509 | Clorazepate Dipotassium CIV (125 mg) | G0B027 |  | $\begin{array}{\|l\|} \hline \text { F-1 (06/03) } \\ \text { F (12/99) } \\ \hline \end{array}$ | [57109-90-7] | \$207 |
| 1140702 | Clorsulon (200 mg) | F1B084 |  | F (01/04) | [60200-06-8] | \$156 |
| 1141002 | Clotrimazole ( 200 mg ) | K0C282 | 2 | $\begin{array}{\|l} \hline J(02 / 05) \\ I ~(05 / 99) \\ \hline \end{array}$ | [23593-75-1] | \$124 |
| 1141024 | Clotrimazole Related Compound A ( 25 mg ) ((0-chlorophenyl)diphenylmethanol) | I |  | $\begin{aligned} & \mathrm{H}(10 / 01) \\ & \mathrm{G}-1(02 / 99) \\ & \hline \end{aligned}$ | [66774-02-5] | \$487 |
| 1141909 | Cloxacillin Benzathine ( 200 mg ) | F-1 |  | F (03/02) | [23736-58-5] | \$156 |
| 1142005 | Cloxacillin Sodium (200 mg) | LOB086 |  | K (01/04) | [7081-44-9] | \$156 |
| 1142107 | Clozapine ( 100 mg ) | F0C032 |  |  | [5786-21-0] | \$260 |
| 1143008 | Cocaine Hydrochloride CII (250 mg) | IOB074 |  | $\begin{array}{\|l\|} \hline \mathrm{H}-2(01 / 04) \\ \mathrm{H}-1(02 / 99) \\ \hline \end{array}$ | [53-21-4] | \$207 |
| 1143802 | Codeine N-Oxide Cl (50 mg) | G0A034 |  | F-1 (11/02) | [3688-65-1] | \$207 |
| 1144000 | Codeine Phosphate CII (100 mg) | J0C200 |  | $\begin{array}{\|l\|l\|} \hline \text { I-1 (10/04) } \\ \text { I (09/02) } \\ \text { H-1 }(01 / 00) \\ \hline \end{array}$ | [41444-62-6] | \$207 |
| 1145003 | Codeine Sulfate CII (250 mg) | H-2 |  | $\mathrm{H}-1$ (01/02) | [6854-40-6] | \$207 |
| 1146006 | Colchicine ( 300 mg ) | $J$ |  | I (05/02) | [64-86-8] | \$156 |
| 1146505 | Colestipol Hydrochloride (200 mg) | F-1 |  |  | [37296-80-3] | \$156 |
| 1147009 | Colistimethate Sodium (200 mg) | H |  |  | [8068-28-8] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1148001 | Colistin Sulfate (200 mg) | G-1 |  | G (09/99) | [1264-72-8] | \$156 |
| 1148500 | Copovidone ( 100 mg ) | F0C194 |  |  | [2586-89-9] | \$156 |
| 1149004 | Corticotropin (5.6 Units/vial; 5 vials) | M |  | L (06/99) | [9002-60-2] | \$124 |
| 1150003 | Cortisone Acetate ( 150 mg ) | I |  |  | [50-04-4] | \$156 |
| 1150353 | Creatinine ( 100 mg ) | F |  |  | [60-27-5] | \$156 |
| 1150502 | Cromolyn Sodium ( 500 mg ) | $J$ |  | I (06/00) | [15826-37-6] | \$156 |
| 1150706 | Crospovidone ( 200 mg ) | G1C273 |  | G (12/04) | [9003-39-8] | \$156 |
| 1151006 | Crotamiton ( 200 mg ) | H-1 |  | H (07/00) | [483-63-6] | \$156 |
| 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) | N |  | M-3 (08/99) | [68-19-9] | \$156 |
| 1152508 | Cyclacillin (200 mg) | G |  |  | [3485-14-1] | \$156 |
| 1152701 | Cyclandelate (200 mg) | F0C384 |  |  | [456-59-7] | \$156 |
| 1154004 | Cyclizine Hydrochloride ( 200 mg ) | G |  |  | [303-25-3] | \$156 |
| 1154503 | Cyclobenzaprine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G0A013 |  | F-3 (07/03) | [6202-23-9] | \$156 |
| 1154558 | Alpha Cyclodextrin ( 50 mg ) | F-1 |  | F (10/00) | [10016-20-3] | \$156 |
| 1154569 | Beta Cyclodextrin (250 mg) | G |  | F-1 (12/02) | [7585-39-9] | \$156 |
| 1154707 | Cyclomethicone 4 (200 mg) | F-2 |  | F-1 (06/02) | [69430-24-6] | \$156 |
| 1154809 | Cyclomethicone 5 ( 125 mg ) | F-2 |  | F-1 (09/99) | [69430-24-6] | \$124 |
| 1154900 | Cyclomethicone 6 (200 mg) | F2B024 |  | F-1 (03/03) | [69430-24-6] | \$156 |
| 1156000 | Cyclopentolate Hydrochloride ( 300 mg ) | H |  | G (04/00) | [5870-29-1] | \$156 |
| 1157002 | Cyclophosphamide ( 500 mg ) | J1B200 | 2 | $J(02 / 05)$ | [6055-19-2] | \$124 |
| 1157501 | 2-Cyclopropylmethylamino-5-chlorobenzophenone ( 50 mg ) | F |  |  | n/f | \$487 |
| 1158005 | Cycloserine ( 200 mg ) | G |  |  | [68-41-7] | \$156 |
| 1158504 | Cyclosporine ( 50 mg ) | H-1 |  | $\begin{aligned} & \text { H (11/02) } \\ & \text { G-2 (03/00) } \end{aligned}$ | [59865-13-3] | \$479 |
| 1158650 | Cyclosporine Resolution Mixture (25 mg) | F |  |  | $\begin{aligned} & \text { [108027-45-8] } \\ & \text { (U) } \\ & \hline \end{aligned}$ | \$412 |
| 1159008 | Cyclothiazide ( 200 mg ) | F-1 |  |  | [2259-96-3] | \$156 |
| 1161000 | Cyproheptadine Hydrochloride ( 500 mg ) | G |  | F-4 (11/02) | [41354-29-4] | \$156 |
| 1161509 | L-Cysteine Hydrochloride ( 200 mg ) | H |  | G (05/00) | [7048-04-6] | \$156 |
| 1162002 | Cytarabine ( 250 mg ) | G-2 |  | G-1 (07/00) | [147-94-4] | \$156 |
| 1162308 | Dacarbazine ( 125 mg ) | H |  | G (01/99) | [4342-03-4] | \$124 |
| 1162320 | Dacarbazine Related Compound A ( 50 mg ) ( 5 -aminoimidazole-4carboxamide Hydrochloride) | H0C052 |  | $\begin{array}{\|l\|} \hline G(03 / 04) \\ F(03 / 00) \\ \hline \end{array}$ | [72-40-2] | \$487 |
| 1162330 | Dacarbazine Related Compound B (50 mg) (2-azahypoxanthine) | G0C325 | 2,3 | $\begin{array}{\|l\|} \hline \text { F-1 (03/05) } \\ \text { F (12/01) } \\ \hline \end{array}$ | [63907-29-9] | \$600 |
| 1162400 | Dactinomycin (50 mg) | 1 |  |  | [50-76-0] | \$427 |
| 1162501 | Danazol ( 200 mg ) | H |  | G (10/00) | [17230-88-5] | \$156 |
| 1164008 | Dapsone (125 mg) | G-3 |  | G-2 (08/99) | [80-08-0] | \$124 |
| 1164700 | Daunorubicin Hydrochloride (200 mg) | LOB307 |  | $\begin{aligned} & \mathrm{K}(11 / 03) \\ & \mathrm{J}(08 / 00) \\ & \hline \end{aligned}$ | [23541-50-6] | \$479 |
| 1165000 | Decamethonium Bromide ( 250 mg ) | F |  |  | [541-22-0] | \$156 |
| 1166003 | Deferoxamine Mesylate ( 500 mg ) | 1 |  |  | [138-14-7] | \$156 |
| 1166309 | Dehydroacetic Acid (200 mg) | F |  |  | [520-45-6] | \$156 |
| 1166400 | Dehydrocarteolol Hydrochloride ( 100 mg ) | F |  |  | n/f | \$487 |
| 1166502 | Dehydrocholic Acid (200 mg) | F-1 |  | F (03/04) | [81-23-2] | \$156 |
| 1169001 | Demecarium Bromide ( 250 mg ) | F |  |  | [56-94-0] | \$156 |
| 1170000 | Demeclocycline Hydrochloride ( 200 mg ) | H1C036 |  | $\begin{array}{\|l\|} \hline H \quad(08 / 04) G-1 \\ (08 / 01) \end{array}$ | [64-73-3] | \$156 |

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| 1171003 | Denatonium Benzoate ( 200 mg ) | IOB129 |  | H (09/02) | [86398-53-0] | \$156 |
| 1171706 | Desacetyl Diltiazem Hydrochloride ( 50 mg ) | 1 |  | H (08/00) | [23515-45-9] | \$487 |
| 1171900 | Desflurane ( 0.5 mL ) | F0C187 |  |  | [57041-67-5] | \$156 |
| 1171910 | Desflurane Related Compound A ( 0.1 mL ) (bis-(1,2,2,2-tetrafluoroethyl) ether) | F0C031 |  |  | n/f | \$487 |
| 1172006 | Desipramine Hydrochloride ( 125 mg ) | H-1 |  | H (10/99) | [58-28-6] | \$124 |
| 1173009 | Deslanoside ( 100 mg ) | H-1 |  |  | [17598-65-1] | \$156 |
| 1173235 | Desogestrel ( 50 mg ) | G0C390 |  | FOB282 (11/04) | [54024-22-5] | \$156 |
| 1173246 | Desogestrel Related Compound A (15 mg) (13-Ethyl-11-methylene-18, 19-dinor-5alpha, 17alpha-preg-3-en-20-yl-17-ol, desogestrel delta-3 isomer) | F0B279 |  |  | n/f | \$487 |
| 1173257 | Desogestrel Related Compound B (15 mg) (3-Hydroxy-desogestrel) | FOB284 |  |  | n/f | \$487 |
| 1173268 | Desogestrel Related Compound C ( 25 mg ) (3-Keto-desogestrel) | FOB281 |  |  | [54048-10-1] | \$487 |
| 1173508 | Desoximetasone ( 200 mg ) | H0B036 |  | G (01/04) | [382-67-2] | \$156 |
| 1174001 | Desoxycorticosterone Acetate ( $200 \mathrm{mg} \mathrm{)}$ | J0C014 |  | $\begin{array}{\|l\|} \hline \text { I (01/04) } \\ \mathrm{H}(05 / 00) \\ \hline \end{array}$ | [56-47-3] | \$156 |
| 1175004 | Desoxycorticosterone Pivalate ( 125 mg ) | H0C276 |  | G (01/04) | [808-48-0] | \$124 |
| 1176007 | Dexamethasone ( 125 mg ) | J |  |  | [50-02-2] | \$124 |
| 1176506 | Dexamethasone Acetate ( 200 mg ) | G |  | F-1 (06/99) | [55812-90-3] | \$156 |
| 1177000 | Dexamethasone Phosphate (200 mg) | J1B070 |  | $\begin{array}{\|l} \hline \mathrm{J}(08 / 03) \\ \mathrm{I}(03 / 00) \\ \hline \end{array}$ | [312-93-6] | \$156 |
| 1178002 | Dexbrompheniramine Maleate (200 mg) | $J$ |  | 1 (03/03) | [2391-03-9] | \$156 |
| 1179005 | Dexchlorpheniramine Maleate ( 500 mg ) | G1A025 |  | G (12/02) | [2438-32-6] | \$156 |
| 1179504 | Dexpanthenol ( 500 mg ) | J0C293 |  | $\begin{aligned} & \hline \text { I (08/04) } \\ & \mathrm{H}(02 / 02) \\ & \hline \end{aligned}$ | [81-13-0] | \$160 |
| 1179708 | Dextran 40 ( 50 mg ) | F0C247 |  |  | [9004-54-0] | \$156 |
| 1179741 | Dextran 70 ( 50 mg ) | F0C260 |  |  | [9004-54-0] | \$156 |
| 1179854 | Dextran 4 Calibration (100 mg) | F0C002 |  |  | [9004-54-0] | \$156 |
| 1179865 | Dextran 10 Calibration ( 100 mg ) | F0C010 |  |  | [9004-54-0] | \$156 |
| 1179876 | Dextran 40 Calibration ( 100 mg ) | F0C011 |  |  | [9004-54-0] | \$156 |
| 1179720 | Dextran 40 System Suitability ( 200 mg ) | F0B181 |  |  | [9004-54-0] | \$156 |
| 1179887 | Dextran 70 Calibration ( 100 mg ) | F0C013 |  |  | [9004-54-0] | \$156 |
| 1179763 | Dextran 70 System Suitability ( 200 mg ) | F0B182 |  |  | [9004-54-0] | \$156 |
| 1179898 | Dextran 250 Calibration ( 100 mg ) | F0C039 |  |  | [9004-54-0] | \$156 |
| 1179800 | Dextran Vo Marker ( 100 mg ) | FOB242 |  |  | [9004-54-0] | \$156 |
| 1180004 | Dextroamphetamine Sulfate CII (500 mg) | H |  | $\begin{aligned} & \hline \text { G (08/03) } \\ & \text { F-6 (12/99) } \end{aligned}$ | [51-63-8] | \$216 |
| 1180503 | Dextromethorphan (2 g) | H |  | G (06/00) | [125-71-3] | \$487 |
| 1181007 | Dextromethorphan Hydrobromide ( 500 mg ) | JOB167 |  | I (07/03) | [6700-34-1] | \$156 |
| 1181302 | Dextrose ( 500 mg ) | J-1 |  | $\begin{array}{\|l} \hline J(11 / 02) \\ I(08 / 99) \\ \hline \end{array}$ | [50-99-7] | \$124 |
| 1181506 | Diacetylated Monoglycerides ( 200 mg ) | G |  |  | [68990-54-5] | \$156 |
| 1182000 | Diacetylfluorescein (200 mg) | H |  | G (01/02) | [596-09-8] | \$156 |
| 1183002 | Diacetylmorphine Hydrochloride CI (25 mg) (AS) (Heroin Hydrochloride) | J |  | I-1 (10/99) | [1502-95-0] | \$207 |
| 1184005 | Diatrizoic Acid ( 100 mg ) | G |  |  | [50978-11-5] | \$156 |
| 1184027 | Diatrizoic Acid Related Compound A ( 50 mg ) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid) | I |  | H (02/00) | [1713-07-1] | \$487 |
| 1185008 | Diazepam CIV (100 mg) | 1 |  | H (12/01) | [439-14-5] | \$207 |
| 1185020 | Diazepam Related Compound A (25 mg) (2-Methyl-amino-5-chlorobenzophenone) | 1 |  | $\begin{array}{\|l} \hline \mathrm{H}-1(11 / 02) \\ \mathrm{H}(04 / 00) \\ \hline \end{array}$ | [1022-13-5] | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1023403 | Diazepam Related Compound B (25 mg) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril) | I1C102 |  | $\begin{array}{\|l\|l\|} \hline I(12 / 04) \\ H & (04 / 01) \\ \hline \end{array}$ | [5220-02-0] | \$487 |
| 1186000 | Diazoxide (200 mg) | G1C017 |  | G (12/03) | [364-98-7] | \$156 |
| 1187003 | Dibucaine Hydrochloride (200 mg) | 1 |  | H-2 (01/03) | [61-12-1] | \$156 |
| 1187207 | Dichloralphenazone CIV (200 mg) | F0B010 |  |  | [480-30-8] | \$207 |
| 1188006 | Dichlorphenamide (200 mg) | G-1 |  |  | [120-97-8] | \$156 |
| 1188800 | Diclofenac Sodium (200 mg) | H0B150 |  | $\begin{aligned} & \text { G-1 (03/04) } \\ & \text { G (05/01) } \\ & \hline \end{aligned}$ | [15307-79-6] | \$156 |
| 1188811 | Diclofenac Related Compound A (100 mg) (N-(2,6-dichlorophenyl)in-dolin-2-one) | H |  | G (05/02) | [15362-40-0] | \$490 |
| 1189009 | Dicloxacillin Sodium (500 mg) | J0C182 |  | $\begin{array}{\|l\|} \hline \text { IOB142 (09/04) } \\ \text { H (05/03) } \\ \hline \end{array}$ | [13412-64-1] | \$156 |
| 1190008 | Dicumarol (200 mg) | G |  |  | [66-76-2] | \$156 |
| 1191000 | Dicyclomine Hydrochloride ( 125 mg ) | H |  | G (03/99) | [67-92-5] | \$124 |
| 1192003 | Dienestrol ( 125 mg ) | 1 |  |  | [84-17-3] | \$124 |
| 1193006 | Diethylcarbamazine Citrate ( 200 mg ) | G-1 |  |  | [1642-54-2] | \$156 |
| 1193301 | Diethylene Glycol Monoethyl Ether ( $0.5 \mathrm{~mL} /$ ampule) | F0B095 |  |  | [111-90-0] | \$156 |
| 1193505 | Diethyl Phthalate ( 200 mg ) | G |  | F-1 (03/00) | [84-66-2] | \$156 |
| 1194009 | Diethylpropion Hydrochloride CIV (200 mg) | H |  |  | [134-80-5] | \$207 |
| 1195001 | Diethylstilbestrol (200 mg) | K5B291 |  | K-4 (05/04) | [56-53-1] | \$156 |
| 1197007 | Diethyltoluamide (3 g) | H |  |  | [134-62-3] | \$124 |
| 1197302 | Diflorasone Diacetate (200 mg) | G |  | F-1 (03/00) | [33564-31-7] | \$156 |
| 1197506 | Diflunisal ( 200 mg ) | G |  |  | [22494-42-4] | \$156 |
| 1198000 | Digitalis (3 g) | F |  |  | [8031-42-3] | \$156 |
| 1199002 | Digitoxin ( 200 mg ) | M |  |  | [71-63-6] | \$156 |
| 1200000 | Digoxin (250 mg) | O0B096 |  | N-1 (04/03) | [20830-75-5] | \$156 |
| 1200600 | Dihydrocapsaicin (25 mg) | G0C071 |  | $\begin{array}{\|l} \hline \text { F-1 (12/03) } \\ \text { F (01/00) } \\ \hline \end{array}$ | [19408-84-5] | \$156 |
| 1200804 | Dihydrocodeine Bitartrate CII (200 mg) | H |  | G (03/01) | [5965-13-9] | \$207 |
| 1201002 | 17alpha-Dihydroequilin ( 50 mg ) | 10C277 |  | H (07/04) | [6639-99-2] | \$208 |
| 1202005 | Dihydroergotamine Mesylate (250 mg) (List Chemical) | J0B085 |  | I (03/03) | [6190-39-2] | \$156 |
| 1203008 | Dihydrostreptomycin Sulfate ( 200 mg ) | J |  |  | [5490-27-7] | \$156 |
| 1204000 | Dihydrotachysterol ( $30 \mathrm{mg} / \mathrm{ampule}$; 4 ampules) | 1 |  |  | [67-96-9] | \$156 |
| 1204102 | Dihydroxyacetone ( 250 mg ) | F |  |  | [96-26-4] | \$156 |
| 1204805 | Diloxanide Furoate (200 mg) | F0C026 |  |  | [3736-81-0] | \$156 |
| 1205003 | Diltiazem Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | I |  |  | [33286-22-5] | \$156 |
| 1206006 | Dimenhydrinate ( 100 mg ) | J0B055 |  | I (06/03) | [523-87-5] | \$156 |
| 1208001 | Dimethisoquin Hydrochloride (2 g) | G |  |  | [2773-92-4] | \$156 |
| 1210105 | N -(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8-germaspiro [4:5]de-cane-1,3-dione (AS) | F |  |  | [41992-23-8] | \$156 |
| 1211006 | Dimethyl Sulfoxide ( 3 g ) | G0C198 |  | $\begin{aligned} & \text { F-3 }(07 / 04) \\ & \text { F- }(05 / 02) \end{aligned}$ | [67-68-5] | \$208 |
| 1213001 | Dinoprost Tromethamine ( 50 mg ) | F |  |  | [38562-01-5] | \$1,525 |
| 1213103 | Dinoprostone ( 50 mg ) | F0C030 |  |  | [363-24-6] | \$1,525 |
| 1214004 | Dioxybenzone ( 150 mg ) | F1B277 |  | F (10/03) | [131-53-3] | \$156 |
| 1216000 | Diphemanil Methylsulfate ( 500 mg ) | H |  |  | [62-97-5] | \$156 |
| 1217909 | Diphenhydramine Citrate ( 125 mg ) | H0B128 |  | G (04/03) | [88637-37-0] | \$124 |
| 1218005 | Diphenhydramine Hydrochloride ( 200 mg ) | J0B013 |  | 1 (07/03) | [147-24-0] | \$156 |
| 1219008 | Diphenoxylate Hydrochloride CII (200 mg) | I |  | H (03/02) | [3810-80-8] | \$207 |

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| 1220302 | Dipivefrin Hydrochloride (200 mg) | 1 |  | H (06/99) | [64019-93-8] | \$156 |
| 1220506 | Dipyridamole (200 mg) | H |  | G-1 (01/99) | [58-32-2] | \$156 |
| 1220700 | Dirithromycin (200 mg) | F |  |  | [62013-04-1] | \$156 |
| 1221000 | Disodium Guanylate ( 300 mg ) (FCC) | F-1 |  |  | [5550-12-9] | \$156 |
| 1222002 | Disodium Inosinate ( 500 mg ) (FCC) | F |  |  | [4691-65-0] | \$156 |
| 1222501 | Disopyramide Phosphate (200 mg) | H-1 |  | H (03/02) | [22059-60-5] | \$156 |
| 1223005 | 2,4-Disulfamyl-5-trifluoromethylaniline ( 125 mg ) | G |  |  | [654-62-6] | \$487 |
| 1224008 | Disulfiram (200 mg) | F-3 |  | F-2 (07/02) | [97-77-8] | \$156 |
| 1224507 | Dobutamine Hydrochloride ( 600 mg ) | H-1 |  | H (01/00) | [49745-95-1] | \$156 |
| 1224700 | Docusate Calcium ( 500 mg ) | H0B044 |  | G-1 (07/02) | [128-49-4] | \$156 |
| 1224802 | Docusate Sodium ( 500 mg ) | J |  | I-1 (05/02) | [577-11-7] | \$156 |
| 1224904 | Docusate Potassium (100 mg) | F-1 |  | F (11/99) | [7491-09-0] | \$156 |
| 1224959 | Dolasetron Mesylate ( 200 mg ) | F0C319 |  |  | [115956-13-3] | \$156 |
| 1224960 | Dolasetron Mesylate Related Compound A ( 25 mg ) (Hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3(4H)-one hydrochloride) | F0C321 |  |  | n/f | \$487 |
| 1225204 | Dopamine Hydrochloride ( 200 mg ) | G |  | F-5 (05/02) | [62-31-7] | \$156 |
| 1225281 | Dorzolamide Hydrochloride ( 500 mg ) | F0C040 |  |  | [130693-82-2] | \$156 |
| 1225292 | Dorzolamide Hydrochloride Related Compound A (20 mg) ( $(4 \mathrm{R}, 6 \mathrm{R})-4-$ (ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide, monohydrochloride) | F0C068 |  |  | n/f | \$487 |
| 1225000 | Doxapram Hydrochloride ( 200 mg ) | F4C053 |  | F-3 (07/04) | [7081-53-0] | \$156 |
| 1225419 | Doxazosin Mesylate ( 200 mg ) | F0C079 |  |  | [77883-43-3] | \$156 |
| 1225500 | Doxepin Hydrochloride ( 500 mg ) | 1 |  |  | [1229-29-4] | \$156 |
| 1225703 | Doxorubicin Hydrochloride ( 50 mg ) | K |  | $J$ (06/02) | [25316-40-9] | \$479 |
| 1226003 | Doxycycline Hyclate (200 mg) | I |  | H (01/00) | [24390-14-5] | \$156 |
| 1227006 | Doxylamine Succinate ( 300 mg ) | IOB266 |  | H (01/04) | [562-10-7] | \$156 |
| 1229001 | Droperidol (250 mg) | 10C029 | 2 | $\begin{aligned} & \text { H-1 (01/05) } \\ & \text { H (04/99) } \\ & \hline \end{aligned}$ | [548-73-2] | \$156 |
| 1230000 | Dyclonine Hydrochloride (200 mg) | G |  |  | [536-43-6] | \$156 |
| 1231003 | Dydrogesterone (200 mg) | IOB114 |  | H (01/04) | [152-62-5] | \$156 |
| 1231502 | Dyphylline ( 200 mg ) | G-2 |  | G-1 (11/02) | [479-18-5] | \$156 |
| 1231728 | Powdered Echinacea Purpurea Extract (1 g) | F0D018 | 1 |  | [90028-20-9] | \$520 |
| 1231706 | Powdered Echinacea Angustifolia Extract (1 g) | F0D019 | 1 |  | [84696-11-7] | \$520 |
| 1231808 | Econazole Nitrate (200 mg) | G |  |  | [68797-31-9] | \$156 |
| 1232006 | Edetate Calcium Disodium ( 200 mg ) | H0B272 |  | $\begin{aligned} & \text { G-3 }(11 / 04) \\ & \text { G-2 }(11 / 99) \\ & \hline \end{aligned}$ | [23411-34-9] | \$156 |
| 1233009 | Edetate Disodium ( 200 mg ) | H |  | G-2 (04/02) | [6381-92-6] | \$156 |
| 1233508 | Edetic Acid ( 200 mg ) | F-1 |  |  | [60-00-4] | \$156 |
| 1234001 | Edrophonium Chloride ( $200 \mathrm{mg} \mathrm{)}$ | H |  | G (08/99) | [116-38-1] | \$156 |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 |  |  | [84696-12-5] | \$520 |
| 1234806 | Emedastine Difumarate ( 100 mg ) | F0C059 |  |  | [87233-62-3] | \$156 |
| 1235004 | Emetine Hydrochloride ( 300 mg ) | H0B201 |  | G (05/03) | [316-42-7] | \$156 |
| 1235274 | Enalaprilat ( 300 mg ) | J0C268 | 2 | $\begin{array}{\|l\|l\|} \hline I(11 / 04) \\ H(03 / 01) \\ G(08 / 99) \\ \hline \end{array}$ | [84680-54-6] | \$124 |
| 1235300 | Enalapril Maleate ( 200 mg ) | $J$ |  | $1(06 / 01)$ | [76095-16-4] | \$156 |
| 1235503 | Endotoxin (10,000 USP Endotoxin Units) | G2B274 |  | $\begin{aligned} & \text { G-1 (12/03) } \\ & \text { G (06/99) } \end{aligned}$ | n/f | \$156 |
| 1235809 | Enflurane (1 mL) | G-1 |  | G (02/01) | [13838-16-9] | \$156 |
| 1236007 | Ephedrine Sulfate (200 mg) (List Chemical) | H-2 |  | H-1 (11/02) | [134-72-5] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1236506 | 4-Epianhydrotetracycline Hydrochloride (50 mg) | J0C041 |  | $\begin{array}{\|l\|l\|} \hline \text { I-1 (12/03) } \\ \text { I (06/00) } \\ \hline \end{array}$ | [4465-65-0] | \$487 |
| 1236801 | Epilactose ( 200 mg ) | G |  | F-1 (06/00) | [103302-12-1] | \$487 |
| 1237000 | Epinephrine Bitartrate (200 mg) | 0 |  |  | [51-42-3] | \$156 |
| 1237509 | Epitetracycline Hydrochloride (200 mg) | F |  |  | [23313-80-6] | \$487 |
| 1238002 | Equilin ( 25 mg ) | 11B290 |  | $\begin{array}{\|l\|} \hline \text { I (11/04) } \\ \text { H-1 }(05 / 00) \\ \hline \end{array}$ | [474-86-2] | \$208 |
| 1239005 | Ergocalciferol (30 mg/ampule; 5 ampules) (Vitamin D2) | P0B275 |  | $\begin{array}{\|l\|} \hline \mathrm{O}(02 / 04) \\ \mathrm{N}(12 / 99) \\ \hline \end{array}$ | [50-14-6] | \$168 |
| 1239504 | Ergoloid Mesylates ( $300 \mathrm{mg} \mathrm{)}$ | 1 |  | $\mathrm{H}-1$ (01/00) | [8067-24-1] | \$156 |
| 1240004 | Ergonovine Maleate (100 mg) (List Chemical) | N |  | M-1 (07/02) | [129-51-1] | \$156 |
| 1241007 | Ergosterol ( 50 mg ) | H |  |  | [57-87-4] | \$156 |
| 1241506 | Ergotamine Tartrate (150 mg) (List Chemical) | IOB174 |  | H (01/04) | [379-79-3] | \$156 |
| 1241550 | Ergotaminine ( 100 mg ) (List Chemical) | G0B177 |  | F-1 (06/04) | [639-81-6] | \$156 |
| 1242000 | Erythromycin (250 mg) | M |  | L (08/99) | [114-07-8] | \$156 |
| 1242010 | Erythromycin B (150 mg) | G1C080 |  | $\begin{aligned} & \hline \text { G (11/04) } \\ & \text { F-1 (09/01) } \\ & \text { F (05/01) } \\ & \hline \end{aligned}$ | [527-75-3] | \$156 |
| 1242021 | Erythromycin C (50 mg) | F-3 |  | $\begin{array}{\|l\|l} \hline \text { F-2 (01/03) } \\ \text { F-1 (02/02) } \\ \text { F (02/99) } \\ \hline \end{array}$ | n/f | \$156 |
| 1242032 | Erythromycin Related Compound N (50 mg) (N-Demethylerythromycin A) | F2A023 |  | $\begin{aligned} & \hline \text { F-1 (06/04) } \\ & \text { F (09/99) } \\ & \hline \end{aligned}$ | n/f | \$156 |
| 1243002 | Erythromycin Estolate (200 mg) | H |  | G (01/03) | [3521-62-8] | \$156 |
| 1245008 | Erythromycin Ethylsuccinate ( 200 mg ) | H |  | G-1 (06/01) | [1264-62-6] | \$156 |
| 1246000 | Erythromycin Gluceptate ( 200 mg ) | H |  | G (07/03) | [23067-13-2] | \$156 |
| 1247003 | Erythromycin Lactobionate ( $200 \mathrm{mg} \mathrm{)}$ | H-1 |  | H (01/02) | [3847-29-8] | \$156 |
| 1248006 | Erythromycin Stearate ( $200 \mathrm{mg} \mathrm{)}$ | H0B187 |  | G-1 (05/03) | [643-22-1] | \$156 |
| 1249009 | Erythrosine Sodium ( 100 mg ) | F |  |  | [49746-10-3] | \$156 |
| 1250008 | Estradiol ( 500 mg ) | K1B007 |  | K (04/03) | [50-28-2] | \$156 |
| 1251000 | Estradiol Benzoate ( 250 mg ) (AS) | G-1 |  |  | [50-50-0] | \$156 |
| 1252003 | Estradiol Cypionate ( $200 \mathrm{mg} \mathrm{)}$ | G-1 |  | G (02/00) | [313-06-4] | \$156 |
| 1254009 | Estradiol Valerate ( 100 mg ) | L |  | K (05/02) | [979-32-8] | \$156 |
| 1254508 | Estriol ( 100 mg ) | $J$ |  | I-1 (06/01) | [50-27-1] | \$156 |
| 1255001 | Estrone ( 200 mg ) | K1B099 |  | $\begin{array}{\|l\|} \hline \mathrm{K}(07 / 03) \\ \mathrm{J}-1(07 / 00) \\ \hline \end{array}$ | [53-16-7] | \$156 |
| 1255500 | Estropipate ( 500 mg ) | J0B262 |  | $\begin{array}{\|l\|} \hline \text { I (12/03) } \\ H(09 / 01) \\ \hline \end{array}$ | [7280-37-7] | \$156 |
| 1256004 | Ethacrynic Acid (200 mg) | F |  |  | [58-54-8] | \$156 |
| 1257007 | Ethambutol Hydrochloride ( 200 mg ) | H |  | G (08/02) | [1070-11-7] | \$156 |
| 1258305 | Ethchlorvynol CIV ( 0.7 ml ) | F0B011 |  |  | [113-18-8] | \$207 |
| 1260001 | Ethinyl Estradiol ( 150 mg ) | Q0C162 | 2 | $\begin{aligned} & \text { P1B193 (11/04) } \\ & \text { P0B052 (01/04) } \\ & \text { P (03/03) } \\ & \text { O (08/99) } \\ & \hline \end{aligned}$ | [57-63-6] | \$156 |
| 1260012 | Ethinyl Estradiol Related Compound A ( 20 mg ) (6-Keto-ethinyl estradiol) | F0B252 |  |  | n/f | \$487 |
| 1261004 | Ethionamide ( 200 mg ) | H0B148 |  | G (03/03) | [536-33-4] | \$156 |
| 1262801 | Ethopabate ( 125 mg ) | F |  |  | [59-06-3] | \$156 |
| 1262823 | Ethopabate Related Compound A ( 25 mg ) (Methyl-4-acetamido-2hydroxybenzoate) | F |  |  | n/f | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1263000 | Ethopropazine Hydrochloride ( 300 mg ) | G |  |  | [1094-08-2] | \$156 |
| 1264002 | Ethosuximide ( 125 mg ) | H |  | $\begin{aligned} & \text { G-2 }(11 / 01) \\ & \text { G-1 }(05 / 99) \\ & \hline \end{aligned}$ | [77-67-8] | \$124 |
| 1264501 | Ethotoin ( 200 mg ) | F |  |  | [86-35-1] | \$156 |
| 1265005 | Ethoxzolamide (200 mg) | F |  |  | [452-35-7] | \$156 |
| 1265504 | Ethylcellulose (1 g) | H-1 |  | H (06/99) | [9004-57-3] | \$156 |
| 1266008 | Ethyl Maltol (1 g) (FCC) | H |  |  | [4940-11-8] | \$156 |
| 1266507 | Ethylnorepinephrine Hydrochloride (200 mg) | F |  |  | [3198-07-0] | \$156 |
| 1267000 | Ethylparaben ( 200 mg ) | IOA016 |  | H (01/04) | [120-47-8] | \$156 |
| 1267500 | Ethyl Vanillin ( 200 mg ) | F2B134 |  | F-1 (04/04) | [121-32-4] | \$156 |
| 1268003 | Ethynodiol Diacetate ( 200 mg ) | 10A033 |  | $\begin{aligned} & \mathrm{H}-1(01 / 03) \\ & \mathrm{H}(04 / 01) \\ & \hline \end{aligned}$ | [297-76-7] | \$156 |
| 1268502 | Etidronate Disodium (200 mg) | G |  | F-2 (02/03) | [7414-83-7] | \$156 |
| 1268604 | Etidronic Acid Monohydrate (1 g) | G |  | F-1 (05/99) | [2809-21-4] | \$156 |
| 1268706 | Etodolac ( 400 mg ) | G |  | F (10/01) | [41340-25-4] | \$156 |
| 1268728 | Etodolac Related Compound A (25 mg) ((+/-)-8-ethyl-1-methyl-1,3,4,9tetrahydropyrano [3,4-b]-indole-1-acetic acid) | F-1 |  | F (05/02) | [109518-50-5] | \$208 |
| 1268808 | Etoposide ( 300 mg ) | H0C315 |  | G (11/04) | [33419-42-0] | \$124 |
| 1268852 | Etoposide Resolution Mixture ( 30 mg ) | F0B209 |  |  | [33419-42-0] | \$208 |
| 1269200 | Famotidine ( 125 mg ) | H-1 |  | $\begin{aligned} & \mathrm{H}(11 / 02) \\ & \mathrm{G}(03 / 99) \\ & \hline \end{aligned}$ | [76824-35-6] | \$124 |
| 1269389 | Felodipine ( 200 mg ) | F-1 |  | F (09/02) | [72509-76-3] | \$156 |
| 1269390 | Felodipine Related Compound A (100 mg) (ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate) | F0B207 |  |  | [96302-71-7] | \$487 |
| 1269403 | Fenbendazole ( 100 mg ) | F |  |  | [43210-67-9] | \$487 |
| 1269458 | Fenoldopam Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | F0C125 |  |  | [67227-57-0] | \$156 |
| 1269469 | Fenoldopam Related Compound A ( 20 mg ) (1-Methyl-3-benzazapine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate) | FOC124 |  |  | n/f | \$487 |
| 1269470 | Fenoldopam Related Compound B ( 20 mg ) (1H-3-Benzazapine-7,8diol, 2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate) | FOC126 |  |  | n/f | \$487 |
| 1269505 | Fenoprofen Calcium ( 500 mg ) | G-1 |  |  | [53746-45-5] | \$156 |
| 1269550 | Fenoprofen Sodium ( 500 mg ) | G |  | F-1 (05/02) | [66424-46-2] | \$156 |
| 1270005 | Fentanyl Citrate CII (100 mg) | K0C264 |  | $\begin{array}{\|l\|} \hline \text { J2B227 (11/04) } \\ \mathrm{J}-1(09 / 03) \\ \mathrm{J}(05 / 02) \\ \mathrm{I}(06 / 00) \\ \hline \end{array}$ | [990-73-8] | \$207 |
| 1270402 | Finasteride ( 200 mg ) | F |  |  | [98319-26-7] | \$156 |
| 1270800 | Flecainide Acetate (200 mg) | F2A022 | 2 | $\begin{array}{\|l\|l\|l\|l\|l\|l\|} \hline \text { F-1 (02/03) } \\ \hline \end{array}$ | [54143-56-5] | \$156 |
| 1270821 | Flecainide Related Compound A (75 mg) (3-[2,5-bis(2,2,2-trifluor-oethoxy)phenyl]-1,5,6,7,8,8a-hexahydroimidazo-[1,5a]pyridine Hydrochloride) | F |  |  | n/f | \$487 |
| 1271008 | Floxuridine ( 250 mg ) | F-2 |  | F-1 (08/01) | [50-91-9] | \$156 |
| 1272000 | Flucytosine ( 200 mg ) | F |  |  | [2022-85-7] | \$156 |
| 1272204 | Fludarabine Phosphate ( 300 mg ) | F0C374 |  |  | [75607-67-9] | \$156 |
| 1273003 | Fludrocortisone Acetate ( 250 mg ) | H |  | G (08/01) | [514-36-3] | \$156 |
| 1273808 | Flumazenil ( 200 mg ) | F0C305 |  |  | [78755-81-4] | \$780 |
| 1274006 | Flumethasone Pivalate ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  | H (01/02) | [2002-29-1] | \$156 |
| 1274505 | Flunisolide ( 200 mg ) | 1 |  | H (01/01) | [77326-96-6] | \$156 |
| 1274607 | Flunixin Meglumine ( $300 \mathrm{mg} \mathrm{)}$ | G |  | $\begin{aligned} & \hline \text { F-1 (04/02) } \\ & \text { F (09/99) } \\ & \hline \end{aligned}$ | [42461-84-7] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1275009 | Fluocinolone Acetonide ( 100 mg ) | J |  | I (11/99) | [67-73-2] | \$156 |
| 1276001 | Fluocinonide ( 100 mg ) | 1 |  |  | [356-12-7] | \$156 |
| 1277004 | Fluorescein (200 mg) | G0B171 |  | F-1 (02/03) | [2321-07-5] | \$156 |
| 1277252 | Fluoride Dentifrice: Sodium Fluoride/Silica (4.5 oz) | J0C294 |  | $\begin{aligned} & \text { I (08/04) } \\ & \text { H (04/99) } \end{aligned}$ | n/f | \$458 |
| 1277274 | Fluoride Dentifrice: Sodium Fluoride/Sodium Bicarbonate Powder (4 oz) | $F$ |  |  | n/f | \$487 |
| 1277300 | Fluoride Dentifrice: Sodium Monofluorophosphate-Calcium Carbonate (4.6 oz) | G |  |  | n/f | \$487 |
| 1277354 | Fluoride Dentifrice: Sodium Monofluorophosphate/Dicalcium Phosphate (4.6 oz) | G |  |  | n/f | \$487 |
| 1277401 | Fluoride Dentifrice: Sodium Monofluorophosphate (1000 ppm)/Silica ( 5.25 oz ) | G-1 |  | G (08/99) | n/f | \$487 |
| 1277423 | Fluoride Dentifrice: Sodium Monofluorophosphate ( 1500 ppm )/Silica ( 5.25 oz ) | F-1 |  | F (07/99) | n/f | \$487 |
| 1277456 | Fluoride Dentifrice: Stannous Fluoride-Silica (4 oz) | H0B105 |  | G (11/02) | n/f | \$487 |
| 1278007 | Fluorometholone ( 200 mg ) | IOB184 |  | H-1 (11/02) | [426-13-1] | \$156 |
| 1278109 | Fluorometholone Acetate ( 200 mg ) | F |  |  | [3801-06-7] | \$156 |
| 1278302 | Fluoroquinolonic Acid ( 50 mg ) | H0C140 | 2 | $\begin{array}{\|l\|l} \hline G(01 / 05) \\ \text { F-1 }(12 / 99) \\ \hline \end{array}$ | [86393-33-1] | \$487 |
| 1279000 | Fluorouracil ( 250 mg ) | H-1 |  | H (01/02) | [51-21-8] | \$156 |
| 1279804 | Fluoxetine Hydrochloride (200 mg) | F2C132 | 2 | $\begin{array}{\|l\|} \hline \text { F-1 (02/05) } \\ \text { F (11/99) } \\ \hline \end{array}$ | [59333-67-4] | \$156 |
| 1279815 | Fluoxetine Related Compound A ( 15 mg ) ( N -methyl-3-phenyl-3-[(al-pha,alpha,alpha-(trifluoro-m-tolyl)oxy]propylamine Hydrochloride) | H0C131 |  | G (06/04) <br> F-1 (05/01) <br> F (06/00) | n/f | \$487 |
| 1279826 | Fluoxetine Related Compound B ( 5 mL of a 0.01 N HCl solution, approx. $2 \mathrm{mg} / \mathrm{mL}$ ) (N-methyl-3-phenylpropylamine) | F3C085 |  | $\begin{array}{\|l} \hline \text { F-2 (06/04) } \\ \text { F-1 (09/02) } \\ \hline \mathrm{F}(09 / 00) \\ \hline \end{array}$ | [23580-89-4] | \$156 |
| 1279837 | Fluoxetine Related Compound C (15 mg) (N-Methyl-N-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-succinamic acid) | F0C352 |  |  | n/f | \$487 |
| 1280009 | Fluoxymesterone CIII ( 200 mg ) | G-2 |  | G-1 (04/00) | [76-43-7] | \$207 |
| 1280803 | Fluphenazine Decanoate Dihydrochloride ( 500 mg ) | G |  | F-1 (10/01) | n/f | \$159 |
| 1281001 | Fluphenazine Enanthate Dihydrochloride ( 125 mg ) | H |  | G (02/99) | [3105-68-8] | \$124 |
| 1282004 | Fluphenazine Hydrochloride ( 125 mg ) | H |  |  | [146-56-5] | \$124 |
| 1284000 | Flurandrenolide ( 100 mg ) | IOB245 |  | H (09/03) | [1524-88-5] | \$156 |
| 1285002 | Flurazepam Hydrochloride CIV ( 200 mg ) | J0C365 | 2 | I (09/03) | [1172-18-5] | \$207 |
| 1285308 | Flurazepam Related Compound C ( 50 mg ) (5-chloro-2-(2-diethylami-noethyl(amino)-2'-fluorobenzophenone Hydrochloride) | H-1 |  |  | n/f | \$487 |
| 1285603 | Flurazepam Related Compound F (50 mg) (7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one) | $10 \mathrm{C092}$ |  | H (01/04) | [2886-65-9] | \$487 |
| 1285750 | Flurbiprofen ( 200 mg ) | G |  |  | [5104-49-4] | \$156 |
| 1285760 | Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid) | H |  | G (03/01) | n/f | \$487 |
| 1285807 | Flurbiprofen Sodium ( 200 mg ) | F |  |  | [56767-76-1] | \$156 |
| 1285851 | Flutamide ( 200 mg ) | H0B278 | 2 | $\begin{array}{\|l\|l\|} \hline \mathrm{G}(11 / 04) \\ \mathrm{F}-1(06 / 00) \\ \hline \end{array}$ | [13311-84-7] | \$156 |
| 1285862 | o-Flutamide ( 50 mg ) | F-1 |  | F (01/00) | n/f | \$156 |
| 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) | P |  | O (07/00) | [59-30-3] | \$156 |
| 1286027 | Folic Acid Related Compound A ( 50 mg ) (Calcium Formyltetrahydrofolate) | 10B176 |  | $\begin{array}{\|l\|} \hline \text { H-1 (04/04) } \\ \text { H (01/00) } \\ \hline \end{array}$ | [1492-18-8] | \$156 |
| 1286060 | Formononetin ( 50 mg ) | F0C196 |  |  | [485-72-3] | \$520 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1286209 | 4-Formylbenzenesulfonamide ( 50 mg ) | F |  |  | n/f | \$487 |
| 1286300 | 10-Formylfolic Acid ( 25 mg ) | F2B226 |  | F-1 (01/04) | [134-05-4] | \$156 |
| 1286366 | Fosphenytoin Sodium ( 250 mg ) | F0C156 |  |  | [92134-98-0] | \$156 |
| 1286504 | Fructose ( 125 mg ) | I-2 |  | $\begin{array}{\|l\|} \hline \text { I-1 (11/02) } \\ \text { I (08/99) } \\ \hline \end{array}$ | [57-48-7] | \$124 |
| 1286708 | Fumaric Acid (200 mg) | G-1 |  | G (04/02) | [110-17-8] | \$156 |
| 1286800 | Furazolidone (200 mg) | G-2 |  | G-1 (01/01) | [67-45-8] | \$156 |
| 1287008 | Furosemide ( 125 mg ) | J1B131 |  | $J(10 / 03)$ | [54-31-9] | \$124 |
| 1287020 | Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfurylami-no-5-sulfamoylbenzoic Acid) | J |  | I (08/02) | n/f | \$487 |
| 1287030 | Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid) | 10 C 248 |  | $\begin{array}{\|l\|} \hline \mathrm{H}(08 / 04) \\ \text { G-3 }(03 / 01) \\ \hline \end{array}$ | [3086-91-7] | \$487 |
| 1287303 | Gabapentin ( 250 mg ) | F |  |  | [60142-96-3] | \$156 |
| 1287325 | Gabapentin Related Compound A (100 mg) (3,3-pentamethylene-5butyrolactam) | F |  |  | [64744-50-9] | \$487 |
| 1287507 | Gadodiamide ( 500 mg ) | F |  |  | [131410-48-5] | \$156 |
| 1287518 | Gadodiamide Related Compound A ( 50 mg ) (gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide) | F |  |  | n/f | \$487 |
| 1287529 | Gadodiamide Related Compound B ( 50 mg ) (gadolinium disodium diethylenetriamine pentaacetic acid) | F |  |  | n/f | \$487 |
| 1287609 | Gadopentetate Monomeglumine ( 500 mg ) | F |  |  | [92923-57-4] | \$156 |
| 1287631 | Gadoteridol ( 500 mg ) | F |  |  | [120066-54-8] | \$156 |
| 1287642 | Gadoteridol Related Compound A ( 50 mg ) (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid) | FOA002 |  |  | [120041-08-9] | \$487 |
| 1287653 | Gadoteridol Related Compound B ( 50 mg ) (1,4,7,10-Tetraazacyclodo-decane-1,4,7-triacetic acid, monogadolinium salt) | FOB198 |  |  | [112188-16-6] | \$487 |
| 1287664 | Gadoteridol Related Compound C (50 mg) (1,4,7,10-Tetraaza-11-oxo-bicyclo[8.2.2]tetradecane-4,7-diacetic acid) | FOB199 |  |  | [220182-19-4] | \$487 |
| 1287675 | Gadoversetamide ( 200 mg ) | F0C172 |  |  | [131069-91-5] | \$156 |
| 1287686 | Gadoversetamide Related Compound A (200 mg) (Hydrogen[8,11,14-tris(carboxymethyl)-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(4-)]gadolinium) | F0C173 |  |  | n/f | \$487 |
| 1287700 | Galactose (200 mg) | F-4 |  | F-3 (05/01) | [59-23-4] | \$487 |
| 1288000 | Gallamine Triethiodide ( 200 mg ) | F |  |  | [65-29-2] | \$156 |
| 1288306 | Ganciclovir ( 200 mg ) | F0C287 |  |  | [82410-32-0] | \$364 |
| 1288317 | Ganciclovir Related Compound A (15 mg) ((RS)-2-Amino-9-(2,3-dihy-droxy-propoxymethyl)-1,9-dihydro-purin-6-one) | F0C288 |  |  | n/f | \$624 |
| 1288500 | Gemfibrozil ( 200 mg ) | H |  |  | [25812-30-0] | \$156 |
| 1288510 | Gemfibrozil Related Compound A (20 mg) (2,2-dimethyl-5-[2,5-di-methyl-4-propene-1-yl)phenoxy]valeric acid) | F0C101 |  |  | n/f | \$487 |
| 1289003 | Gentamicin Sulfate (200 mg) | L0C279 | 2 | $\begin{aligned} & \mathrm{K}(12 / 04) \\ & \mathrm{J}-1(04 / 00) \\ & \hline \end{aligned}$ | [1405-41-0] | \$156 |
| 1290002 | Gentian Violet (650 mg) | F |  |  | [548-62-9] | \$156 |
| 1291005 | Gibberellic Acid (200 mg) (FCC) | G |  | F (04/01) | [77-06-5] | \$156 |
| 1291504 | Powdered Ginger ( 500 mg ) | F |  |  | n/f | \$156 |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | F0B289 |  |  | [50647-08-0] | \$520 |
| 1292008 | Gitoxin ( 50 mg ) | G |  | F-3 (07/00) | [4562-36-1] | \$487 |
| 1292507 | Glipizide ( 125 mg ) | G1C174 |  | G (07/04) | [29094-61-9] | \$124 |
| 1292609 | Glipizide Related Compound A (25 mg) ( N -\{2-[(4-aminosulfony))pheny-l]ethyl\}-5-methyl-pyrazinecarboxamide) | G-1 |  | G (04/99) | n/f | \$487 |
| 1294003 | Glucagon ( $25 \mathrm{mg}, 0.95 \mathrm{U} / \mathrm{mg}$ ) |  |  | H (01/05) | [16941-32-5] | \$156 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 |  |  | [66-84-2] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1294976 | Glutamic Acid ( 200 mg ) | F0C069 |  |  | [56-86-0] | \$156 |
| 1294808 | Glutamine ( 100 mg ) | F0B244 |  |  | [56-85-9] | \$156 |
| 1294848 | gamma-Glutamyl-S-allyl-L-cysteine ( 25 mg ) | F |  |  | n/f | \$675 |
| 1295006 | Glutethimide CII ( 500 mg ) | F |  |  | [77-21-4] | \$207 |
| 1295505 | Glyburide ( 200 mg ) | G |  | F-2 (11/02) | [10238-21-8] | \$156 |
| 1295607 | Glycerin (2 mL) | H0C073 |  | $\begin{aligned} & \text { G1A001 (04/04) } \\ & \text { G (12/02) } \\ & \text { F (04/99) } \\ & \hline \end{aligned}$ | [56-81-5] | \$156 |
| 1295709 | Glyceryl Behenate ( 200 mg ) | F3B113 |  | F-2 (03/03) | [18641-57-1] | \$156 |
| 1295800 | Glycine ( 200 mg ) | F-3 |  | F-2 (02/00) | [56-40-6] | \$156 |
| 1296009 | Glycopyrrolate ( 200 mg ) | H0B304 |  | G (05/04) | [596-51-0] | \$156 |
| 1295888 | Glycyrrhizic Acid ( 25 mg ) | F0C006 |  |  | [1405-86-3] | \$487 |
| 1297001 | Human Chorionic Gonadotropin (1 vial, 5,760 USP Units per package) | H |  | G (07/00) | [9002-61-3] | \$156 |
| 1298004 | Gramicidin ( 200 mg ) | 1 |  | H-1 (07/02) | [1405-97-6] | \$156 |
| 1299007 | Griseofulvin (200 mg) | 1 |  | H-1 (09/02) | [126-07-8] | \$156 |
| 1299200 | Griseofulvin Permeability Diameter (2 g) | J0C380 |  | $\begin{aligned} & \text { 10C138 (10/04) } \\ & \mathrm{H}(08 / 03) \\ & \hline \end{aligned}$ | [126-07-8] | \$156 |
| 1300004 | Guaiacol ( 1 g ) | K |  | $J(04 / 00)$ | [90-05-1] | \$156 |
| 1301007 | Guaifenesin (200 mg) | 1 |  | H (09/02) | [93-14-1] | \$156 |
| 1301404 | Guanabenz Acetate ( $200 \mathrm{mg} \mathrm{)}$ | G |  | F-1 (06/00) | [23256-50-0] | \$156 |
| 1301608 | Guanadrel Sulfate (200 mg) | F-1 |  |  | [22195-34-2] | \$156 |
| 1301801 | Guanethidine Monosulfate ( 200 mg ) | F |  |  | [645-43-2] | \$156 |
| 1302000 | Guanethidine Sulfate ( 500 mg ) | G-1 |  |  | [60-02-6] | \$156 |
| 1302101 | Guanfacine Hydrochloride (125 mg) | G0B123 |  | $\begin{array}{\|l\|l\|} \hline \text { F-1 (02/03) } \\ \text { F (11/99) } \\ \hline \end{array}$ | [29110-48-3] | \$124 |
| 1302305 | Halazepam CIV (200 mg) (AS) | F1C224 |  | F (12/04) | [23092-17-3] | \$207 |
| 1302509 | Halcinonide ( 300 mg ) | F |  |  | [3093-35-4] | \$156 |
| 1303002 | Haloperidol ( 200 mg ) | 1 |  | H-1 (05/02) | [52-86-8] | \$156 |
| 1303013 | Haloperidol Related Compound A (15 mg) (4,4-Bis[(4-p-chlorophenyl)-4-hydroxy-piperidino]-butyrophenone) | K0C362 |  | J (12/04) | [67987-08-0] | \$487 |
| 1303308 | Haloprogin ( 200 mg ) | F |  |  | [777-11-7] | \$156 |
| 1303501 | Halothane ( 1 mL ) |  |  | F-1 (03/05) | [151-67-7] | \$156 |
| 1304005 | Heparin Sodium ( $10 \times 1 \mathrm{~mL}$ ) | K-5 |  | $\begin{aligned} & \text { K-4 (08/03) } \\ & \text { K-3 (02/99) } \\ & \hline \end{aligned}$ | [9041-08-1] | \$156 |
| 1305008 | Hexachlorophene ( 500 mg ) | 1 |  | H-2 (01/01) | [70-30-4] | \$156 |
| 1305507 | 2E, 4E-Hexadienoic Acid Isobutylamide ( 25 mg ) | F0C353 | 1 |  | [82240-09-3] | \$540 |
| 1307003 | Hexobarbital CIII ( 500 mg ) | F |  |  | [56-29-1] | \$207 |
| 1308006 | Hexylcaine Hydrochloride (1 g) | F-1 |  |  | [532-76-3] | \$156 |
| 1308200 | Hexylene Glycol (125 mg) | G |  | $\begin{array}{\|l\|l\|l\|l\|l\|l\|} \hline \text { F-2 } \\ \text { F-1 } & (04 / 99) \\ \hline \end{array}$ | [107-41-5] | \$156 |
| 1308307 | Hexylresorcinol (200 mg) | F |  |  | [136-77-6] | \$156 |
| 1308505 | L-Histidine (200 mg) | G0A018 |  | $\begin{array}{\|l\|l} \mathrm{F}-2(01 / 03) \\ \mathrm{F}-1(04 / 00) \\ \hline \end{array}$ | [71-00-1] | \$156 |
| 1309009 | Histamine Dihydrochloride ( 250 mg ) | M0C280 |  | L (07/04) | [56-92-8] | \$156 |
| 1310008 | Homatropine Hydrobromide ( 200 mg ) | H2C049 | 2 | $\begin{aligned} & \hline \text { H-1(02/05) } \\ & \text { H (08/02) } \\ & \hline \end{aligned}$ | [51-56-9] | \$156 |
| 1311000 | Homatropine Methylbromide ( 250 mg ) | J |  | $\begin{array}{\|l\|l} \hline \mathrm{I}-1(06 / 01) \\ \mathrm{H}-1(10 / 01) \\ \hline \end{array}$ | [80-49-9] | \$156 |
| 1311408 | Homosalate ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | F0B102 |  |  | [118-56-9] | \$156 |
| 1312003 | Hyaluronidase ( 500 mg ) | H |  |  | [9001-54-1] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| 1313006 | Hydralazine Hydrochloride (200 mg) | K |  | J-1 (09/02) | [304-20-1] | \$156 |
| 1314009 | Hydrochlorothiazide ( 200 mg ) | I |  | H (05/02) | [58-93-5] | \$156 |
| 1315001 | Hydrocodone Bitartrate CII (250 mg) | K0C217 | 2 | $\begin{array}{\|l\|} \hline \text { JOA026 (01/05) } \\ \text { I-1 (12/02) } \\ \text { I (07/02) } \\ \text { H-2 (11/99) } \\ \hline \end{array}$ | [34195-34-1] | \$207 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl) | F0C214 |  |  | [847-86-9] | \$513 |
| 1316004 | Hydrocortisone (200 mg) | M1C110 |  | $\begin{aligned} & \text { M (10/04) } \\ & \text { L (09/00) } \\ & \hline \end{aligned}$ | [50-23-7] | \$156 |
| 1317007 | Hydrocortisone Acetate ( $200 \mathrm{mg} \mathrm{)}$ | K |  | J (10/99) | [50-03-3] | \$156 |
| 1317302 | Hydrocortisone Butyrate (200 mg) | H |  |  | [13609-67-1] | \$156 |
| 1318000 | Hydrocortisone Cypionate ( 200 mg ) | F |  |  | [508-99-6] | \$156 |
| 1319002 | Hydrocortisone Hemisuccinate (200 mg) | H |  | $\begin{aligned} & \text { G-3 (03/02) } \\ & \text { G-2 (08/99) } \end{aligned}$ | [83784-20-7] | \$156 |
| 1320001 | Hydrocortisone Phosphate Triethylamine (200 mg) | F-1 |  |  | n/f | \$156 |
| 1321004 | Hydrocortisone Valerate ( 200 mg ) | F-1 |  | F (07/02) | [57524-89-7] | \$156 |
| 1322007 | Hydroflumethiazide ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  |  | [135-09-1] | \$156 |
| 1323000 | Hydromorphone Hydrochloride CII (50 mg) | J0C372 | 2 | $\begin{array}{\|l} \hline \text { I (01/05) } \\ H-2(03 / 01) \\ \hline \end{array}$ | [71-68-1] | \$207 |
| 1324002 | Hydroquinone ( 500 mg ) | H0C249 |  | $\begin{aligned} & \hline \text { G-1 (10/04) } \\ & \text { G (11/01) } \\ & \text { F-4 (02/99) } \\ & \hline \end{aligned}$ | [123-31-9] | \$156 |
| 1325005 | Hydroxyamphetamine Hydrobromide (200 mg) | G |  | F (06/01) | [306-21-8] | \$156 |
| 1327000 | Hydroxychloroquine Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | J0B297 |  | I (05/04) | [747-36-4] | \$156 |
| 1329006 | Hydroxyprogesterone Caproate ( 200 mg ) | H |  |  | [630-56-8] | \$156 |
| 1329709 | Hydroxypropyl Betadex ( 200 mg ) | F0B295 |  |  | [128446-35-5] | \$156 |
| 1329800 | Hydroxypropyl Cellulose (200 mg) | F-1 |  |  | [9004-64-2] | \$156 |
| 1332000 | Hydroxyurea (200 mg) | H |  | G (01/00) | [127-07-1] | \$156 |
| 1333003 | Hydroxyzine Hydrochloride ( 500 mg ) | H |  |  | [2192-20-3] | \$156 |
| 1333058 | Hydroxyzine Related Compound A ( 25 mg ) (p-Chlorobenzhydrylpiperazine) | H |  |  | [303-26-4] | \$208 |
| 1334006 | Hydroxyzine Pamoate ( 500 mg ) | H0C016 |  | G-1 (07/03) | [10246-75-0] | \$156 |
| 1335009 | Hyoscyamine Sulfate ( 125 mg ) | H0C193 | 2 | $\begin{array}{\|l\|} \hline \text { G2A007 (09/04) } \\ \text { G-1 (08/02) } \\ \text { G (10/99) } \\ \hline \end{array}$ | [6835-16-1] | \$124 |
| 1335202 | Hyperoside ( 50 mg ) | F |  |  | [482-36-0] | \$855 |
| 1330005 | Hypromellose (250 mg) (Hydroxypropyl Methylcellulose) | H0C387 |  | $\begin{aligned} & \text { G-1 (11/04) } \\ & \text { G (02/02) } \\ & \hline \end{aligned}$ | [9004-65-3] | \$156 |
| 1335304 | Hypromellose Phthalate ( 100 mg ) | F-1 |  | F (12/00) | [9050-31-1] | \$156 |
| 1335508 | Ibuprofen ( 750 mg ) | J |  | I (06/02) | [15687-27-1] | \$156 |
| 1335701 | Idarubicin Hydrochloride ( 50 mg ) | H0C061 |  | $\begin{aligned} & G(11 / 03) \\ & F(06 / 00 \end{aligned}$ | [57852-57-0] | \$479 |
| 1336001 | Idoxuridine ( 250 mg ) | H1B230 |  | H (07/04) | [54-42-2] | \$156 |
| 1336205 | Ifosfamide ( 500 mg ) | G |  | $\begin{aligned} & \hline \text { F-1 (11/00) } \\ & \text { F (02/99) } \\ & \hline \end{aligned}$ | [3778-73-2] | \$156 |
| 1336500 | Imidazole (200 mg) | G1B132 |  | G (01/04) | [288-32-4] | \$487 |
| 1336806 | Imidurea ( 200 mg ) | H |  | G (10/99) | [39236-46-9] | \$156 |
| 1337004 | Iminodibenzyl (25 mg) | 10C253 |  | H (11/04) | [494-19-9] | \$487 |
| 1337809 | Imipenem Monohydrate ( 100 mg ) | G1C296 | 2 | $\begin{aligned} & \mathrm{G}(01 / 05) \\ & \mathrm{F}(01 / 01) \\ & \hline \end{aligned}$ | [74431-23-5] | \$156 |
| 1338007 | Imipramine Hydrochloride (200 mg) | 1 |  | H (09/01) | [113-52-0] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1338801 | Indapamide (250 mg) | H |  | G (07/02) | [26807-65-8] | \$156 |
| 1339000 | Indigotindisulfonate Sodium ( 500 mg ) | H1B153 |  | H (06/03) | [860-22-0] | \$156 |
| 1340009 | Indocyanine Green (200 mg) | IOB045 |  | H (09/01) | [3599-32-4] | \$156 |
| 1341001 | Indomethacin (200 mg) | JOB165 |  | $\begin{array}{\|l\|} \hline \text { I (01/04) } \\ \mathrm{H}(05 / 99) \\ \hline \end{array}$ | [53-86-1] | \$156 |
| 1342004 | Insulin (100 mg) | H |  |  | [9004-10-8] | \$156 |
| 1342106 | Insulin Human (100 mg) | H1A031 |  | $\begin{aligned} & \hline \text { H }(11 / 02) \\ & \text { G }(04 / 00) \end{aligned}$ | [11061-68-0] | \$156 |
| 1342208 | Insulin (Beef) ( 100 mg ) | F |  |  | [11070-73-8] | \$156 |
| 1342300 | Insulin (Pork) (100 mg) | F |  |  | [12584-58-6] | \$156 |
| 1342503 | locetamic Acid ( 200 mg ) | F |  |  | [16034-77-8] | \$156 |
| 1343007 | lodipamide ( 200 mg ) | G | 4 |  | [606-17-7] | \$156 |
| 1343517 | lodixanol (200 mg) | FOB240 |  |  | [92339-11-2] | \$156 |
| 1343540 | lodixanol Related Compound C (25 mg) (5-Acetyl[3-[[3,5-bis[[2,3-dihydroxypropyl)amino]carbonyl]-2,4,6-triiodophenyl]amino]-2-hydroxy-propyl]amino]-N,N'-bis-(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B236 |  |  | n/f | \$487 |
| 1343550 | lodixanol Related Compound D (50 mg) (5-[Acetyl(2-hydroxy-3-methyl-propyl)amino]-N,N'-bis(2,3-dihydroxypropyl)2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B231 |  |  | [89797-00-2] | \$487 |
| 1343561 | lodixanol Related Compound E ( 25 mg ) ( $5-[[3-[[3-[[(2,3-$ Dihydoxypro-pyl)amino]carbonyl]-5-[[amino]carbonyl]-2,4,6-triiodophenyl](acetylimi-no)]-2-hydroxypropyl]-(acetylimino)]-N,N'-bis(2,3-dihydoxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B229 |  |  | n/f | \$487 |
| 1344305 | o-lodohippuric Acid ( 100 mg ) | F |  |  | [147-58-0] | \$156 |
| 1344509 | Iodoquinol ( 100 mg ) | H |  | G (07/02) | [83-73-8] | \$156 |
| 1344600 | lohexol ( 100 mg ) | F-1 |  | F (01/99) | [66108-95-0] | \$124 |
| 1344622 | Iohexol Related Compound A (100 mg) (5-(acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F-1 |  | F (10/01) | n/f | \$487 |
| 1344644 | lohexol Related Compound B ( 50 mg ) ( 5 -amino-N,N'-bis(2,3-dihydrox-ypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F-1 |  | F (01/04) | [76801-93-9] | \$487 |
| 1344666 | lohexol Related Compound C (100 mg) (N,N'-bis(2,3-dihydroxypropyl)-5-nitro-1,3-benzenedicarboxamide) | F-1 |  | F (09/03) | n/f | \$156 |
| 1344702 | lopamidol (200 mg) | G |  |  | [60166-93-0] | \$156 |
| 1344724 | lopamidol Related Compound A (50 mg) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoiso-phthalamide) | G |  |  | [60166-98-5] | \$487 |
| 1344735 | lopamidol Related Compound B (100 mg) (5-Glycolamido-N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodoisophthalamide) | F |  |  | n/f | \$487 |
| 1344804 | lopromide ( 400 mg ) | F |  |  | [73334-07-3] | \$156 |
| 1344826 | lopromide Related Compound A ( 50 mg ) ( 5 -Amino-N,N'-bis(2,3-dihy-droxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide) | F |  |  | n/f | \$487 |
| 1344837 | lopromide Related Compound B ( 50 mg ) (5-(Acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide) | F |  |  | n/f | \$487 |
| 1345002 | lothalamic Acid (200 mg) | G |  |  | [2276-90-6] | \$156 |
| 1345104 | loversol (200 mg) | F |  |  | [87771-40-2] | \$156 |
| 1345115 | loversol Related Compound A (50 mg) (5-Amino-N,N'-bis(2,3-dihydrox-ypropyl)-2,4,6-triiodoisophthalamide) | F |  |  | [76801-93-9] | \$487 |
| 1345126 | loversol Related Compound B ( 50 mg ) (N,N'-bis(2,3-dihydroxypropyl)-5-[(N-(2-hydroxyethyl)-carbonyl)methoxy]-2,4,6-triiodoisophthalamide) | F |  |  | n/f | \$487 |
| 1345159 | loxaglic Acid (100 mg) | F |  |  | [59017-64-0] | \$156 |
| 1345206 | Ioxilan (400 mg) | F |  |  | [107793-72-6] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1345228 | Ioxilan Related Compound A (100 mg) (5-amino-2,4,6-triiodo-3 N-(2hydroxyethyl)carbamoyl benzoic acid) | F |  |  | [22871-58-5] | \$487 |
| 1346005 | Ipodate Calcium (200 mg) | F |  |  | [1151-11-7] | \$156 |
| 1347008 | Ipodate Sodium (200 mg) | F-1 |  |  | [1221-56-3] | \$156 |
| 1347755 | Isoamyl Methoxycinnamate ( $750 \mathrm{mg} / \mathrm{ampule} \mathrm{)}$ | F0B017 |  |  | [71617-10-2] | \$156 |
| 1348000 | Isocarboxazid (200 mg) | F-1 |  |  | [59-63-2] | \$156 |
| 1348500 | Isoetharine Hydrochloride ( 250 mg ) | F-2 |  |  | [2576-92-3] | \$156 |
| 1348907 | Isoflupredone Acetate ( 200 mg ) | F0C109 |  |  | [338-98-7] | \$156 |
| 1349003 | Isoflurane ( 1 mL ) | H1C199 |  | H (12/04) | [26675-46-7] | \$156 |
| 1349014 | Isoflurane Related Compound A ( 0.1 mL ) (1-Chloro-2,2,2-trifluoroethyl chlorodifluoromethyl ether) | F0C232 |  |  | n/f | \$487 |
| 1349025 | Isoflurane Related Compound B ( 0.1 mL ) (2,2,2-Trifluoroethyldifluoromethyl ether) | F0C233 |  |  | n/f | \$487 |
| 1349502 | L-Isoleucine ( 200 mg ) | F-2 |  | F-1 (09/02) | [73-32-5] | \$156 |
| 1349604 | Isomalathion ( 50 mg ) | F1B107 |  | F (01/03) | [3344-12-5] | \$487 |
| 1349659 | Isometheptene Mucate ( 200 mg ) | F |  |  | [7492-31-1] | \$156 |
| 1349706 | Isoniazid (200 mg) | H |  |  | [54-85-3] | \$156 |
| 1350002 | Isopropamide lodide (200 mg) | F-2 |  |  | [71-81-8] | \$156 |
| 1350400 | Isopropyl Myristate ( 500 mg ) | I1C183 | 2 | I (01/05) | [110-27-0] | \$156 |
| 1350603 | Isopropyl Palmitate ( 500 mg ) | 1 |  | H (10/99) | [142-91-6] | \$156 |
| 1351005 | Isoproterenol Hydrochloride ( 125 mg ) | K |  |  | [51-30-9] | \$124 |
| 1352008 | Isosorbide ( $75 \%$ solution, 1 g ) | I |  | H-2 (10/00) | [652-67-5] | \$156 |
| 1353000 | Diluted Isosorbide Dinitrate ( 500 mg of $25 \%$ mixture with mannitol) | I-1 |  | I (10/99) | [87-33-2] | \$156 |
| 1353500 | Isotretinoin (200 mg) | 1 |  | H (10/00) | [4759-48-2] | \$156 |
| 1354003 | Isoxsuprine Hydrochloride (200 mg) | F-3 |  |  | [579-56-6] | \$156 |
| 1354207 | Isradipine ( 200 mg ) | G0B054 |  | F (05/03) | [75695-93-1] | \$156 |
| 1354218 | Isradipine Related Compound A ( 25 mg ) (Isopropyl methyl 4-(4-benzofurazanyl)-2,6-dimethyl-3,5-pyridinedicarboxylate) | F |  |  | n/f | \$487 |
| 1354309 | Ivermectin (200 mg) | FOB196 |  |  | [70288-86-7] | \$156 |
| 1355006 | Kanamycin Sulfate (200 mg) | J |  | I (06/99) | [25389-94-0] | \$156 |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 |  |  | n/f | \$260 |
| 1355753 | Kawain (200 mg) | F0C160 |  |  | [500-64-1] | \$208 |
| 1356009 | Ketamine Hydrochloride CIIII (250 mg) | G-2 |  | G-1 (07/00) | [1867-66-9] | \$207 |
| 1356020 | Ketamine Related Compound A ( 50 mg ) (1-[(2-Chlorophenyl)(methylimino)methyl]cylcopentanol) | F0C118 |  |  | [6740-87-0] | \$487 |
| 1356508 | Ketoconazole (200 mg) | G4B179 |  | $\begin{array}{\|l\|} \hline \text { G-3 }(01 / 04) \\ \text { G-2 }(06 / 01) \\ \text { G-1 }(01 / 99) \\ \hline \end{array}$ | [65277-42-1] | \$156 |
| 1356632 | Ketoprofen (200 mg) | H0B216 |  | $\begin{array}{\|l} \hline \mathrm{G}(07 / 04) \\ \mathrm{F}-2(05 / 99) \\ \hline \end{array}$ | [22071-15-4] | \$156 |
| 1356643 | Ketoprofen Related Compound A ( 25 mg ) (alpha-Methyl-3-(4-methylbenzoyl) benzeneacetic acid) | G |  |  | [107257-20-5] | \$487 |
| 1356665 | Ketorolac Tromethamine (200 mg) | G |  | F-2 (04/99) | [74103-07-4] | \$156 |
| 1356654 | Labetalol Hydrochloride (200 mg) | G |  | $\begin{array}{\|l} \hline \text { F-2 (01/02) } \\ \text { F-1 (03/01) } \\ \hline \end{array}$ | [32780-64-6] | \$156 |
| 1356676 | Anhydrous Lactose (100 mg) | G1C004 | 2 | $\begin{aligned} & \text { G (12/04) } \\ & \text { F (06/01) } \end{aligned}$ | [63-42-3] | \$156 |
| 1356687 | Lactitol ( 500 mg ) | FOB005 |  |  | [81025-04-9] | \$156 |
| 1356701 | Lactose Monohydrate ( 500 mg ) | G-1 |  | G (08/02) | [5989-81-1] | \$156 |
| 1356803 | Lactulose (1 g) | H |  | G-1 (08/00) | [4618-18-2] | \$156 |
| 1356836 | Lamivudine ( 200 mg ) | F0C361 |  |  | [134678-17-4] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1356880 | Lanolin (20 g) | F |  |  | [8006-54-0] | \$156 |
| 1356905 | Lanolin Alcohols (5 g) | F |  |  | [8027-33-6] | \$156 |
| 1356916 | Lansoprazole ( 200 mg ) | F0B310 |  |  | [103577-45-3] | \$156 |
| 1356927 | Lansoprazole Related Compound A (25 mg) (2-[[[3-methyl-4-(2,2,2-triflouroethoxy)-2-pyridyl]methyl]sulfonyl]benzimidazole) | F0B311 |  |  | n/f | \$487 |
| 1356971 | Letrozole ( 200 mg ) | FOB170 |  |  | [112809-51-5] | \$156 |
| 1356982 | Letrozole Related Compound A ( 15 mg ) ( $4,4^{\prime}$-( $1 \mathrm{H}-1,3,4$-triazol-1ylmethylene)dibenzonitrile) | F0B168 |  |  | n/f | \$487 |
| 1357001 | L-Leucine (200 mg) | H0B237 |  | $\begin{aligned} & \text { G-1 (04/04) } \\ & \text { G (08/00) } \\ & \hline \end{aligned}$ | [61-90-5] | \$156 |
| 1358004 | Leucovorin Calcium (500 mg) | J2B219 |  | $\begin{aligned} & \hline \mathrm{J}-1(07 / 04) \\ & \mathrm{J}(05 / 02) \\ & \hline \end{aligned}$ | [1492-18-8] | \$160 |
| 1359007 | Levallorphan Tartrate (200 mg) DISCONTINUED |  |  | $\begin{aligned} & \text { G-1 (09/04) } \\ & \text { G }(11 / 02) \end{aligned}$ | [71-82-9] | \$156 |
| 1359302 | Levamisole Hydrochloride ( 125 mg ) | F2C122 |  | F-1 (05/04) | [16595-80-5] | \$124 |
| 1359506 | Levmetamfetamine ClII (75 mg) | F |  |  | [33817-09-3] | \$207 |
| 1359801 | Levobunolol Hydrochloride ( 200 mg ) | G |  |  | [27912-14-7] | \$156 |
| 1359903 | Levocarnitine (400 mg) | G0B197 |  | $\begin{aligned} & \text { F-2 }(06 / 03) \\ & \text { F-1 }(12 / 00) \\ & \hline \end{aligned}$ | [541-15-1] | \$156 |
| 1359925 | Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride) | F-1 |  | F (08/01) | [6538-82-5] | \$208 |
| 1361009 | Levodopa ( 200 mg ) | I |  | H (09/00) | [59-92-7] | \$156 |
| 1361010 | Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydroxyphenyl)alanine) | K |  | $\begin{aligned} & \hline J(01 / 03) \\ & I(06 / 00) \\ & \hline \end{aligned}$ | [27244-64-0] | \$487 |
| 1420006 | Levodopa Related Compound B (50 mg) (3-Methoxytyrosine) | 10 C 300 |  | H (07/04) |  | \$487 |
| 1362500 | Levonordefrin ( 200 mg ) | F-1 |  |  | [829-74-3] | \$156 |
| 1363004 | Levopropoxyphene Napsylate ( 300 mg ) | G |  |  | [55557-30-7] | \$156 |
| 1364007 | Levorphanol Tartrate CII (500 mg) | H |  | G (03/01) | [5985-38-6] | \$207 |
| 1365000 | Levothyroxine ( 500 mg ) | K |  | $J$ (10/00) | [51-48-9] | \$156 |
| 1366002 | Lidocaine ( 250 mg ) | L |  |  | [137-58-6] | \$156 |
| 1367005 | Lincomycin Hydrochloride ( 200 mg ) | H2B130 |  | H-1 (01/04) | [7179-49-9] | \$156 |
| 1367504 | Lindane ( 200 mg ) | F-2 |  |  | [58-89-9] | \$156 |
| 1368008 | Liothyronine ( 250 mg ) | L1C262 |  | $\begin{aligned} & \hline \text { L (08/04) } \\ & \text { K (08/01) } \\ & \hline \end{aligned}$ | [6893-02-3] | \$156 |
| 1368609 | Lisinopril (300 mg) | 11-045 | 2 | $\begin{aligned} & \text { I (11/04) } \\ & H(09 / 01) \\ & G(10 / 99) \\ & \hline \end{aligned}$ | [83915-83-7] | \$156 |
| 1369000 | Lithium Carbonate ( 300 mg ) | G0B031 |  | $\begin{aligned} & \hline \text { F-2 (01/03) } \\ & \text { F-1 (01/01) } \\ & \hline \end{aligned}$ | [554-13-2] | \$156 |
| 1370000 | Loperamide Hydrochloride (200 mg) | H0C202 |  | $\begin{aligned} & \text { G-2 (09/04) } \\ & \text { G-1 (02/03) } \end{aligned}$ | [34552-83-5] | \$156 |
| 1370203 | Loracarbef (200 mg) | F |  |  | [121961-22-6] | \$156 |
| 1370225 | Loracarbef L-Isomer ( 25 mg ) | F |  |  | n/f | \$156 |
| 1370270 | Loratadine (200 mg) | F0C414 |  |  | [79794-75-5] | \$260 |
| 1370305 | Lorazepam CIV (200 mg) | 10 C 048 |  | H0B023 (06/04) | [846-49-1] | \$207 |
| 1370327 | Lorazepam Related Compound A ( 25 mg ) (7-Chloro-5-(o-chlorophe-nyl)-1,3-dihydro-3-acetoxy-2H-1,4-benzodiazepin-2-one) | G |  | F-1 (06/01) | [2848-96-6] | \$487 |
| 1370338 | Lorazepam Related Compound B ( 25 mg ) (2-Amino-2',5-dichlorobenzophenone) | G |  | F-2 (01/04) | [2958-36-3] | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1370349 | Lorazepam Related Compound C ( 25 mg ) (6-Chloro-4-(o-chlorophe-nyl)-2-quinazolinecarboxaldehyde) | H |  | $\begin{array}{\|l\|} \hline \text { G (01/03) } \\ \text { F-3 (01/02) } \\ \hline \end{array}$ | n/f | \$487 |
| 1370350 | Lorazepam Related Compound D ( 25 mg ) (6-Chloro-4-(o-chlorophe-nyl)-2-quinazolinecarboxylic Acid) | G0A014 |  | F-2 (01/04) | [54643-79-7] | \$487 |
| 1370360 | Lorazepam Related Compound E ( 25 mg ) (6-Chloro-4-(o-chlorophe-nyl)-2-quinazoline Methanol) | G |  | $\begin{array}{\|l\|l\|l\|} \hline \text { F-3 (07/02) } \\ \text { F-2 (04/99) } \\ \hline \end{array}$ | n/f | \$487 |
| 1370600 | Lovastatin ( 125 mg ) | H2C012 |  | $\begin{aligned} & \text { H1B067 (01/04) } \\ & \text { H (08/03) } \\ & \hline \end{aligned}$ | [75330-75-5] | \$124 |
| 1370611 | Lovastatin Related Compound A (20 mg) (Butanoic acid, 2-methyl-,1,2,3,4,4a,7,8,8a-octahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[alpha(R*), 3alpha,7beta,8beta( $\left.2 \mathrm{~S}^{*}, 4 \mathrm{~S}^{*}\right)$, 8 alpha beta]]-) | G0C326 |  | F0B235 (09/04) | n/f | \$487 |
| 1370702 | Loxapine Succinate ( 125 mg ) | G0B026 |  | $\begin{array}{\|l\|} \hline \text { F-2 (06/03) } \\ \text { F-1 (07/01) } \\ \hline \end{array}$ | [27833-64-3] | \$124 |
| 1370906 | Lynestrenol (20 mg) | F0B314 |  |  | [52-76-6] | \$203 |
| 1371002 | Lysergic Acid Diethylamide Tartrate CI (10 mg) (AS) (LSD) | I |  |  | [50-37-3] | \$207 |
| 1371501 | L-Lysine Acetate ( 200 mg ) | F1C027 |  | F (11/04) | [57282-49-2] | \$156 |
| 1372005 | L-Lysine Hydrochloride ( 200 mg ) | H |  | G (07/00) | [657-27-2] | \$156 |
| 1373008 | Mafenide Acetate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [13009-99-9] | \$156 |
| 1374000 | Magaldrate ( 200 mg ) | F-1 |  |  | [74978-16-8] | \$156 |
| 1374306 | Magnesium Salicylate ( $200 \mathrm{mg} \mathrm{)}$ | F2B081 |  | F-1 (01/04) | [18917-95-8] | \$156 |
| 1374408 | Malathion ( 500 mg ) | F-1 |  | F (08/01) | [121-75-5] | \$156 |
| 1374500 | Maleic Acid ( 300 mg ) | G |  | F-2 (12/00) | [110-16-7] | \$487 |
| 1374601 | Malic Acid (200 mg) | G0B158 |  | F-1 (04/03) | [617-48-1] | \$156 |
| 1374907 | Maltitol (200 mg) | G |  | F-1 (12/99) | [585-88-6] | \$156 |
| 1375003 | Maltol (4 g) (FCC) | G |  | F-1 (12/99) | [118-71-8] | \$156 |
| 1375058 | Mandelic Acid ( 500 mg ) | F |  |  | [90-64-2] | \$156 |
| 1375105 | Mannitol ( 200 mg ) | IOB212 |  | H (03/04) | [69-65-8] | \$156 |
| 1375207 | Maprotiline Hydrochloride ( 200 mg ) | H |  | G (07/02) | [10347-81-6] | \$156 |
| 1375309 | Mazindol CIV ( 350 mg ) | H |  | G (02/03) | [22232-71-9] | \$207 |
| 1375502 | Mebendazole ( 200 mg ) | G1C195 |  | G (11/04) | [31431-39-7] | \$156 |
| 1375706 | Mebrofenin ( 100 mg ) | F |  |  | [78266-06-5] | \$156 |
| 1376006 | Mecamylamine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  |  | [826-39-1] | \$156 |
| 1376505 | Mechlorethamine Hydrochloride ( 100 mg ) | F-1 |  | F (09/00) | [55-86-7] | \$156 |
| 1377009 | Meclizine Hydrochloride ( 500 mg ) | $\mathrm{I}-1$ |  |  | [31884-77-2] | \$156 |
| 1377508 | Meclocycline Sulfosalicylate ( 300 mg ) | G |  |  | [73816-42-9] | \$156 |
| 1377803 | Meclofenamate Sodium ( 500 mg ) | H |  |  | [6385-02-0] | \$156 |
| 1378001 | Medroxyprogesterone Acetate (200 mg) | H-2 |  | H-1 (04/03) | [71-58-9] | \$156 |
| 1378012 | Medroxyprogesterone Acetate Related Compound A ( 25 mg ) (4,5-betaDihydromedroxyprogesterone acetate) | F0C427 | 1 |  | n/f | \$500 |
| 1379004 | Medrysone ( 500 mg ) | F |  |  | [2668-66-8] | \$156 |
| 1379605 | Mefenamic Acid (200 mg) | G0C025 |  | $\begin{array}{\|l\|} \hline \text { F3A032 (08/04) } \\ \text { F-2 (01/03) } \\ \hline \end{array}$ | [61-68-7] | \$156 |
| 1379106 | Megestrol Acetate (500 mg) | 1 |  | H (05/00) | [595-33-5] | \$156 |
| 1379300 | Melphalan Hydrochloride ( 100 mg ) | H0B296 | 2,3 | G (01/05) | [3223-07-2] | \$156 |
| 1381006 | Menadione (200 mg) (Vitamin K3) | H-3 |  | H-2 (02/00) | [58-27-5] | \$156 |
| 1381709 | Menthol ( 250 mg ) | IOB049 |  | H (04/03) | [2216-51-5] | \$156 |
| 1381742 | Menthyl Anthranilate ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | F0B103 |  |  | [134-09-8] | \$156 |
| 1382009 | Mepenzolate Bromide ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [76-90-4] | \$156 |
| 1383001 | Meperidine Hydrochloride CII (200 mg) | I |  | H-1 (12/99) | [50-13-5] | \$207 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1384004 | Mephentermine Sulfate ( 250 mg ) | F-1 |  |  | [1212-72-2] | \$156 |
| 1385007 | Mephenytoin (250 mg) | G |  |  | [50-12-4] | \$156 |
| 1386000 | Mephobarbital CIV (250 mg) | G |  | F (01/01) | [115-38-8] | \$207 |
| 1387002 | Mepivacaine Hydrochloride ( 200 mg ) | H |  | G-4 (02/99) | [1722-62-9] | \$156 |
| 1388005 | Meprednisone ( 200 mg ) | G |  |  | [1247-42-3] | \$156 |
| 1389008 | Meprobamate CIV (200 mg) | G-1 |  | G (03/02) | [57-53-4] | \$207 |
| 1390007 | Meprylcaine Hydrochloride (200 mg) | F |  |  | [956-03-6] | \$156 |
| 1391000 | 3-Mercapto-2-methylpropanoic Acid 1,2-Diphenylethylamine Salt ( 75 mg ) | G |  |  | n/f | \$487 |
| 1392002 | Mercaptopurine ( 500 mg ) | I2C263 |  | $\begin{array}{\|l} \hline \text { I-1 (10/04) } \\ \text { I (07/02) } \\ \text { H (12/99) } \\ \hline \end{array}$ | [6112-76-1] | \$156 |
| 1392454 | Meropenem ( 300 mg ) | F0C201 |  |  | [119478-56-7] | \$182 |
| 1392705 | Mesalamine (200 mg) | G1B001 |  | $\begin{array}{\|l\|} \hline \text { G (01/03) } \\ \text { F-1 }(03 / 00) \\ \hline \end{array}$ | [89-57-6] | \$156 |
| 1393005 | Mesoridazine Besylate ( 250 mg ) | J0C117 |  | I-1 (12/04) | [32672-69-8] | \$156 |
| 1394008 | Mestranol (200 mg) | K0C065 |  | $\begin{array}{\|l\|} \hline J \text { (07/04) } \\ \text { I-1 (09/99) } \\ \hline \end{array}$ | [72-33-3] | \$156 |
| 1395500 | Metaproterenol Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | F-3 |  |  | [5874-97-5] | \$156 |
| 1396003 | Metaraminol Bitartrate ( 200 mg ) | F-3 |  |  | [33402-03-8] | \$156 |
| 1396309 | Metformin Hydrochloride ( 200 mg ) | F0C209 |  |  | [1115-70-4] | \$182 |
| 1396310 | Metformin Related Compound A (50 mg) (1-Cyanoguanidine) | F0C210 |  |  | [461-58-5] | \$487 |
| 1396400 | Methacrylic Acid Copolymer Type A (200 mg) | G0B140 |  | F-2 (04/03) | n/f | \$156 |
| 1396502 | Methacrylic Acid Copolymer Type B (200 mg) | G0B141 |  | F-2 (04/03) | n/f | \$156 |
| 1396604 | Methacrylic Acid Copolymer Type C (100 mg) | G1B088 |  | G (08/03) | n/f | \$124 |
| 1397006 | Methacycline Hydrochloride ( 200 mg ) | H |  | G (04/01) | [3963-95-9] | \$156 |
| 1398009 | Methadone Hydrochloride CII (200 mg) | IOB163 |  | H-1 (08/03) | [1095-90-5] | \$207 |
| 1399001 | Methamphetamine Hydrochloride CII (125 mg) | I |  |  | [51-57-0] | \$207 |
| 1401001 | Methantheline Bromide ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [53-46-3] | \$156 |
| 1402004 | Methapyrilene Fumarate ( 200 mg ) | F-1 |  |  | [33032-12-1] | \$156 |
| 1404000 | Methaqualone Cl ( 500 mg ) | F-1 |  |  | [72-44-6] | \$207 |
| 1405002 | Metharbital CIII ( 200 mg ) | F-2 |  | F-1 (07/99) | [50-11-3] | \$207 |
| 1406005 | Methazolamide ( 500 mg ) | H0B239 |  | G-1 (05/04) | [554-57-4] | \$156 |
| 1407008 | Methdilazine ( 200 mg ) | F-1 |  |  | [1982-37-2] | \$156 |
| 1408000 | Methdilazine Hydrochloride ( 200 mg ) | G |  |  | [1229-35-2] | \$156 |
| 1409003 | Methenamine ( 500 mg ) | H0C047 |  | G (05/04) | [100-97-0] | \$156 |
| 1409502 | Methenamine Hippurate (200 mg) | F |  |  | [5714-73-8] | \$156 |
| 1409604 | Methenamine Mandelate ( $200 \mathrm{mg} \mathrm{)}$ | G0C304 | 2 | $\begin{array}{\|l\|l} \hline \text { F-2 }(01 / 05) \\ \text { F-1 }(11 / 00) \\ \hline \end{array}$ | [587-23-5] | \$156 |
| 1410002 | Methicillin Sodium (500 mg) | J0C333 | 2 | $\begin{aligned} & \text { I1B186 (11/04) } \\ & \text { I (03/03) } \\ & \text { H (03/00) } \\ & \hline \end{aligned}$ | [7246-14-2] | \$156 |
| 1411005 | Methimazole (200 mg) | G |  | F (02/01) | [60-56-0] | \$156 |
| 1411504 | L-Methionine ( 200 mg ) | G |  | F-2 (11/99) | [63-68-3] | \$156 |
| 1412008 | Methocarbamol (200 mg) | H2B029 |  | H-1 (03/04) | [532-03-6] | \$156 |
| 1413000 | Methohexital CIV (500 mg) | F-2 |  |  | [18652-93-2] | \$207 |
| 1414003 | Methotrexate ( 500 mg ) | 1 |  |  | [59-05-2] | \$156 |
| 1415006 | Methotrimeprazine ( 125 mg ) | F-2 |  | F-1 (05/99) | [60-99-1] | \$124 |
| 1416009 | Methoxamine Hydrochloride ( 200 mg ) | F |  |  | [61-16-5] | \$156 |
| 1417001 | Methoxsalen (500 mg) | H |  |  | [298-81-7] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1418004 | Methoxyflurane (1 mL) | G |  |  | [76-38-0] | \$156 |
| 1419007 | Methoxyphenamine Hydrochloride ( 250 mg ) | F |  |  | [5588-10-3] | \$156 |
| 1421009 | Methscopolamine Bromide ( $200 \mathrm{mg} \mathrm{)}$ | G1D004 | 2 | G (02/05) | [155-41-9] | \$156 |
| 1422001 | Methsuximide ( 500 mg ) | F-2 |  | F-1 (08/99) | [77-41-8] | \$156 |
| 1424007 | Methyclothiazide ( 200 mg ) | G |  |  | [135-07-9] | \$156 |
| 1424018 | Methyclothiazide Related Compound A (100 mg) (4-amino-6-chloro-N-3-methyl-m-benzenedisulfonamide) | G |  | F-2 (12/00) | n/f | \$487 |
| 1424222 | Methyl Benzylidene Camphor (200 mg) | F0B118 |  |  | [36861-47-9] | \$156 |
| 1424233 | Methyl Caprate ( 300 mg ) | F |  |  | [110-42-9] | \$156 |
| 1424244 | Methyl Caproate ( 300 mg ) | F |  |  | [106-70-7] | \$156 |
| 1424255 | Methyl Caprylate ( 300 mg ) | F |  |  | [111-11-5] | \$156 |
| 1424506 | Methylcellulose (1 g) (AS) | G0B222 |  | F-2 (05/03) | [9004-67-5] | \$156 |
| 1425000 | 4-Methyl-2,5-dimethoxyamphetamine Hydrochloride CI ( 25 mg ) (AS) (STP) | F |  |  | [15589-00-1] | \$207 |
| 1426002 | Methyldopa ( 500 mg ) | 1 |  |  | [41372-08-1] | \$156 |
| 1427005 | Methyldopate Hydrochloride ( 200 mg ) | G-2 |  |  | [2508-79-4] | \$156 |
| 1428008 | Methylene Blue ( $250 \mathrm{mg} \mathrm{)}$ | G |  |  | [7220-79-3] | \$156 |
| 1429000 | Methylenedioxy-3,4-amphetamine Hydrochloride $\mathbf{C l}(25 \mathrm{mg})(\mathrm{AS})$ (MDA) | F-1 |  |  | [6292-91-7] | \$207 |
| 1430000 | Methylergonovine Maleate ( 50 mg ) (List Chemical) | J |  | I (05/02) | [57432-61-8] | \$156 |
| 1430305 | Methyl Laurate ( 500 mg ) | F |  |  | [111-82-0] | \$156 |
| 1430327 | Methyl Linoleate ( $5 \times 50 \mathrm{mg}$ ) | F |  |  | [112-63-0] | \$156 |
| 1430349 | Methyl Linolenate ( $5 \times 50 \mathrm{mg}$ ) | F |  |  | [301-00-8] | \$156 |
| 1430509 | $3-\mathrm{O}-\mathrm{Methylmethyldopa} \mathrm{( } 50 \mathrm{mg}$ ) | G-1 |  |  | n/f | \$487 |
| 1431002 | Methyl 5-methyl-3-isoxazolecarboxylate ( 25 mg ) | F-1 |  | F (01/01) | n/f | \$487 |
| 1431501 | Methyl Myristate ( 300 mg ) | F |  |  | [124-10-7] | \$156 |
| 1431556 | Methyl Oleate ( 500 mg ) | G0C148 |  | F (04/04) | [112-62-9] | \$156 |
| 1431603 | Methyl Palmitate ( 300 mg ) | F |  |  | [112-39-0] | \$156 |
| 1431625 | Methyl Palmitoleate ( 300 mg ) | F |  |  | n/f | \$156 |
| 1432005 | Methylparaben ( 125 mg ) | J-1 |  | J (03/03)) | [99-76-3] | \$124 |
| 1433008 | Methylphenidate Hydrochloride CII (125 mg) | 1 |  | H (05/01) | [298-59-9] | \$165 |
| 1434000 | Methylphenidate Hydrochloride Erythro Isomer CII ( 25 mg ) | J0B294 |  | $\begin{aligned} & \text { IOA006 (09/03) } \\ & \text { H-1 (01/03) } \\ & \text { H (06/01) } \\ & \hline \end{aligned}$ | [298-59-9] | \$560 |
| 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution CII ( 0.5 mL ) | F0C368 | 1 |  | n/f | \$560 |
| 1434022 | Methylphenidate Related Compound A ( 50 mg ) (alpha-Phenyl-2piperidineacetic Acid Hydrochloride) | G |  | F-2 (10/99) | n/f | \$487 |
| 1435003 | Methylprednisolone ( 200 mg ) | H |  |  | [83-43-2] | \$156 |
| 1436006 | Methylprednisolone Acetate ( 200 mg ) | G-2 |  | G-1 (02/00) | [53-36-1] | \$156 |
| 1437009 | Methylprednisolone Hemisuccinate (200 mg) | IOC146 |  | H (07/04) | [2921-57-5] | \$156 |
| 1437508 | Methyl Stearate ( 300 mg ) | F |  |  | [112-61-8] | \$156 |
| 1438001 | Methyltestosterone CIII ( 200 mg ) | J |  | I (11/01) | [58-18-4] | \$207 |
| 1440003 | Methysergide Maleate ( 200 mg ) | H |  |  | [129-49-7] | \$156 |
| 1440808 | Metoclopramide Hydrochloride ( 500 mg ) | G |  | F-2 (06/99) | [54143-57-6] | \$156 |
| 1441006 | Metocurine lodide ( $300 \mathrm{mg} \mathrm{)}$ | G |  |  | [7601-55-0] | \$156 |
| 1441200 | Metolazone ( 200 mg ) | G0B246 |  | F-1 (05/03) | [17560-51-9] | \$156 |
| 1441287 | Metoprolol Fumarate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [119637-66-0] | \$156 |
| 1441232 | Metoprolol Related Compound A (20 mg) ((+/-)1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol) | F0C343 |  |  | n/f | \$520 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1441243 | Metoprolol Related Compound B (50 mg) ((+/-)1-chloro-2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]-propane) | F0C377 |  |  | n/f | \$520 |
| 1441254 | Metoprolol Related Compound C (20 mg) ((+/-)4-[2-Hydroxy-3-(1methylethyl)aminopropoxy]benzaldehyde) | F0C344 |  |  | n/f | \$520 |
| 1441265 | Metoprolol Related Compound D ( 50 mg ) ( $(+/-$ )N,N-bis-[2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl](1-methylethyl)amine) | F0C378 |  |  | n/f | \$520 |
| 1441298 | Metoprolol Succinate ( $200 \mathrm{mg} \mathrm{)}$ | F0C415 | 1 |  | [98418-47-4] | \$156 |
| 1441301 | Metoprolol Tartrate ( 200 mg ) | H1B059 |  | $\begin{aligned} & \hline \text { H (01/04) } \\ & \text { G-1 (11/99) } \end{aligned}$ | [56392-17-7] | \$156 |
| 1441505 | Metrizamide ( 500 mg ) | F |  |  | [31112-62-6] | \$156 |
| 1442009 | Metronidazole ( 100 mg ) | 1 |  |  | [443-48-1] | \$156 |
| 1443001 | Metyrapone ( 200 mg ) | H |  | G (06/01) | [54-36-4] | \$156 |
| 1443205 | Metyrosine ( 200 mg ) | F |  |  | [672-87-7] | \$156 |
| 1443250 | Mexiletine Hydrochloride ( 200 mg ) | F-2 |  | F-1 (09/02) | [5370-01-4] | \$156 |
| 1443307 | Mezlocillin Sodium ( 350 mg ) | G |  |  | [59798-30-0] | \$156 |
| 1443409 | Miconazole ( 200 mg ) | G-1 |  | G (07/02) | [22916-47-8] | \$156 |
| 1443500 | Miconazole Nitrate ( $200 \mathrm{mg} \mathrm{)}$ | I |  | H (06/99) | [22832-87-7] | \$156 |
| 1443850 | Powdered Milk Thistle Extract (250 mg) | F0B321 |  |  | [84604-20-6] | \$260 |
| 1443908 | Milrinone ( 500 mg ) | F0C050 |  |  | [78415-72-2] | \$260 |
| 1443919 | Milrinone Related Compound A (50 mg) (1,6-Dihydro-2-methyl-6-oxo(3,4'-bipyridine)-5-carboxamide) | F0C051 |  |  | [80047-24-1] | \$487 |
| 1444004 | Minocycline Hydrochloride (200 mg) | 10 C 178 |  | $\begin{array}{\|l} \mathrm{H}-3(04 / 04) \\ \mathrm{H}-2(07 / 02) \\ \hline \end{array}$ | [13614-98-7] | \$156 |
| 1444208 | Minoxidil (125 mg) | H1C168 |  | $\begin{aligned} & \hline \text { H }(03 / 04) \\ & \mathrm{G}(05 / 99) \end{aligned}$ | [38304-91-5] | \$124 |
| 1444707 | Mitomycin ( 50 mg ) | K |  | $J(07 / 01)$ | [50-07-7] | \$479 |
| 1445007 | Mitotane ( 500 mg ) | GOC044 |  | F (07/04) | [53-19-0] | \$156 |
| 1445200 | Mitoxantrone Hydrochloride ( 400 mg ) | H |  | G (03/01) | [70476-82-3] | \$498 |
| 1445222 | Mitoxantrone Related Compound A Hydrochloride ( 30 mg ) ( 8 -amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione Hydrochloride) DISCONTINUED; Please order 1445211 |  | 9 | $\begin{aligned} & \text { F-1 (07/04) } \\ & \text { F (03/01) } \end{aligned}$ | n/f | \$208 |
| 1445211 | Mitoxantrone System Suitability Mixture ( 0.3 mg ) | F0D010 | 1 |  | n/f | \$500 |
| 1445459 | Molindone Hydrochloride ( 500 mg ) | F |  |  | [15622-65-8] | \$156 |
| 1445470 | Mometasone Furoate (200 mg) | G0B073 |  | $\begin{array}{\|l\|} \hline \text { F-1 (04/03) } \\ \text { F (02/01) } \\ \hline \end{array}$ | [83919-23-7] | \$156 |
| 1445481 | Monensin Sodium (200 mg) | F0B293 |  |  | [22373-78-0] | \$156 |
| 1445506 | Monobenzone ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [103-16-2] | \$156 |
| 1445801 | Mono- and Di-acetylated Monoglycerides (200 mg) | F |  |  | [68990-54-5] | \$156 |
| 1446000 | Monoglycerides (125 mg) | H |  |  | [68990-53-4] | \$124 |
| 1446804 | Monostearyl Maleate ( 100 mg ) | G |  | F-2 (04/00) | [2424-62-6] | \$487 |
| 1446950 | Moricizine Hydrochloride ( 100 mg ) | F |  |  | [29560-58-5] | \$156 |
| 1447002 | Morphine Monohydrate CII (50 mg) (AS) | G |  |  | [6009-81-0] | \$207 |
| 1448005 | Morphine Sulfate CII (500 mg) | LOB056 |  | $\begin{aligned} & \hline \mathrm{K}(06 / 03) \\ & \mathrm{J}-1(07 / 00) \\ & \hline \end{aligned}$ | [6211-15-0] | \$332 |
| 1448504 | Moxalactam Disodium ( 500 mg ) | F-1 |  |  | [64953-12-4] | \$156 |
| 1448901 | Mupirocin ( 50 mg ) | F2C158 | 2 | $\begin{array}{\|l} \hline \text { F-1 (12/04) } \\ \text { F (03/02) } \\ \hline \end{array}$ | [12650-69-0] | \$156 |
| 1448923 | Mupirocin Lithium (100 mg) | G |  | F (02/01) | [73346-79-9] | \$156 |
| 1449008 | Myristyl Alcohol (1 g) | G |  | F (02/02) | [112-72-1] | \$156 |
| 1449518 | Nabumetone (200 mg) | F0C072 |  |  | [42924-53-8] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1449700 | Nadolol (200 mg) | F-3 |  | F-2 (04/02) | [42200-33-9] | \$156 |
| 1450007 | Nafcillin Sodium (200 mg) | H |  |  | [7177-50-6] | \$156 |
| 1450404 | Naftifine Hydrochloride ( 200 mg ) | F |  |  | [65473-14-5] | \$156 |
| 1451000 | Nalidixic Acid (200 mg) | G |  |  | [389-08-2] | \$156 |
| 1452002 | Nalorphine Hydrochloride CIII (250 mg) | 1 |  |  | [57-29-4] | \$207 |
| 1453005 | Naloxone (125 mg) | LOB124 |  | $\begin{aligned} & \text { K-1 (12/02) } \\ & \text { K (07/01) } \\ & \hline \end{aligned}$ | [465-65-6] | \$124 |
| 1453504 | Naltrexone (200 mg) | H0C150 |  | $\begin{aligned} & \text { G1B039 (03/04) } \\ & \text { G (02/03) } \\ & \hline \end{aligned}$ | [16590-41-3] | \$156 |
| 1453526 | Naltrexone Related Compound A CII (30 mg) (N-(3-butenyl)-noroxymorphone Hydrochloride) | F |  |  | n/f | \$207 |
| 1454008 | Nandrolone CIII ( 50 mg ) | F-3 |  |  | [434-22-0] | \$560 |
| 1455000 | Nandrolone Decanoate CIII ( $250 \mathrm{mg} \mathrm{)}$ | 1 |  |  | [360-70-3] | \$207 |
| 1456003 | Nandrolone Phenpropionate CIII (250 mg) | H |  |  | [62-90-8] | \$207 |
| 1457006 | Naphazoline Hydrochloride (200 mg) | K |  |  | [550-99-2] | \$156 |
| 1457301 | Naproxen (200 mg) | I-1 |  | $\begin{aligned} & \text { I (03/03) } \\ & \text { H-1 (01/01) } \end{aligned}$ | [22204-53-1] | \$156 |
| 1457403 | Naproxen Sodium (200 mg) | 1 |  |  | [26159-34-2] | \$156 |
| 1457469 | Naratriptan Hydrochloride ( 125 mg ) | F0C360 | 1 |  | [143388-64-1] | \$208 |
| 1457505 | Natamycin (200 mg) | I |  | H (11/99) | [7681-93-8] | \$156 |
| 1458009 | Neomycin Sulfate (200 mg) | L-2 |  | $\begin{array}{\|l\|l} \hline \text { L-1 (09/01) } \\ \text { L (02/99) } \\ \hline \end{array}$ | [1405-10-3] | \$156 |
| 1459001 | Neostigmine Bromide (200 mg) | G |  |  | [114-80-7] | \$156 |
| 1460000 | Neostigmine Methylsulfate ( 200 mg ) | 1 |  | H (07/00) | [51-60-5] | \$156 |
| 1460500 | Netilmicin Sulfate ( 500 mg ) | 10 C 388 | 2 | $\begin{aligned} & \mathrm{H}(01 / 05) \\ & \mathrm{G}(05 / 02) \end{aligned}$ | [56391-57-2] | \$156 |
| 1461003 | Niacin (200 mg) | H2C121 | 2 | H-1 (01/05) | [59-67-6] | \$156 |
| 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) | M-1 |  | M (02/01) | [98-92-0] | \$156 |
| 1463304 | Nicotine Bitartrate Dihydrate ( 500 mg ) | G |  | F (05/99) | [6019-06-3] | \$156 |
| 1463508 | Nifedipine ( 125 mg ) | J0B243 |  | I-1 (04/04) | [21829-25-4] | \$124 |
| 1463600 | Nifedipine Nitrophenylpyridine Analog ( 25 mg ) | K |  | J (04/01) | n/f | \$487 |
| 1463701 | Nifedipine Nitrosophenylpyridine Analog ( 25 mg ) | K |  | $J$ (07/02) | n/f | \$487 |
| 1464001 | Nitrofurantoin ( 500 mg ) | $J$ |  | I-1 (11/02) | [67-20-9] | \$156 |
| 1465004 | Nitrofurazone ( 200 mg ) | H-1 |  | H (09/01) | [59-87-0] | \$156 |
| 1465503 | Nitrofurfural Diacetate ( 100 mg ) |  |  | F-1 (12/04) | [92-55-7] | \$487 |
| 1466007 | Nitrofurazone Related Compound A (500 mg) (5-Nitro-2-furfuraldazine) | H0B100 |  | G (07/03) | n/f | \$487 |
| 1466506 | Diluted Nitroglycerin ( 5 ampules, approx. 200 mg of a $0.948 \%$ solution in propylene glycol each) | G |  |  | [55-63-0] | \$156 |
| 1467804 | Nizatidine (200 mg) | G |  | F-1 (06/00) | [76963-41-2] | \$156 |
| 1467950 | Nonoxynol 9 ( 0.5 mL ) | H-1 |  | H (03/02) | [26027-38-3] | \$156 |
| 1468002 | Nonoxynol 10 (200 mg) | F |  |  | [26027-38-3] | \$156 |
| 1468400 | Nordazepam CIV (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-ben-zodiazepin-2-one) | H1B035 |  | $\begin{aligned} & \mathrm{H}(03 / 03) \\ & \mathrm{G}(03 / 00) \end{aligned}$ | [1088-11-5] | \$560 |
| 1468501 | Norepinephrine Bitartrate ( 125 mg ) | H |  |  | [69815-49-2] | \$124 |
| 1469005 | Norethindrone ( 200 mg ) | J1B065 |  | $\begin{array}{\|l} \hline J-1(05 / 03) \\ \mathrm{J}(07 / 02) \\ \mathrm{l}-1(03 / 01) \\ \hline \end{array}$ | [68-22-4] | \$156 |
| 1470004 | Norethindrone Acetate ( 100 mg ) | J0B072 |  | $\begin{array}{\|l\|} \hline 1(04 / 03) \\ H(06 / 99) \\ \hline \end{array}$ | [51-98-9] | \$156 |
| 1471007 | Norethynodrel ( 200 mg ) | G |  |  | [68-23-5] | \$156 |
| 1471506 | Norfloxacin (200 mg) | H |  | G (04/01) | [70458-96-7] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1471914 | Norgestimate (200 mg) | F0C086 |  |  | [35189-28-7] | \$156 |
| 1472000 | Norgestrel (125 mg) | J0C269 |  | $\begin{aligned} & \mathrm{I}(07 / 04) \\ & \mathrm{H}(05 / 99) \\ & \hline \end{aligned}$ | [6533-00-2] | \$124 |
| 1473002 | Noroxymorphone Hydrochloride CII (50 mg) | H1C177 |  | H (11/04) | n/f | \$560 |
| 1474005 | Nortriptyline Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  | H (04/00) | [894-71-3] | \$156 |
| 1474504 | Noscapine ( 500 mg ) | G |  |  | [128-62-1] | \$156 |
| 1475008 | Novobiocin ( 200 mg ) | G-2 |  |  | [303-81-1] | \$156 |
| 1476000 | Nylidrin Hydrochloride ( 200 mg ) | F-2 |  |  | [849-55-8] | \$156 |
| 1477003 | Nystatin ( 200 mg ) | N1B004 |  | N (01/03) | [1400-61-9] | \$156 |
| 1477900 | Octinoxate ( 500 mg ) (Octyl Methoxycinnamate) | G0C024 |  | FOB032 (12/03) | [5466-77-3] | \$156 |
| 1477411 | Octocrylene ( 500 mg ) | G0C211 |  | FOB104 (05/04) | [6197-30-4] | \$156 |
| 1477502 | Octoxynol 9 (200 mg) | G |  | F-2 (07/00) | [9002-93-1] | \$156 |
| 1477808 | Octyldodecanol (200 mg) | G |  | F-1 (07/99) | [5333-42-6] | \$156 |
| 1477943 | Octyl Salicylate (400 mg) | F0B091 |  |  | [118-60-5] | \$156 |
| 1478108 | Ofloxacin (200 mg) | F-2 |  | F-1 (08/02) | [82419-36-1] | \$156 |
| 1478505 | Omeprazole (200 mg) | H1B211 |  | $\begin{array}{\|l} \hline \mathrm{H}(05 / 04) \\ \mathrm{G}-1(04 / 02) \\ \mathrm{G}(09 / 01) \\ \hline \end{array}$ | [73590-58-6] | \$156 |
| 1478582 | Ondansetron Hydrochloride ( 300 mg ) | F0C222 |  |  | [103639-04-9] | \$208 |
| 1478593 | Ondansetron Related Compound A ( 50 mg ) (3[(Dimethylamino)-methyll-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride) | FOC191 |  |  | [119812-29-2] | \$487 |
| 1478618 | Ondansetron Related Compound C (50 mg) (1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4-one) | F0C251 |  |  | [27397-31-1] | \$487 |
| 1478629 | Ondansetron Related Compound D (50 mg) (1,2,3,9-Tetrahydro-9-methyl-3-methylene-4H-carbazol-4-one) | F0C226 |  |  | n/f | \$487 |
| 1479009 | Orphenadrine Citrate (200 mg) | G |  | F-4 (05/02) | [4682-36-4] | \$156 |
| 1481000 | Oxacillin Sodium ( 200 mg ) | $J$ |  | I (03/02) | [7240-38-2] | \$156 |
| 1481500 | Oxamniquine ( 200 mg ) | F |  |  | [21738-42-1] | \$156 |
| 1481703 | Oxamniquine Related Compound A (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolinemethyl methanesulfonate) | F |  |  | n/f | \$487 |
| 1481805 | Oxamniquine Related Compound B (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-5-nitro-6-quinolinemethanol) | F |  |  | n/f | \$487 |
| 1482003 | Oxandrolone CIII ( 50 mg ) | G0B220 |  | F-4 (07/03) | [53-39-4] | \$207 |
| 1482207 | Oxaprozin (200 mg) | F0C115 |  |  | [21256-18-8] | \$156 |
| 1483006 | Oxazepam CIV (200 mg) | G-1 |  | G (12/00) | [604-75-1] | \$207 |
| 1483301 | Oxfendazole (200 mg) | F0C128 |  |  | [53716-50-0] | \$156 |
| 1483505 | Oxprenolol Hydrochloride ( 200 mg ) | I0C344 | 2 | H (02/05) | [6452-73-9] | \$156 |
| 1484009 | Oxtriphylline ( 500 mg ) | G |  |  | [4499-40-5] | \$156 |
| 1485001 | Oxybenzone (150 mg) | H0B263 |  | $\begin{array}{\|l} \hline \text { G (11/03) } \\ \mathrm{F}-2(12 / 99) \\ \hline \end{array}$ | [131-57-7] | \$156 |
| 1485103 | Oxybutynin Chloride (200 mg) | G-1 |  | G (11/02) | [1508-65-2] | \$156 |
| 1485114 | Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid) | G |  | F-2 (01/00) | [4335-77-7] | \$487 |
| 1485191 | Oxycodone CII (200 mg) | 10B046 |  | $\begin{array}{\|l\|} \hline \text { H }(01 / 03) \\ \text { G-1 }(01 / 01) \\ \hline \end{array}$ | [76-42-6] | \$207 |
| 1486004 | Oxymetazoline Hydrochloride (200 mg) | J0C206 | 2 | I (03/05) | [2315-02-8] | \$156 |
| 1487007 | Oxymetholone CIII (200 mg) | G1B247 |  | G (10/03) | [434-07-1] | \$207 |
| 1488000 | Oxymorphone CII ( 500 mg ) | H0B214 |  | G (03/03) | [76-41-5] | \$207 |
| 1489002 | Oxyphenbutazone (1 g) | H |  |  | [7081-38-1] | \$156 |
| 1490103 | Oxyquinoline Sulfate (200 mg) | F-1 |  | F (07/02) | [134-31-6] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1491004 | Oxytetracycline (200 mg) | J0C084 | 2 | I-1 (10/04) | [6153-64-6] | \$156 |
| 1491300 | Oxytocin (5 vials, 46 USP units per vial) | F |  |  | [50-56-6] | \$156 |
| 1491332 | Paclitaxel ( 200 mg ) | F0C180 |  |  | [33069-62-4] | \$1,508 |
| 1491343 | Paclitaxel Related Compound A (20 mg) (Cephalomannine) | FOC179 |  |  | [71610-00-9] | \$754 |
| 1491354 | Paclitaxel Related Compound B (20 mg) (10-Deacetyl-7-epipaclitaxel) | F0C181 |  |  | nf | \$754 |
| 1491503 | Padimate O ( 300 mg ) | H0B154 |  | G (04/03) | [21245-02-3] | \$156 |
| 1492007 | Palmitic Acid ( 500 mg ) | 1 |  |  | [57-10-3] | \$156 |
| 1493000 | Pamoic Acid (250 mg) | G-4 |  | G-3 (01/03) | [130-85-8] | \$156 |
| 1494057 | Pancreatin Amylase and Protease (2 g) | 1 |  | H (10/00) | [8049-47-6] | \$156 |
| 1494079 | Pancreatin Lipase (2 g) | 1 |  | H-1 (03/01) | [8049-47-6] | \$156 |
| 1494501 | Panthenol, Racemic ( 200 mg ) | G |  | F-1 (02/00) | [16485-10-2] | \$156 |
| 1494807 | Pantolactone ( 500 mg ) | F |  |  | [599-04-2] | \$487 |
| 1495005 | Papain (1 g) | H |  | G (12/01) | [9001-73-4] | \$156 |
| 1496008 | Papaverine Hydrochloride ( 200 mg ) | H |  |  | [61-25-6] | \$156 |
| 1497000 | Paramethadione ( 500 mg ) | G |  |  | [115-67-3] | \$156 |
| 1498003 | Paramethasone Acetate ( 200 mg ) | G |  | F-1 (05/01) | [1597-82-6] | \$156 |
| 1498706 | Parbendazole (200 mg) | F |  |  | [14255-87-9] | \$156 |
| 1499006 | Pargyline Hydrochloride (200 mg) | F-1 |  |  | [306-07-0] | \$156 |
| 1500003 | Paromomycin Sulfate ( 125 mg ) | G |  | F-3 (01/01) | [1263-89-4] | \$156 |
| 1500218 | Paroxetine Hydrochloride ( 350 mg ) | G0D003 | 2,3 | FOB288 (09/04) | [110429-35-1] | \$156 |
| 1500229 | Paroxetine Related Compound A (20 mg) (trans-4-(p-methoxyphenyl)-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine Hydrochloride) | F0B172 |  |  | n/f | \$487 |
| 1500230 | Paroxetine Related Compound B ( 20 mg ) (trans-4-phenyl-3-([(3,4methylenedioxy)phenoxy]methylpiperidine acetate) | F0B189 |  |  | n/f | \$487 |
| 1500240 | Paroxetine Related Compound C ( 25 mg ) ((+)-trans-Paroxetine hydrochloride) | FOB192 |  |  | [130855-30-0] | \$487 |
| 1500251 | Paroxetine Related Compound D (15 mg) ((-)-cis-Paroxetine hydrochloride) | F0C228 |  |  | n/f | \$487 |
| 1500400 | Parthenolide ( 25 mg ) | F |  |  | [20554-84-1] | \$156 |
| 1500502 | Particle Count Set (2 blanks and 2 suspensions) | 1 |  | H (09/02) | n/f | \$487 |
| 1500808 | Penbutolol Sulfate (200 mg) | F |  |  | [38363-32-5] | \$156 |
| 1501006 | Penicillamine (200 mg) | H1B164 |  | H (01/04) | [52-67-5] | \$156 |
| 1501108 | Penicillamine Disulfide ( 100 mg ) | H |  | G (07/00) | [20902-45-8] | \$487 |
| 1502009 | Penicillin G Benzathine ( 200 mg ) | J |  |  | [41372-02-5] | \$156 |
| 1502508 | Penicillin G Potassium ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  | H (02/99) | [113-98-4] | \$156 |
| 1502552 | Penicillin G Procaine ( 200 mg ) | G0C271 |  | $\begin{aligned} & \hline \text { F-1 (08/04) } \\ & \text { F (03/99) } \\ & \hline \end{aligned}$ | [6130-64-9] | \$156 |
| 1502701 | Penicillin G Sodium ( 200 mg ) | L-3 |  | L-2 (09/01) | [69-57-8] | \$156 |
| 1504489 | Penicillin V ( 200 mg ) | F |  |  | [87-08-1] | \$156 |
| 1504503 | Penicillin V Potassium ( 200 mg ) | H0C213 |  | $\begin{aligned} & \text { G-1 (06/04) } \\ & \text { G (06/00) } \end{aligned}$ | [132-98-9] | \$156 |
| 1505007 | Pentazocine CIV (500 mg) | 10 C 418 | 2 | $\begin{aligned} & \text { H (01/05) } \\ & \text { G-1 }(11 / 00) \\ & \hline \end{aligned}$ | [359-83-1] | \$207 |
| 1505506 | Pentetic Acid (100 mg) | F-1 |  | F (09/01) | [67-43-6] | \$156 |
| 1507002 | Pentobarbital CII (200 mg) | H3C144 |  | $\begin{array}{\|l\|l\|} \hline \mathrm{H}-2(07 / 04) \\ \mathrm{H}-1 & (08 / 02) \\ \hline \end{array}$ | [76-74-4] | \$207 |
| 1508901 | Pentoxifylline (200 mg) | F0B202 |  |  | [6493-05-6] | \$156 |
| 1510007 | Pepsin (5 g) | F-2 |  |  | [9001-75-6] | \$156 |
| 1510801 | Perflubron ( 0.5 mL ) | G0C103 |  | F (04/04) | [423-55-2] | \$156 |
| 1510845 | Pergolide Mesylate ( 200 mg ) | F1C225 |  | F (07/04) | [66104-23-2] | \$194 |

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## USP Reference Standards and Authentic Substances

| Cat. <br> No. | Description | Curr. <br> Lot. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1510867 | Pergolide Sulfoxide ( 50 mg ) | F0B014 |  |  | [72822-01-6] | \$194 |
| 1511000 | Perphenazine ( 200 mg ) | J0B249 |  | I (10/03) | [58-39-9] | \$156 |
| 1511203 | Perphenazine Sulfoxide ( 100 mg ) | G-1 |  | G (07/02) | [10078-25-8] | \$487 |
| 1512002 | Phenacemide ( 250 mg ) | F |  |  | [63-98-9] | \$156 |
| 1513005 | Phenacetin ( 500 mg ) | H-1 |  | H (09/00) | [62-44-2] | \$156 |
| 1514008 | Phenacetin Melting Point Standard ( 500 mg ) (Approximately 135 degrees) | H3A009 |  | $\begin{aligned} & \mathrm{H}-2(02 / 03) \\ & \mathrm{H}-1(06 / 01) \end{aligned}$ | [62-44-2] | \$92 |
| 1515000 | Phenazopyridine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H0C426 | 2 | G-4 (12/04) | [136-40-3] | \$156 |
| 1516003 | Phencyclidine Hydrochloride CII ( 25 mg ) (AS) | G1B025 |  | G (12/02) | [956-90-1] | \$207 |
| 1516502 | Phendimetrazine Tartrate CIII ( 350 mg ) | G |  | F (01/01) | [50-58-8] | \$207 |
| 1517006 | Phenelzine Sulfate (200 mg) | G |  | F-1 (04/02) | [156-51-4] | \$156 |
| 1517301 | D-Phenethicillin Potassium (200 mg) | F |  |  | n/f | \$487 |
| 1517607 | L-Phenethicillin Potassium (200 mg) | F |  |  | n/f | \$156 |
| 1520000 | Phenformin Hydrochloride (200 mg) | G |  |  | [834-28-6] | \$156 |
| 1522006 | Phenindione (250 mg) | F |  |  | [83-12-5] | \$156 |
| 1522301 | Pheniramine Maleate ( 100 mg ) | F1C342 |  | F (08/04) | [132-20-7] | \$156 |
| 1523009 | Phenmetrazine Hydrochloride CII (200 mg) | F-2 |  |  | [1707-14-8] | \$207 |
| 1524001 | Phenobarbital CIV (200 mg) | $J$ |  |  | [50-06-6] | \$207 |
| 1524908 | Phenolphthalein ( 250 mg ) | F-3 |  |  | [77-09-8] | \$156 |
| 1525004 | Phenolsulfonphthalein ( 100 mg ) | F-2 |  |  | [143-74-8] | \$156 |
| 1526007 | Phenoxybenzamine Hydrochloride ( $250 \mathrm{mg} \mathrm{)}$ | G |  |  | [63-92-3] | \$156 |
| 1528002 | Phensuximide ( 500 mg ) | G |  | F-1 (03/01) | [86-34-0] | \$156 |
| 1528501 | Phentermine Hydrochloride CIV (200 mg) | H0B309 |  | G (08/03) | [1197-21-3] | \$207 |
| 1529005 | Phentolamine Hydrochloride ( 300 mg ) | F |  |  | [73-05-2] | \$156 |
| 1530004 | Phentolamine Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  |  | [65-28-1] | \$156 |
| 1530503 | L-Phenylalanine (200 mg) | H |  | G (02/02) | [63-91-2] | \$156 |
| 1530809 | Phenylbenzimidazole Sulfonic Acid (200 mg) | F |  |  | [27503-81-7] | \$156 |
| 1531007 | Phenylbutazone (250 mg) | J0A008 |  | I-1 (02/03) | [50-33-9] | \$156 |
| 1533002 | Phenylephrine Hydrochloride (125 mg) | K |  | J (02/99) | [61-76-7] | \$124 |
| 1533308 | 5-Phenylhydantoin ( 100 mg ) | F |  |  | [89-24-7] | \$487 |
| 1533851 | Phenylpropanediol ( 100 mg ) | F |  |  | n/f | \$487 |
| 1533909 | Phenylpropanolamine Bitartrate (100 mg) (List Chemical) | F |  |  | [67244-90-0] | \$156 |
| 1534005 | Phenylpropanolamine Hydrochloride (250 mg) (List Chemical) | J |  | 1 (02/02) | [154-41-6] | \$156 |
| 1535008 | Phenytoin (200 mg) | 12B233 |  | $\begin{array}{\|l\|} \hline \text { I-1 (03/04) } \\ \text { I (04/01) } \\ \hline \end{array}$ | [57-41-0] | \$156 |
| 1535507 | Phenytoin Sodium (200 mg) | H |  | G (05/99) | [630-93-3] | \$156 |
| 1535019 | Phenytoin Related Compound A (50 mg) (2,2-Diphenylglycine) | F0C155 |  |  | [3060-50-2] | \$487 |
| 1535020 | Phenytoin Related Compound B ( 50 mg ) (alpha-((aminocarbonyl)ami-no)-alpha-phenyl benzeneacetic acid) | F0C157 |  |  | [6802-95-5] | \$487 |
| 1535700 | Phosphated Riboflavin ( 100 mg ) | G1B286 |  | G (07/04) | [6184-17-4] | \$124 |
| 1537003 | Physostigmine Salicylate ( 200 mg ) | H-1 |  | H (06/00) | [57-64-7] | \$156 |
| 1538006 | Phytonadione (500 mg) (Vitamin K1) | N0B303 |  | $\begin{array}{\|l\|} \hline \mathrm{M}-1(07 / 04) \\ \mathrm{M}(09 / 01) \\ \hline \end{array}$ | [84-80-0] | \$156 |
| 1538505 | Pilocarpine ( 300 mg ) | F |  |  | [92-13-7] | \$156 |
| 1538902 | Pilocarpine Hydrochloride (200 mg) | H |  |  | [54-71-7] | \$156 |
| 1539009 | Pilocarpine Nitrate (200 mg) | 1 |  |  | [148-72-1] | \$156 |
| 1539508 | Pimozide ( 200 mg ) | G |  |  | [2062-78-4] | \$156 |
| 1539701 | Pindolol ( 200 mg ) | IOB210 |  | H-1 (12/04) | [13523-86-9] | \$156 |
| 1541000 | Piperacetazine (250 mg) | F |  |  | [3819-00-9] | \$156 |

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| 1541500 | Piperacillin ( 500 mg ) | H |  |  | [66258-76-2] | \$156 |
| 1541703 | Piperazine Adipate ( 200 mg ) | F |  |  | [142-88-1] | \$156 |
| 1541805 | Piperazine Citrate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  | [144-29-6] | \$156 |
| 1541907 | Piperazine Dihydrochloride (200 mg) | F |  |  | [142-64-3] | \$156 |
| 1542003 | Piperazine Phosphate ( 200 mg ) | F |  |  | [14538-56-8] | \$156 |
| 1543006 | Piperidolate Hydrochloride ( 200 mg ) | F |  |  | [129-77-1] | \$156 |
| 1544508 | Piroxicam (200 mg) | H |  | G (01/99) | [36322-90-4] | \$156 |
| 1545205 | Plicamycin (50 mg) | H |  | G (04/00) | [18378-89-7] | \$479 |
| 1545409 | Polacrilex Resin (100 mg) | F |  |  | n/f | \$156 |
| 1545500 | Polacrilin Potassium (200 mg) | F-2 |  | F-1 (09/00) | n/f | \$156 |
| 1546106 | Poloxalene ( 500 mg ) | F0C009 |  |  | [9003-11-6] | \$156 |
| 1546300 | Polydimethylsiloxane ( 500 mg ) | H0C020 |  | $\begin{aligned} & \text { G-5 (05/04) } \\ & \text { G-4 }(06 / 01) \end{aligned}$ | [9016-00-6] | \$156 |
| 1546707 | Polyethylene, High Density (3 strips) | G |  | F-1 (04/01) | [9002-88-4] | \$156 |
| 1546809 | Polyethylene, Low Density (3 strips) | G1B166 |  | $\begin{array}{\|l\|} \hline \text { G (06/04) } \\ \text { F-2 (12/99) } \\ \hline \end{array}$ | [9002-88-4] | \$156 |
| 1546853 | Polyethylene Oxide ( 100 mg ) | F-1 |  |  | [25322-68-3] | \$156 |
| 1546900 | Polyethylene Terephthalate (PET) (3 Strips) | F |  |  | [25038-59-9] | \$156 |
| 1546922 | Polyethylene Terephthalate G (PETG) (3 Strips) | F |  |  | [25640-14-6] | \$156 |
| 1547007 | Polymyxin B Sulfate (200 mg) | K |  | J-1 (09/99) | [1405-20-5] | \$156 |
| 1547404 | Polyoxyl 50 Stearate ( 200 mg ) | F |  |  | [9004-99-3] | \$156 |
| 1547903 | Polyoxyl 40 Stearate ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  | F-1 (05/00) | [9004-99-3] | \$156 |
| 1548000 | Polythiazide ( 200 mg ) | F-1 |  |  | [346-18-9] | \$156 |
| 1550001 | Potassium Gluconate (200 mg) | H0C064 |  | G (06/04) | [299-27-4] | \$156 |
| 1551004 | Potassium Guaiacolsulfonate ( 500 mg ) | J0B292 |  | $\begin{array}{\|l} \hline \text { I-1 (07/03) } \\ \text { I (11/00) } \\ \hline \end{array}$ | [78247-49-1] | \$156 |
| 1551150 | Potassium Sucrose Octasulfate ( 300 mg ) | IOB283 |  | $\begin{array}{\|l\|} \hline \text { HOB119 (04/04) } \\ \text { G-1 (04/03) } \\ \text { G (02/01) } \\ \hline \end{array}$ | [76578-81-9] | \$156 |
| 1551300 | Potassium Trichloroammineplatinate ( 20 mg ) |  |  | $\begin{array}{\|l\|} \hline \text { H0B149 (12/04) } \\ \text { G-1 (01/03) } \\ \text { G (07/99) } \\ \hline \end{array}$ | [13820-91-2] | \$487 |
| 1551503 | Povidone ( 100 mg ) | F-1 |  | F (11/01) | [9003-39-8] | \$156 |
| 1553000 | Pralidoxime Chloride ( $200 \mathrm{mg} \mathrm{)}$ | G-2 |  | $\begin{aligned} & \text { G-1 (03/01) } \\ & \text { G (08/99) } \end{aligned}$ | [51-15-0] | \$156 |
| 1554002 | Pramoxine Hydrochloride ( 500 mg ) | 1 |  | H (11/02) | [637-58-1] | \$156 |
| 1554501 | Prazepam CIV ( 500 mg ) | G0C066 |  | F-1 (11/02) | [2955-38-6] | \$207 |
| 1554603 | Praziquantel ( 200 mg ) | G |  | $\begin{aligned} & \hline \text { F-3 }(07 / 02) \\ & \text { F-2 (09/00) } \\ & \hline \end{aligned}$ | [55268-74-1] | \$156 |
| 1554658 | Praziquantel Related Compound A (50 mg) (2-benzoyl-1,2,3,6,7,11b-hexahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one) | F-1 |  |  | n/f | \$487 |
| 1554669 | Praziquantel Related Compound B ( 50 mg ) (2-(cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one) | F-2 |  | F-1 (06/00) | n/f | \$487 |
| 1554670 | Praziquantel Related Compound C ( 50 mg ) ( 2 -(N-formylhexahydrohip-puroyl-1,2,3,4-tetrahydroisoquinolin-1-one) | F-2 |  | F-1 (06/00) | n/f | \$487 |
| 1554705 | Prazosin Hydrochloride ( 500 mg ) | H0B254 | 2 | $\begin{aligned} & \text { G-1 (02/05) } \\ & \text { G (02/01) } \\ & \hline \end{aligned}$ | [19237-84-4] | \$156 |
| 1555005 | Prednisolone (200 mg) | M |  | L-1 (04/02) | [50-24-8] | \$156 |
| 1556008 | Prednisolone Acetate ( 200 mg ) | J |  | I-1 (02/02) | [52-21-1] | \$156 |
| 1556507 | Prednisolone Hemisuccinate ( 125 mg ) | H-1 |  | H (02/99) | [2920-86-7] | \$124 |
| 1558003 | Prednisolone Tebutate ( 200 mg ) | F |  |  | [7681-14-3] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1559006 | Prednisone ( 250 mg ) | L1B251 |  | $\begin{array}{\|l} \hline \text { L (11/04) } \\ \text { K-1 (01/02) } \\ \text { K (02/00) } \\ \hline \end{array}$ | [53-03-2] | \$156 |
| 1559505 | Prednisone Tablets (Dissolution Calibrator, Disintegrating) (30 tablets) | O0C056 |  | $\begin{array}{\|l} \hline N(06 / 04) \\ M(09 / 02) \\ L(11 / 00) \\ \hline \end{array}$ | [53-03-2] | \$180 |
| 1561008 | Prilocaine Hydrochloride (200 mg) | F3B215 |  | F-2 (03/04) | [1786-81-8] | \$156 |
| 1561507 | Primaquine Phosphate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | [63-45-6] | \$156 |
| 1562000 | Primidone ( 200 mg ) | G |  | F-6 (04/99) | [125-33-7] | \$156 |
| 1563003 | Probenecid ( 200 mg ) | IOA011 |  | H-1 (03/03) | [57-66-9] | \$156 |
| 1563309 | Probucol (200 mg) | G |  | F-1 (01/02) | [23288-49-5] | \$156 |
| 1563320 | Probucol Related Compound A ( 25 mg ) (2,2',6,6'-tetra-tert-butyldiphenoquinone) | F-2 |  | F-1 (11/04) | n/f | \$487 |
| 1563331 | Probucol Related Compound B (25 mg) (4,4'-dithio-bis(2,6-di-tertbutylphenol)) | F-2 |  | F-1 (08/03) | n/f | \$487 |
| 1563342 | Probucol Related Compound C ( 25 mg ) (4-[(3,5-di-tert-butyl-2-hydro-xyphenylthio)isopropylidenethio]-2,6-di-tert-butylphenol) | F-2 |  | F-1 (05/00) | n/f | \$487 |
| 1563502 | Procainamide Hydrochloride ( 200 mg ) | H1B117 |  | H (04/03) | [614-39-1] | \$156 |
| 1564006 | Procaine Hydrochloride (200 mg) | H |  |  | [51-05-8] | \$156 |
| 1565009 | Procarbazine Hydrochloride ( 200 mg ) | F |  |  | [366-70-1] | \$156 |
| 1566001 | Prochlorperazine Maleate ( 200 mg ) | H-1 |  |  | [84-02-6] | \$156 |
| 1567004 | Procyclidine Hydrochloride ( 200 mg ) | G |  |  | [1508-76-5] | \$156 |
| 1568007 | Progesterone (200 mg) | H6C088 |  | $\begin{array}{ll} \hline \text { H-5 (11/04) } \\ \text { H-4 (07/02) } \\ \hline \end{array}$ | [57-83-0] | \$124 |
| 1568506 | L-Proline (200 mg) | F-2 |  | F-1 (01/02) | [147-85-3] | \$156 |
| 1569000 | Promazine Hydrochloride ( 200 mg ) | H0B261 |  | G (10/03) | [53-60-1] | \$156 |
| 1570009 | Promethazine Hydrochloride ( 500 mg ) | K |  | J-1 (10/00) | [58-33-3] | \$156 |
| 1570304 | Propafenone Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G1C184 |  | $\begin{aligned} & \mathrm{G}(12 / 04) \\ & \mathrm{F}-1(01 / 01) \end{aligned}$ | [34183-22-7] | \$156 |
| 1570508 | Propantheline Bromide ( $200 \mathrm{mg} \mathrm{)}$ | IOA019 |  | H (11/02) | [50-34-0] | \$156 |
| 1329505 | Propantheline Bromide Related Compound A (50 mg) (9-Hydroxypropantheline bromide) | G0B258 |  | F-1 (12/03) | n/f | \$487 |
| 1571001 | Proparacaine Hydrochloride ( 200 mg ) | G |  |  | [5875-06-9] | \$156 |
| 1573007 | Propoxycaine Hydrochloride ( 200 mg ) | F |  |  | [550-83-4] | \$156 |
| 1574000 | Propoxyphene Hydrochloride CII (1 g) | L0C285 |  | K (09/04) | [1639-60-7] | \$207 |
| 1575002 | Propoxyphene Napsylate CII (1 g) | H |  |  | [26570-10-5] | \$207 |
| 1575206 | Propoxyphene Related Compound A ( 50 mg ) (alpha-d-4-dimethylami-no-1,2-diphenyl-3-methyl-2-butanol Hydrochloride) | G-5 |  |  | n/f | \$487 |
| 1576005 | Propranolol Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | 10 C 170 | 2 | $\begin{aligned} & \hline \text { H-1 (12/04) } \\ & \text { H (09/01) } \\ & \hline \end{aligned}$ | [318-98-9] | \$156 |
| 1576504 | Propylene Carbonate (200 mg) | F |  |  | [108-32-7] | \$156 |
| 1576708 | Propylene Glycol (1 mL) | $10 \mathrm{C022}$ |  | $\begin{aligned} & \hline \mathrm{H}(03 / 04) \\ & \mathrm{G}(02 / 99) \\ & \hline \end{aligned}$ | [57-55-6] | \$156 |
| 1576720 | Propylene Glycol Diacetate ( 250 mg ) | F |  |  | [623-84-7] | \$156 |
| 1576800 | Propyl Gallate ( 200 mg ) | G-1 |  | G (01/03) | [121-79-9] | \$156 |
| 1577008 | Propylparaben ( 200 mg ) | 1 |  | H (02/00) | [94-13-3] | \$156 |
| 1578000 | Propylthiouracil (200 mg) | G |  | F-1 (01/00) | [51-52-5] | \$156 |
| 1578500 | Prostaglandin A1 (25 mg) | H0B108 |  | G (04/03) | [14152-28-4] | \$529 |
| 1580002 | Protriptyline Hydrochloride (200 mg) | F-1 |  |  | [1225-55-4] | \$156 |
| 1581005 | Pseudoephedrine Hydrochloride (125 mg) (List Chemical) | J1B203 |  | $\begin{array}{\|l\|} \hline J(01 / 04) \\ \mathrm{I}(05 / 02) \end{array}$ | [345-78-8] | \$124 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| 1581504 | Pseudoephedrine Sulfate (200 mg) (List Chemical) | G1C135 |  | $\begin{array}{\|l\|} \hline \mathrm{G}(06 / 04) \\ \mathrm{F}-2(05 / 02) \\ \hline \end{array}$ | [7460-12-0] | \$156 |
| 1584003 | Pyrantel Pamoate (1 g) | 1 |  | H-1 (04/00) | [22204-24-6] | \$156 |
| 1585006 | Pyrazinamide ( 200 mg ) | G |  | F-2 (02/00) | [98-96-4] | \$156 |
| 1586009 | Pyridostigmine Bromide ( $200 \mathrm{mg} \mathrm{)}$ | 10C324 | 2 | H (01/05) | [101-26-8] | \$156 |
| 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) | P |  | O-1 (04/00) | [58-56-0] | \$156 |
| 1588004 | Pyrilamine Maleate (200 mg) | IOB276 |  | H (12/03) | [59-33-6] | \$156 |
| 1589007 | Pyrimethamine (200 mg) | H |  | G (07/02) | [58-14-0] | \$156 |
| 1592001 | Pyrvinium Pamoate ( 500 mg ) | G |  |  | [3546-41-6] | \$156 |
| 1592205 | Quazepam CIV (200 mg) | F |  |  | [36735-22-5] | \$207 |
| 1592227 | Quazepam Related Compound A (30 mg) (7-Chloro-1-(2,2,2-trifluor-oethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one) | F |  |  | n/f | \$487 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 |  |  | [6151-25-3] | \$156 |
| 1593004 | Quinacrine Hydrochloride ( 200 mg ) | F-1 |  |  | [6151-30-0] | \$156 |
| 1593412 | Quinapril Related Compound A (50 mg) (Ethyl[3S-[2(R*),3a, 11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-phenylethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate) | FOC114 |  |  | [103733-49-9] | \$487 |
| 1593423 | Quinapril Related Compound B ( 50 mg ) ( 3 -Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahy-dro-,[3S-[2[R*(R*)],3R*]]-) | F0C116 |  |  | [85441-60-7] | \$487 |
| 1594007 | Quinethazone ( 1.5 g ) | G |  |  | [73-49-4] | \$156 |
| 1594506 | Quinic Acid ( 200 mg ) | F |  |  | [77-95-2] | \$156 |
| 1595000 | Quinidine Gluconate (200 mg) | H1A028 |  | H (04/03) | [7054-25-3] | \$156 |
| 1595509 | Quinidine Sulfate ( 500 mg ) | H-1 |  | H (12/99) | [6591-63-5] | \$156 |
| 1596807 | Quinine Hydrochloride Dihydrate (1 g) | F0C108 |  |  | [6119-47-7] | \$156 |
| 1597005 | Quinine Sulfate (200 mg) | H |  |  | [6119-70-6] | \$156 |
| 1597504 | Quininone ( 50 mg ) | H0B034 |  | G-1 (03/04) | [84-31-1] | \$487 |
| 1598008 | 3-Quinuclidinyl Benzilate ( 25 mg ) (FOR U.S. SALE ONLY) | H | 3 | G (11/01) | [6581-06-2] | \$515 |
| 1598303 | Ramipril ( 200 mg ) | F0C099 |  |  | [87333-19-5] | \$156 |
| 1598314 | Ramipril Related Compound A (20 mg) ((2S,3aS,6aS)-1-[(S)2-[[(S)1-(methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclo-penta[b]pyrrole-2-carboxylic acid) | F0C100 |  |  | [91224-69-0] | \$487 |
| 1598405 | Ranitidine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H0B268 |  | G (01/04) | [66357-59-3] | \$156 |
| 1598507 | Ranitidine Related Compound A (50 mg) (5-[[(2-aminoethyl)thio]-methyl]-N,N-dimethyl-2-furanmethanamine hemifumarate) | H1B137 |  | $\begin{array}{\|l\|} \hline \mathrm{H}(01 / 04) \\ \mathrm{G}(01 / 01) \\ \hline \end{array}$ | [91224-69-0] | \$487 |
| 1598609 | Ranitidine Related Compound B ( 50 mg ) ( $\mathrm{N}, \mathrm{N}$ '-bis[2-[[[5-[(dimethyla-mino)methyl]-2-furanyl]methyl]thio]ethyl]-2-nitro-1,1-ethenediamine) | G |  | F-4 (04/02) | [72126-78-4] | \$487 |
| 1598700 | Ranitidine Related Compound C (50 mg) ( N -[2-[[[5-[(dimethylamino)-methyl]-2-furanyl]methyl]sulfinyl]ethyl]-N-methyl-2-nitro-1,1-ethenediamine) | 11B136 |  | $\begin{aligned} & \text { I (01/04) } \\ & \text { H (05/01) } \end{aligned}$ | [73851-70-4] | \$487 |
| 1599000 | Rauwolfia Serpentina (15 g) | G |  |  | [8063-17-0] | \$156 |
| 1599500 | Powdered Red Clover Extract ( 500 mg ) | F0C188 |  |  | n/f | \$260 |
| 1600813 | Repaglinide ( 200 mg ) | F0B265 |  |  | [135062-02-1] | \$156 |
| 1600824 | Repaglinide Related Compound A (50 mg) ((S)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butylamine, N -acetyl-L-glutamate salt) | FOB267 |  |  | n/f | \$487 |
| 1600835 | Repaglinide Related Compound B ( 50 mg ) (3-Ethoxy-4-ethoxycarbo-nyl-phenylacetic acid) | F0B269 |  |  | [99469-99-5] | \$487 |
| 1600846 | Repaglinide Related Compound C (25 mg) ((S)-2-Ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl] benzoic acid) | FOB271 |  |  | [107362-12-9] | \$487 |
| 1601000 | Reserpine ( 200 mg ) | O0C106 |  | N (06/03) | [50-55-5] | \$156 |
| 1601102 | Residual Solvent Mixture - Class 1 ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C407 | 1 |  | n/f | \$156 |
| 1601146 | Residual Solvent Class 1 - Benzene (1.2 mL/ampule; 3 ampules) | F0C408 | 1 |  | n/f | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1601168 | Residual Solvent Class 1-Carbon Tetrachloride ( $1.2 \mathrm{~mL} / \mathrm{ampule}$; 3 ampules) | FOC409 | 1 |  | n/f | \$156 |
| 1601180 | Residual Solvent Class 1-1,2-Dichloroethane (1.2 mL/ampule; 3 ampules) | F0C412 | 1 |  | n/f | \$156 |
| 1601204 | Residual Solvent Class 1-1,1-Dichloroethene (1.2 mL/ampule; 3 ampules) | F0C411 | 1 |  | n/f | \$156 |
| 1601226 | Residual Solvent Class 1-1,1,1-Trichloroethane (1.2 mL/ampule; 3 ampules) | F0C410 | 1 |  | n/f | \$156 |
| 1602003 | Resorcinol ( 200 mg ) | H-1 |  | H (04/01) | [108-46-3] | \$156 |
| 1602706 | Ribavirin (200 mg) | H |  | G (08/01) | [36791-04-5] | \$289 |
| 1603006 | Riboflavin (500 mg) (Vitamin B2) | N0C021 |  | $\begin{aligned} & \text { M-1 (09/04) } \\ & M(11 / 00) \\ & \hline \end{aligned}$ | [83-88-5] | \$156 |
| 1603800 | Rifabutin ( 50 mg ) | G0B040 |  | F (11/02) | [72559-06-9] | \$156 |
| 1604009 | Rifampin ( 300 mg ) | $J$ |  | I (09/00) | [13292-46-1] | \$156 |
| 1604202 | Rifampin Quinone ( 50 mg ) | H |  | G (12/01) | [13983-13-6] | \$156 |
| 1604508 | Rimantadine Hydrochloride ( $300 \mathrm{mg} \mathrm{)}$ | F0C266 |  |  | [1501-84-4] | \$156 |
| 1604600 | Rimexolone ( 100 mg ) | F |  |  | [49697-38-3] | \$156 |
| 1604701 | Ritodrine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G-1 |  |  | [23239-51-2] | \$156 |
| 1606208 | Roxarsone ( 200 mg ) | F |  |  | [121-19-7] | \$156 |
| 1606503 | Rutin ( 100 mg ) | F |  |  | [153-18-4] | \$156 |
| 1607007 | Saccharin (200 mg) | G-3 |  | G-2 (12/01) | [81-07-2] | \$156 |
| 1608000 | Salicylamide (200 mg) | F-4 |  | F-3 (05/03) | [65-45-2] | \$156 |
| 1609002 | Salicylic Acid (125 mg) | J2B147 |  | $\begin{array}{\|l} \hline \mathrm{J}-1(10 / 03) \\ \mathrm{J}(10 / 02) \\ \mathrm{I}(07 / 99) \\ \hline \end{array}$ | [69-72-7] | \$124 |
| 1609501 | Salicylic Acid Tablets (Dissolution Calibrator, Non-disintegrating) (33 tablets) | 0 |  | N(02/02) | [69-72-7] | \$156 |
| 1609807 | Salsalate ( 125 mg ) | G |  |  | [552-94-3] | \$124 |
| 1609829 | Saquinavir Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | F0B008 |  |  | [149845-06-7] | \$156 |
| 1609831 | Saquinavir Related Compound A ( 25 mg ) ( N -tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-D-asparaginyl]a-mino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide) | F0B009 |  |  | n/f | \$487 |
| 1610001 | Scopolamine Hydrobromide ( 250 mg ) | J0B051 |  | I-1 (01/03) | [6533-68-2] | \$156 |
| 1610090 | Scopoletin (20 mg) | F0C329 |  |  | [92-61-5] | \$156 |
| 1611004 | Secobarbital CII (200 mg) | H |  |  | [76-73-3] | \$207 |
| 1611900 | Selegiline Hydrochloride (200 mg) | G |  |  | [14611-52-0] | \$156 |
| 1611955 | Selenomethionine ( 100 mg ) | F0B006 |  |  | [1464-42-2] | \$156 |
| 1612007 | Sennosides (250 mg) | H1B223 |  | H (04/04) | $\begin{array}{\|ll} {[81-27-6]} & \text { (A) } \\ {[128-57-4]} & \text { (B) } \\ \hline \end{array}$ | \$156 |
| 1612506 | L-Serine (200 mg) | G |  | F-3 (11/00) | [56-45-1] | \$156 |
| 1612540 | Sevoflurane (1 mL) | F0C219 |  |  | [28523-86-6] | \$156 |
| 1612550 | Sevoflurane Related Compound A ( 0.2 mL ) (1,1,3,3,3-Pentafluoroisopropenyl fluoromethyl ether) | F0C261 |  |  | [58109-34-5] | \$487 |
| 1612608 | Silver Sulfadiazine ( 200 mg ) | 1 |  | H (04/01) | [22199-08-2] | \$156 |
| 1612630 | Silybin ( 50 mg ) | F |  |  | [22888-70-6] | \$156 |
| 1612641 | Silydianin (20 mg) | F |  |  | [29782-68-1] | \$156 |
| 1612652 | Simethicone (50 g) |  |  | $\begin{aligned} & \mathrm{G}(01 / 05) \\ & \mathrm{F}(07 / 00) \\ & \hline \end{aligned}$ | [8050-81-5] | \$156 |
| 1612700 | Simvastatin (200 mg) | H1B093 |  | $\begin{array}{\|l\|} \hline H(07 / 03) \\ G(02 / 02) \\ \text { F-1 (05/99) } \end{array}$ | [79902-63-9] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1612801 | Sisomicin Sulfate (500 mg) | 10 C 238 |  | $\begin{aligned} & \text { H (04/04) } \\ & \text { G (10/00) } \end{aligned}$ | [53179-09-2] | \$156 |
| 1613509 | Sodium Ascorbate ( $200 \mathrm{mg} \mathrm{)}$ | G2C067 | 2 | G-1 (03/05) | [134-03-2] | \$156 |
| 1613600 | Sodium Butyrate ( 25 mg ) | F |  |  | [156-54-7] | \$156 |
| 1614002 | Sodium Fluoride ( 1 g ) | H-1 |  | H (05/01) | [7681-49-4] | \$156 |
| 1614308 | Sodium Lactate (200 mg) | H |  | G (06/00) | [867-56-1] | \$156 |
| 1614501 | Sodium Nitroprusside ( 500 mg ) | H |  | G (11/99) | [13755-38-9] | \$156 |
| 1614603 | Sodium Propionate ( 200 mg ) | F-1 |  | F (03/02) | [6700-17-0] | \$156 |
| 1614669 | Sodium Starch Glycolate ( 400 mg ) | F0C087 |  |  | [9063-38-1] | \$156 |
| 1614705 | Sodium Stearyl Fumarate ( 200 mg ) | G |  | F-2 (05/01) | [4070-80-8] | \$156 |
| 1616008 | 1,4-Sorbitan ( 200 mg ) | 10A003 |  | $\begin{aligned} & \mathrm{H}(04 / 03) \\ & \mathrm{G}(02 / 00) \\ & \hline \end{aligned}$ | [27299-12-3] | \$156 |
| 1617000 | Sorbitol ( 125 mg ) | H1B139 |  | H (01/04) | [50-70-4] | \$124 |
| 1617408 | Sotalol Hydrochloride ( 300 mg ) | F0C234 |  |  | [959-24-0] | \$182 |
| 1617419 | Sotalol Related Compound A ( 50 mg ) (N-[4-[[(1-Methylethyl)amino]acetyl]phenyl]methanesulfonamide monohydrochloride) | F0C235 |  |  | n/f | \$487 |
| 1617420 | Sotalol Related Compound B (50 mg) (N-(4-Formylphenyl)methanesulfonamide) | F0C236 |  |  | n/f | \$487 |
| 1617430 | Sotalol Related Compound C (50 mg) (N-[4-[2-[(1-Methylethyl)aminojethyl]phenyl]methanesulfonamide hydrochloride) | F0C237 |  |  | n/f | \$487 |
| 1618003 | Spectinomycin Hydrochloride (200 mg) | G0C310 | 2 | F-2 (01/05) | [22189-32-8] | \$156 |
| 1619006 | Spironolactone ( 125 mg ) | J-1 |  |  | [52-01-7] | \$124 |
| 1619505 | Squalane ( 500 mg ) | G-1 |  |  | [111-01-3] | \$156 |
| 1620005 | Stanozolol CIII (200 mg) | F-3 |  | F-2 (02/01) | [10418-03-8] | \$207 |
| 1621008 | Stearic Acid ( 500 mg ) | J |  | I (10/01) | [57-11-4] | \$156 |
| 1621507 | Stearoyl Polyoxyglycerides (100 mg) | F0C286 |  |  | n/f | \$156 |
| 1622000 | Stearyl Alcohol (125 mg) | H2B217 |  | $\begin{aligned} & \hline \text { H-1 (12/04) } \\ & \text { H (09/99) } \\ & \hline \end{aligned}$ | [112-92-5] | \$124 |
| 1623003 | Streptomycin Sulfate (200 mg) | J0B195 |  | I (04/03) | [3810-74-0] | \$156 |
| 1623502 | Succinylcholine Chloride ( 500 mg ) | H |  |  | [71-27-2] | \$156 |
| 1623604 | Succinylmonocholine Chloride ( 150 mg ) | G |  | F-1 (02/01) | n/f | \$487 |
| 1623626 | Sucralose ( 400 mg ) | G0B028 |  | F (04/03) | [56038-13-2] | \$156 |
| 1623637 | Sucrose ( 100 mg ) | H1C223 |  | $\begin{aligned} & \text { HOB002 (11/04) } \\ & \text { G-1 (03/03) } \\ & \text { G (05/99) } \end{aligned}$ | [57-50-1] | \$156 |
| 1623648 | Sufentanil Citrate ClI (25 mg) | H0B208 |  | $\begin{aligned} & \text { G (05/03) } \\ & F-1(04 / 02) \\ & F(09 / 99) \\ & \hline \end{aligned}$ | [60561-17-3] | \$207 |
| 1623670 | Sulbactam ( 250 mg ) | G |  | F-1 (05/00) | [68373-14-8] | \$156 |
| 1623681 | Sulconazole Nitrate ( 200 mg ) | F-1 |  | F (05/02) | [61318-91-0] | \$156 |
| 1623706 | Sulfabenzamide ( 200 mg ) | G |  |  | [127-71-9] | \$156 |
| 1623808 | Sulfacetamide ( 300 mg ) | G-1 |  |  | [144-80-9] | \$156 |
| 1624006 | Sulfacetamide Sodium (500 mg) | 11B318 |  | $\begin{aligned} & \hline \text { I (09/04) } \\ & H(08 / 01) \\ & \hline \end{aligned}$ | [6209-17-2] | \$156 |
| 1624505 | Sulfachlorpyridazine (200 mg) | F |  |  | [80-32-0] | \$156 |
| 1625009 | Sulfadiazine ( 200 mg ) | $J$ |  | 1 (03/04) | [68-35-9] | \$156 |
| 1626001 | Sulfadimethoxine ( 200 mg ) | F4C298 |  | $\begin{aligned} & \text { F-3 (11/04) } \\ & \text { F-2 (03/99) } \\ & \hline \end{aligned}$ | [122-11-2] | \$156 |
| 1626500 | Sulfadoxine (200 mg) | F-2 |  | F-1 (07/02) | [2447-57-6] | \$156 |
| 1628007 | Sulfamerazine ( 500 mg ) | H1C171 |  | H (12/04) | [127-79-7] | \$156 |
| 1629000 | Sulfamethazine (1 g) | G-3 |  |  | [57-68-1] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1630009 | Sulfamethizole (200 mg) | F-3 |  | F-2 (01/03) | [144-82-1] | \$156 |
| 1631001 | Sulfamethoxazole ( 200 mg ) | I-1 |  | I (04/02) | [723-46-6] | \$156 |
| 1631500 | Sulfamethoxazole N4-glucoside ( 25 mg ) | H |  | G (11/01) | n/f | \$487 |
| 1632004 | Sulfanilamide (5 g) | OOB047 |  | N (01/04) | [63-74-1] | \$156 |
| 1633007 | Sulfanilamide Melting Point Standard (500 mg) (Approximately 165 degrees) | K0B133 |  | $\begin{array}{\|l\|} \hline \mathrm{J}-1(03 / 04) \\ \mathrm{J}(09 / 99) \\ \hline \end{array}$ | [63-74-1] | \$75 |
| 1633506 | Sulfanilic Acid ( $200 \mathrm{mg} \mathrm{)}$ | G |  | F-2 (09/00) | [121-57-3] | \$487 |
| 1634000 | Sulfapyridine (200 mg) | IOB298 |  | H (07/04) | [144-83-2] | \$156 |
| 1635002 | Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees) | J |  | I (07/00) | [144-83-2] | \$92 |
| 1635206 | Sulfaquinoxaline ( 200 mg ) | FOA005 |  |  | [59-40-5] | \$156 |
| 1636005 | Sulfasalazine ( 125 mg ) | G-2 |  | G-1 (06/99) | [599-79-1] | \$124 |
| 1636504 | Sulfathiazole ( 350 mg ) | H |  | G (08/00) | [72-14-0] | \$156 |
| 1637008 | Sulfinpyrazone ( $200 \mathrm{mg} \mathrm{)}$ | H0C416 | 2 | G (03/05) | [57-96-5] | \$156 |
| 1638000 | Sulfisoxazole (200 mg) | J |  | I-1 (06/99) | [127-69-5] | \$156 |
| 1639003 | Sulfisoxazole Acetyl ( 200 mg ) | H-1 |  |  | [80-74-0] | \$156 |
| 1640002 | Sulfisoxazole Diolamine ( 500 mg ) | F |  |  | [4299-60-9] | \$156 |
| 1642008 | Sulindac ( 200 mg ) | H |  | G-1 (12/01) | [38194-50-2] | \$156 |
| 1642154 | Sumatriptan ( 50 mg ) | F0C220 |  |  | [103628-46-2] | \$208 |
| 1642201 | Sumatriptan Succinate ( 200 mg ) | F0C231 |  |  | [103628-48-4] | \$208 |
| 1642212 | Sumatriptan Succinate Related Compound A ( 15 mg ) ([3-[2-(dimethy-lamino)ethyl]-2-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-1H-in-dol-5-yl]-N-methylmethansulfonamide, succinate salt) | F0C221 |  |  | n/f | \$624 |
| 1642223 | Sumatriptan Succinate Related Compound C ( 50 mg ) ([3-[2-(dimethy-lamino)ethyl]-1-(hydroxymethyl)-1H-indol-5-yl]-N-methylmethanesulfonamide succinate salt) | F0C230 |  |  | n/f | \$624 |
| 1642507 | Suprofen (200 mg) | F |  |  | [40828-46-4] | \$156 |
| 1642700 | Tacrine Hydrochloride ( 500 mg ) | F0C119 |  |  | [1684-40-8] | \$156 |
| 1643000 | Talbutal CIII (250 mg) | F |  |  | [115-44-6] | \$207 |
| 1643306 | Tamoxifen Citrate (200 mg) | H |  | $\begin{aligned} & \text { G-2 (09/01) } \\ & \text { G-1 }(05 / 00) \\ & \hline \end{aligned}$ | [54965-24-1] | \$156 |
| 1643361 | Taurine ( 100 mg ) | F0C104 |  |  | [107-35-7] | \$156 |
| 1643408 | Temazepam CIV (200 mg) | H0C205 |  | $\begin{aligned} & \hline G(06 / 04) \\ & F(12 / 99) \\ & \hline \end{aligned}$ | [846-50-4] | \$207 |
| 1643452 | Terazosin Hydrochloride (200 mg) | F0C244 |  |  | [70024-40-7] | \$156 |
| 1643463 | Terazosin Related Compound A (50 mg) (1-(4-Amino-6,7-dimethoxy-2quinazolinyl)piperazine dihydrochloride) | F0C245 |  |  | n/f | \$487 |
| 1643474 | Terazosin Related Compound B (50 mg) (1-(4-hydroxy-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]piperazine) | F0C218 |  |  | n/f | \$487 |
| 1643485 | Terazosin Related Compound C (25 mg) (1,4-bis(4-amino-6,7-di-methoxy-2-quinazolinyl)piperazine dihydrochloride) | F0C257 |  |  | n/f | \$487 |
| 1643500 | Terbutaline Sulfate ( 125 mg ) | H |  | G (04/99) | [23031-32-5] | \$124 |
| 1643703 | Terconazole (200 mg) | G-2 |  | $\begin{aligned} & \text { G-1(04/01) } \\ & \text { G (03/99) } \end{aligned}$ | [67915-31-5] | \$156 |
| 1643805 | Terfenadine (200 mg) | H |  | G (12/99) | [50679-08-8] | \$156 |
| 1643907 | Terfenadine Related Compound A (100 mg) (1-[4-(1,1-dimethylethyl)-phenyl]-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-butanone) | G |  |  | n/f | \$487 |
| 1643929 | Terfenadine Related Compound B (50 mg) (Terfenadine-N-oxide) | F |  |  | n/f | \$487 |
| 1644003 | Terpin Hydrate ( 750 mg ) | G |  |  | [2451-01-6] | \$156 |
| 1645006 | Testolactone CIII ( 125 mg ) | F-1 |  |  | [968-93-4] | \$165 |
| 1646009 | Testosterone CIII (125 mg) | I1B253 |  | I (08/04) | [58-22-0] | \$165 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1647001 | Testosterone Cypionate CIII ( 200 mg ) | G-1 |  | G (08/01) | [58-20-8] | \$207 |
| 1648004 | Testosterone Enanthate CIII ( 200 mg ) | $J$ |  |  | [315-37-7] | \$207 |
| 1649007 | Testosterone Propionate CIII ( $200 \mathrm{mg} \mathrm{)}$ | L1C005 |  | $\begin{array}{\|l\|} \hline \text { L (08/04) } \\ \text { K-1 (11/01) } \\ \hline \end{array}$ | [57-85-2] | \$207 |
| 1650006 | Tetracaine Hydrochloride ( 200 mg ) | J |  |  | [136-47-0] | \$156 |
| 1651009 | Tetracycline Hydrochloride ( 200 mg ) | L0C216 | 2 | K (12/04) | [64-75-5] | \$156 |
| 1652001 | Tetrahydrozoline Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G1A015 |  | G (03/03) | [522-48-5] | \$156 |
| 1652500 | Thalidomide ( 200 mg ) | F0C107 |  |  | [50-35-1] | \$182 |
| 1653004 | Theophylline (200 mg) | JOB180 |  | I (01/04) | [58-55-9] | \$156 |
| 1653106 | Theophylline Extended-Release Beads (Drug Release Calibrator, Multiple Unit) (20 g) |  |  | F-1 (11/04) | [58-55-9] | \$156 |
| 1655000 | Thiabendazole (100 mg) | G0A027 |  | $\begin{aligned} & \hline \text { F-1 (04/03) } \\ & F(04 / 01) \\ & \hline \end{aligned}$ | [148-79-8] | \$156 |
| 1656002 | Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride) | 0 |  | $\begin{array}{\|l\|} \mathrm{N}(11 / 02) \\ \mathrm{M}-1(04 / 99) \\ \hline \end{array}$ | [67-03-8] | \$156 |
| 1656308 | Thiamylal CIII ( 200 mg ) | F |  |  | [77-27-0] | \$207 |
| 1657005 | Thiethylperazine Malate ( $200 \mathrm{mg} \mathrm{)}$ | G |  | F-1 (09/00) | [52239-63-1] | \$156 |
| 1658008 | Thiethylperazine Maleate ( 200 mg ) | F-1 |  |  | [1179-69-7] | \$156 |
| 1659000 | Thimerosal ( 500 mg ) | H1B205 |  | $\begin{aligned} & \text { H (09/04) } \\ & \text { G (12/99) } \\ & \hline \end{aligned}$ | [54-64-8] | \$156 |
| 1660000 | Thioguanine ( 200 mg ) | F-1 |  |  | [154-42-7] | \$156 |
| 1661002 | Thiopental CIII ( 250 mg ) | 1 |  |  | [76-75-5] | \$207 |
| 1662504 | Thioridazine ( 200 mg ) | H |  |  | [50-52-2] | \$156 |
| 1663008 | Thioridazine Hydrochloride ( 200 mg ) | H |  |  | [130-61-0] | \$156 |
| 1663700 | Thiostrepton (200 mg) | F1B022 |  | F (11/02) | [1393-48-2] | \$156 |
| 1664000 | Thiotepa ( 500 mg ) | 1 |  | H (01/99) | [52-24-4] | \$156 |
| 1665003 | Thiothixene ( 250 mg ) | G |  |  | [3313-26-6] | \$156 |
| 1666006 | (E)-Thiothixene (100 mg) | H |  | G-1 (05/00) | [3313-27-7] | \$487 |
| 1667100 | Thonzonium Bromide (200 mg) | F |  |  | [553-08-2] | \$156 |
| 1667202 | L-Threonine ( 200 mg ) | G |  | F-3 (12/00) | [72-19-5] | \$156 |
| 1667279 | Thromboplastin, Human Recombinant (set) (1 vial Thromboplastin and 1 vial Diluent) DISCONTINUED |  |  | F (10/04) | [9002-05-5] | \$156 |
| 1667290 | Tiamulin Fumarate ( $250 \mathrm{mg} \mathrm{)}$ | F0C327 |  |  | [55297-96-6] | \$156 |
| 1667337 | Tiamulin Related Compound A (50 mg) (Tosyl pleuromutilin) | F0C328 |  |  | n/f | \$494 |
| 1667304 | Ticarcillin Monosodium Monohydrate ( 200 mg ) | H |  | G-1 (03/99) | [74682-62-5] | \$156 |
| 1667359 | Tiletamine Hydrochloride ( 200 mg ) | F0C019 |  |  | [14176-50-2] | \$156 |
| 1667406 | Timolol Maleate ( 200 mg ) | G-1 |  |  | [26921-17-5] | \$156 |
| 1667520 | Tinidazole (200 mg) | F0C093 |  |  | [19387-91-8] | \$156 |
| 1667530 | Tinidazole Related Compound A (100 mg) (2-methyl-5-nitroimidazole) | F0C091 |  |  | [696-23-1] | \$487 |
| 1667439 | Tioconazole ( 200 mg ) | H |  | G (04/02) | [65899-73-2] | \$156 |
| 1667450 | Tioconazole Related Compound A (25 mg) (1-[2,4-Dichloro-beta-[(3-thenyl)-oxy]phenethyl]jimidazole Hydrochloride) | G |  |  | n/f | \$487 |
| 1667461 | Tioconazole Related Compound B (25 mg) (1-[2,4-Dichloro-beta-[(2,5-dichloro-3-thenyl)oxy]phenethyl]imidazole Hydrochloride) | G |  |  | n/f | \$487 |
| 1667472 | Tioconazole Related Compound C (25 mg) (1-[2,4-Dichloro-beta-[(5-bromo-2-chloro-3-thenyl)-oxy]-phenethyl]jimidazole Hydrochloride) | G |  |  | n/f | \$487 |
| 1667508 | Tobramycin (250 mg) | K0B248 |  | J (08/03) | [32986-56-4] | \$156 |
| 1667552 | Tocainide Hydrochloride ( 125 mg ) | F-1 |  | F (04/99) | [35891-93-1] | \$124 |
| 1667600 | Alpha Tocopherol ( 250 mg ) (Vitamin E Alcohol) | M |  | L-1 (01/00) | [10191-41-0] | \$156 |
| 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) | K |  | J (06/99) | [7695-91-2] | \$156 |

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## USP Reference Standards and Authentic Substances

| Cat. <br> No. | Description | Curr. <br> Lot. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \hline \text { CAS } \\ \text { No. } \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1667803 | Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate) | F-5 |  | F-4 (01/02) | [4345-03-3] | \$156 |
| 1668001 | Tolazamide (200 mg) | G-2 |  | G-1 (06/00) | [1156-19-0] | \$156 |
| 1669004 | Tolazoline Hydrochloride ( 300 mg ) | F |  |  | [59-97-2] | \$156 |
| 1670003 | Tolbutamide (200 mg) | 1 |  | H (06/00) | [64-77-7] | \$156 |
| 1670502 | Tolmetin Sodium ( 500 mg ) | IOB064 |  | H (09/03) | [64490-92-2] | \$156 |
| 1671006 | Tolnaftate (200 mg) | J0C405 | 2 | I (02/05) | [2398-96-1] | \$156 |
| 1672009 | Toluenesulfonamides, ortho and para (200 mg of each supplied in a set) | F-4 |  | F-3 (11/99) | $\begin{array}{\|l} \hline[88-19-7](\mathrm{o}) \\ {[70-55-3](\mathrm{p})} \\ \hline \end{array}$ | \$487 |
| 1672304 | Torsemide ( 200 mg ) | F0B090 |  |  | [56211-40-6] | \$156 |
| 1672315 | Torsemide Related Compound A (75 mg) (4-[(3-methylphenyl)amino]-3-pyridinesulfonamide) | F0B071 |  |  | n/f | \$487 |
| 1672326 | Torsemide Related Compound B (75 mg) (N-[(n-butylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide) | F0B083 |  |  | n/f | \$487 |
| 1672337 | Torsemide Related Compound C (75 mg) (N-[(ethylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide) | F0B078 |  |  | n/f | \$487 |
| 1672803 | Transplatin (25 mg) | H0B287 |  | G (03/04) | [14913-33-8] | \$487 |
| 1673500 | Trazodone Hydrochloride (200 mg) | F-2 |  |  | [25332-39-2] | \$156 |
| 1674004 | Tretinoin ( $30 \mathrm{mg} / \mathrm{ampule;} 5$ ampules) | I2B185 |  | $\begin{array}{\|l\|l} \hline I-1(01 / 04) \\ I(01 / 02) \\ H(06 / 01) \\ \hline \end{array}$ | [302-79-4] | \$156 |
| 1675007 | Triacetin (1 g) | H0C413 | 2 | $\begin{aligned} & \text { G-1 (02/05) } \\ & \text { G (06/01) } \end{aligned}$ | [102-76-1] | \$156 |
| 1676000 | Triamcinolone ( 250 mg ) | H-1 |  |  | [124-94-7] | \$156 |
| 1677002 | Triamcinolone Acetonide ( 500 mg ) | K |  | J (03/99) | [76-25-5] | \$156 |
| 1678005 | Triamcinolone Diacetate ( 200 mg ) | G |  |  | [67-78-7] | \$156 |
| 1679008 | Triamcinolone Hexacetonide ( 125 mg ) | G |  |  | [5611-51-8] | \$124 |
| 1680007 | Triamterene ( 200 mg ) | 1 |  |  | [396-01-0] | \$156 |
| 1680506 | Triazolam CIV (200 mg) | H0B041 |  | G-1 (03/03) | [28911-01-5] | \$207 |
| 1680608 | Tributyl Citrate ( 500 mg ) | G0C227 | 2 | F (01/05) | [77-94-1] | \$156 |
| 1680801 | Trichlorfon (200 mg) | F |  |  | [52-68-6] | \$156 |
| 1681000 | Trichlormethiazide ( 200 mg ) | H |  |  | [133-67-5] | \$156 |
| 1682206 | Triclosan (200 mg) | F0B135 |  |  | [3380-34-5] | \$156 |
| 1683005 | Tridihexethyl Chloride ( 200 mg ) | F-1 |  |  | [4310-35-4] | \$156 |
| 1683504 | Trientine Hydrochloride (125 mg) | F2B257 |  | $\begin{array}{\|l} \hline \text { F-1 (09/03) } \\ \text { F (08/96) } \end{array}$ | [38260-01-4] | \$124 |
| 1683606 | Triethyl Citrate ( 500 mg ) | F-1 |  | F (03/02) | [77-93-0] | \$156 |
| 1685000 | Trifluoperazine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H0A010 |  | G (03/03) | [440-17-5] | \$156 |
| 1685500 | 2-[ N -(2,2,2-Trifluoro-ethyl)amino-5]-chlorobenzophenone ( 25 mg ) | F |  |  | n/f | \$487 |
| 1686003 | Triflupromazine Hydrochloride ( 200 mg ) | F-2 |  | F-1 (03/04) | [1098-60-8] | \$156 |
| 1686309 | Trifluridine ( 200 mg ) | F |  |  | [70-00-8] | \$156 |
| 1686310 | Trifluridine Related Compound A (20 mg) (5-Carboxy-2'-deoxyuridine) | F |  |  | [14599-46-3] | \$487 |
| 1687006 | Trihexyphenidyl Hydrochloride ( 200 mg ) | $J$ |  | I (07/01) | [52-49-3] | \$156 |
| 1689001 | Trimeprazine Tarrrate (200 mg) | F-3 |  | F-2 (08/01) | [4330-99-8] | \$156 |
| 1690000 | Trimethadione (200 mg) | G |  |  | [127-48-0] | \$156 |
| 1692006 | Trimethobenzamide Hydrochloride ( 500 mg ) | H-2 |  | H-1 (06/02) | [554-92-7] | \$156 |
| 1692505 | Trimethoprim ( 300 mg ) | J0B228 |  | I (01/04) | [738-70-5] | \$156 |
| 1693009 | Trioxsalen (200 mg) | H0C278 |  | G (04/04) | [3902-71-4] | \$156 |
| 1694001 | Tripelennamine Citrate ( 200 mg ) | G |  | F (02/03) | [6138-56-3] | \$156 |
| 1695004 | Tripelennamine Hydrochloride (200 mg) | $J$ |  |  | [154-69-8] | \$156 |
| 1696007 | Triprolidine Hydrochloride ( 500 mg ) | I |  | H-1 (02/02) | [6138-79-0] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1696109 | Triprolidine Hydrochloride Z-Isomer (100 mg) | G |  | F-1 (02/02) | n/f | \$487 |
| 1696200 | Trisalicylic Acid (100 mg) | G |  | F-1 (10/99) | n/f | \$487 |
| 1697000 | Troleandomycin (250 mg) | F-1 |  |  | [2751-09-9] | \$156 |
| 1698002 | Tromethamine ( 125 mg ) | G |  | F-3 (07/99) | [77-86-1] | \$124 |
| 1699005 | Tropicamide ( 125 mg ) | G-1 |  | G (02/99) | [1508-75-4] | \$124 |
| 1700002 | Trypsin Crystallized ( 300 mg ) | H |  | G (12/99) | [9002-07-7] | \$156 |
| 1700501 | L-Tryptophan (200 mg) | G-1 |  | G (09/00) | [73-22-3] | \$156 |
| 1702008 | Tubocurarine Chloride ( 250 mg ) | K-1 |  |  | [6989-98-6] | \$156 |
| 1703805 | Tylosin (250 mg) | F0C008 |  |  | [1401-69-0] | \$156 |
| 1704003 | Tyloxapol ( 600 mg ) | H |  | G (02/00) | [25301-02-4] | \$156 |
| 1704502 | Tyropanoate Sodium ( 500 mg ) | F |  |  | [7246-21-1] | \$156 |
| 1705006 | L-Tyrosine ( 500 mg ) | $J$ |  |  | [60-18-4] | \$156 |
| 1705301 | Ubidecarenone ( $200 \mathrm{mg} \mathrm{)}$ | F0B191 |  |  | [303-98-0] | \$156 |
| 1705312 | Ubidecarenone for System Suitability ( 25 mg ) | F0B194 |  |  | [303-98-0] | \$156 |
| 1705505 | Undecylenic Acid (200 mg) | G2C018 |  | $\begin{aligned} & \text { G-1 (11/04) } \\ & \text { G (01/02) } \end{aligned}$ | [112-38-9] | \$156 |
| 1705800 | Uracil Arabinoside ( 50 mg ) | G |  | F-1 (06/99) | [3083-77-0] | \$156 |
| 1706009 | Uracil Mustard ( 500 mg ) | F |  |  | [66-75-1] | \$156 |
| 1706701 | Urea C 13 (100 mg) | F0C078 |  |  | [57-13-6] | \$182 |
| 1707806 | Ursodiol ( 125 mg ) | G |  | $\begin{array}{\|l} \hline \text { F-1 (11/01) } \\ \text { F (09/99) } \\ \hline \end{array}$ | [128-13-2] | \$124 |
| 1707908 | Valerenic Acid (25 mg) | G0B146 |  | F (01/04) | [3569-10-6] | \$696 |
| 1708503 | L-Valine (200 mg) | F-2 |  | F-1 (05/02) | [72-18-4] | \$156 |
| 1708707 | Valproic Acid ( 500 mg ) | J1B127 |  | $\begin{array}{\|l\|} \hline J(01 / 04) \\ I-1(11 / 00) \\ \hline \end{array}$ | [99-66-1] | \$156 |
| 1708729 | Valproic Acid Related Compound A ( 0.25 mL ) (diallylacetic acid) | F1B156 |  | F (01/03) | [99-67-2] | \$208 |
| 1708762 | Valsartan ( 350 mg ) | F0C147 | 1 |  | [137862-53-4] | \$156 |
| 1708773 | Valsartan Related Compound A (20 mg) ((R)-N-Valeryl-N-([2'-(1-H-tetrazole)-5-yl)-biphenyl-4-yl]-methyl)-valine) | F0C215 |  |  | n/f | \$624 |
| 1708795 | Valsartan Related Compound C (10 mg) ((S)-N-Valeryl-N-([2'-(1-H-tetrazole)-5-yl)biphenyl-4-yl]-methyl)valine benzyl ester) | F0C208 |  |  | n/f | \$624 |
| 1709007 | Vancomycin Hydrochloride (4 vials, each vial contains $100,500 \mathrm{mcg}$ of vancomycin activity) | L |  | K (08/01) | [1404-93-9] | \$156 |
| 1710006 | Vanillin (200 mg) | J0A021 | 2 | $\begin{aligned} & \hline \text { I (03/05) } \\ & H(04 / 99) \\ & \hline \end{aligned}$ | [121-33-5] | \$156 |
| 1711009 | Vanillin Melting Point Standard (1 g) (Approximately 82 degrees) | J |  | $\begin{array}{\|l\|} \hline \text { I-1 (03/03) } \\ \text { I (11/00) } \\ \hline \end{array}$ | [121-33-5] | \$92 |
| 1711155 | Vecuronium Bromide ( 60 mg ) | F0C367 |  |  | [50700-72-6] | \$156 |
| 1711166 | Vecuronium Bromide Related Compound A ( 25 mg ) (3alpha, 17beta-diacetyl-oxy-2beta, 16beta-bispiperidinyl-5alpha-androstan) | F0B178 |  |  | n/f | \$487 |
| 1711202 | Verapamil Hydrochloride ( 200 mg ) | G |  | F-4 (06/00) | [152-11-4] | \$156 |
| 1711304 | Verapamil Related Compound A (50 mg) (3,4-Dimethoxy-alpha-[3-(methylamino)propyl]-alpha-(1-methylethyl)-benzeneacetonitrile monoHydrochloride) | H |  | G (01/01) | n/f | \$487 |
| 1711406 | Verapamil Related Compound B ( 50 mg ) (alpha-[2-[[2-(3,4-dimethox-yphenyl)-ethyl]methylamino]ethyl]-3,4-dimethoxy-alpha-(1-methylethyl)benzeneacetonitrile monoHydrochloride) | G |  |  | [1794-55-4] | \$487 |
| 1711461 | Verteporfin ( 200 mg ) | F0C166 |  |  | [129497-78-5] | \$156 |
| 1711472 | Verteporfin Related Compound A (50 mg) ((+/-)18-Ethenyl-4,4a-dihy-dro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23H,25H-ben-zo[b]prophine-9,13-dipropanoic acid) | F0C167 |  |  | n/f | \$487 |
| 1711508 | Vidarabine (200 mg) | G-1 |  |  | [24356-66-9] | \$156 |

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| 1713004 | Vinblastine Sulfate ( 50 mg ) | M0B308 |  | $\begin{array}{\|l\|l} \hline \mathrm{L}(12 / 04) \\ \mathrm{K}(05 / 99) \\ \hline \end{array}$ | [143-67-9] | \$354 |
| 1714007 | Vincristine Sulfate ( $50 \mathrm{mg} /$ ampule) | O0B062 |  | $\begin{aligned} & N(01 / 03) \\ & M(04 / 99) \end{aligned}$ | [2068-78-2] | \$479 |
| 1714506 | Vinorelbine Tartrate ( 200 mg ) | F0C243 |  |  | [125317-39-7] | \$156 |
| 1714528 | Vinorelbine Related Compound A ( 25 mg ) (4-O-Deacetylvinorelbine tartrate) | FOC242 |  |  | n/f | \$487 |
| 1715000 | Viomycin Sulfate (200 mg) | F |  |  | [37883-00-4] | \$156 |
| 1716002 | Vitamin A (10 ampules containing vitamin A acetate in cottonseed/ peanut oil) | V0C258 |  | U (04/04) | [127-47-9] | \$156 |
| 1717504 | Vitamin D Assay System Suitability (1.5 g) | F |  |  | [67-97-0] | \$156 |
| 1717708 | Vitexin ( 30 mg ) | F0C142 |  |  | [3681-93-4] | \$520 |
| 1719000 | Warfarin (200 mg) | 10B305 |  | $\begin{array}{\|l\|l} \hline \mathrm{H}-2(08 / 04) \\ \mathrm{H}-1(11 / 01) \\ \hline \end{array}$ | [81-81-2] | \$156 |
| 1719102 | Warfarin Related Compound A (50 mg) (3-(o-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one) | G1B111 |  | G (01/04) | [37209-23-7] | \$156 |
| 1720000 | Xanthanoic Acid (100 mg) | G-1 |  | G (12/00) | [82-07-5] | \$487 |
| 1720203 | Xanthone (100 mg) | F-1 |  |  | [90-47-1] | \$487 |
| 1720407 | Xylazine ( 200 mg ) | F1C001 | 2 | F (02/05) | [7361-61-7] | \$156 |
| 1720429 | Xylazine Hydrochloride (200 mg) | F |  |  | [23076-35-9] | \$156 |
| 1720600 | Xylitol (1 g) | G0B037 |  | $\begin{array}{\|l\|l\|} \hline \text { F-3 }(11 / 02) \\ \text { F-2 (05/00) } \\ \hline \end{array}$ | [87-99-0] | \$156 |
| 1721002 | Xylometazoline Hydrochloride (125 mg) | IOB101 |  | H-1 (05/03) | [1218-35-5] | \$124 |
| 1722005 | Xylose (1 g) | F |  |  | [58-86-6] | \$156 |
| 1724000 | Yohimbine Hydrochloride ( 200 mg ) | F |  |  | [65-19-0] | \$156 |
| 1724306 | Zalcitabine ( 200 mg ) | F |  |  | [7481-89-2] | \$156 |
| 1724317 | Zalcitabine Related Compound A (50 mg) (2',3'-Didehydro-2',3'-dideoxycytidine) | F0B234 |  |  | [7481-88-1] | \$487 |
| 1724500 | Zidovudine ( 400 mg ) | G |  | F (09/01) | [30516-87-1] | \$156 |
| 1724521 | Zidovudine Related Compound B ( 25 mg ) ( 3 '-chloro-3'-deoxythymidine) | G0B116 |  | $\begin{array}{\|l} \hline \text { F-1 (03/03) } \\ \text { F (06/01) } \\ \hline \end{array}$ | [25526-94-7] | \$487 |
| 1724532 | Zidovudine Related Compound C (100 mg) (thymine) | F-1 |  | F (09/01) | [65-71-4] | \$487 |
| 1724656 | Zileuton ( 150 mg ) | F0C062 |  |  | [111406-87-2] | \$156 |
| 1724667 | Zileuton Related Compound A ( 50 mg ) ( N -(1-Benzo[b]thien-2-ylethyl) urea) | F0B316 |  |  | n/f | \$487 |
| 1724678 | Zileuton Related Compound B ( 50 mg ) (2-(Benzo[b]thien-2-oyl)benzo[b]thiophene) | F0B313 |  |  | n/f | \$487 |
| 1724689 | Zileuton Related Compound C (50 mg) (1-Benzo[b]thien-2-ylethanone) | F0B299 |  |  | n/f | \$487 |
| 1724805 | Zolazepam Hydrochloride ( 500 mg ) | G0C023 |  | $\begin{aligned} & \hline \text { F-1 (03/04) } \\ & \text { F (05/02) } \end{aligned}$ | [33754-49-3] | \$156 |

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## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. No. | New Description |
| :---: | :---: | :---: | :---: |
| 00200-6 | 5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid ( 50 mg ) (Limit Test) | 1184027 | Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid) |
| 02200-3 | 3-Amino-4-carboxamidopyrazole Hemisulfate ( 50 mg ) (Limit Test) | 1013024 | Allopurinol Related Compound A ( 50 mg ) (3-Amino-4-carboxamidopyrazole Hemisulfate) |
| 02250-2 | 4-Amino-6-chloro-1,3-benzenedisulfonamide ( 100 mg ) (Lim- it Test) | 1057507 | Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide) |
| 1023403 | 3-Amino-6-chloro-1-methyl-4-phenylcarbostyril (25 mg) | 1023403 | Diazepam Related Compound B ( 25 mg ) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril) |
| 02380-0 | 2-Amino-2'-chloro-5-nitrobenzophenone ( 25 mg ) (Limit Test) | 1140338 | Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5-nitrobenzophenone) |
| 02420-2 | 4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide ( 100 mg ) (Limit Test) | 1424018 | Methyclothiazide Related Compound A (100 mg) (4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide) |
| 02240-6 | 2-Amino-4-chlorophenol (50 mg) (Limit Test) | 1130527 | Chlorzoxazone Related Compound A (25 mg) ( 2-Amino-4chlorophenol) |
| 02460-0 | 3-Amino-4-(2-chloro-phenyl)-6-nitrocarbostyril (25 mg) (Limit Test) | 1140327 | Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril) |
| 02490-5 | 2-Amino-2',5-dichlorobenzophenone (25 mg) (Limit Test) | 1370338 | Lorazepam Related Compound B ( 25 mg ) (2-Amino-2',5dichlorobenzophenone) |
| 02610-6 | 3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid ( 25 mg ) (Limit Test) | 1078325 | Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid) |
| 02620-8 | alpha-Aminopropiophenone Hydrochloride ( 50 mg ) (Limit Test) | 1096804 | Cathinone Hydrochloride CI (50 mg) (alpha-Aminopropiophenone Hydrochloride) |
| 06300-0 | 5-Benzyl-3,6-dioxo-2-piperazineacetic Acid ( 250 mg ) (Limit Test) | 1043728 | Aspartame Related Compound A ( 75 mg ) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid) |
| 07350-3 | 2-(4-Biphenylyl)propionic Acid (100 mg) (Limit Test) | 1285760 | Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid) |
| 07480-1 | N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide ( 50 mg ) (Limit Test) | 1344724 | Iopamidol Related Compound A (50 mg) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide) |
| 07500-4 | 4,4'-Bis[4-(p-chlorophenyl)-4-hydroxypiperidino]-butyrophenone ( 25 mg ) (Limit Test) | 1303013 | Haloperidol Related Compound A ( 25 mg ) ( $4,4-\mathrm{Bis}[4-\mathrm{p}-$ chlorophenyl)-4-hydroxypiperidino]-butyrophenone |
| 08650-5 | Calcium Formyltetrahydrofolate ( 50 mg ) (AS) (For Qualitiative Use Only) | 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) |
| 11230-0 | p -Chlorobenzhydrylpiperazine ( 25 mg ) | 1333058 | Hydroxyzine Related Compound A ( 25 mg ) (p-Chlorobenzhydrylpiperazine) |
| 11310-9 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxaldehyde ( 25 mg ) (Limit Test) | 1370349 | Lorazepam Related Compound C (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde) |
| 11320-0 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxylic Acid ( 25 mg ) (Limit Test) | 1370350 | Lorazepam Related Compound D ( 25 mg ) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid) |
| 11330-2 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazoline Methanol ( 25 mg ) (Limit Test) | 1370360 | Lorazepam Related Compound E (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol) |
| 11400-0 | 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one ( 50 mg ) (Limit Test) | 1468400 | Nordazepam CIV ( 50 mg ) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) |
| 11500-2 | 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one $4-\mathrm{oxide}$ ( 25 mg ) (Limit Test) | 1110020 | Chlordiazepoxide Related Compound A ( 25 mg ) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide) |
| 11510-4 | 2-Chloro-4-N-furfuryl-amino-5-sulfamolybenzoic acid ( 50 mg ) (Limit Test) | 1287020 | Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid) |
| 11550-1 | 2-Chloro-3,5-dimethyl-phenol (50 mg) (Limit Test) | 1122722 | Chloroxylenol Related Compound A (50 mg) (2-Chloro-3,5-dimethyl-phenol) |
| 11650-4 | (o-Chlorophenyl)diphenyl-methanol (25 mg) (Limit Test) | 1141024 | Clotrimazole Related Compound A ( 25 mg ) ((0-Chlorophe-nyl)diphenyl-methanol ) |
| 11670-8 | 4-(4-Chlorophenyl)-2-pyrrolidinone (75 mg) (Limit Test) | 1048222 | Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone) |
| 11900-3 | 4-Chloro-5-sulfamoylanthranilic Acid (100 mg) (Limit Test) | 1287030 | Furosemide Related Compound B (100 mg) (4-Chloro-5sulfamoylanthranilic Acid) |

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| :---: | :---: | :---: | :---: |
| 1119309 | 4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid ( 100 mg ) | 1119309 | Chlorthalidone Related Compound A ( 25 mg ) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid) |
| 1153001 | Cyclizine ( 1 g ) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F (04/04) |
| 15870-8 | Cyclosporine U (25 mg) DISCONTINUED | 1158650 | Cyclosporine Resolution Mixture ( 25 mg ) (Replaces Cat. No. 15870-8 Cyclosporine U ( 25 mg )) |
| 21000-3 | alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride (125 mg) (Limit Test) | 1575206 | Propoxyphene Related Compound A ( 50 mg ) (alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride) |
| 1268820 | Etoposide Related Compound A ( 25 mg ) (4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-alpha-D-glucopyranoside) DISCONTINUED | 1268852 | Etoposide Resolution Mixture ( 30 mg ) |
| 1269006 | Evans Blue ( 200 mg ) | N/A | DISCONTINUED, Last Lot/Valid Use Date: G (04/04) |
| 1277208 | Fluoride Dentifrice: Sodium Fluoride-Calcium Pyrophosphate (high beta-phase) ( 180 g ) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F (01/04) |
| 32720-4 | 3-Hydroxy-1-methylquinuclidinium Bromide ( 250 mg ) (Limit Test) | 1135021 | Clidinium Bromide Related Compound A ( 250 mg ) (3-Hydroxy -1-methylquinuclindinium Bromide) |
| 1329505 | 9-Hydroxypropantheline Bromide ( 50 mg ) | 1329505 | Propantheline Bromide Related Compound A ( 50 mg ) (9Hydroxypropantheline bromide) |
| 1330005 | Hydroxypropyl Methylcellulose ( $250 \mathrm{mg} \mathrm{)}$ | 1330005 | Hypromellose (250 mg) (Hydroxypropyl Methylcellulose) |
| 33010-7 | Hydroxypropyl Methylcellulose Phthalate ( 100 mg ) | 1335304 | Hypromellose Phthalate ( 100 mg ) |
| 1362001 | Levo-alpha-acetylmethadol Hydrochloride CII ( 25 mg ) (AS) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F-1 (08/03) |
|  | Melting Point Standard - Acetanilide ( 500 mg ; approximately 114 degrees) | 1004001 | Acetanilide Melting Point Standard ( 500 mg ) (Approximately 114 degrees) |
|  | Melting Point Standard - Caffeine (1 g; approximately 236 degrees) | 1086006 | Caffeine Melting Point Standard (1 g) (Approximately 236 degrees) |
|  | Melting Point Standard - Phenacetin ( 500 mg ; approximately 135 degrees) | 1514008 | Phenacetin Melting Point Standard (500 mg) (Approximately 135 degrees) |
|  | Melting Point Standard - Sulfanilamide ( 1 g ; approximately 165 degrees) | 1633007 | Sulfanilamide Melting Point Standard ( 500 mg ) (Approximately 165 degrees) |
|  | Melting Point Standard - Sulfapyridine (2 g; approximately 191 degrees) | 1635002 | Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees) |
|  | Melting Point Standard - Vanillin (1 g; approximately 82 degrees) | 1711009 | Vanillin Melting Point Standard (1 g) (Approximately 82 degrees) |
| 1420006 | 3 -Methoxytyrosine ( 50 mg ) | 1420006 | Levodopa Related Compound B (50 mg) (3-Methoxytyrosine) |
| 42420-0 | 2-Methylamino-5-chlorobenzophenone (25 mg) (Limit Test) | 1185020 | Diazepam Related Compound A ( 25 mg ) (2-Methylamino-5chlorobenzophenone) |
| 42430-2 | 3-O-Methylcarbidopa ( 50 mg ) | 1095517 | Carbidopa Related Compound A ( 50 mg ) (3-O-Methylcarbidopa) |
| 1445222 | Mitoxantrone Related Compound A Hydrochloride ( 30 mg ) (8-amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]a-mino]-9,10-anthracenedione Hydrochloride) DISCONTINUED; Please order 1445211 | 1445211 | Mitoxantrone System Suitability Mixture ( 0.3 mg ) |
| 46600-7 | 5-Nitro-2-furfuraldazine (500mg) | 1466007 | Nitrofurazone Related Compound A (500mg) (5-Nitro-2furfuraldazine) |
| 46660-8 | 3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid ( 25 mg ) (Limit Test) | 1078336 | Bumetanide Related Compound B ( 25 mg ) (3-Nitro-4-phe-noxy-5-sulfamoylbenzoic Acid) |
| 1477900 | Octyl Methoxycinnamate ( 500 mg ) | 1477900 | Octinoxate ( 500 mg ) (Octyl Methoxycinnamate) |
| 49400-2 | Pancreatin (2 g) | $\begin{array}{\|l} \hline 1494057 \\ \text { and/or } \\ 1494079 \\ \hline \end{array}$ | Pancreatin Amylase and Protease (2 g) and/or Pancreatin Lipase (2 g) |
| 1527000 | Phenprocoumon (200 mg) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F-1 (02/04) |
| 53180-1 | Phenylcyclohexylglycolic Acid (100 mg) (Limit Test) | 1485114 | Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid) |

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## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. No. | New Description |
| :---: | :---: | :---: | :---: |
| 53350-1 | alpha-Phenyl-2-piperidineacetic Acid Hydrochloride ( 50 mg ) (Limit Test) | 1434022 | Methylphenidate Related Compound A ( 50 mg ) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride) |
| 54500-1 | Plastic, Negative Control | 1546707 | Polyethylene, High Density (3 strips) |
| 61500-5 | Sodium Taurocholate (20 g) | 1071304 | Bile Salts (10 g) (Sodium Taurocholate) |
| 68800-9 | 3 -(3,4,6-Trihydroxyphenyl)-alanine (50 mg) (Limit Test) | 1361010 | Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydrox-yphenyl)-alanine) |
|  | Vitamin B1 Hydrochloride | 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) |
|  | Vitamin B2 | 1603006 | Riboflavin ( 500 mg ) (Vitamin B2) |
|  | Vitamin B3 | 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) |
|  | Vitamin B5 | 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) |
|  | Vitamin B6 | 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) |
|  | Vitamin B12 | 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) |
|  | Vitamim Bc | 1286005 | Folic Acid (500 mg) (Vitamin M or Vitamin Bc) |
|  | Vitamin C | 1043003 | Ascorbic Acid (1 g) (Vitamin C) |
|  | Vitamin D2 | 1239005 | Ergocalciferol ( $150 \mathrm{mg} ; 30 \mathrm{mg} / \mathrm{ampule} ; 5$ ampules) (Vitamin D2) |
|  | Vitamin D3 | 1131009 | Cholecalciferol (30 mg/ampul; 5 ampuls) (Vitamin D3) |
|  | Vitamin E Alcohol | 1667600 | Alpha Tocopherol ( 250 mg ) (Vitamin E Alcohol) |
|  | Vitamin E Acetate | 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) |
|  | Vitamin E Acid Succinate | 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) |
|  | Vitamin K1 | 1538006 | Phytonadione ( 500 mg ) (Vitamin K1) |
|  | Vitamin K3 | 1381006 | Menadione (200 mg) (Vitamin K3) |
|  | Vitamin M | 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) |

## Dietary Supplement Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| AMINO ACIDS |  |  |  |
| 1012509 | L-Alanine (200 mg) | F-2 | \$156 |
| 1021000 | Aminocaproic Acid (200 mg) | F-4 | \$156 |
| 1042500 | L-Arginine (200 mg) | G-1 | \$156 |
| 1042601 | Arginine Hydrochloride ( 125 mg ) | G0B060 | \$124 |
| 1161509 | L-Cysteine Hydrochloride ( 200 mg ) | H | \$156 |
| 1294976 | Glutamic Acid ( 200 mg ) | F0C069 | \$156 |
| 1294808 | Glutamine ( 100 mg ) | FOB244 | \$156 |
| 1295800 | Glycine ( 200 mg ) | F-3 | \$156 |
| 1308505 | L-Histidine ( 200 mg ) | G0A018 | \$156 |
| 1349502 | L-Isoleucine ( 200 mg ) | F-2 | \$156 |
| 1357001 | L-Leucine (200 mg) | H0B237 | \$156 |
| 1359903 | Levocarnitine ( 400 mg ) | G0B197 | \$156 |
| 1359925 | Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride) | F-1 | \$208 |
| 1371501 | L-Lysine Acetate ( 200 mg ) | F1C027 | \$156 |
| 1372005 | L-Lysine Hydrochloride (200 mg) | H | \$156 |
| 1411504 | L-Methionine ( 200 mg ) | G | \$156 |
| 1530503 | L-Phenylalanine ( 200 mg ) | H | \$156 |
| 1568506 | L-Proline (200 mg) | F-2 | \$156 |
| 1612506 | L-Serine (200 mg) | G | \$156 |
| 1667202 | L-Threonine ( 200 mg ) | G | \$156 |
| 1700501 | L-Tryptophan (200 mg) | G-1 | \$156 |
| 1705006 | L-Tyrosine ( 500 mg ) | $J$ | \$156 |
| 1708503 | L-Valine ( 200 mg ) | F-2 | \$156 |
| BOTANICALS |  |  |  |
| CAPSAICIN/CAPSICUM |  |  |  |
| 1091108 | Capsaicin (100 mg) | G-1 | \$156 |
| 1200600 | Dihydrocapsaicin (25 mg) | G0C071 | \$156 |
| CHAMOMILE |  |  |  |
| 1040708 | Apigenin-7-Glucoside ( 30 mg ) | F | \$487 |
| CHASTE TREE |  |  |  |
| 1105009 | Powdered Chaste Tree Extract (1.5 g) | F0C406 | \$520 |
| CRANBERRY LIQUID |  |  |  |
| 1134368 | Citric Acid (200 mg) | F1B092 | \$156 |
| 1181302 | Dextrose ( 500 mg ) | J-1 | \$124 |
| 1286504 | Fructose ( 125 mg ) | I-2 | \$124 |
| 1374601 | Malic Acid (200 mg) | G0B158 | \$156 |
| 1594506 | Quinic Acid ( 200 mg ) | F | \$156 |
| 1617000 | Sorbitol ( 125 mg ) | H1B139 | \$124 |
| 1623637 | Sucrose (100 mg) | H1C223 | \$156 |
| ELEUTHERO |  |  |  |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | \$520 |
| ECHINACEA |  |  |  |
| 1115545 | Chlorogenic Acid ( 50 mg ) | FOC420 | \$156 |
| 1231728 | Powdered Echinacea Purpurea Extract (1 g) | F0D018 | \$520 |
| 1231706 | Powdered Echinacea Angustifolia Extract (1 g) | F0D019 | \$520 |
| 1305507 | 2E, 4E-Hexadienoic Acid Isobutylamide ( 25 mg ) | F0C353 | \$540 |
| FEVERFEW |  |  |  |
| 1500400 | Parthenolide (25 mg) | F | \$156 |

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## Dietary Supplement Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| GARLIC |  |  |  |
| 1012145 | Agigenin (25 mg) | F | \$156 |
| 1012950 | Alliin (25 mg) | F | \$1,525 |
| 1115556 | beta-Chlorogenin ( 20 mg ) | F | \$156 |
| 1294848 | gamma-Glutamyl-S-allyl-L-cysteine ( 25 mg ) | F | \$675 |
| 1411504 | L-Methionine (200 mg) | G | \$156 |
| GARLIC FLUID EXTRACT |  |  |  |
| 1013057 | S-Allyl-L-Cysteine (25 mg) | F | \$487 |
| GINGER |  |  |  |
| 1091108 | Capsaicin (100 mg) | G-1 | \$156 |
| 1291504 | Powdered Ginger ( 500 mg ) | F | \$156 |
| GINKGO |  |  |  |
| 1115545 | Chlorogenic Acid ( 50 mg ) | FOC420 | \$156 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| AMERICAN GINSENG |  |  |  |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | F0B289 | \$520 |
| ASIAN GINSENG |  |  |  |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | FOB289 | \$520 |
| HAWTHORN LEAF WITH FLOWER |  |  |  |
| 1115545 | Chlorogenic Acid ( 50 mg ) | FOC420 | \$156 |
| 1335202 | Hyperoside ( 50 mg ) | F | \$855 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| 1717708 | Vitexin ( 30 mg ) | FOC142 | \$520 |
| KAVA |  |  |  |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 | \$260 |
| KAWAIN |  |  |  |
| 1355753 | Kawain (200 mg) | FOC160 | \$208 |
| LICORICE |  |  |  |
| 1295888 | Glycyrrhizic Acid (25 mg) | F0C006 | \$487 |
| MILK THISTLE |  |  |  |
| 1443850 | Powdered Milk Thistle Extract (250 mg) | F0B321 | \$260 |
| 1612630 | Silybin ( 50 mg ) | F | \$156 |
| 1612641 | Silydianin (20 mg) | F | \$156 |
| RED CLOVER |  |  |  |
| 1286060 | Formononetin ( 50 mg ) | F0C196 | \$520 |
| 1599500 | Powdered Red Clover Extract (500 mg) | FOC188 | \$260 |
| SAW PALMETTO |  |  |  |
| 1424233 | Methyl Caprate ( 300 mg ) | F | \$156 |
| 1424244 | Methyl Caproate ( 300 mg ) | F | \$156 |
| 1424255 | Methyl Caprylate ( 300 mg ) | F | \$156 |
| 1430305 | Methyl Laurate ( 500 mg ) | F | \$156 |
| 1430327 | Methyl Linoleate ( $5 \times 50 \mathrm{mg}$ ) | F | \$156 |
| 1430349 | Methyl Linolenate ( $5 \times 50 \mathrm{mg}$ ) | F | \$156 |
| 1431501 | Methyl Myristate ( 300 mg ) | F | \$156 |
| 1431556 | Methyl Oleate ( 500 mg ) | G0C148 | \$156 |
| 1431603 | Methyl Palmitate ( 300 mg ) | F | \$156 |

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## Dietary Supplement Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1431625 | Methyl Palmitoleate ( 300 mg ) | F | \$156 |
| 1437508 | Methyl Stearate ( 300 mg ) | F | \$156 |
| ST. JOHN S WORT |  |  |  |
| 1115545 | Chlorogenic Acid (50 mg) | F0C420 | \$156 |
| 1335202 | Hyperoside ( 50 mg ) | F | \$855 |
| 1485001 | Oxybenzone ( 150 mg ) | H0B263 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| VALERIAN |  |  |  |
| 1707908 | Valerenic Acid (25 mg) | G0B146 | \$696 |
| MISCELLANEOUS DIETARY SUPPLEMENTS |  |  |  |
| 1133570 | Chondroitin Sulfate Sodium ( 300 mg ) | F0B256 | \$156 |
| 1133638 | Chromium Picolinate ( 100 mg ) | F | \$156 |
| 1150353 | Creatinine ( 100 mg ) | F | \$156 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 | \$156 |
| 1611955 | Selenomethionine ( 100 mg ) | F0B006 | \$156 |
| VITAMINS-MINERALS |  |  |  |
| 1043003 | Ascorbic Acid (1 g) (Vitamin C) | Q0B012 | \$156 |
| 1071508 | Biotin ( 200 mg ) | H1B019 | \$156 |
| 1086356 | Calcium Ascorbate (200 mg) | F-1 | \$156 |
| 1087009 | Calcium Pantothenate ( $200 \mathrm{mg} \mathrm{)} \mathrm{(Vitamin} \mathrm{B5)}$ | N-1 | \$156 |
| 1131009 | Cholecalciferol ( $30 \mathrm{mg} / \mathrm{ampule}$; 5 ampules) (Vitamin D3) | M0B157 | \$159 |
| 1131803 | Delta-4,6-cholestadienol ( 30 mg ) | F | \$156 |
| 1152009 | Cyanocobalamin (1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) | N | \$156 |
| 1179504 | Dexpanthenol ( 500 mg ) | J0C293 | \$160 |
| 1239005 | Ergocalciferol ( $30 \mathrm{mg} / \mathrm{ampule}$; 5 ampules) (Vitamin D2) | P0B275 | \$168 |
| 1241007 | Ergosterol ( 50 mg ) | H | \$156 |
| 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) | P | \$156 |
| 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) | IOB176 | \$156 |
| 1381006 | Menadione (200 mg) (Vitamin K3) | H-3 | \$156 |
| 1461003 | Niacin (200 mg) | H2C121 | \$156 |
| 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) | M-1 | \$156 |
| 1494501 | Panthenol, Racemic ( $200 \mathrm{mg} \mathrm{)}$ | G | \$156 |
| 1494807 | Pantolactone ( 500 mg ) | F | \$487 |
| 1538006 | Phytonadione ( 500 mg ) (Vitamin K1) | N0B303 | \$156 |
| 1550001 | Potassium Gluconate ( $200 \mathrm{mg} \mathrm{)}$ | H0C064 | \$156 |
| 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) | P | \$156 |
| 1603006 | Riboflavin ( 500 mg ) (Vitamin B2) | N0C021 | \$156 |
| 1613509 | Sodium Ascorbate (200 mg) | G2C067 | \$156 |
| 1614002 | Sodium Fluoride (1 g) | H-1 | \$156 |
| 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) | 0 | \$156 |
| 1667600 | Alpha Tocopherol ( 250 mg ) (Vitamin E Alcohol) | M | \$156 |
| 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) | K | \$156 |
| 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) | F-5 | \$156 |
| 1716002 | Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil) | V0C258 | \$156 |
| 1717504 | Vitamin D Assay System Suitability (1.5 g) | F | \$156 |

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## Controlled Substances Reference Standards Available from USP

| $\begin{aligned} & \text { Cat. } \\ & \text { No. } \\ & \hline \end{aligned}$ | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1012906 | Alfentanil Hydrochloride CII (500 mg) | F0B016 | \$207 |
| 1014005 | Alphaprodine Hydrochloride CII (250 mg) | F | \$207 |
| 1015008 | Alprazolam CIV (200 mg) | H | \$207 |
| 1030001 | Amobarbital CII (200 mg) | F-2 | \$207 |
| 1036008 | Anileridine Hydrochloride CII ( $250 \mathrm{mg} \mathrm{)}$ | F | \$207 |
| 1042000 | Aprobarbital CIII (200 mg) (AS) | F-1 | \$207 |
| 1059003 | Benzphetamine Hydrochloride CIII (200 mg) (AS) | F-1 | \$207 |
| 1078700 | Buprenorphine Hydrochloride CIII ( 50 mg ) | F-1 | \$207 |
| 1079000 | Butabarbital CIII (200 mg) | H0C007 | \$207 |
| 1081002 | Butalbital CIII (200 mg) | H0C054 | \$207 |
| 1082504 | Butorphanol Tartrate CIV (500 mg) | J | \$207 |
| 1089004 | Cannabidiol Cl (25 mg) (AS) | F-2 | \$207 |
| 1090003 | Cannabinol CI (25 mg) (AS) |  | \$207 |
| 1096804 | Cathinone Hydrochloride CI (50 mg) (alpha-Aminopropiophenone Hydrochloride) | 1 | \$560 |
| 1109000 | Chlordiazepoxide CIV (200 mg) | 10B063 | \$207 |
| 1110009 | Chlordiazepoxide Hydrochloride CIV (200 mg) | G-4 | \$207 |
| 1140305 | Clonazepam CIV (200 mg) | G1B175 | \$207 |
| 1140509 | Clorazepate Dipotassium CIV (125 mg) | G0B027 | \$207 |
| 1143008 | Cocaine Hydrochloride CII (250 mg) | IOB074 | \$207 |
| 1143802 | Codeine N-Oxide Cl (50 mg) | G0A034 | \$207 |
| 1144000 | Codeine Phosphate CII (100 mg) | J0C200 | \$207 |
| 1145003 | Codeine Sulfate CII (250 mg) | H-2 | \$207 |
| 1180004 | Dextroamphetamine Sulfate CII (500 mg) | H | \$216 |
| 1183002 | Diacetylmorphine Hydrochloride (Heroin Hydrochloride) CI (25 mg) (AS) | J | \$207 |
| 1185008 | Diazepam CIV (100 mg) | 1 | \$207 |
| 1187207 | Dichloralphenazone CIV (200 mg) | F0B010 | \$207 |
| 1194009 | Diethylpropion Hydrochloride CIV (200 mg) | H | \$207 |
| 1200804 | Dihydrocodeine Bitartrate CII (200 mg) | H | \$207 |
| 1219008 | Diphenoxylate Hydrochloride CII (200 mg) | 1 | \$207 |
| 1258305 | Ethchlorvynol CIV ( 0.7 ml ) | F0B011 | \$207 |
| 1270005 | Fentanyl Citrate CII (100 mg) | K0C264 | \$207 |
| 1280009 | Fluoxymesterone CIII (200 mg) | G-2 | \$207 |
| 1285002 | Flurazepam Hydrochloride CIV (200 mg) | J0C365 | \$207 |
| 1295006 | Glutethimide CII ( 500 mg ) | F | \$207 |
| 1302305 | Halazepam CIV (200 mg) (AS) | F1C224 | \$207 |
| 1307003 | Hexobarbital CIII ( 500 mg ) | F | \$207 |
| 1315001 | Hydrocodone Bitartrate CII (250 mg) | K0C217 | \$207 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl) | F0C214 | \$513 |
| 1323000 | Hydromorphone Hydrochloride CII (50 mg) | J0C372 | \$207 |
| 1356009 | Ketamine Hydrochloride CIII ( 250 mg ) | G-2 | \$207 |
| 1359506 | Levmetamfetamine CII ( 75 mg ) | F | \$207 |
| 1364007 | Levorphanol Tartrate CII (500 mg) | H | \$207 |
| 1370305 | Lorazepam CIV (200 mg) | $10 \mathrm{CO48}$ | \$207 |
| 1371002 | Lysergic Acid Diethylamide Tartrate (LSD) Cl (10 mg) (AS) | 1 | \$207 |
| 1375309 | Mazindol CIV ( 350 mg ) | H | \$207 |
| 1383001 | Meperidine Hydrochloride CII (200 mg) | 1 | \$207 |
| 1386000 | Mephobarbital CIV (250 mg) | G | \$207 |
| 1389008 | Meprobamate CIV (200 mg) | G-1 | \$207 |
| 1398009 | Methadone Hydrochloride CII (200 mg) | IOB163 | \$207 |

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## Controlled Substances Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1399001 | Methamphetamine Hydrochloride CII (125 mg) | I | \$207 |
| 1404000 | Methaqualone $\mathbf{C l}(500 \mathrm{mg}$ ) | F-1 | \$207 |
| 1405002 | Metharbital CIII ( $200 \mathrm{mg} \mathrm{)}$ | F-2 | \$207 |
| 1413000 | Methohexital CIV ( 500 mg ) | F-2 | \$207 |
| 1425000 | 4-Methyl-2,5-dimethoxyamphetamine Hydrochloride (STP) CI (25 mg) (AS) | F | \$207 |
| 1429000 | Methylenedioxy-3,4-amphetamine Hydrochloride (MDA) CI (25 mg) (AS) | F-1 | \$207 |
| 1433008 | Methylphenidate Hydrochloride CII (125 mg) | 1 | \$165 |
| 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution CII ( 0.5 mL ) | F0C368 | \$560 |
| 1434000 | Methylphenidate Hydrochloride Erythro Isomer CII ( 25 mg ) | J0B294 | \$560 |
| 1438001 | Methyltestosterone CIII ( 200 mg ) | J | \$207 |
| 1447002 | Morphine Monohydrate CII (50 mg) (AS) | G | \$207 |
| 1448005 | Morphine Sulfate CII ( 500 mg ) | LOB056 | \$332 |
| 1452002 | Nalorphine Hydrochloride CIII (250 mg) | 1 | \$207 |
| 1453526 | Naltrexone Related Compound A CII (30 mg) ( N -(3-butenyl)-noroxymorphone hydrochloride) | F | \$207 |
| 1454008 | Nandrolone CIII ( 50 mg ) | F-3 | \$560 |
| 1455000 | Nandrolone Decanoate CIII ( $250 \mathrm{mg} \mathrm{)}$ | 1 | \$207 |
| 1456003 | Nandrolone Phenpropionate CIII (250 mg) | H | \$207 |
| 1468400 | Nordazepam CIV (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) | H1B035 | \$560 |
| 1473002 | Noroxymorphone Hydrochloride CII (50 mg) | H1C177 | \$560 |
| 1482003 | Oxandrolone CIII ( 50 mg ) | G0B220 | \$207 |
| 1483006 | Oxazepam CIV (200 mg) | G-1 | \$207 |
| 1485191 | Oxycodone CII (200 mg) | IOB046 | \$207 |
| 1487007 | Oxymetholone CIII (200 mg) | G1B247 | \$207 |
| 1488000 | Oxymorphone CII ( 500 mg ) | H0B214 | \$207 |
| 1505007 | Pentazocine CIV ( 500 mg ) | 10 C 418 | \$207 |
| 1507002 | Pentobarbital CII ( $200 \mathrm{mg} \mathrm{)}$ | H3C144 | \$207 |
| 1516003 | Phencyclidine Hydrochloride CII (25 mg) (AS) | G1B025 | \$207 |
| 1516502 | Phendimetrazine Tartrate CIII ( 350 mg ) | G | \$207 |
| 1523009 | Phenmetrazine Hydrochloride CII (200 mg) | F-2 | \$207 |
| 1524001 | Phenobarbital CIV (200 mg) | J | \$207 |
| 1528501 | Phentermine Hydrochloride CIV (200 mg) | H0B309 | \$207 |
| 1554501 | Prazepam CIV (500 mg) | G0C066 | \$207 |
| 1574000 | Propoxyphene Hydrochloride CII (1 g) | L0C285 | \$207 |
| 1575002 | Propoxyphene Napsylate CII (1 g) | H | \$207 |
| 1592205 | Quazepam CIV (200 mg) | F | \$207 |
| 1611004 | Secobarbital CII ( 200 mg ) | H | \$207 |
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## The Journal of Standards Development and Official Compendia Revision

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[^157]
## STANDARDS DEVELOPMENT

This section presents an overview of the public review and comment process, conducted through Pharmacopeial Forum $(P F)$, for the development of official pharmaceutical standards.

USP publishes Pharmacopeial Forum ( $P F$ ) bimonthly as the working vehicle of the USP Council of Experts. PF provides interested parties an opportunity to review and comment as the Council of Experts develops or revises standards for the United States Pharmacopeia and the National Formulary (USP-NF).
$P F$ includes the following:

1. Potential revisions-entirely new standards, revision ideas, and drafts not yet targeted for official adoption (Pharmacopeial Previews)
2. Proposed revisions-new or revised standards targeted for official adoption (In-Process Revision)
3. Adopted revisions-new or revised standards that become official and binding before the publication of the next $U S P-$ NF or Supplement (Interim Revision Announcement)

USP welcomes comments and data on potential, proposed, or official standards.* Comments, along with USP's responses, will be published either in PF Briefings, the Commentary section of $P F$, the Commentary section of Supplements to USP-NF, or the Commentary section of $U S P-N F$.

[^158]The chart below shows the public review and comment process and its relationship to standards development.

# Public Review and Comment Process for Standards Development 



Questions on the process should be addressed to John W. Gasper, M.A., J.D., Director, Office of the Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: jg@usp.org).

## HOW TO USE PF

This section provides descriptions of the various parts of $P F$. It also includes Committee Designations and the Staff Directory.

The contents of the different sections of $P F$ are briefly described below. Readers will get an idea of how each section is relevant to their job functions. They may contact USP scientific staff liaisons or staff members of the Executive Secretariat (listed in the Staff Directory) if they have any questions. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a Request for Revision is available on the USP website (www.usp.org/standards/revisionguideline/).

# Proposed and Adopted Revisions 

| Section | Content | How Readers Can Respond |
| :---: | :---: | :---: |
| Pharmacopeial <br> Previews <br> Early ideas for revisions | -Briefing: Scientific rationale for potential inclusion or change. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -Potential revisions not yet targeted for official adoption that require a longer public review and comment process because of issues such as: <br> - the controversial nature of an item; <br> - the application of new technologies that require further study; and <br> - articles produced by multiple sources. | Review drafts and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview. |
| In-Process Revision Revisions targeted for adoption | -Briefing: Scientific rationale for proposed changes. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -New and revised standards that have been approved for publication by the appropriate USP Committee when it is considering whether to advance standards to official status (see Standards Development). New or revised text is marked with symbols ( ${ }^{\square}$ or ) to specify the tentative earliest date on which the revision would be officially adopted. | Review material and send comments promptly to USP staff liaison (see the Staff Directory). Guidelines on how to comment are found at the end of the Policies and Announcements section. |
| Harmonization <br> Items the Pharmacopeial Discussion Group (PDG) is trying to harmonize internationally | - Briefing: Scientific rationale for the potential inclusion or change or for the proposed change. The designated stage of harmonization. The stage determines whether an item appears under Pharmacopeial Previews or under In-Process Revision, both separate sections of Harmonization. <br> -For In-Process Revision, new or revised text is marked with symbols (■) to specify the tentative, earliest date on which the revision would be officially adopted. | Review material and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview or In-Process Revision. |
| Interim Revision <br> Announcement <br> Adopted standards | Standards that have been adopted and will become officially binding on the specified date. Effective date is specified in the section's introductory page or within parentheses following a particular item. New or revised text is set off by the symbols ${ }^{\circ}$. | Review to see if affected by any of the changes. Note effective date when standards become official and ensure compliance. |

## Other Sections

## Committee Designations

Names of the committees (composed of volunteer scientific experts) that USP staff work with on the development of standards.

## Staff Directory

Names of all USP scientific staff liaisons with contact information.

## Policies and Announcements

- General scientific and policy issues affecting $U S P-N F$ standards and processes
- Update on standards-related issues being considered by USP
- Summaries of meetings of the Council of Experts
- Guidelines on how to comment
- Publication and comment schedules


## Stimuli to the Revision Process

- Articles on standards development issues authored by the USP Council of Experts, USP staff, or other interested parties
- Discussions of issues on which USP desires public input prior to further development


## Nomenclature

- Latest adopted United States Adopted Names (USAN) and International Nonproprietary Names (INN) for drugs
- Revisions to existing names as a supplement to the USP Dictionary of USAN and International Drug Names
- Suggested, proposed, and recommended USAN and INN
- Information on how nonproprietary drug names are devised
- Articles relevant to compendial nomenclature issues


## Index

Cumulative directory for the content of all issues of $P F$ beginning with $P F$ 30(1).

## Reference Standards Catalog

List of official USP Reference Standards specified in $U S P-N F$, along with availability and ordering information.

## Chromatographic Reagents Used in USP-NF and Pharmacopeial Forum

Update of chromatographic reagents based on the proposals published in this issue of $P F$.

## EXPERT COMMITTEE DESIGNATIONS*

The names of the Committees and their abbreviations are as follows:

| AER | Aerosols |
| :---: | :---: |
| AMB | Analytical Microbiology |
| BBP | Blood and Blood Products |
| BNA | Bioavailability and Nutrient Absorption |
| BNT | Biotechnology and Natural Therapeutics and Diagnostics |
| BPC | Biopharmaceutics |
| BST | Biostatistics |
| CRX | Compounding Pharmacy |
| DSB | Dietary Supplements-Botanicals |
| DSI | Dietary Supplements-Information |
| DSN | Dietary Supplements-Non-Botanicals |
| EMC | Excipient Monograph Content |
| ETM | Excipients-Test Methods |
| GCT | Gene Therapy, Cell Therapy, and Tissue Engineering |
| GTB | General Toxicity and Biocompatibility |
| NL | Nomenclature and Labeling |
| PA1 | Pharmaceutical Analysis 1 |
| PA2 | Pharmaceutical Analysis 2 |
| PA3 | Pharmaceutical Analysis 3 |
| PA4 | Pharmaceutical Analysis 4 |
| PA5 | Pharmaceutical Analysis 5 |
| PA6 | Pharmaceutical Analysis 6 |
| PA7 | Pharmaceutical Analysis 7-Antibiotics |
| PDF | Pharmaceutical Dosage Forms |
| PPC | Parenteral Products-Compounding and Preparation |
| PPI | Parenteral Products-Industrial |
| PSD | Packaging, Storage, and Distribution |
| PW | Pharmaceutical Waters |
| RMI | Radiopharmaceuticals and Medical Imaging |
| SMU | Safe Medication Use |
| VET | Veterinary Drugs |
| VVI | Vaccines, Virology, and Immunology |

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## STAFF DIRECTORY

This is an updated directory that reflects assignment changes based on the reorganization of USP. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Committee is not identified. The Fax number is (301) 816-8373.

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| William E. Brown, Scientist | web@usp.org | $(301) 816-8278$ | USP Correspondence |

## STAFF DIRECTORY (continued)

\(\left.\left.$$
\begin{array}{llll}\hline \text { STAFF } & \text { E-MAIL } & \text { PHONE } & \text { ASSIGNMENT } \\
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\text { Scientist and Latin American } \\
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\text { cals (DSB); Dietary } \\
\text { Supplements-Bioavail- }\end{array}
$$ <br>

ability and Nutrient\end{array}\right] $$
\begin{array}{c}\text { Absorption (BNA) }\end{array}
$$\right]\)| Pharmaceutical Analysis 4 |
| :---: |
| (PA4) |

## STAFF DIRECTORY (continued)

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| Eric B. Sheinin, Vice President, <br> Information and Standards <br> Development | es@usp.org | $(301) 816-8103$ |  |
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| William W. Wright, Scientific <br> Fellow | www@usp.org | $(301) 816-8335$ | Pharmaceutical Analysis 7- <br> Antibiotics (PA7a) |
| Kahkashan Zaidi, <br> Scientist | kxz@usp.org | (301) 816-8269 | Aerosols (AER) |

## POLICIES AND ANNOUNCEMENTS

In this section, readers may find statements about general scientific and policy issues that may have an impact on $U S P-N F$ standards and processes, announcements about issues being considered by USP, and summaries of Council of Experts meetings. This section also includes publication and comment schedules.

USP TO HOLD FIRST ANNUAL SCIENTIFIC MEETING. MEETING FOCUSES ON PRODUCT AND PROCESS STANDARDS. The United States Pharmacopeia (USP) is pleased to announce that it will hold its first USP Annual Scientific Meeting at the Sheraton Woodbridge Place in Iselin, N.J. from Sept. 27 to 29, 2004. The new USP Annual Scientific Meeting, which replaces the organization's open conference format, will allow stakeholders the opportunity to learn about and discuss science topics that are the foundation of USP's standards-setting activities.
"We are creating one annual meeting to allow USP to address multiple topics and to allow more people to participate in USP's standards-setting activities," said Roger L. Williams, M.D., USP executive vice president and chief executive officer. "This one-stop approach allows stakeholders the opportunity to meet with USP at one time and in one convenient location."

Preliminary USP Annual Scientific Meeting topics to be presented are the following:

- Biologics and Biotechnology Products
- Chromatography
- Dissolution
- Excipients and Pharmaceutical Waters
- Making the $U S P-N F$ Work for You
- Microbiology
- Process Analytical Technology
- Specifications

In addition, USP will offer its Pharmacopeial Education courses on Analytical Method Validation, Basic Statistics and their Practical Applications to USP, Dissolution, Microbiology, and USP 100 and 101. These courses and the USP Annual Scientific Meeting session tracks will be approved for continuing pharmaceutical education units (CEUs). Attendees of the USP Annual Scientific Meeting also can learn about other USP initiatives and how to become involved in USP's processes through the various USP volunteer bodies.

The USP Annual Scientific Meeting is designed for $U S P-$ $N F$ and USP Reference Standards customers and other USP stakeholders including pharmaceutical scientists focusing on chemistry, microbiology, biologics and biotechnology, Process Analytical Technology, excipients, dissolution, and chromatography.

For further information about the USP Annual Scientific Meeting, please visit www.usp.org/conferences, or call 301-816-8226.

USAN COUNCIL SECRETARIAT REVISES USAN FEE-FOR-SERVICE CHARGES. A revised schedule of fee-for-service charges has been placed in effect as of January 1, 2004. The increased fees appear on the USAN submission forms that are provided under Appendix XI of the 2004 edition of the USP Dictionary of USAN and International Drug Names. This announcement will be important to inform users of the USP Dictionary who are not yet using the revised 2004 edition of the changes.

For further information please contact:
United States Adopted Names (USAN) Program
American Medical Association
515 North State Street
Chicago, IL 60610
Phone: 312-464-4046
Fax: 312-464-4028
Web site: http://www.ama-assn.org/go/usan

## USP GUIDELINE FOR SUBMITTING REQUESTS

 FOR REVISION TO THE USP-NF. We are pleased to announce the availability of the USP Guideline for Submitting Requests for Revision to the USP-NF. This document was developed in conjunction with the USP Council of Experts and its Expert Committees, USP Staff, and the Drug Substance, Complex Actives, and Excipients Project Teams of the Prescription/Nonprescription Stakeholders Forum. This document includes information to aid submission of new monographs and revisions to existing monographs for Non-Complex Active Substances and Products, Biological and Biotech Substances and Products, Excipients, and Vaccines. It incorporates many of the concepts and suggestions included in the ICH Q3A, Q3B, Q3C, Q6A, and Q6B guidelines. These include the definition of a specification and incorporate much of the terminology of Q3A for the control of impurities. The guideline clearly defines the information needed for the USP's Council of Experts and its Expert Committees to evaluate a request for revision. The document is approximately 75 pages in length with about 25 pages of addenda and is available in PDF format from the USP website at www.usp.org. Hard copies will be provided upon request.PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education series has been developed to enhance the knowledge, skills, and expertise of pharmaceutical industry personnel.

The following list indicates tentatively scheduled course dates. For further information, contact Laura A. McCurry, Manager, Pharmacopeial Education, lam@usp.org, 301-816-8285; Diana Lenahan, Program Associate, dpl@usp.
org, 301-816-8530; or visit the website at www.usp.org/ education to register. Call 301-816-8530 to get information on customized courses offered at USP or at your site.

Calendar of Pharmacopeial Education Courses, 2004

| Date | Name of course | Location |
| :--- | :--- | :--- |
| July 19 and 20 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| August 10 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| August 11 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ <br> and the Standards Development Process | USP Headquarters, Rockville, MD |
| August 12 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| October 14 | Fundamentals of Microbiological Testing | USP Headquarters, Rockville, MD |
| October 18 and 19 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| November 11 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| November 11 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| November 12 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| November 12 | Fundamentals of Dissolution (Lecture) | USP Headquarters, Rockville, MD |
| December 2 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| December 8 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| December 9 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |

VISIT THE USP WEB SITE AT <http://www.usp.org $\rangle$. Various resources related to Pharmacopeial standards are presented, including highlights from $P F$.

## USP-NF AVAILABLE IN THREE ELECTRONIC

FORMATS. The trusted reference for official pharmaceutical standards is available in three convenient electronic formats-CD, intranet, and online. The CD is ideal for single users who prefer to have $U S P-N F$ on their hard drives. The intranet format allows Web browser-based access to multiple users within a company, through their own intranet server. The online format can be accessed by individual registered users through the World Wide Web. All three electronic formats provide fast and easy access to official $U S P-N F$ content. More information can be obtained by visiting www.usp.org/products or by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

## CHROMATOGRAPHIC REAGENTS NOW AVAILABLE.

 Chromatographic Reagents lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic test methods that has been published in Pharmacopeial Forum (PF) since1980. Chromatographic Reagents also helps to track which column reagents were used to validate methods that have become official and are included in $U S P-N F$. The branded column reagents list is updated bimonthly through Pharmacopeial Forum. Chromatographic Reagents can be ordered by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

INTERNATIONAL CORRESPONDENCE. Individuals who wish to correspond with the European and Japanese Pharmacopoeias concerning monographs in the Official Inquiry and Consensus stages of international harmonization should address their comments to the coordinating pharmacopeia for a given article. The addresses for the European and Japanese Pharmacopoeias are as follows:

Technical Secretariat of the
European Pharmacopoeia Commission
B.P. 907

F 67029 Strasbourg Cedex 1
France

## NAKASHIMA Nobumasa

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HOW TO SUBMIT COMMENTS. The USP welcomes and encourages interested parties to submit comments and data regarding potential, proposed, or adopted (official) standards. Submissions concerning a particular item that
has appeared in a $P F$ should be submitted to the appropriate USP scientific staff liaison identified at the end of the Briefing accompanying each item. To submit comments and data to a liaison, use the e-mail address and telephone numbers listed in the Staff Directory included in every PF.

Please note that $U S P-N F$ is being published in an annual edition with one main book and two Supplements a year. In addition, the following schedule will repeat every year so that users will know what to expect and become familiar with the deadlines.

The publication and comment schedule for USP 27-NF 22 is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2003 | November 2003 | January 2004 |
| Supplement One | October 15, 2003 | February 2004 | April 2004 |
| Supplement Two | February 17, 2004 | June 2004 | August 2004 |

The publication and comment schedule for USP $28-N F 23$ is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2004 | November 2004 | January 2005 |
| Supplement One | October 15, 2004 | February 2005 | April 2005 |
| Supplement Two | February 17, 2005 | June 2005 | August 2005 |

In the future, USP anticipates including the comment submission deadline in each briefing of every revision proposal when it is published for public review and comment.

For general inquiries or in cases where a particular liaison is not identified, use the general USP telephone number 301-881-0666 or FAX number 301-816-8373.

All official revisions are published in Supplements to $U S P-N F$ (twice yearly). Between Supplements, official revisions are published in $P F$ in the Interim Revision Announcement; these revisions are also incorporated in the upcoming Supplement. The electronic version of $U S P-N F$ is updated as each Supplement becomes available and, therefore, contains all official text up to and including the contents of the latest Supplement.

Publication Schedules

| Publication | Publication Date | Official Date |
| :---: | :---: | :---: |
| $1{ }^{\text {st }}$ Supplement | Feb. 2004 | Apr. 1, 2004 |
| PF 30(2) [Mar.-Apr. 2004] | Mar. 2004 | Not Applicable |
| $22^{\text {nd }}$ IRA [published in PF 30(2)] | Mar. 2004 | Apr. 1, 2004 |
| PF 30(3) [May-June 2004] | May 2004 | Not Applicable |
| $3{ }^{\text {rd }}$ IRA [published in PF 30(3)] | May 2004 | June 1, 2004 |
| $2^{\text {nd }}$ Supplement | June 2004* | Aug. 1, 2004* |
| PF 30(4) [July-Aug. 2004] | July 2004 | Not Applicable |
| $4^{\text {th }}$ IRA [published in $P F$ 30(4)] | July 2004 | Aug. 1, 2004 |
| PF 30(5) [Sept.-Oct. 2004] | Sept. 2004* | Not Applicable |
| $5^{\text {th }}$ IRA [published in $P F 30(5)$ ] | Sept. 2004* | Oct. 1, 2004* |
| PF 30(6) [Nov.-Dec. 2004] | Nov. 2004 ${ }^{*}$ | Not Applicable |
| $6^{\text {th }}$ IRA [published in $P F 30(6)$ ] | Nov. 2004 ${ }^{*}$ | Dec. 1, 2004* |

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## INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

- The list of new USP Reference Standards that have become available
- The list of assays or tests that are adopted but held in abeyance pending availability of required USP Reference Standards
- New adopted (official) revisions to the $U S P-N F$ that become effective before the effective date of the next Supplement or that were not ready for adoption by the closing date for the upcoming Supplement. (The effective date for these revisions is stated on the next page.)

Readers should review this section to determine if they are affected by any of the changes.
Symbols-Interim revisions are shown with new text (if any) enclosed in circles, ${ }^{\bullet}$ new text $\boldsymbol{m}_{\bullet}$. Text enclosed in squares, $\boldsymbol{\square}_{\text {new }}$ text $_{\boldsymbol{\bullet}}$, has already been adopted in a Supplement. Where the symbols appear together with no enclosed text, such as ${ }^{\bullet}$ • or $\boldsymbol{m}^{\boldsymbol{\bullet}} \boldsymbol{\square}$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the $I R A$ or Supplement in which the revision first appeared. For example, $\bullet 2$ indicates that the revision was officially adopted in the Second Interim Revision Announcement, and $\boldsymbol{m}_{2 \mathrm{~S}(\text { USP27) }}$ indicates that the revision was officially adopted in the Second Supplement to USP 27.

Errata-At the end of the Interim Revision Announcement section is a list of errata and corrections to USP 27-NF 22. The page number indicates where the item is found in $U S P-N F$. If necessary, this list will be updated with every issue of $P F$. This information will also be cumulative in the next available Supplement, and will appear in its corrected form in the next annual edition of $U S P-N F$. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.
FOURTH INTERIM REVISION ANNOUNCEMENT ..... 1141
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Acyclovir ..... 1143
Acyclovir Capsules ..... 1143
Acyclovir for Injection ..... 1144
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Alendronic Acid Tablets ..... 1146
Methionine C 11 Injection ..... 1146
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# FOURTH INTERIM REVISION ANNOUNCEMENT <br> to USP 27 and to NF 22 

By authority of the United States Pharmacopeial Convention, Inc. Prepared by the Council of Experts and published by the Board of Trustees

Larry L. Braden, Chair<br>USP Board of Trustees<br>Roger L. Williams, Executive Vice President and Chairman, USP Council of Experts<br>John W. Gasper, Director, Executive Secretariat

Official August 1, 2004.
Released July 1, 2004.

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## New USP Reference Standards

The following USP Reference Standards, which were indicated in past Supplements to $U S P-N F$ as being not yet available, have since become available. Thus, the official date of each USP 27 or NF 22 standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list.

USP Benazepril Hydrochloride RS (July 1, 2004)
USP Benazepril Related Compound C RS (January 1, 2005)
USP Positive Bioreaction RS (November 1, 2004)
USP Cefpiramide RS (September 1, 2004)
USP Cefpodoxime Proxetil RS (January 1, 2005)
USP Powdered Chaste Tree Extract RS (November 1, 2004)
USP Chlorhexidine RS (July 1, 2004)
USP Chlorhexidine Acetate RS (July 1, 2004)
USP Chlorhexidine Related Compounds RS (November 1, 2004)
USP Chlorogenic Acid RS (November 1, 2004)
USP Clonazepam Related Compound C RS (July 1, 2004)
USP Clonidine RS (September 1, 2004)
USP Clonidine Related Compound A RS (September 1, 2004)
USP Clonidine Related Compound B RS (November 1, 2004)
USP Cyclandelate RS (September 1, 2004)
USP Dolasetron Mesylate RS (July 1, 2004)
USP Dolasetron Mesylate Related Compound A RS (July 1, 2004)
USP Powdered Echinacea purpurea Extract RS (November 1, 2004)

USP Powdered Eleuthero Extract RS (July 1, 2004)
USP Fenbendazole Related Compound A RS (January 1, 2005)
USP Fenbendazole Related Compound B RS (January 1, 2005)
USP Fludarabine RS (September 1, 2004)
USP Fluoxetine Related Compound C RS (July 1, 2004)
USP Ganciclovir Related Compound A RS (July 1, 2004)
USP Glucosamine Hydrochloride RS (July 1, 2004)
USP $2 E, 4 E$-Hexadienoic Acid Isobutylamide RS (November 1, 2004)

USP Homopolymer Polypropylene RS (January 1, 2005)
USP Isoflurane Related Compound A RS (September 1, 2004)
USP Isoflurane Related Compound B RS (September 1, 2004)
USP Lamivudine RS (July 1, 2004)
USP Lamivudine Resolution Mixture A RS (November 1, 2004)
USP Leuprolide Acetate RS (January 1, 2005)
USP Linoleoyl Polyoxylglycerides RS (January 1, 2005)
USP Loratadine RS (September 1, 2004)
USP Medroxyprogesterone Acetate Related Compound A RS (November 1, 2004)
USP Methylphenidate Hydrochloride Erythro Isomer Solution CII RS (November 1, 2004)
USP Metoprolol Related Compound A RS (July 1, 2004)
USP Metoprolol Related Compound B RS (September 1, 2004)
USP Metoprolol Related Compound C RS (September 1, 2004)
USP Metoprolol Related Compound D RS (September 1, 2004)
USP Metoprolol Succinate RS (November 1, 2004)
USP Mitoxantrone System Suitability Mixture RS (November 1, 2004)

USP Naratriptan Hydrochloride RS (November 1, 2004)
USP Nevirapine Hemihydrate RS (January 1, 2005)
USP Nevirapine Related Compound A RS (January 1, 2005)
USP Nevirapine Related Compound B RS (January 1, 2005)
USP Oxybutynin Related Compound B RS (January 1, 2005)
USP Oxybutynin Related Compound C RS (January 1, 2005)
USP Oleoyl Polyoxylglycerides RS (January 1, 2005)
USP Phenytoin Related Compound B RS (July 1, 2004)
USP Potassium Bicarbonate RS (January 1, 2005)
USP Residual Solvent Class 1 -Benzene RS (November 1, 2004)
USP Residual Solvent Class 1-1,2 Dichloroethane RS (November 1, 2004)

USP Residual Solvent Class 1-1,2 Dichloroethene RS (November 1, 2004)
USP Residual Solvent Class 1-Carbon Tetrachloride RS (November 1, 2004)
USP Residual Solvent Class 1-1,1,1-Trichloroethane RS (November 1, 2004)
USP Residual Solvent Class 2-Chlorobenzene RS (January 1, 2005)

USP Residual Solvent Class 2-1,4-Dioxane RS (January 1, 2005)
USP Residual Solvent Class 2-Methanol RS (January 1, 2005)
USP Residual Solvent Class 2-Methylene Chloride RS (January 1, 2005)
USP Residual Solvent Class 2-Tetrahydrofuran RS (January 1, 2005)

USP Residual Solvent Class 2-Toluene RS (January 1, 2005)
USP Residual Solvent Class 2-Xylenes RS (January 1, 2005)
USP Residual Solvent Mixture-Class 1 RS (November 1, 2004)
USP Rimantidine Hydrochloride RS (July 1, 2004)
USP Scopoletin RS (July 1, 2004)
USP Sotalol Hydrochloride RS (July 1, 2004)
USP Tiamulin Fumarate RS (July 1, 2004)
USP Tiamulin Related Compound A RS (July 1, 2004)
USP Valsartan RS (November 1, 2004)
USP Vecuronium Bromide RS (September 1, 2004)

The official dates of any USP 27 or NF 22 standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards.

USP Alteplase RS
USP Amiloxate RS
USP Bupropion Hydrochloride Related Compound A RS
USP Bupropion Hydrochloride Related Compound B RS
USP Bupropion Hydrochloride Related Compound C RS
USP Bupropion Hydrochloride Related Compound D RS
USP Bupropion Hydrochloride Related Compound E RS
USP Bupropion Hydrochloride Related Compound F RS
USP Cinoxate RS
USP Decoquinate RS
USP Diethylstilbestrol Diphosphate RS
USP Enalapril Related Compound B RS
USP Enzacamene RS
USP Fludeoxyglucose RS
USP Ginseng Extract RS
USP Gonadorelin Hydrochloride RS
USP Hypericin RS
USP Lactase RS
USP Menotropins RS
USP Methyldopa-Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Ondansetron Related Compound B RS
USP Potassium Perchlorate RS
USP Pyrethrum Extract RS
USP Sargramostim RS
USP Sulisobenzone RS
USP Terbutaline Related Compound A RS
USP $\Delta^{8}$-tetrahydrocannabinol RS
USP $\Delta^{9}$-tetrahydrocannabinol RS
USP Thiacetarsamide RS
USP Tilmicosin RS
USP Tinidazole Related Compound B RS
USP Trenbolone RS
USP Trenbolone Acetate RS
USP Powdered Valerian RS
USP Vasopressin RS

## MONOGRAPHS (USP)

## Acyclovir

## Change to read:

## Assay and limit for guanine-

Mobile phase-Prepare a filtered and degassed solution of glacial acetic acid in water ( 1 in 1000). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
-System suitability solution 1-Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having known concentrations of about 0.1 mg of each per mL .

System suitability solution 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about $0.7 \mu \mathrm{~g}$ per mL . $\bullet 4$

Guanine standard preparation-Transfer about 8.75 mg of guanine, accurately weighed, to a $500-\mathrm{mL}$ volumetric flask. Dissolve in 50 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. ${ }^{\bullet}$ Transfer 2.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix to obtain a solution having a known concentration of about $0.7 \mu \mathrm{~g}$ per $\mathrm{mL} .{ }^{4}$

Standard preparation-Dissolve about 25 mg of USP Acyclovir RS, accurately weighed, in 5 mL of 0.1 N sodium hydroxide in a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution ${ }^{\bullet}$ to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix to obtain a solution having ${ }^{\bullet}$ a known concentration of about 0.1 mg of USP Acyclovir RS per mL. $\bullet 4$

Assay preparation-Dissolve about 100 mg of Acyclovir, accurately weighed, in 20 mL of 0.1 N sodium hydroxide in a 200mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.2-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph ${ }^{\bullet}$ System suitability solution 1, $\bullet_{4}$ and record the peak responses as directed for Procedure: the resolution, $R$, between acyclovir and guanine is not less than 2.0 ; the tailing factor for the analyte peak is not more than 2 ; and the relative standard deviation for replicate injections ${ }^{\bullet}$ for the acyclovir peak ${ }_{04}$ is not more than $2.0 \%$. ${ }^{\circ}$ Chromatograph System suitability solution 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$. 4

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation, ${ }^{\bullet}$ Guanine standard preparation, $\bullet_{4}$ and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in $\mu \mathrm{g}$, of guanine in the portion of Acyclovir taken by the formula:
$1000 C\left(r_{U} / r_{S}\right)$,
in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of guanine in the ${ }^{\bullet}$ Guanine standard preparation; ${ }^{4}$ and $r_{U}$ and $r_{S}$ are the peak responses due to guanine in the Assay preparation and the ${ }^{\bullet}$ Guanine standard preparation, $\bullet 4$ respectively: not more than $0.7 \%$ of gua-
nine is found. Calculate the quantity, in mg , of $\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}$ in the portion of Acyclovir taken by the formula:

$$
1000 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses due to acyclovir in the Assay preparation and the Standard preparation, respectively.

## Acyclovir Capsules

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed solution of 0.02 M acetic acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
-System suitability preparation 1-Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.1 mg of each per mL .

System suitability preparation 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about $2.0 \mu \mathrm{~g}$ per mL. $\bullet 4$

Standard preparation-Dissolve an accurately weighed quantity of USP Acyclovir RS ${ }^{\bullet}{ }^{4}$ in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.1 mg per mL . ${ }_{\bullet}^{\bullet}$
Assay preparation-Remove, as completely as possible, the contents of not fewer than 10 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 10 mg of acyclovir, to a $100-\mathrm{mL}$ volumetric flask, dissolve in 10 mL of 0.1 N sodium hydroxide, dilute with water to volume, mix, and filter.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.2-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph ${ }^{8}$ System suitability preparation $1, \bullet_{4}$ and record the peak responses ${ }^{\bullet}$ for acyclovir ${ }_{\bullet}$ as directed for Procedure: the relative retention times are about 0.6 for guanine and 1.0 for acyclovir; the resolution, $R$, between guanine and acyclovir is not less than 2.0; and the relative standard deviation for replicate injections ${ }^{\bullet}$ of acyclovir ${ }_{\bullet 4}$ is not more than $2.0 \%$. ${ }^{\bullet}$ Chromatograph System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \% . \bullet 4$
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg , of acyclovir $\left(\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}\right)$ in the portion of Capsules taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Acyclovir for Injection

## Change to read:

## Chromatographic purity-

Solution A-Prepare a filtered and degassed mixture of 0.17 M acetic acid and methanol ( $125: 8$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Solution B: methanol, filtered and degassed.
Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments to either solution as necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve suitable quantities of purine and USP Acyclovir RS in Solution $A$ to obtain a solution containing about $0.5 \mu \mathrm{~g}$ of each per mL .
${ }^{\wedge}$ Acyclovir standard solution-Dissolve an accurately weighed quantity of USP Acyclovir RS in Solution A, and dilute quantitatively, and stepwise if necessary, with Solution $A$ to obtain a solution having a known concentration of about $5 \mu \mathrm{~g}$ per mL .

Guanine solution-Dissolve about 25 mg of guanine, accurately weighed, in 50 mL of 0.1 N sodium hydroxide in a $500-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.
${ }^{\bullet}$ Standard solution $1 \bullet$-Transfer 5.0 mL of Acyclovir standard solution $\bullet 4$ to a $50-\mathrm{mL}$ volumetric flask, dilute with Solution $A$ to volume, and mix.
-Standard solution 2-Transfer 5.0 mL of Guanine solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Solution $A$ to volume, and mix. $\bullet 4$

Test solution-Constitute and combine not fewer than 10 vials of Acyclovir for Injection. Transfer an accurately measured quantity, equivalent to about 100 mg of acyclovir, to a $200-\mathrm{mL}$ volumetric flask, dilute with Solution $A$ to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a 254-nm detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-15$ | 100 | 0 | isocratic |
| $15-45$ | $100 \rightarrow 65$ | $0 \rightarrow 35$ | linear gradient |
| $45-46$ | $65 \rightarrow 100$ | $35 \rightarrow 0$ | linear gradient |
| $46-56$ | 100 | 0 | re-equilibration |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between purine and acyclovir is not less than 2.0. Chromatograph ${ }^{\bullet}$ Standard solution 1 and Standard solution 2,94 and record the peak responses as directed for Procedure: the typical ${ }^{4}$ retention times for guanine and acyclovir are about ${ }^{\bullet} 5.8$ minutes and 14 minutes, $\bullet 4$ respectively; and the relative standard deviation $\mathbf{N}^{\text {of }}$ of the acyclovir peak area and the guanine peak $\operatorname{area}_{\Delta U S P 27}$ for replicate injections is not more than $\mathbf{\Delta} 1 \%$. $\Delta$ USP2

Procedure-【Separately inject equal volumes ■1S (USP27) (about $50 \mu \mathrm{~L}$ ) of $\boldsymbol{\Delta}^{\boldsymbol{t}}$ the Standard solution and $\mathbf{\Delta U S P 2 7}$ the Test solution into the chromatograph, record the chromatograms, and measure the peak ${ }^{\boldsymbol{\Delta}} \operatorname{area}_{\mathbf{U S P 2 7}}$ responses. ${ }^{\boldsymbol{\wedge}}$ Calculate the percentage of guanine in the Acyclovir for Injection by the formula:

$$
20,000(C / W)\left(r_{g} / r_{s g}\right)
$$

in which $C$ is the concentration, in $m g$ per mL , of guanine in the Standard solution; $W$ is the total weight, in mg , of acyclovir in the Test solution based on the label claim; $r_{g}$ is the peak response for guanine, if present, in the Test solution; and $r_{s g}$ is the peak response of guanine in the Standard solution: not more than $1.0 \%$ is
 rity in the ${ }^{2}$ $\triangle U S P 27$ Acyclovir for Injection $\boldsymbol{\Delta}$ $\Delta U S P 27$ by the formula:

$$
20,000(C / W)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Acyclovir RS in the Standard solution; $W$ is the $\mathbf{}_{\text {total }}^{\mathbf{\Delta U S P} 2 Z}$ weight, ${ }^{\mathbf{\Delta}}$ in $\mathrm{mg}, \mathbf{\Delta U S P 2 7}$ of acyclovir $\mathbf{\Delta}_{\mathbf{\Delta S P 2 7}}$ in the Test solution ${ }^{\text {based on }}$ on the label claim; $\boldsymbol{\Delta U S P 2 7} r_{i}$ is the peak response for each impurity; and $r_{S}$ is the peak response of acyclovir in the Standard solution: $\mathbf{\lambda}_{\mathbf{\Delta S P} 27}$ not more than $0.15 \%$ for any peak having a relative retention time of about ${ }^{\boldsymbol{\Delta}} 0.7$ compared to the acyclovir peak ${ }_{\mathbf{\Delta} U S P 27}$ is found; not more than $0.5 \%$ of any other individual impurity is found; and the total of all other impurities is not more than $1.0 \%$.

## Change to read:

Assay-
Mobile phase-Prepare a filtered and degassed solution of 0.02 M acetic acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

- System suitability preparation 1-Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having known concentrations of about 0.1 mg of each per mL .

System suitability preparation 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having a known concentration of about $2.0 \mu \mathrm{~g}$ per mL . $\bullet 4$

Standard preparation-Dissolve accurately weighed quantities of USP Acyclovir RS $\bullet$ - in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having a known concentration of about 0.1 mg per mL . ${ }^{\bullet}$

Assay preparation-Constitute, with water, 1 vial of Acyclovir for Injection. Transfer an accurately weighed amount of this solution, equivalent to about 10 mg of acyclovir, to a $100-\mathrm{mL}$ volumetric flask, and dilute with water to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.2-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph ${ }^{6}$ System suitability preparation $1, \bullet$ and record the peak responses ${ }^{\bullet}$ for acyclovir ${ }_{\bullet}$ as directed for Procedure: the relative retention times are about 0.6 for guanine and 1.0 for acyclovir; the resolution, $R$, between guanine and acyclovir is not less than 2.0; and the relative standard deviation for replicate injections ${ }^{\bullet}$ for the acyclovir peak ${ }_{\bullet 4}$ is not more than $2.0 \%$. ${ }^{\bullet}$ Chromatograph System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than 2.0\%. 4

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of acyclovir $\left(\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}\right)$ in the portion of Acyclovir for Injection taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Acyclovir Ointment

## Change to read:

## Assay-

Mobile phase_Prepare a filtered and degassed solution of 0.02 M acetic acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve accurately weighed quantities of USP Acyclovir RS ${ }^{\bullet}$ - in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having known concentrations of about 0.1 mg per mL . ${ }^{\bullet}$

- System suitability preparation 1-Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having known concentration of about 0.1 mg of each per mL .

System suitability preparation 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having a known concentration of about $2.0 \mu \mathrm{~g}$ per $\mathrm{mL} . \bullet 4$

Assay preparation-Transfer an accurately weighed quantity of Ointment, equivalent to about 10 mg of acyclovir, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with 0.1 N sodium hydroxide to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a 254 -nm detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph ${ }^{\bullet}$ System suitability preparation 1,4 and record the peak responses as directed for Procedure: the relative retention times are about 0.6 for guanine and 1.0 for acyclovir; the resolution, $R$, between guanine and acyclovir is not less than 2.0 ; and the relative standard deviation for replicate injections ${ }^{\bullet}$ for acyclovir ${ }_{\bullet 4}$ is not more than $2.0 \%$. ${ }^{\bullet}$ Chromatograph System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$. $\bullet 4$

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg , of acyclovir $\left(\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}\right)$ in the portion of Ointment taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Acyclovir Oral Suspension

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed solution of 0.02 M acetic acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve ${ }^{\bullet}$ an accurately weighed quantity of USP Acyclovir $\mathrm{RS}_{\bullet 4}$ in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having ${ }^{\bullet}$ a known concentration of 0.1 mg per mL .

System suitability preparation 1-Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having known concentrations of about 0.1 mg of each per mL .
System suitability preparation 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with 0.1 N sodium hydroxide to obtain a solution having a known concentration of about $2.0 \mu \mathrm{~g}$ per mL .4
Assay preparation - Transfer an accurately measured quantity of well-shaken Oral Suspension, equivalent to about 200 mg of acyclovir, to a $200-\mathrm{mL}$ volumetric flask, add 100 mL of 0.1 N sodium hydroxide, shake by mechanical means for 15 minutes, and sonicate, if necessary, to dissolve the Oral Suspension completely. Dilute with 0.1 N sodium hydroxide to volume, and mix. Transfer 10.0 mL of the solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, mix, and filter.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph ${ }^{\bullet}$ System suitability preparation 1,04 and record the peak responses as directed for Procedure: the relative retention times are about 0.6 for guanine and 1.0 for acyclovir; the resolution, $R$, between guanine and acyclovir is not less than 2.0; and the relative standard deviation for replicate injections ${ }^{\bullet}$ for the acyclovir ${ }_{4}$ is not more than $2.0 \%$. ${ }^{\bullet}$ Chromatograph System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$. 4
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of acyclovir $\left(\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}\right)$ in the portion of Oral Suspension taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Acyclovir Tablets

## Change to read:

## Assay-

Mobile phase_Prepare a filtered and degassed solution of 0.02 M acetic acid. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
-System suitability preparation 1-Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.1 mg of each per mL .

System suitability preparation 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about $2.0 \mu \mathrm{~g}$ per $\mathrm{mL} . \bullet 4$

Standard preparation-Dissolve an accurately weighed ${ }^{\bullet}$ quantity $\bullet_{4}$ of USP Acyclovir RS ${ }_{\bullet 4}$ in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration $\bullet_{\bullet}$ of about 0.1 mg per mL . ${ }^{\bullet}-4$

Assay preparation-Weigh and finely powder not fewer than 10 Tablets. Transfer an accurately weighed quantity of powder, equivalent to about 10 mg of acyclovir, to a $100-\mathrm{mL}$ volumetric flask, dissolve in 10 mL of 0.1 N sodium hydroxide, dilute with water to volume, mix, and filter.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The column temperature is maintained at $40^{\circ}$. The flow rate is about 1.5 mL per minute. Chromatograph ${ }^{\bullet}$ System suitability preparation 1, $\bullet_{4}$ and record the peak responses for acyclovir ${ }_{\bullet 4}$ as directed for Procedure: the relative retention times are about 0.6 for guanine and 1.0 for acyclovir; the resolution, $R$, between guanine and acyclovir is not less than 2.0; and the relative standard deviation for replicate injections ${ }^{\circ}$ for the acyclovir peak ${ }_{\bullet 4}$ is not more than $2.0 \%$. ${ }^{\circ}$ Chromatograph System suitability preparation 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of acyclovir $\left(\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}\right)$ in the portion of Tablets taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Alendronic Acid Tablets

-(Title for this new monograph—to become official July 1, 2006)

## Methionine C 11 Injection

## Delete the following:



## Change to read:

» Methionine C 11 Injection is a sterile isotonic solution, suitable for intravenous administration of ${ }^{\bullet} \mathrm{L}\left[{ }^{11} \mathrm{C}\right]$ methionine, $\bullet 4$ in which a portion of the molecules are labeled with radioactive ${ }^{11} \mathrm{C}$. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ${ }^{11} \mathrm{C}$ expressed in MBq (or in mCi ) at the time indicated in the labeling. It may contain preservatives and stabilizers.

## Cellaburate

${ }^{\bullet}$ (Title for this new monograph—to become official January 1, 2010)

## NOTICE OF POSTPONEMENT

The following revisions to the Doxorubicin Hydrochloride monograph, which were published in the First Supplement to USP 27-NF 22 and originally meant to become official on April 1, 2004, have been postponed indefinitely. This postponement is to provide additional time to further evaluate the use of amorphous doxorubicin hydrochloride.
The Pharmaceutical Analysis 7 Expert Committee is presently reviewing comments received concerning these items. The USP intends to publish, if necessary, another proposed revision in a future issue of Pharmacopeial Forum for further public review and comment. The USP proposes going forward to official text for these revisions after the public comments have been considered.

## Doxorubicin Hydrochloride

## Change to read:

Packaging and storage-Preserve in tight containers, ${ }^{\bullet}$ and store at controlled room temperature, except where it is labeled as amorphous, in which case it should be stored in the freezer. $e_{4}$
${ }^{\bullet}$ (Postponed indefinitely) ${ }_{\bullet 4}$
Add the following:
${ }^{\bullet}$ Labeling-The amorphous form is so labeled. $\bullet 4$
${ }^{\bullet}$ (Postponed indefinitely) ${ }^{\bullet}$

## Change to read:

Crystallinity $\langle 695\rangle$ : meets the requirements, ${ }^{\bullet}$ except that where it is labeled as amorphous, most of the particles do not exhibit birefringence and extinction positions. $\bullet 4$
${ }^{\bullet}$ (Postponed indefnitely) $\bullet_{4}$

## NOTICE OF POSTPONEMENT

The following revisions to the Hydrocodone Bitartrate monograph, which were published in the First Supplement to USP 27-NF 22 and originally meant to become official on April 1, 2004, have been postponed indefinitely. The USP has postponed the official date for Ordinary impurities, Related compounds, and the Assay. This postponement is to accommodate the approved products on the market that cannot meet the requirement and is intended to provide sufficient time to evaluate different proposals via the regular revision process.

## Hydrocodone Bitartrate

## Delete the following:

${ }^{\bullet}$ Ordinary impurities $\langle 466\rangle$ -
Test solution: a mixture of methanol and water (1:1). Standard solution: a mixture of methanol and water (1:1).
Eluant: a mixture of hexanes, acetone, methanol, and ammonium hydroxide ( $60: 40: 20: 1.5$ ).

Visualization: 3, followed by overspraying with hydrogen peroxide TS. [NOTE-Cover the thin-layer chromatographic plate with a glass plate to slow fading of the spots. Exclude the origin spot, if present, from the determination of the total impurities.]
${ }^{\bullet}$ (Postponed indefinitely) ${ }^{4}$

## Add the following:

- Related compounds-[NOTE-For the test for Related compounds and in the Assay, dry both USP Hydrocodone Bitartrate RS and USP Dihydrocodeine Bitartrate RS under vacuum at $105^{\circ}$ for 2 hours. Immediately transfer the dried materials to a desiccator containing phosphorus pentoxide. Immediately weigh each dried material.]

Solution A, Solution B, Mobile phase, and Chromatographic system-Proceed as directed in the Assay.

Test solution-Use the Assay preparation
System suitability solution-Combine about 1.5 mg of USP Dihydrocodeine Bitartrate RS and 1.0 mL of the Standard preparation prepared for the Assay in a $200-\mathrm{mL}$ volumetric flask. Dilute with Solution $A$ to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—Proceed as directed in the Assay. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.89 for dihydrocodeine and 1.0 for hydrocodone; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Test solution and the System suitability solution into the chromatograph, record the chromatograms, and measure the peak responses.

Calculate the percentage of dihydrocodeine bitartrate and any unknown impurities in the portion of Hydrocodone Bitartrate taken by the formula:

$$
10,000(C / W) F\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Hydrocodone Bitartrate RS in the System suitability solution; $W$ is the quantity, in mg , of Hydrocodone Bitartrate taken to prepare the Test solution; $F$ is the relative response factor and is equal to the values given in the following table; $r_{U}$ is the individual peak response of each impurity in the test solution; and $r_{S}$ is the response of hydrocodone bitartrate in the System suitability solution: not more than $0.5 \%$ of any individual impurity is found, and not more than $2.0 \%$ of total impurities is found.

| Hydrocodone Bitartrate <br> and <br> Related Compounds | Relative <br> Retention Time | Relative <br> Response <br> Factor |
| :--- | :---: | :---: |
| dihydrocodeine bitartrate <br> hydrocodone diol <br> bitartrate | 0.89 | 0.81 |
| hydrocodone bitartrate <br> dihydrothebainone <br> bitartrate | 0.92 | 0.76 |
| hydrocodone aldol dimer <br> bitartrate | 1.00 | 1.00 |
| 7-cyclohexenyl hydroco- <br> done bitartrate | 1.03 | 0.96 |
| benzophenone <br> other impurities | 1.50 | 1.00 |
| (Postponed indefinitely) $\bullet_{\bullet 4}{ }^{\bullet 4}$ |  |  |

## Change to read:

Assay- ${ }^{\bullet}$ [NOTE-See the Note in the test for Related compounds before performing the Assay.]

Solution A-Dissolve 5.75 g of monobasic ammonium phosphate in about 900 mL of water in a $1000-\mathrm{mL}$ volumetric flask, adjust with phosphoric acid to a pH of $3.0 \pm 0.1$, dilute with methanol to volume, and mix.
Solution $B$-Prepare a filtered and degassed mixture of methanol and water $(80: 20)$.

## NOTICE OF POSTPONEMENT (continued)

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Hydrocodone Bitartrate RS in Solution $A$ to obtain a solution having a known concentration of about 1.5 mg per mL .

Assay preparation-Transfer an accurately weighed quantity of previously dried Hydrocodone Bitartrate, equivalent to about 150 mg of hydrocodone bitartrate, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Solution $A$ to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The column temperature is maintained at $60^{\circ}$. The flow rate is about 1.2 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibrium |
| $0-6$ | 100 | 0 | isocratic |
| $6-30$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| $30-31$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |

Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 1.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg , of hydrocodone bitartrate $\left(\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{3} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}\right)$ in the portion of Hydrocodone Bitartrate taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Hydrocodone Bitartrate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\bullet$
${ }^{\bullet}$ (Postponed indefinitely) ${ }_{\bullet 4}$

## Paroxetine Tablets

-(Title for this new monograph—to become official February 1, 2006)

## GENERAL CHAPTERS

General Tests and Assays
General Requirements for Tests and Assays

## 〈11 ${ }^{\text {USP REFERENCE }}$ STANDARDS

## Change to read:

USP Denatonium Benzoate RS-- This material is the anhydrous form of denatonium benzoate. $\bullet_{4}$ Dry portion at $105^{\circ}$ for 2 hours before using. Keep container tightly closed.

## Change to read:

USP Desacetyl Diltiazem Hydrochloride RS $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{~S} \cdot \mathrm{HCl}\right.$ $\diamond$ 408.95)-Do not dry. $\bullet 4$ Keep container tightly closed. Protect from light.

## Change to read:

USP Emedastine ${ }^{\boldsymbol{\bullet}}$ Difumarate ${ }_{\bullet 4}$ RS-- ${ }^{\boldsymbol{\Delta}}$ Dry portion at $105^{\circ}$ for 3 hours before using. Keep container tightly closed. $\Delta U S P 27$

## Change to read:

USP 4-Formylbenzenesulfonamide RS-- (NAME CHANGE) See USP Mafenide Related Compound A RS.七4

## Add the following:

- USP Homopolymer Polypropylene RS-Exercise care in handling and storage to avoid scratching surface of strips. Prepare samples as directed in the respective USP General Test Chapter. $\bullet 4$


## Add the following:

-USP Mafenide Related Compound A RS [4-formylbenzenesulfonamide] $\mathrm{C}_{7} \mathrm{H}_{7} \mathrm{NO}_{3} \mathrm{~S} \diamond 185.20$-Dry portion in vacuum at $60^{\circ}$ for 4 hours before using. Keep container tightly closed. Protect from light. $\bullet 4$

## Change to read:

USP Nitrofurfural Diacetate RS $\quad\left(\mathrm{C}_{9} \mathrm{H}_{0} \mathrm{NO}_{7} \diamond 243.17\right)-{ }^{\circ}$ Do not dry.@4 Keep container tightly closed. ${ }^{\bullet}$ Protect from light. $\bullet 4$

## Change to read:

USP Pilocarpine Hydrochloride RS-Dry portion at $105^{\circ}$ for 2 hours before using. Keep container tightly closed. Protect from light. ${ }^{\bullet}$ Store in a refrigerator. $\bullet 4$

## Change to read:

USP Spectinomycin Hydrochloride RS-- ${ }^{\circ}$ This is the pentahydrate form of spectinomycin hydrochloride. $\bullet_{4}$ Do not dry before using. Keep container tightly closed. Protect from light. Store in a refrigerator. $\bullet 4$

## Change to read:

USP Vanillin Melting Point RS-- ${ }^{\bullet}$ Do not dry. ${ }_{\bullet 4}$ When melted by the USP capillary tube method, Class Ia in the general chapter Melting Range or Temperature $\langle 741\rangle$, the observed range falls within the indicated acceptance range. Keep container tightly closed and protected from light.

## GENERAL CHAPTERS

## General Information

## 〈1196〉 PHARMACOPEIAL HARMONIZATION

## Change to read:

## PDG WORKING PROCEDURES

## General

Harmonization may be carried out retrospectively for existing monographs or chapters or prospectively for new monographs or chapters.

The three pharmacopeias have a commitment to respect the agreed working procedures and the associated time deadlines as an essential part of the harmonization procedure.

Harmonization of pharmacopeial documents in the PDG occurs based on decisions of the expert bodies of each pharmacopeia. The PDG works transparently in many ways, but principally through the public notice and comment procedures of each pharmacopeia.

Where necessary, meetings of experts are held to identify potential solutions to difficult problems.

The specific stages of the PDG process involved in harmonization are described below.

## Stage 1: Identification

On the basis of an inquiry among its users, the PDG identifies subjects to be harmonized among PDG pharmacopeias and nominates a coordinating pharmacopeia for each subject.

The PDG distributes the work by consensus among the three pharmacopeias and strives for a balance in the distribution of assignments to coordinating pharmacopeias.

## Stage 2: Investigation

For a subject to be harmonized retrospectively, the coordinating pharmacopeia collects the information on the existing specifications in the three pharmacopeias, on the grades of products marketed, and on the potential analytical procedures.

The coordinating pharmacopeia prepares a draft monograph or chapter, accompanied by a report giving the rationale for the proposal with validation data.

Stage 2 ends with the proposal draft, which is mentioned in this procedure as a Stage 3 draft. The Stage 3 draft, accompanied by supporting comments or data that explain the reasons for each test procedure or limit proposed, is sent by the coordinating pharmacopeia to the secretariats of the other two PDG pharmacopeias.

## Stage 3: Proposal for Expert Committee Review

The three pharmacopeias forward the Stage 3 draft to their expert committee (through meetings or consultation by correspondence).

Comments by the experts resulting from this preliminary survey are sent to their respective pharmacopeial secretariat, preferably within 2 months. However, the comment period should not exceed 4 months. Within 2 months of receipt of the comments, the pharmacopeial secretariat should consolidate the comments and forward them to the coordinating pharmacopeia.

The coordinating pharmacopeia reviews the comments received and prepares a harmonized document (Stage 4 draft) accompanied by a commentary discussing comments received regarding the previous text and providing reasons for action taken in response to those comments.

The Stage 4 draft, as far as possible written in global style-a style easily understood by a variety of readers-together with the commentary, are sent to the secretariats of the other pharmacopeias (end of Stage 3).

## Stage 4: Official Inquiry

The Stage 4 draft and the commentary are published in the revision document of each pharmacopeia in a section entitled International Harmonization. The draft is published in its entirety.

The corresponding secretariats may have to add information essential to the understanding of the implementation of the texts (e.g., the addition of the description of an analytical procedure or of reagents that do not exist in the pharmacopeia) and a translation is added by the European and Japanese Pharmacopoeias. The style may be adapted to that of the pharmacopeia concerned or global style may be used. ${ }^{\bullet}$ A pharmacopeia can add additional text, either to amplify some of the requirements with additional information or because national requirements and compendial policy dictate that the addition is necessary. However, these must be a clear indication that this additional information is not part of the harmonized document. This will avoid additional text being included after the harmonization process is completed, but will allow interested parties to review a complete text. $\bullet_{4}$ The three pharmacopeias endeavor to publish the drafts simultaneously or as close together as possible.

Comments regarding this draft are sent by readers of the revision document to their respective pharmacopeial secretariat, preferably within 4 months, and at most within 6 months of its publication.

Each pharmacopeia analyzes the comments received and submits its consolidated comments to the coordinating pharmacopeia within 2 months of the end of the review/comment period.

The coordinating pharmacopeia reviews the comments received and prepares a draft harmonized document (Stage 5A draft), accompanied by a commentary discussing comments received regarding the previous text and providing reasons for action taken in response to those comments.

The Stage 5 A draft together with the commentary is sent to the
secretariats of the other two PDG pharmacopeias.

## Stage 5. Consensus

## 5A. PROVISIONAL

The Stage 5A draft is reviewed and commented on by the other two PDG pharmacopeias within 4 months of receipt. The three pharmacopeias shall do their utmost to reach full agreement at this stage to obtain a final consensus document.

If a consensus has not been reached, the coordinating pharmacopeia prepares a revised version (Stage $5 \mathrm{~A} / 2$ ), taking relevant, substantiated comments on the Stage 5A document from the two other pharmacopeias into consideration. The revised document (Stage $5 \mathrm{~A} / 2$ ), together with the commentary, are sent to the secre-
tariats of the other two PDG pharmacopeias. The revised document is reviewed and commented on by the other two PDG pharmacopeias, preferably within 2 months of receipt. This review/comment and revision process of the 5A document is repeated (Stage 5A/n) until the three PDG pharmacopeias reach a consensus or until the coordinating pharmacopeia considers that harmonization by attribute should be applied.

If the coordinating pharmacopeia considers certain attributes in the monograph or provisions in a general chapter (especially for retroactive harmonization) are such that it will not be possible to harmonize within a reasonable time period, harmonization by attribute will be applied. If harmonization by attribute is applied, a special cover page (see the table in the Appendix) indicating harmonization is included with the draft. The text contains ${ }^{\circ}$ harmonized attributes and provisions, and ${ }_{44}$ nonharmonized and local attributes are not included. ${ }^{\circ}$ The nonharmonized attributes are clearly indicated in the text as such. $\bullet 4$ The table is prepared as follows: if three pharmacopeias agree on the attribute, there will be a $(+)$ in all columns; if two pharmacopeias agree that the attribute should be included and have agreed on the method and limit, there will be a $(+)$ in the column for those two pharmacopeias, and a $(-)$ in the column for the pharmacopeia that will not stipulate the test.

For nonharmonized or local requirements, if three pharmacopeias agree that the attribute should be included, but have not come to agreement on the method and/or limit: state attribute under "nonharmonized attributes." If only one pharmacopeia will include an attribute: state under "local requirement."

If the Stage 5 A draft is substantially different from the Stage 4 draft, the PDG may decide that it should be published again in the revision documents; the draft then reverts technically to Stage 4 , revised.

## 5B. DRAFT SIGN-OFF

When ${ }^{\bullet}$ - agreement is reached, the 5 B draft is sent by the coordinating pharmacopeia to the other pharmacopeias no later than 4 weeks before a PDG meeting for final confirmation. The document is then presented for sign-off at the PDG meeting. ${ }^{\bullet}$ This document includes nonharmonized attributes clearly marked as such. $\bullet 4$

## Stage 6: •Regional Adoption and Implementation

NOTE-The last two stages of the implementation of the "harmonized" chapters and monographs take place independently according to the procedures established by each pharmacopeial organization.

## 6A. REGIONAL ADOPTION ${ }_{\bullet}$

The document is submitted for adoption to the organization responsible for each pharmacopeia. Each pharmacopeia incorporates the harmonized draft according to its own procedures. ${ }^{\bullet}$ Stylistic and editorial differences may occur. $\bullet 4$

Adopted texts are published by the three pharmacopeias in their supplements, or where applicable, in a new edition.

If necessary, the Stage 5B draft may be adopted with some amendments (local requirements) corresponding to a general policy in the national or regional (European) area. If a pharmacopeia includes a local attribute after the sign-off of a text, it will inform the PDG. ${ }^{\circ}$ It is, however, preferred to include the nonharmonized text in Stage 5B as an alert to the other pharmacopeias that there will be some differences in text in the final document. 04

Users of the pharmacopeias are appropriately informed of the harmonization status of monographs and general chapters. In the European Pharmacopoeia $(E P)$ and $U S P-N F$, for general chapters,
this is done via a preliminary paragraph. For the Japanese Pharmacopoeia ( $J P$ ), a notification is made by the MHLW, and information is given in a general chapter.

## ${ }^{\bullet}$ 6B. IMPLEMENTATION ${ }_{\bullet 4}$

The pharmacopeias will inform each other of the date of implementation in their particular region.

The date of implementation of a harmonized document varies in the three PDG regions depending on their legal requirements, need of translation, and publication schedules. Each pharmacopeia generally allows some period of time after publication for implementation to allow manufacturers and other users to achieve conformity. Harmonization is not achieved until the text becomes official in all three pharmacopeias.

## -Stage 7: Inter-Regional Implementation

When a harmonized text has become official in all three pharmacopeias, EP and USP publish a statement indicating the harmonization status of the text; JP publishes a statement to the same effect at Stage 6B. These statements are intended to promote regulatory acceptance of interchangeability of harmonized monographs and general chapters. $\bullet 4$

## Revision

The procedure for the revision of harmonized monographs and chapters is as follows.
The pharmacopeias participating in the PDG have agreed not to revise unilaterally any harmonized document (monograph or chapter) after sign-off or after publication.
A pharmacopeia requesting the revision of a monograph or chapter shall apply the following criteria for justification of the revision:

- Public health and safety reasons.
- Insufficient supply of pharmacopeial-quality product on the market.
- Specified analytical reagents or equipment are not available.
- New methods of preparation of products or reagents are not covered by the current monograph.
- Analytical procedures can be replaced by more appropriate, accurate, or precise procedures.
The PDG as a whole has to agree to initiate the revision. A coordinating pharmacopeia will be nominated. The coordinating pharmacopeia will prepare a Stage 3 draft, based on the validation of data provided by the pharmacopeia requesting the revision.

The PDG Working Procedures will then be followed. The revisions of a sign-off document prepared for this or other reasons are indicated as revision $1,2,3$, etc.

In case of health and safety issues, and whenever agreed to by the PDG, an accelerated procedure shall be applied (shortening and/or eliminating stages).

## Discussion

Harmonization of general chapters and monographs benefits manufacturers of pharmaceutical products intended for human use, regulatory agencies, and ultimately, practitioners and patients. Benefits are derived from (1) reduced development effort; (2) simplification of regulatory filings; and (3) reduced release testing.

Pharmacopeial harmonization amplifies the work of the ICH, particularly for Quality topics. While the PDG is not part of the ICH , the PDG periodically provides updates to the ICH Steering Committee, and in the past participated in a joint task force. This
task force focused on harmonization of general chapters considered important to the ICH harmonized document Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Q6A). USP also participates in the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH). As with the ICH, some of the quality guidelines developed in VICH depend upon harmonization of pharmacopeial general chapters. A major difference between the PDG and ICH/ VICHs is that the ICH/VICH guidelines generally are applicable only to ingredients and drug products not previously registered in an ICH/VICH region or nation, whereas the PDG harmonization applies to all marketed products in the applicable region or nation.

In the case of harmonization by attribute, nonharmonization or divergence will be indicated in $U S P-N F$ and $E P$ by the symbol $\leqslant$. For these nonharmonized attributes, reliance upon the individual pharmacopeia is required. A monograph or general chapter in one PDG pharmacopeia may unilaterally include additional local or national attributes that are not included in the corresponding text of the other pharmacopeias. Such text is not considered by the PDG to be a divergence from the PDG harmonized text.

As with other $U S P-N F$ revisions, draft harmonization texts are published for comment in Pharmacopeial Forum. Final harmonized official text in $U S P-N F$ is presented in the latest edition, Supplement, or Interim Revision Announcement. The current status of all harmonization projects appears in Table 1 and Table 2. These status tables will be updated in subsequent editions of $U S P-N F$ and its Supplements.

In the U.S., cases of noncompliance and/or dispute are resolved through performance of the official procedure in $U S P$ or $N F$. If the procedure and its acceptance criteria are harmonized in the PDG, then a manufacturer may follow the relevant compendial instructions in $U S P-N F, E P$, or $J P$.

Table 1. Status of Harmonization-Excipient Monographs

| Excipient Name | Coordinating Pharmacopeia | Harmonization Stage |
| :---: | :---: | :---: |
| Alcohol | EP | 6 |
| Benzyl Alcohol | EP | 6 |
| Dehydrated Alcohol | EP | 6 |
| Butylparaben | EP | ${ }^{\bullet} 6$ |
| ${ }^{\mathbf{4}}$ Calcium Carbonate | USP | $2 \pm$ USP27 |
| Calcium Disodium Edetate | JP | 5A2 |
| Calcium Phosphate Dibasic (and anhydrous) | JP | ${ }^{\bullet} 5 \mathrm{~B}{ }^{4}$ |
| Carboxymethylcellulose Calcium | USP | 6 |
| Carboxymethylcellulose Sodium | USP | 4 |
| ${ }^{4}$ Carmellose | JP | 2 \USP27 |
| Cellulose Acetate | USP | 6 |
| Cellulose Acetate Phthalate | USP | 6 |
| Microcrystalline Cellulose | USP | ${ }^{\bullet} 6$ |
| Cellulose, Powdered | USP | ${ }^{\bullet} 6$ |
| Citric Acid, Anhydrous | EP | 6 |
| Citric Acid, Monohydrate | EP | 6 |
| ${ }^{4}$ Copovidone | JP | $2 \mathbf{4}$ USP27 |
| Croscarmellulose Sodium | USP | 6 |
| Crospovidone | EP | 4 |
| Ethylcellulose | EP | 6 |
| Ethylparaben | EP | ${ }^{6} 6$ |
| ${ }^{\Delta}$ Gelatin | EP | 2 \USP27 |
| ${ }^{\text {A }}$ Glucose | EP | $2 \pm$ USP 27 |
| Glycerin | USP | 3 |
| ${ }^{\text {S }}$ Glyceryl Monostearate | USP | 2 \USP27 |
| Hydroxyethyl Cellulose | EP | 4 |
| Hydroxypropyl Cellulose | USP | 4 |

Table 1. Status of Harmonization-Excipient Monographs (Continued)

| Excipient Name | Coordinating Pharmacopeia | Harmonization Stage |
| :---: | :---: | :---: |
| Hydroxypropyl Cellulose, Low Substituted | USP | 4 |
| Hydroxypropylmethyl Cellulose | JP | ${ }^{\bullet}{ }^{\text {•4 }}$ |
| Hydroxypropylmethyl Cellulose Phthalate | USP | ${ }^{\bullet} 5 \mathrm{~A} \bullet 4$ |
| Lactose, Anhydrous | USP | 6 |
| Lactose, Monohydrate | USP | 6 |
| Magnesium Stearate | USP | ${ }^{-4}$ |
| ${ }^{\Delta}$ Mannitol | EP | 2 USP27 |
| Methylcellulose | JP | ${ }_{604}$ |
| Methylparaben | EP | ${ }^{\bullet} 6$ |
| Petrolatum, White | USP | 4 |
| Polyethylene Glycol | USP | 4 |
| Polysorbate 80 | EP | 3 |
| Povidone | JP | 5A |
| ${ }^{\text {A }}$ Propylene Glycol | $\mathrm{EP}_{\mathbf{\triangle U S P 2 7}}$ | ${ }_{-} 3$ |
| Propylparaben | EP | ${ }^{\bullet} 6$ |
| Saccharin | USP | ${ }^{4} 6{ }_{\text {UUSP27 }}$ |
| Saccharin, Calcium | USP | ${ }^{\mathbf{4}} 6_{\mathbf{4} \text { USP27 }}$ |
| Saccharin, Sodium | USP | ${ }^{4} 6 \mathbf{4}$ USP27 |
| Silicon Dioxide | JP | 4 |
| Silicon Dioxide, Collodial | JP | 4 |
| Sodium Chloride | EP | 6 |
| ${ }^{4}$ Sodium Lauryl Sulfate | USP | $2^{4}$ USP27 |
| Sodium Starch Glycolate | USP | $6_{64}$ |
| Starch, Corn | USP | 6 |
| Starch, Potato | EP | 6 |
| ${ }^{\mathbf{A}}$ Starch, Pregelatinized | JP | 2 USSP27 |
| Starch, Rice | EP | $4^{\text {® }}$ Revised ${ }^{\text {a }}$ |
| Starch, Wheat | EP | 6 |
| Stearic Acid | EP | 4 |
| Sucrose | EP | 3 |
| Talc | EP | ${ }^{\bullet} 6{ }_{\bullet 4}$ |
| Titanium Dioxide | JP | 5A2 |

Table 2. Status of Harmonization-General Chapters

| Chapter Title | Coordinating Pharmacopeia | Harmonization Stage |
| :---: | :---: | :---: |
| Amino Acid Determination | USP | 6 |
| Bacterial Endotoxins | JP | 7 |
| Bulk Density and Tapped Density | EP | 3 |
| ${ }^{\bullet}$ Conductivity | EP | 2 |
| Degree of Color of Liquids; Clarity and Degree of Opalescence of Liquids | EP | 3 |
| Density of Solids | EP | 3 |
| Disintegration | USP | 4 |
| Dissolution | USP | 4 |
| Capillary Electrophoresis | EP | 6 |
| Polyacrylamide Gel Electrophoresis | EP | 6 |
| Extractable Volume of Parenterals | EP | 6 |
| Flowability (Powder Flow) | USP | 4 |
| Heavy Metals | USP | 3 |
| Inhalation | EP | 3 |
| Isoelectric Focusing | EP | 6 |

Table 2. Status of Harmonization-General Chapters (Continued)

| Chapter Title | Coordinating Pharmacopeia | Harmonization Stage |
| :---: | :---: | :---: |
| Light Diffraction Measure of Particle Size | EP | 3 |
| Microbial Contamination |  |  |
| - Tests for specified microorganisms | EP | 4 |
| Microbial Enumeration | EP | 4 |
| Microbial Attributes | EP | 4 |
| Optical Microscopy | USP | ${ }^{-5}{ }^{\text {¢ }}$ |
| Particle Size Distribution Estimation by Analytical Sieving | USP | ${ }^{-5} \mathrm{~A}_{\bullet 4}$ |
| Peptide Mapping | USP | 6 |
| Porosimetry by Mercury Intrusion | EP | 3 |
| Powder Fineness | USP | ${ }^{\bullet} 5 \mathrm{~A}_{\bullet 4}$ |
| Protein Determination | USP | 6 |
| Residue on Ignition | JP | 6 |
| $\bullet$ (Revision 1) $\bullet 4$ |  |  |
| Specific Surface Area | EP | ${ }^{\bullet} 6$ |
| Sterility Tests | EP | 6 |
| Tablet Friability | USP | 3 |
| ${ }^{\bullet}$ Thermal Behavior of Powders | EP | 2 |
| Uniformity of Content/Mass | USP | ${ }^{\bullet} 5 \mathrm{~A}_{2}{ }_{4}$ |
| X-Ray Diffraction-Solids | EP | 3 |

## ${ }^{\wedge}$ Harmonized Monographs and Chapters

## HARMONIZED CHAPTERS

$\langle\mathbf{8 5}\rangle$ Bacterial Endotoxins Test-This chapter has been harmonized by PDG and published in the European Pharmacopoeia and in the Japanese Pharmacopoeia. Portions of the chapter that are not harmonized with the other two pharmacopeias are marked by the symbol . Footnotes 1, 2, and 4 are in the $U S P$ while they are not in the $E P$ or $J P$. These footnotes give additional information, such as the calculation of endotoxin limits for different classes of products (Footnote 4) or reference USP chapters (Footnote 2).

The USP Endotoxin Reference Standard is harmonized with the International Reference Standard for Endotoxin and the EP Endotoxin Reference Standard and indirectly harmonized with the JP Endotoxin Reference Standard that is indexed to the International Reference Standard. The result is that 1 USP Endotoxin Unit $=1$ International Endotoxin Unit = 1 EP Endotoxin Unit. $\Delta U S P 27$

## ERRATA

Following is a list of errata and corrections to USP 27-NF 22. The page number indicates where the item is found in USP 27-NF 22. If necessary, this list will be updated with every issue of $P F$. This information will also be available as a cumulative table in the next available Supplement and will appear in its corrected form in the next annual edition of USP-NF. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff are available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

| Page | Title | Section | Description |
| :--- | :--- | :--- | :--- |
| 242 | Bethanechol Chloride | Related compounds | Line 6 under Procedure: Change " $2500 C(F / W)\left(r_{i} /\right.$ <br> $\left.r_{S}\right), "$ to: $25,000 C(F / W)\left(r_{i} / r_{S}\right)$, |
| 1235 | Metrifonate | Chromatographic purity | Break subsection Solution $B$ as follows: Change "Solu- <br> tion $B-\operatorname{Use}$ variable mixtures of..." to: <br> Solution $B-U s e ~ a c e t o n i t r i l e . ~$ |
|  |  |  | Mobile phase-Use variable mixtures of ... |
| 1253 | Mitoxantrone Injection | Assay | Lines 1-2: Change "Resolution solution," to: System <br> suitability solution, |
| Supplement 1 |  | Line 2 under Mobile phase: Change "(4:1)" to: (1:4) |  |

## IN-PROCESS REVISION

This section contains proposals for adoption as official USP or NF standards (either proposed new standards or proposed revisions of current $U S P$ or $N F$ standards). These may be any of the following: (1) items that previously appeared under Pharmacopeial Previews and are now formally proposed as revisions; (2) proposed revisions placed directly under In-Process Revision; or (3) modifications of revisions previously proposed under In-Process Revision. Readers should review material in this section and provide comments to the staff liaison (use the Staff Directory to find the contact information). Information on how to comment is found in the Policies and Announcements section. It is important to send comments promptly so that the Committee members can consider readers' input as they are deciding whether to advance standards to official status.

Briefings Each Proposal is preceded by a Briefing in the following format:

## BRIEFING

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being proposed, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see How to Use PF), the name of the scientific staff liaison who handled the particular issue, and the USP tracking correspondence number, as shown in the example below:
(PA5: K. Russo) RTS-55678-1

Symbols Proposed revisions are shown with language proposed for deletion or replacement crossed off. New text (if any) follows, and is enclosed in symbols and set off from the current official text by a paragraph break and by larger type, as shown in the examples below:
${ }^{\bullet}$ new text ${ }^{\circ}$
if slated for an Interim Revision Announcement to USP 27-NF 22 (IRA);
$\Delta_{\text {new text }}^{\text {USPP28 }}$
if slated for USP $28-N F 23$; and
-new text.
if slated for a Supplement to $U S P-N F$. The same symbols not set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as ${ }^{\bullet}$ 。 or $\boldsymbol{\bullet}^{\boldsymbol{\wedge}}$ or $^{\boldsymbol{\Delta}}$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular IRA or Supplement or indicates the USP or NF as the publication where the revision will appear if approved. For example, $\bullet 2$ indicates that the revision is proposed for the Second Interim Revision Announcement, and $\mathbf{a S S}_{\text {(USP 27) }}$ indicates that the proposed revision is slated for the Second Supplement to USP 27, and $\Delta_{\triangle S P 28}$ and ${ }_{\Delta N F 23}$ indicate that the revisions are proposed for USP 28 and $N F 23$, respectively.

Official Title Changes Where the specification "Monograph title change" is found, it indicates that the official title stated after that specification will be substituted for the former title in the appropriate places throughout that monograph once this revision becomes official.
IN-PROCESS REVISION ..... 1157
MONOGRAPHS (USP) ..... 116
Acepromazine Maleate Injection (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 1161
Acetaminophen Extended-Release Tablets [new] (1 $1^{\text {st }}$ Supp to USP 28) ..... 161
Albendazole Oral Suspension ( $1^{\text {st }}$ Supp to USP 28) ..... 1163
Aminopentamide Sulfate ( $1^{\text {st }}$ Supp to USP 28) ..... 1163
Aspartic Acid (1st Supp to USP 28) ..... 1163
Aspirin ( $1^{\text {st }}$ Supp to USP 28) ..... 1164
Avobenzone ( ${ }^{\text {st }}$ Supp to USP 28) ..... 1164
Benzoyl Peroxide Gel ( $1^{\text {st }}$ Supp to USP 28) ..... 1165
Betamethasone Sodium Phosphate ( $1^{\text {st }}$ Supp to USP 28) ..... 1166
Bismuth Subsalicylate Oral Suspension [new] (1 $1^{\text {st }}$ Supp to USP 28) ..... 1166
Bismuth Subsalicylate Tablets [new] ( $1^{\text {st }}$ Supp to USP 28) ..... 116
Caffeine ( $1^{\text {st }}$ Supp to USP 28) ..... 1168
Calcitonin Salmon [new] ( $1^{\text {st }}$ Supp to USP 28) ..... 1169
Calcitonin Salmon Injection [new] (1 $1^{\text {st }}$ Supp to USP 28) ..... 177
Calcitonin Salmon Nasal Solution [new] (1 $1^{\text {st }}$ Supp to USP 28) ..... 1178
Clarithromycin ( $1^{\text {st }}$ Supp to USP 28) ..... 1179
Clarithromycin Tablets ( $1^{\text {st }}$ Supp to USP 28) ..... 1182
Clarithromycin Extended-Release Tablets [new] ( $1^{\text {st }}$ Supp to USP 28) ..... 1183
Cyclophosphamide Tablets ( $1^{\text {st }}$ Supp to USP 28) ..... 1186
Desflurane ( $1^{\text {st }}$ Supp to USP 28) ..... 1187
Diethylstilbestrol Diphosphate Tablets [new] ( $1^{\text {st }}$ Supp to USP 28) ..... 1187
Dimenhydrinate Oral Solution (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 190
Dimenhydrinate Syrup (1 $1^{\text {st }}$ Supp to USP 28) ..... 1190
Dimenhydrinate Tablets (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 191
Ensulizole ( $1^{\text {st }}$ Supp to USP 28 ) ..... 191
Epinephrine Nasal Solution ( $1^{\text {st }}$ Supp to USP 28) ..... 1192
Epinephryl Borate Ophthalmic Solution ( $1^{\text {st }}$ Supp to USP 28) ..... 192
Ergoloid Mesylates Tablets ( $1^{\text {st }}$ Supp to USP 28) ..... 193
Ergoloid Mesylates Tablets [new] (1st Supp to USP 28) ..... 1194
Ergotamine Mesylates Sublingual Tablets [new] ( $1^{\text {st }}$ Supp to USP 28) ..... 196
Ergotamine Tartrate Tablets ( $1^{\text {st }}$ Supp to USP 28) ..... 198
Ergotamine Tartrate Tablets [new] ( $1^{\text {st }}$ Supp to USP 28) ..... 1198
Ergotamine Tartrate Sublingual Tablets [new] (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 199
Estradiol Transdermal System [new] ( $1^{\text {st }}$ Supp to USP 28) ..... 120
Etodolac Extended-Release Tablets [new] (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 1203
Fenbendazole [new] ( $1^{\text {st }}$ Supp to USP 28) ..... 1205
Fexofenadine Hydrochloride [new] (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 1208
Cryopreserved Human Fibroblast-Derived Dermal Substitute [new] (1 $1^{\text {st }}$ Supp to USP 28) ..... 1211
Human Fibroblast-Derived Temporary Skin Substitute [new] (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 22
Flumazenil [new] (1 ${ }^{\text {st }}$ Supp to USP 28 ..... 1223
Flurazepam Hydrochloride ( $1^{\text {st }}$ Supp to USP 28) ..... 1229
Fluticasone Propionate [new] (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 1230
Fluvastatin Sodium [new] ( $1^{\text {st }}$ Supp to USP 28) ..... 1234
Fluvastatin Capsules [new] (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 1237
Fluvoxamine Maleate [new] ( $1^{\text {st }}$ Supp to USP 28) ..... 1240
Fluvoxamine Maleate Tablets [new] ( $1^{\text {st }}$ Supp to USP 28) ..... 1243
Gemcitabine for Injection ( $1^{\text {st }}$ Supp to USP 28) ..... 1246
Gemfibrozil Capsules ( $1^{\text {st }}$ Supp to USP 28) ..... 246
Gemfibrozil Tablets (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 1247
Glimepiride [new] (1 $1^{\text {st }}$ Supp to USP 28) ..... 1247
Gonadorelin Acetate [new] (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 1250
Hydromorphone Hydrochloride ( $1^{\text {st }}$ Supp to USP 28) ..... 1254
Isoflurane ( $1^{\text {st }}$ Supp to USP 28) ..... 1255
Ketoconazole Tablets ( ${ }^{\text {st }}$ Supp to USP 28) ..... 1256
Lidocaine Hydrochloride (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 1256
Lidocaine Hydrochloride and Epinephrine Injection ( $1^{\text {st }}$ Supp to USP 28) ..... 1257
Loratadine Oral Solution (Proposal for $6^{\text {th }}$ IRA) ..... 1258
Mafenide Acetate ( $1^{\text {st }}$ Supp to USP 28) ..... 1258
Mafenide Acetate for Topical Solution (1 $1^{\text {st }}$ Supp to USP 28) ..... 1259
Mefloquine Hydrochloride [new] (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 1260
Mercaptopurine Tablets ( $1^{\text {st }}$ Supp to USP 28) ..... 1261
Mesoridazine Besylate (1 ${ }^{\text {st }}$ Supp to USP 28) ..... 1262
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## MONOGRAPHS (USP)

BRIEFING

Acepromazine Maleate Injection, USP 27 page 15 and page 3037 of the First Supplement. It is proposed to add a test for Bacterial endotoxins.
(VET: I. DeVeau; AMB: D. Porter) RTS-41314-1

## Add the following:

■Bacterial endotoxins $\langle 85\rangle$ : not more than 4.5 USP Endotoxin Units per mg of acepromazine maleate.■1s (USP28)

BRIEFING

Acetaminophen Extended-Release Tablets. Because there is no existing $U S P$ monograph for this drug product, a new monograph is being proposed. The liquid chromatographic procedure in the Assay is based on analyses performed with the Waters $\mu$ Bondapak ${ }^{\circledR} \mathrm{C} 18$ brand of L1 column.
(PA2: C. Anthony) RTS-40239-1

## Add the following:

## Acetaminophen Extended-Release Tablets

## » Acetaminophen Extended-Release Tablets con-

 tain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$.Packaging and storage-Preserve in tight containers.
Labeling-Where the Tablets are gelatin-coated, the label so states.

USP Reference standards $\langle 11\rangle$ —USP Acetaminophen $R S$.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$ —Use a portion of powdered Tablets.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, obtained as directed in the Assay.

Drug release $\langle 724\rangle$ -
Medium: simulated gastric fluid TS (without enzyme); 900 mL .

Apparatus 2: 50 rpm .
Times: 15 minutes, 1 hour, and 3 hours.
Procedure-Determine the amount of $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ dissolved from UV absorbances at 243 nm using a filtered portion of the solution under test in comparison with a Standard solution having a known concentration of USP Acetaminophen RS in the same Medium.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ dissolved at the times specified conform to Acceptance Table 1.

| Time | Amount dissolved |
| :---: | :--- |
| 15 minutes | between $45 \%$ and $65 \%$ |
| 1 hour | between $60 \%$ and $85 \%$ |
| 3 hours | not less than $85 \%$ |

## FOR GELATIN-COATED TABLETS-

Medium, Apparatus, and Procedure-Proceed as directed above.

Times: 30 minutes, 90 minutes, and 4 hours.
Tolerances-The percentage of the labeled amount of $\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}$ dissolved at the times specified conform to Acceptance Table 2.

| Time | Amount dissolved |
| :---: | :--- |
| 30 minutes | between $40 \%$ and $60 \%$ |
| 90 minutes | between $55 \%$ and $85 \%$ |
| 4 hours | not less than $80 \%$ |

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Assay-

Mobile phase-Prepare a mixture of water and phosphoric acid ( $9: 1$ ). Combine 1 mL of this solution with a mixture of water and methanol ( $700: 300$ ). Filter, and degas. Make adjustments if necessary (see System Suitability under Chromatograph $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Acetaminophen RS in methanol, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.65 mg per mL .

Assay preparation-Transfer 10 Tablets into a $250-\mathrm{mL}$ volumetric flask containing 50 mL of water and a magnetic stir bar. Stir at least 30 minutes or until the coating has dissolved. Add 150 mL of methanol, and stir for 45 minutes. Tablet cores should be disintegrated at least 15 minutes prior to ending the stirring. Remove the magnetic stir bar and rinse into the flask with methanol. Dilute with methanol to volume, mix well, and centrifuge. Transfer 5 mL of the clear supernatant to a $200-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix well.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $295-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 3.0, and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of acetaminophen $\left(\mathrm{C}_{8} \mathrm{H}_{9} \mathrm{NO}_{2}\right)$ in each Tablet taken by the formula:

$$
1000 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Acetaminophen RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the acetaminophen peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Albendazole Oral Suspension, USP 27 page 54, page 3040 of the First Supplement, and page 991 of $P F$ 29(4) [July-Aug. 2003]. It was proposed in $P F 29(4)$ to change the specified labeling requirements from "Label it to indicate that it is for veterinary use only" to "Oral Suspension intended for veterinary use only is so labeled." This change was proposed to allow use of the Albendazole Oral Suspension monograph by manufacturers who distribute albendazole oral suspension that is approved for human use outside the United States. Comments received by USP indicate a concern that the labeling changes proposed in $P F$ 29(4) would create confusion, because Albendazole Oral Suspension has not been approved for human use in the United States. To prevent any possible confusion, it is now proposed to delete the Labeling specifications in the Albendazole Oral Suspension monograph. This would allow manufacturers to use the monograph for the albendazole oral suspension products that they distribute in countries where the appropriate authorities have given approval for human use. The proposal would also now have the labeling default to the specification of the governing regulatory authority for a given country.
(NL: W. Paul; VET: I. DeVeau) RTS-40621-2

## Delete the following:

Gabeling Label it to indient that it is for veterinary use only.
Oral-Suspension intended for veterinary use only is so labe

```
lec!1S (USP28)
```


## BRIEFING

Aminopentamide Sulfate, USP 27 page 122 and page 1844 of PF 29(6) [Nov.-Dec. 2003]. In the Assay, it is proposed to replace the solvent used to prepare the titrant to avoid the use of benzene.
(BPC: M. Marques) RTS-41333-1

## Change to read:

Labeling-Label it to indicate that it is for veterinary use only.
${ }^{\Delta}$ Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. $\Delta$ USP28

## Change to read:

USP Reference standards $\langle 11\rangle —$ USP Aminopentamide Sulfate $R S$.
${ }^{\Delta}$ USP Endotoxin RS. ■USP28

## Add the following:

${ }^{\Delta}$ Other requirements-Where the label states that Aminopentamide Sulfate is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Aminopentamide Sulfate Injection. Where the label states that Aminopentamide Sulfate must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Aminopentamide

Sulfate Injection. $\mathbf{\Delta U S P 2 8}$

## Change to read:

Assay-Dissolve about 500 mg of Aminopentamide Sulfate, accurately weighed, in 100 mL of dimethylformamide in a suitable container. Add 5 drops of thymol blue TS, and titrate with 0.1 N lithium methoxide VS

ㅂin benzene
$\boldsymbol{m}_{\text {in toluene }} \mathbf{n}_{1 S}$ (USP28)
to a deep blue endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N lithium methoxide is equivalent to 19.72 mg of $\mathrm{C}_{19} \mathrm{H}_{24} \mathrm{~N}_{2} \mathrm{O} \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$.

## BRIEFING

Aspartic Acid, USP 27 page 170. On the basis of comments received, it is proposed to clarify the composition of the Standard solution in the test for Chromatographic purity.
(DSN: L. Evans) RTS-41194-1

## Change to read:

Chromatographic purity-
Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture.

System suitability solution-Dissolve 10 mg each of USP Aspartic Acid RS and glutamic acid, each accurately weighed, in 2 mL of ammonia TS, dilute with water to 25.0 mL , and mix.

Test solution-Transfer 0.1 g of Aspartic Acid to a $10-\mathrm{mL}$ volumetric flask, dissolve in 2 mL of $17 \%$ ammonia solution (prepared by diluting ammonium hydroxide, 6 in 10), dilute with water to volume, and mix.

Standard solution-Transfer 5 mg of USP Aspartic Acid RS to a $100-\mathrm{mL}$ volumetric flask, dissolve in 2 mL of $17 \%$ ammonia solution (prepared by diluting ammonium hydroxide, 6 in 10), nitm hydroxide,

■11S (USP28)
dilute with water to volume, and mix.
Application volume: $5 \mu \mathrm{~L}$.
Developing solvent system: a mixture of butyl alcohol, glacial acetic acid, and water $(6: 2: 2)$.

Spray reagent-Dissolve 0.2 g of ninhydrin in 100 mL of a mixture of butyl alcohol and 2 N acetic acid (95:5).

Procedure-Proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$, except to dry the plate at $80^{\circ}$ for 30 minutes, spray with Spray reagent, and heat at $80^{\circ}$ for 30 minutes. Examine the plate under white light. The chromatogram obtained from the System suitability solution exhibits two clearly separated spots, and no secondary spot in the chromatogram of the Test solution is larger or more intense than the principal spot in the chromatogram of the Standard solution: not more than $0.5 \%$ of any individual impurity is found; and not more than $2.0 \%$ of total impurities is found.

## Briefing

Aspirin, USP 27 page 171. It is proposed to delete the incorrect chapter number, $\langle 211\rangle$, for Sulfate.
(PA2: C. Anthony) RTS-41283-1

## Change to read:

Sulfate $\langle z 14\rangle$
$\square_{\text {■1S (USP28) }}$
-Dissolve 6.0 g in 37 mL of acetone, and add 3 mL of water. Titrate potentiometrically with 0.02 M lead perchlorate, prepared by dissolving 9.20 g of lead perchlorate in water to make 1000 mL of solution, using a pH meter capable of a minimum reproducibility of $\pm 0.1 \mathrm{mV}$ (see $p H\langle 791\rangle$ ) and equipped with an electrode system consisting of a lead-specific electrode and a silver-silver chloride reference glass-sleeved electrode containing a solution of tetraethylammonium perchlorate in glacial acetic acid ( 1 in 44) (see Titrimetry $\langle 541\rangle$ ): not more than 1.25 mL of 0.02 M lead perchlorate is consumed $(0.04 \%)$. [NOTE-After use, rinse the lead-specific electrode with water, drain the reference electrode, flush with water, rinse with methanol, and allow to dry.]

## BRIEFING

Avobenzone, USP 27 page 194. It is proposed to revise the Chromatographic system in the Assay to include system suitability requirements.

$$
\text { (PA6: L. Evans) } \quad \text { RTS-41185-1 }
$$

## Change to read:

## Assay-

Standard preparation-Dilute an accurately measured quantity of USP Avobenzone RS in acetone, and dilute quantitatively, and stepwise if necessary, with acetone to obtain a solution having a known concentration of about 50 mg per mL .

Assay preparation-Transfer about 500 mg of Avobenzone, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dilute with acetone to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The gas chromatograph is equipped with a flame-ionization detector and a $0.32-\mathrm{mm} \times 25-\mathrm{m}$ fused silica capillary column coated with phase G1. The column temperature is maintained at about $200^{\circ}$ until the time of injection, then increased at a rate of $4^{\circ}$ per minute to $280^{\circ}$. The injection port temperature is maintained at $200^{\circ}$, and the detector temperature is maintained at about $280^{\circ}$. Helium is used as the carrier gas.
-Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between avobenzone and any adjacent peak is not less than 1.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$. 1 IS (USP28)

Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{20} \mathrm{H}_{22} \mathrm{O}_{3}$ in the portion of Avobenzone taken by the formula:

$$
10 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Avobenzone RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Benzoyl Peroxide Gel, USP 27 page 224 and page 455 of $P F$ 30(2) [Mar.-Apr. 2004]. It is proposed to revise the column dimensions in Chromatographic system in the Assay to be consistent with the original method. In addition, an editorial change has been made.
(PA7b: B. Davani) RTS-41307-1

## Change to read:

## Related compounds-

Solution A-Prepare a filtered and degassed mixture of acetonitrile and glacial acetic acid (1000:1).

Solution B-Prepare a filtered and degassed mixture of water and glacial acetic acid (1000:1).

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Prepare a solution in acetonitrile containing $100 \mu \mathrm{~g}$ of benzoic acid and $60 \mu \mathrm{~g}$ of methylparaben per mL.

Test preparation-Transfer an accurately weighed quantity of Gel, equivalent to about 100 mg of benzoyl peroxide, to a $50-$ mL volumetric flask, add 25 mL of acetonitrile, shake vigorously to disperse the specimen, sonicate for 5 minutes, dilute with acetonitrile to volume, mix, and filter.

Standard preparation A-Prepare a solution of benzoic acid in acetonitrile containing $500 \mu \mathrm{~g}$ per mL .

Standard preparation B-Prepare a solution of ethyl benzoate in acetonitrile containing $20 \mu \mathrm{~g}$ per mL .

Standard preparation $C$-Prepare a solution of benzaldehyde in acetonitrile containing $20 \mu \mathrm{~g}$ per mL .

Standard preparation D-Prepare a solution of hydrous benzoyl peroxide, previously subjected to the Assay under Hydrous Benzoyl Peroxide, in acetonitrile containing the equivalent of $40 \mu \mathrm{~g}$ of anhydrous benzoyl peroxide per mL.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $235-\mathrm{nm}$ detector and a $3.9 \mathrm{~mm} \times 15 \mathrm{~cm}$
${ }^{\boldsymbol{\Delta}} 4.6-\mathrm{mm} \times 25-\mathrm{cm}_{\mathbf{\Delta} U S P 28}$
column containing packing L1. The flow rate is about 1.2 mL per minute. The chromatograph is programmed as follows.

| Time <br> $($ minutes $)$ | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :---: |
| 0 | 18 | 82 | equilibration |
| $0-10$ | $18 \rightarrow 60$ | $82 \rightarrow 40$ | linear gradient |
| $\mathbf{\Delta}_{0}-20_{\mathbf{\Delta} U S P 28}$ <br> $10-22$ | 60 | 40 | isocratic |
| $\mathbf{\Delta}_{20-30_{\mathbf{\Delta S P 2 8}}}$ |  |  |  |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between benzoic acid and methylparaben is not less than 3.0;

## ${ }^{-} 2.0 ;_{\mathbf{\Delta S P} 28}$

and the tailing factors for the benzoic acid and methylparaben peaks are not more than 2.0.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparations and the Test preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. The responses of any peaks obtained from the Test preparation corresponding to benzoic acid, ethyl benzoate, and benzaldehyde are not greater than those of the main peaks obtained from Standard preparation A (25\%), Standard preparation B (1\%), and Standard preparation C (1\%), respectively; the response of any other impurity peak obtained from the Test preparation, other than the main benzoyl peroxide peak, any benzoic acid, ethyl benzoate, benzaldehyde, methylparaben, or propylparaben peak, and any solvent peak, is not more than that obtained from Standard preparation $D(2 \%)$; and the sum of the responses of all the impurity peaks, other than those of benzoic acid, ethyl benzoate, and benzaldehyde is not more than that obtained from Standard preparation $D(2 \%)$.

## Change to read:

## Assay-

Mobile phase-Prepare a solution of acetonitrile in water (about 5 in 10) such that the retention times for ethyl benzoate and benzoyl peroxide are about 7 and 14 minutes, respectively.

Internal standard solution-Dissolve ethyl benzoate in acetonitrile to obtain a solution having a concentration of about 3.6 mg per mL .

Standard preparation-Place a suitable quantity of hydrous benzoyl peroxide, recently subjected to the Assay under Hydrous Benzoyl Peroxide, in an accurately weighed conical flask fitted with a glass stopper, weigh again to obtain the weight of the specimen, and quantitatively dissolve in acetonitrile to obtain a solution containing a known concentration of about 0.8 mg of benzoyl peroxide per mL . Pipet 10 mL of this solution and 5 mL of Internal standard solution into a $25-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix. This Standard preparation contains about 0.32 mg of benzoyl peroxide per mL .

Assay preparation-Transfer an accurately weighed quantity of Gel, equivalent to about 40 mg of benzoyl peroxide, to a $50-\mathrm{mL}$ volumetric flask. Add 40 mL of acetonitrile, and shake until the material is thoroughly dispersed. Sonicate the mixture for $5 \mathrm{~min}-$ utes, dilute with acetonitrile to volume, mix, and filter. Pipet 10 mL of the filtrate and 5 mL of Internal standard solution into a $25-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a 4 mm
$\boxed{\square} .9-\mathrm{mm}_{\square 1 \mathrm{~S}}$ (USP28)
$\times 30-\mathrm{cm}$ stainless steet
■1S (USP28)
column that contains packing L 1 , and is operated at room temperature. The flow rate is about 1 mL per minute. Chromatograph three replicate injections of the Standard preparation, and record the peak responses as directed for Procedure: the lowest and highest peak response ratios $\left(R_{S}\right)$ agree within $2.0 \%$; the resolution, $R$, between ethyl benzoate and benzoyl peroxide is not less than 2.0 ; and the tailing factors for the ethyl benzoate and benzoyl peroxide peaks are not more than 2.0.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of benzoyl peroxide $\left(\mathrm{C}_{14} \mathrm{H}_{10} \mathrm{O}_{4}\right)$ in the portion of Gel taken by the formula:

$$
125 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of benzoyl peroxide in the Standard preparation; and $R_{U}$ and $R_{S}$ are the peak response
ratios of benzoyl peroxide to ethyl benzoate obtained from the $A s$ say preparation and the Standard preparation, respectively.

## Briefing

Betamethasone Sodium Phosphate, USP 27 page 237. It is proposed to revise Identification test $B$ to update the text in accordance with the Thin-Layer Chromatographic Identification Test $\langle 201\rangle$.
(PA1: C. Anthony) RTS-41352-1

## Change to read:

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$.
B: Prepare a solution in methanol containing 1 mg per mL . Apply $10 \mu \mathrm{~L}$ of this solution and $10 \mu \mathrm{~L}$ of a solution of USP Be tamethasene Sodium Phosphate $R$ SS in methanol containing 1 mg per mL to a suitable thin layer chromatographic plate (see Chromatography ( 624 ) ) conted with -0.25 mm layer of chroma tographic silien gel. Allow the spots dry. Place 500 mL of butyl aleehol and 200 mL of dilute hydrochleric acid ( 1 in 12 ) in a sepa ratory funnel, and mix. Use the organie layer as the developing sol went. Develop the chromatogram in the developing solvent until the-solvent fromt has moved about three fourths of the length of the plate. Proee as directed in the Identification test under Beta methasone Cream, beginning with "Remove the plate."
-Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -

$$
\text { Test solution: } \quad 1 \mathrm{mg} \text { per } \mathrm{mL} \text {. }
$$

Standard solution-Prepare a solution of USP Betamethasone Sodium Phosphate RS in methanol having a concentration of 1 mg per mL .

Developing solvent system—Place 500 mL of butyl alcohol and 200 mL of dilute hydrochloric acid (1 in 12) in a separatory funnel, and mix. Use the organic layer as the developing solvent.
Spray reagent: a mixture of sulfuric acid, methanol, and nitric acid ( $10: 10: 1$ ).

Procedure-Proceed as directed in the chapter except to spray the plate with Spray reagent, and heat at $105^{\circ}$ for 10 minutes.■1S (USP28)

C: Ignite it at $800^{\circ}$ (see Residue on Ignition $\langle 281\rangle$ ): the residue responds to the tests for Sodium $\langle 191\rangle$ and for Phosphate $\langle 191\rangle$.

## BRIEFING

Bismuth Subsalicylate Oral Suspension, page 627 of $P F$ 28(2) [Mar.-Apr. 2002]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded to In-Process Revision with changes to Packaging and storage.
(PA2: C. Anthony) RTS-40957-1

## Add the following:

## Bismuth Subsalicylate Oral Suspension

## » Bismuth Subsalicylate Oral Suspension is a sus-

 pension that contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\mathrm{C}_{7} \mathrm{H}_{5} \mathrm{BiO}_{4}$. It may contain one or more suitable buffers, coloring agents, flavors, preservatives, stabilizers, sweeteners, and suspending agents.Packaging and storage-Preserve in tight containers, and avoid freezing. Store between $15^{\circ}$ and $30^{\circ}$.

## Identification-

A: It responds to the tests for Bismuth $\langle 191\rangle$.
B: It meets the requirements of the tests for Salicylate $\langle 191\rangle$, after acidifying with nitric acid.
$\mathbf{p H}\langle 791\rangle$ : between 3.0 and 5.0.
Microbial limits $\langle 61\rangle$ —The total aerobic microbial count does not exceed 100 cfu per g, the combined yeast and mold count does not exceed 50 cfu per $g$, and it meets the requirements of the tests for absence of Escherichia coli and of Salmonella species.

## Assay-

Standard preparation—Transfer about 500 mg of bismuth metal, accurately weighed, into a $200-\mathrm{mL}$ volumetric flask, dissolve in 12 mL of nitric acid, and dilute with 0.01 N nitric acid to volume. Transfer 10.0 mL of this solution into a 500mL volumetric flask, and dilute with 1 N nitric acid to volume to obtain solution having a concentration of $50 \mu \mathrm{~g}$ of bismuth per mL.

Assay preparation-Transfer an accurately measured quantity of about 10 g of Oral Suspension, previously well-shaken in its original container to ensure homogeneity, to a $200-\mathrm{mL}$ volumetric flask. Add about 100 mL of 1 N nitric acid, mix, and dilute with 1 N nitric acid to volume. Mix well without shaking, and transfer 10.0 mL of this mixture into a $100-\mathrm{mL}$ volumetric flask, and dilute with 1 N nitric acid to volume. Centrifuge about 20 mL at 4500 rpm for at least 10 minutes.

Procedure-Transfer an accurately measured volume of the Assay preparation that contains about 0.9 mg of bismuth subsalicylate and 10 mL of the Standard preparation to separate $50-\mathrm{mL}$ volumetric flasks. Add 10.0 mL of $10 \%$ ascorbic acid solution and 25.0 mL of $20 \%$ potassium iodide solution into each volumetric flask, dilute with water to volume, and mix well. Concomitantly determine the absorbances of both solutions in $1.0-\mathrm{cm}$ cells at a wavelength of $463-\mathrm{nm}$ with a suitable spectrophotometer using the reagent blank to set the spectrophotometer. Calculate the
quantity, in mg , of $\mathrm{C}_{7} \mathrm{H}_{5} \mathrm{BiO}_{4}$ in the portion of Oral Suspension taken by the formula:

$$
(362.11 / 208.98) 20(C / V)\left(A_{U} / A_{S}\right) \text {, }
$$

in which 362.11 and 208.98 are the molecular weights of bismuth subsalicylate and bismuth, respectively; $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of bismuth in the Standard preparation; $V$ is the volume, in mL , of the Assay preparation taken; and $A_{U}$ and $A_{S}$ are the absorbances of the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Bismuth Subsalicylate Tablets, page 1603 of PF 28(5) [Sept.Oct. 2002]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded to In-Process Revision with changes to Packaging and storage.
(PA2: C. Anthony) RTS-40960-1

## Add the following:

## ■Bismuth Subsalicylate Tablets

» Bismuth Subsalicylate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of bismuth subsalicylate

Packaging and storage-Preserve in tight containers.
Store between $15^{\circ}$ and $30^{\circ}$.

Labeling-Label chewable Tablets to indicate that they are to be chewed before swallowing.

## Identification-

A: It meets the requirements of the tests for Bismuth $\langle 191\rangle$.

B: After acidifying with nitric acid, it meets the requirements of the test for Salicylate $\langle 191\rangle$ with ferric chloride TS.

Assay-
Standard preparation-Transfer about 500 mg of bismuth, accurately weighed, to a $200-\mathrm{mL}$ volumetric flask, dissolve in 12 mL of nitric acid, and dilute with 0.01 N nitric acid to volume. Transfer 10.0 mL of the solution so obtained into a $500-\mathrm{mL}$ volumetric flask, and dilute with 1 N nitric acid to volume to obtain a concentration of $50 \mu \mathrm{~g}$ of bismuth per mL.

Assay preparation-Transfer an accurately weighed portion of finely powdered Tablets, equivalent to about 90 mg of bismuth subsalicylate, to a $200-\mathrm{mL}$ volumetric flask, add about 150 mL of 1 N nitric acid, and sonicate for 2 minutes. Dilute with 1 N nitric acid to volume. Transfer 20.0 mL of the solution so obtained to a $100-\mathrm{mL}$ volumetric flask, and dilute with 1 N nitric acid to volume. Centrifuge a portion at 4500 rpm for at least 10 minutes.

Procedure-Transfer 10.0 mL , accurately measured, of the Assay preparation and the Standard preparation to separate $50.0-\mathrm{mL}$ volumetric flasks. Add 10.0 mL of $10 \%$ ascorbic acid solution and 25.0 mL of $20 \%$ potassium iodide solution into each volumetric flask, and dilute with 1 N nitric acid to volume. Concomitantly determine the absorbance of the solutions at the wavelength of maximum absorbance at about 463 nm with a suitable spectrophotometer using the combined reagent solutions as the blank.

Calculate the quantity, in mg , of $\mathrm{C}_{7} \mathrm{H}_{5} \mathrm{BiO}_{4}$ in the portion of Tablets taken by the formula:

$$
(362.11 / 208.98)(C)\left(A_{U} / A_{S}\right),
$$

in which 362.11 and 208.98 are the molecular weights of bismuth subsalicylate and bismuth, respectively; $C$ is the concentration, in $\mu \mathrm{mg}$ per mL , of bismuth in the Standard preparation; and $A_{U}$ and $A_{S}$ are the absorbances of the solutions from the Assay preparation and the Standard preparation, respectively. $\quad$ IS (USP28)

## BRIEFING

Caffeine, USP 27 page 295 and page 1852 of $P F 29(6)$ [Nov.Dec. 2003]. It is proposed to replace the undefined term "fixed alkali" in the Identification test $B$ with the name of the reagent used.
(PA3: S. Salado) RTS-41195-1

## Add the following:

${ }^{\mathbf{4}}$ Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. $\Delta$ USP28

## Change to read:

USP Reference standards $\langle 11\rangle$-USP Caffeine RS.
${ }^{\triangle}$ USP Endotoxin RS. $\mathbf{\Delta U S P 2 8}$

## Change to read:

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$.
B: Dissolve about 5 mg in 1 mL of hydrochloric acid in a porcelain dish, add 50 mg of potassium chlorate, and evaporate on a steam bath to dryness. Invert the dish over a vessel containing a
few drops of 6 N ammonium hydroxide: the residue acquires a purple color, which disappears upon the addition of a solution of a fixed alkali.
$\square_{1} \mathrm{~N}$ sodium hydroxide.■1S (USP28)

## Add the following:

${ }^{4}$ Other requirements-Where the label states that Caffeine is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Caffeine and Sodium Benzoate Injection. Where the label states that Caffeine must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Caffeine and Sodium Benzoate Injection. $\triangle U S P 28$

## BRIEFING

Calcitonin Salmon; Calcitonin Salmon Injection; Calcitonin Salmon Nasal Solution. Because there are no existing USP monographs for this drug substance and its dosage forms, new monographs, based on validated methods of analysis, are being proposed. The liquid chromatographic procedure in the test for $R e$ lated peptides and related substances and in the Assay is based on analyses performed with the Nucleosil 100-5 C18 brand of L1 column. The typical retention time for calcitonin salmon is about 16 minutes. The liquid chromatographic procedure in the test for Limit of trifluoroacetic acid is based on analyses performed with the Dionex AS11 column. The typical retention times for chloride and trifluoroacetate are about 8 and 11 minutes, respectively. The gas chromatographic procedure in the test for Limit of residual solvents is based on analyses performed with the Restek Rtx-1 brand of G38 column. The approximate retention times for methanol, acetonitrile, dichloromethane, tert-butyl methyl ether, and dimethylformamide are about 5.1, 7.1, 9.3, 11.4, and 21.3 minutes, respectively. The test for Bioidentity used the Amersham cAMP Direct Biotrak EIA kit to quantify the amount of cAMP produced by stimulation.
(BNT: L. Callahan) RTS-34296-1

## Add the following:

## ■Calcitonin Salmon

```
CSNLSTCVLG KLSQELHKLQ TYPRTNTGSG TP
C
```

» Calcitonin Salmon is a synthetic polypeptide that has the same sequence as that of the hor-mone-regulating calcium metabolism secreted by the ultimobranchial gland of salmon. It lowers the calcium concentration in plasma of mammals by diminishing the rate of bone resorption. It contains not less than 90.0 percent and not more than 105.0 percent of calcitonin salmon, calculated on an acetic acid-free and dried basis.

NOTE-1 mg of acetic acid-free, anhydrous Calcitonin Salmon is equivalent to 6000 USP Calcitonin Salmon Units.

Packaging and storage-Preserve in tight containers.
Store protected from light in a refrigerator.
Labeling-The labeling states that the material is synthetic.
USP Reference standards $\langle\mathbf{1 1}\rangle$ —USP Calcitonin Salmon RS. USP Calcitonin Salmon Related Compound A RS ( $N$ -acetyl-cys ${ }^{1}$-calcitonin). USP Endotoxin RS.

## Identification-

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, obtained as directed in the Assay.

B: The UV absorption spectrum of a $0.1 \%$ solution (based on free peptide) in 0.01 N hydrochloric acid exhibits a minima and a maxima at the same wavelengths as those of a similar solution of USP Calcitonin Salmon RS, concomitantly measured. The absorbance at approximately 275 nm (maxima) is about 0.40 to 0.55 , and the ratio of the absorbance at 275 nm (maxima) and 254 nm (minima) is between 1.6 and 2.5 .

Amino acid profile (see Amino Acid Analysis, Method 1, under Biotechnology-Derived Articles-Tests $\langle 1047\rangle$ )-

Internal standard solution-Prepare a 1 mM solution of $\gamma$-aminobutyric acid.
Standard amino acid solution-Prepare a mixture containing equimolar amounts of ammonia and the L form of lysine, histidine, arginine, aspartic acid, threonine, serine, proline, valine, glutamic acid, glycine, leucine, and tyrosine, together with half the equimolar amount of L-cystine, in 0.1 M hydrochloric acid. The final concentration is about 2.5 mM for each amino acid.

Standard solution-Transfer 5 mL of the Internal standard solution and 2 mL of the Standard amino acid solution into a $50-\mathrm{mL}$ volumetric flask, and dilute with 0.1 M hydrochloric acid to volume.

Test solution-Place about 1.5 mg of an accurately weighed quantity of Calcitonin Salmon into a heavy-wall ignition tube, add 1.0 mL of 6 N hydrochloric acid, allow to cool, immerse the lower half of the tube in a freezing mixture until the contents are frozen, evacuate to approximately $10 \mu \mathrm{M}$, purge with nitrogen (repeat the evacuation and nitrogen purge three times), and seal the tube while it is under a $10-\mu \mathrm{M}$ vacuum. Heat for 16 hours at $110^{\circ}$ to $115^{\circ}$ in an air oven. Cool, open the tube, dry in a vacuum desiccator, remove the contents, and allow to cool to room temperature.

Dissolve in 0.1 M hydrochloric acid, transfer to a $10-\mathrm{mL}$ volumetric flask, add 1 mL of Internal standard solution, and dilute with 0.1 M hydrochloric acid to volume.

Procedure-Standardize the amino acid analyzer, using the Standard solution. Inject the Test solution into the amino acid analyzer, and determine the relative proportion of amino acids.

Calculation of amino acid profile-Express the content of each amino acid in moles, using an internal standard calibration technique. Calculate the relative proportions of the amino acids by taking as equivalent to 1 the sum divided by 20 of the number of moles of aspartic acid, glutamic acid, proline, glycine, valine, leucine, histidine, arginine, and lysine. For threonine and serine, perform the same calculation, and correct the concentrations for degradation by adding $5 \%$ and $10 \%$, respectively, to their indicated results. The requirements are met if the values fall within the following limits: aspartic acid, 1.8 to 2.2 ; glutamic acid, 2.7 to 3.3 ; proline, 1.7 to 2.3 ; glycine, 2.7 to 3.3 ; valine, 0.9 to 1.1 ; leucine, 4.5 to 5.3 ; histidine, 0.9 to 1.1 ; arginine, 0.9 to 1.1 ; lysine, 1.8 to 2.2; serine, 3.2 to 4.2 ; threonine, 4.2 to 5.2 ; tyrosine, 0.7 to 1.1; half cystine, 1.4 to 2.1 .

Bacterial endotoxins $\langle 85\rangle$-It contains not more than 1000 USP Endotoxin Units per mg of calcitonin salmon.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed 100 cfu per g. It meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.
$\mathbf{p H}\langle 791\rangle$ : between 4.0 and 6.0 in a $1 \%$ solution in carbon dioxide-free water.

Water, Method Ic $\langle 921\rangle$ : not more than $10 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $0.005 \%$.

Limit of trifluoroacetic acid- [NOTE-Use deionized, degassed water where water is indicated.]

Solution A: water.
Solution B: 0.005 N sodium hydroxide.
Solution C: 0.1 N sodium hydroxide.
Mobile phase-Use variable mixtures of Solution A, Solution B, and Solution C as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Chloride stock standard solution-Dissolve an accurately weighed quantity of sodium chloride in water to obtain a solution having a concentration of the chloride ion of about 0.1 mg per mL .

Trifluoroacetic acid stock standard solution-Dissolve an accurately weighed quantity of trifluoroacetic acid in water to obtain a solution having a concentration of trifluoroacetic acid of about 0.1 mg per mL .
Resolution solution-Pipet 0.2 mL of Chloride stock standard solution and 0.5 mL of Trifluoroacetic acid stock standard solution into a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain a solution that contains $0.2 \mu \mathrm{~g}$ of chloride and $0.5 \mu \mathrm{~g}$ of trifluoroacetate per mL , respectively.
Standard solutions-Pipet $0.2 \mathrm{~mL}, 0.5 \mathrm{~mL}, 1.0 \mathrm{~mL}$, and 2.0 mL of Trifluoroacetic acid stock standard solution into ordered $100-\mathrm{mL}$ volumetric flasks. Dilute with water to volume and mix to obtain solutions that contain concentrations of about $0.2 \mu \mathrm{~g}, 0.5 \mu \mathrm{~g}, 1.0 \mu \mathrm{~g}$, and $2.0 \mu \mathrm{~g}$ of trifluoroacetate per mL , respectively.

Test solution-Transfer about 10 mg of Calcitonin Salmon, accurately weighed, to a $5-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The ion chromatograph is equipped with a conductivity detector, a 4-mm $\times 5-\mathrm{cm}$ anion-exchange guard column con-
taining packing L31, a $4-\mathrm{mm} \times 25-\mathrm{cm}$ anion-exchange analytical column containing packing L31, a high-capacity anion trap column in hydroxide form in the eluent line in front of the injection valve, and a micromembrane anion self-regenerating suppressor. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows.

| Time | Solution | Solution | Solution |  |
| :---: | :---: | :---: | :---: | :--- |
| (Minutes) | $A(\%)$ | $B(\%)$ | $C(\%)$ | Elution |
| $0-2$ | 90 | 10 | 0 | isocratic |
| $2-5$ | $90 \rightarrow 0$ | $10 \rightarrow 100$ | 0 | linear gradient |
| $5-15$ | 0 | $100 \rightarrow 65$ | $0 \rightarrow 35$ | linear gradient |
| $15-20$ | $0 \rightarrow 90$ | $65 \rightarrow 10$ | $35 \rightarrow 0$ | linear gradient |

Chromatograph the Resolution solution, and record the peak responses as directed for the Procedure: the resolution, $R$, between the chloride peak and the trifluoroacetic acid peak is not less than 3 ; and the relative standard deviation for replicate injections is not more than $5.0 \%$.

Procedure—Separately inject equal volumes (about 100 $\mu \mathrm{L}$ ) of each of the Standard solutions and the Test solution into the chromatograph, record the chromatograms, and measure the area of peak responses. Plot the response of the trifluoroacetic acid peak in the Standard solutions versus the concentration of trifluoroacetic acid, and draw the straight line best fitting the plotted points. From the graphs so obtained, determine a concentration value, $C$, in $\mu \mathrm{g}$ per mL for trifluoroacetic acid. Calculate the quantity, in ppm, for trifluoroacetic acid in Calcitonin Salmon by the formula:

$$
5000(C / W)
$$

in which $W$ is the weight in mg of Calcitonin Salmon taken to prepare the Test solution: not more than 200 ppm of trifluoroacetic acid is found.

## Limit of residual solvents-

Standard stock solution—Prepare a solution containing about $300 \mu \mathrm{~g}$ of methanol, $40 \mu \mathrm{~g}$ of acetonitrile, $60 \mu \mathrm{~g}$ of methylene chloride, $500 \mu \mathrm{~g}$ of tert-butyl methyl ether, and $90 \mu \mathrm{~g}$ of dimethylformamide per mL of methyl sulfoxide.

Standard solution-Transfer 5 mL of the Standard stock solution to a $25-\mathrm{mL}$ volumetric flask, and dilute with dimethyl sulfoxide to volume. Transfer 1 mL of the Standard solution to a $20-\mathrm{mL}$ headspace vial fitted with a septum and a crimp cap, and seal the vial.

Test solution 1-Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a $20-\mathrm{mL}$ headspace vial fitted with a septum and a crimp cap, add 1 mL of dimethyl sulfoxide, seal the vial, and mix.

Test solution 2-Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a $20-\mathrm{mL}$ headspace vial fitted with a septum and a crimp cap, add 1 mL of Standard solution, seal the vial, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a headspace injector and a flame-ionization detector and contains a $0.32-\mathrm{mm}$ $\times 60-\mathrm{m}$ fused silica column coated with a $1.0-\mu \mathrm{m}$ film of stationary phase G38. Nitrogen is used as the carrier gas, flowing at a rate of about 25 mL per minute. The column temperature is maintained at $45^{\circ}$ for 2 minutes, then increased at a rate of $10^{\circ}$ per minute to $75^{\circ}$, then increased at a rate of $5^{\circ}$ per minute to $170^{\circ}$ and maintained at $170^{\circ}$ for 3 minutes. The split injector temperature is maintained at about $200^{\circ}$, and the detector temperature is maintained at about $170^{\circ}$. The transfer loop and transfer line temperature is $170^{\circ}$, and the pressurize time is 0.5 minute. The Standard solution vial and the Test solutions 1 and 2 vials are maintained at about $90^{\circ}$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.55 for methanol, 0.76 for
acetonitrile, 1.0 for methylene chloride, 1.2 for tert-butyl methyl ether, and 2.3 for dimethylformamide; and the relative standard deviation, determined from peak areas for each peak, for six replicate injections is not more than $10 \%$.

Procedure-Separately inject equal volumes (about 1 mL ) of headspace from vials of Test solution 1 and Test solution 2 into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of methanol, acetonitrile, methylene chloride, tert-butyl methyl ether, and dimethylformamide in the Calcitonin Salmon taken by the formula:

$$
100\left(r_{T 1}\right)(C) /\left(r_{T 2}\right)\left(W_{T 1}\right)-\left(r_{T 1}\right)\left(W_{T 2}\right),
$$

in which $C$ is the concentration, in mg per mL , of the relevant analyte in the Standard solution; $W_{T 1}$ and $W_{T 2}$ are the weights, in mg, of Calcitonin Salmon taken to prepare Test solution 1 and Test solution 2, respectively; and $r_{T 1}$ and $r_{12}$ are the peak areas of the corresponding analyte obtained from Test solution 1 and Test solution 2, respectively: not more than $3000 \mu \mathrm{~g}$ of methanol, $400 \mu \mathrm{~g}$ of acetonitrile, $600 \mu \mathrm{~g}$ of methylene chloride, $5000 \mu \mathrm{~g}$ of tert-butyl methyl ether, and $900 \mu \mathrm{~g}$ of dimethylformamide per g of Calcitonin Salmon are found.

## Acetic acid content-

Internal standard stock solution-Mix 1 mL of dioxane with water to obtain 100 mL of solution.
Standard solution-Transfer approximately 100 mg of glacial acetic acid, accurately weighed, and 10 mL of Internal standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Test solution-Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, add 1 mL of Internal standard stock solution, dissolve in and dilute with water to volume, and mix.

Chromatographic system see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and a $2-\mathrm{mm} \times 3-\mathrm{m}$ glass column packed with $10 \%$ liquid phase G35, $1 \%$ phosphoric acid, on support S 1 A . Nitrogen is the carrier gas, flowing at a rate of about 30 mL per minute. The column is maintained at $70^{\circ}$ for 4 minutes, then increased at a rate of $8^{\circ}$ per minute to $120^{\circ}$, then maintained at $120^{\circ}$ for 4 minutes. The injection port and detector are maintained isothermally at temperatures of about $200^{\circ}$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the resolution, $R$, between dioxane and acetic acid is not less than 8 ; and the relative standard deviation for replicate injections is not more than 5.0\%.

Procedure-Separately inject equal volumes (about $4 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses of the major peaks. The retention times are about 3 minutes for acetic acid and 1 minute for dioxane. Calculate the percentage of acetic acid in the portion of Calcitonin Salmon taken by the formula:

$$
1000(C / W)\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of acetic acid in the Standard solution; and $R_{U}$ and $R_{S}$ are the peak response ratios of acetic acid to dioxane obtained from the Test solution and the Standard solution, respectively: not less than $4.0 \%$ and not more than $15.0 \%$ is found.

## Bioidentity-

RPMI 1640 with L-glutamine-Prepare a mixture of the ingredients in the quantities shown in sufficient water to obtain 1 L of medium, and sterilize by filtration.

Calcium Nitrate
Potassium Chloride
100.00 mg
400.00 mg

| Thiamine Hydrochloride | 1 mg |
| :--- | :---: |
| Vitamin $\mathrm{B}_{12}$ | 0.005 mg |

Medium $A$ (growth medium)-Using aseptic technique, prepare the following tissue culture medium.

| RPMI 1640 with L-glutamine | 500 mL |
| :--- | ---: |
| Fetal bovine serum | 50 mL |
| 1 M HEPES | 5 mL |
| Penicillin/streptomycin solution |  |
| $\quad(10,000$ IU per mL $/ 10 \mathrm{mg}$ per mL$)$ | 5 mL |
| Human insulin | 10 IU |
| Hydrocortisone | 0.5 mg |

Medium $B$ (stimulation medium)-Dissolve 5 g of albumin bovine serum (BSA), in 500 mL of RPMI 1640 with $2 m M L$-glutamine.
$2 \%$ BSA solution-Dissolve 50 mg of albumin bovine serum in 25 mL of water. [NOTE-Use within 1 day.]

Formic acid/BSA solution-Add 25 mL of 0.1 M formic acid and 5 mL of $2 \%$ BSA solution to a $50-\mathrm{mL}$ volumetric flask, and dilute with water to volume. [NOTE-Use within 2 days.]

Trypsin-tetrasodium ethylenediaminetetraacetate (EDTA) solution-Prepare a sterile filtered solution containing $0.25 \%$ trypsin and 0.53 mM EDTA.

Dulbecco's phosphate buffered saline-Dissolve 8 g of sodium chloride, 1.15 g of dibasic sodium phosphate, 0.2 g of monobasic potassium phosphate, 0.2 g of potassium chloride, 0.1 g of calcium chloride, and 0.1 g of magnesium chloride in 1 L of water.

Standard stock solution-Dissolve an accurately weighed quantity of USP Calcitonin Salmon RS in Formic acid/BSA solution to obtain a solution having a known concentration of about $20 \mu \mathrm{~g}$ per mL .

Positive control solution-Quantitatively dilute the Standard stock solution with Medium B to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 1 ng per mL .

Negative control solution: Medium B.
Standard solution $A-$ Quantitatively dilute the Standard stock solution with Medium $B$ to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.1 ng per mL .

Standard solution B-Dilute Standard solution A quantitatively with Medium $B$ to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.033 ng per mL.

Standard solution C-Dilute Standard solution B quantitatively $(1: 2)$ with Medium $B$ to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.011 ng per mL .

Standard solution D-Dilute Standard solution C quantitatively ( $1: 2$ ) with Medium $B$ to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.0037 ng per mL.

Test stock solution-Dissolve an accurately weighed quantity of Calcitonin Salmon in Formic acid/BSA solution to obtain a solution having concentration of about $20 \mu \mathrm{~g}$ per mL .

Test solution $A$ - Quantitatively dilute the Test stock solution with Medium B to obtain a solution of Calcitonin Salmon having a concentration of 0.1 ng per mL .
Test solution $B$ - Quantitatively dilute Test solution $A$ with Medium $B(1: 2)$ to obtain a solution of Calcitonin Salmon having a concentration of 0.033 ng per mL .
Test solution $C$ - Quantitatively dilute Test solution $B$ with Medium $B(1: 2)$ to obtain a solution of Calcitonin Salmon having a concentration of 0.011 ng per mL .

Test solution $D$ - Quantitatively dilute Test solution $C$ with Medium $B(1: 2)$ to obtain a solution of Calcitonin Salmon having a concentration of 0.0037 ng per mL .

Cell culture preparation-Prepare cell culture of the human mammary tumor cell line T-47D. Cells are propagated using Medium $A$ at $37^{\circ}$ and $5 \%$ carbon dioxide. The medium is changed every 2 days, and cells are passaged every 5 to 9 days, using Trypsin-EDTA solution with a $1: 4$ subculture.

Cell suspension-For the test, use a cell culture that is 5 to 9 days old. Remove the cell culture medium from the flask by aspiration, add 10 mL of Dulbecco's phosphate buffered saline, and rock the culture flask to rinse the entire monolayer. Remove the liquid by aspiration, add 2 mL of Tryp-sin-EDTA solution, spread over the entire monolayer, allow to stand for 3 to 5 minutes, and add 10 mL of Medium $A$. Homogenize the cell suspension using a pipet, transfer to a $15-\mathrm{mL}$ polypropylene tube, centrifuge at about 220 g for 5 minutes, pour off the supernatant, and resuspend the cell pellet in 10 mL of Medium $A$. Count the cells, and adjust cell density to $2.5 \times 10^{4}$ cells per mL through dilution, using

## Medium $A$.

Procedure—Place $200 \mu \mathrm{~L}$ of the Cell suspension into each well of a 96-well culture plate (the tissue culture plate), and incubate for 18 to 24 hours at $37^{\circ}$ and $5 \%$ carbon dioxide. Fill each well of an empty round-bottomed 96-well culture plate (the prepared plate) with $150 \mu \mathrm{~L}$ of one of the following solutions: Positive control solution, Negative control solution, Standard solutions $A-D$, and Test solutions $A-$ $D$, so that each solution fills at least five wells on the prepared plate. After incubation, remove the culture medium from the tissue culture plate. Using an 8-channel or 12-channel pipet, rapidly transfer $100 \mu \mathrm{~L}$ of solution from each well of the prepared plate to each well of the tissue culture plate. Incubate for 15 minutes at ambient temperature, remove solution from each well, stop stimulation by immediately
adding an appropriate cell-lysis buffer, and quantitate cAMP, produced within the cells, using a validated kit. Perform the test three times, using three different 96-well culture plates. [NOTE-Some kits include a cell-lysis reagent and a sequestering agent for the cell-lysis reagent. The range of the test kit is between 0.05 ng and 10 ng per mL of cAMP.] Potency is determined by a 3 -dose, 6 -point paral-lel-line assay, using standard statistical methods. The calculation is carried out using both the lower three concentrations and the upper three concentrations. For the assay to be valid, the requirements for regression and parallelism must be met. If the requirements for validity are met to the same extent in both assessments (the lower and the higher assessments), the final result is determined from the concentration range that shows the higher value when the common slope is divided by the mean square error. The potency levels determined from all three performances of the test are homogeneous, and the confidence limits for all three determinations are between $64 \%$ and $156 \%$ of the calculated potency.

## Related peptides and other related substances-

Test solution-Prepare as directed for the Assay preparation in the Assay.

Solution A, Solution B, Mobile phase, Resolution solution, and Chromatographic system-Prepare as directed in the Assay.

Procedure-Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the area percentage of each peak observed in the chromatogram. Disregard any peaks due to the solvent and any peaks whose area is less than $0.1 \%$ of the principal peak. No peak other than the principal peak constitutes more than $3.0 \%$ of the total
area of all peaks. The sum of the area of all peaks apart from the principal peak is not greater than $5.0 \%$ of the area of all peaks.

Other requirements-Where the label states that Calcitonin Salmon is sterile, it meet the requirements for Sterility under Calcitonin Salmon Injection.

Assay-
Solution A-Dissolve 3.62 g of tetramethylammonium hydroxide pentahydrate in 900 mL of water, add 100 mL of acetonitrile, and mix. Adjust with phosphoric acid to a pH of 2.5 , pass through a filter having a $0.5-\mu \mathrm{m}$ or finer porosity, and degas.

Solution B—Dissolve 1.45 g of tetramethylammonium hydroxide pentahydrate in 400 mL of water, add 600 mL of acetonitrile, and mix. Adjust with phosphoric acid to a pH of 2.5 , pass through a filter having a $0.5-\mu \mathrm{m}$ or finer porosity, and degas.

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability underChroamtography $\langle 621\rangle$ ).

Standard preparation-Transfer about 10.0 mg of USP Calcitonin Salmon RS, accurately weighed, into a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Solution $A$ to volume, and mix.

Resolution solution-Dissolve the contents of a vial of USP Calcitonin Salmon Related Compound A RS in 0.4 mL of Solution $A$, add 0.1 mL of the Standard preparation, and mix.

Assay preparation-Transfer about 10.0 mg of Calcitonin Salmon, accurately weighed, into a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Solution $A$, to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing

L1. The column temperature is maintained at about $65^{\circ}$. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Time | Solution A | Solution B |  |
| :---: | :---: | :---: | :--- |
| (Minutes) | $(\%)$ | $(\%)$ | Elution |
| $0-30$ | $72 \rightarrow 48$ | $28 \rightarrow 52$ | linear gradient |
| $30-32$ | $48 \rightarrow 72$ | $52 \rightarrow 28$ | linear gradient |
| $32-55$ | 72 | 28 | isocratic |

Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.15 for calcitonin salmon related compound A and 1.0 for calcitonin salmon; the resolution, $R$, between calcitonin salmon related compound A and calcitonin salmon is not less than 3 ; the tailing factor is not more than 2.5 ; and the relative standard deviation for replicate injections is not more than $3 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses of the major peaks. Calculate the percentage of calcitonin salmon in the portion of Calcitonin Salmon taken by the formula:

$$
P\left(W_{s} / W_{U}\right)\left(r_{U} / r_{s}\right),
$$

in which $P$ is the percentage of calcitonin salmon in USP Calcitonin Salmon RS; $W_{S}$ is the weight, in mg , of USP Calcitonin Salmon RS used to prepare the Standard preparation; $W_{U}$ is the weight, in mg, of Calcitonin Salmon used to prepare the Assay preparation; and $r_{U}$ and $r_{s}$ are the main peak areas from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Calcitonin Salmon Injection-See briefing under Calcitonin Salmon.
(BNT: L. Callahan) RTS-41052-3

## Add the following:

## ■Calcitonin Salmon Injection

" Calcitonin Salmon Injection is a sterile solution of Calcitonin Salmon in a suitable diluent. Each mL of Calcitonin Salmon Injection possesses an activity of not less than 80 percent and not more than 110 percent of that stated on the label.

Packaging and storage-Preserve in single-dose or multi-ple-dose containers, preferably of Type I glass. Avoid freezing. Store in refrigerator.

Labeling-Label it to indicate the activity in USP Calcitonin Salmon Units per mL. The labeling states that the material is synthetic. Label it to state that it is to be stored in a refrigerator and that freezing is to be avoided.

USP Reference standards $\langle 11\rangle$ —USP Calcitonin Salmon RS. USP Calcitonin Salmon Related Compound A RS. USP Endotoxin RS.

Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Bacterial endotoxins $\langle 85\rangle$ - It contains not more than 0.625 USP Endotoxin Units per USP Calcitonin Salmon Unit.

Sterility $\langle 71\rangle$ —It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.
$\mathbf{p H}\langle 791\rangle$ : between 3.9 and 4.5.
Particulate matter $\langle 788\rangle$ : meets the requirements for small-volume injections.

Other requirements-It meets the requirements under $I n$ jections $\langle 1\rangle$.

Assay-
Solution A, Solution B, Mobile phase, and Chromatographic system-Prepare as directed in the Assay under Calcitonin Salmon.

Standard stock preparation-Transfer about 10.0 mg of USP Calcitonin Salmon RS, accurately weighed, into a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Solution $A$ to volume, and mix.
Standard preparation-Transfer 1 mL of the Standard stock preparation into a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Solution $A$ to volume, and mix.
Resolution solution-Dissolve the contents of a vial of USP Calcitonin Salmon Related Compound A RS and 0.4 mL of Solution $A$, add 0.1 mL of the Standard preparation, and mix. Take 0.1 mL of this solution, add 0.9 mL of Solution $A$, and mix.

Assay preparation-Use the solution from an undiluted injection vial.

Procedure-Separately inject equal volumes (about 200 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the potency, in USP Calcitonin Salmon Units per mL, in the portion of Injection taken by the formula:

$$
C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration of the Standard preparation, in USP Calcitonin Salmon Units per mL; and $r_{U}$ and $r_{s}$ are the main peak areas from the Assay preparation and Standard preparation, respectively.■1S (USP28)

## Briefing

Calcitonin Salmon Nasal Solution-See briefing under Calcitonin Salmon.
(BNT: L. Callahan) RTS-41052-2

## Add the following:

## ■Calcitonin Salmon Nasal Solution

» Calcitonin Salmon Nasal Solution is a solution of Calcitonin Salmon in a suitable diluent. It contains suitable preservatives, and is packaged in a form suitable for nasal administration so that the required dosage can be controlled as required. Each mL of Calcitonin Salmon Nasal Solution possesses an activity of not less than 80 percent and not more than 110 percent of that stated on the label.

Packaging and storage-Preserve in containers suitable for spraying the contents into the nasal cavities in a controlled individualized dosage. Store unopened containers in a refrigerator, and opened containers at room temperature.

Labeling-Label it to indicate that it is for intranasal administration only. Label it to state that the origin is synthetic.

USP Reference standards $\langle 11\rangle —$ USP Calcitonin Salmon RS. USP Calcitonin Salmon Related Compound A RS.
$\mathbf{p H}\langle 791\rangle$ : between 3.5 and 4.5.
Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Microbial limits $\langle 61\rangle$ —The total aerobic microbial count does not exceed 100 cfu per g , and the total combined molds and yeast count does not exceed 50 cfu per g. It meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.

## Assay-

Solution A, Solution B, Mobile phase, Standard preparation, Resolution solution, and Chromatographic systemPrepare as directed in the Assay under Calcitonin Salmon Injection.

Diluent-Dissolve 0.75 g of sodium chloride, 0.2 g of sodium acetate, and 0.2 g of glacial acetic acid in 100 mL of water.

Assay preparation-Transfer 1 mL of Nasal Solution to a $10-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.

Procedure-Separately inject equal volumes (about 200 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the potency, in USP Calcitonin Salmon Units per mL, in the Nasal Solution taken by the formula:

$$
10 C\left(r_{U} / r_{S}\right),
$$

in which $C$ is the concentration of the Standard preparation, in USP Calcitonin Salmon Units per mL; and $r_{U}$ and $r_{S}$ are the main peak areas from the Assay preparation and Standard preparation, respectively.■1S (USP28)

| Letter <br> code | Related substance | Relative <br> retention <br> time |
| :---: | :---: | :---: |
| N | 10,11 -anhydro-6- $O$-methylerythro- <br> mycin A | 1.15 |
| O | $6-O-$-methylerythromycin A-9- <br> oxime (Z) | 1.38 |
| P | $6,4^{\prime \prime}$-di- $O$-methylerythromycin A | 1.35 |

(PA7: W. Wright) RTS-40852-1

## Change to read:

» Clarithromycin contains not less than $960 \mu \mathrm{~g}$ and net more than $1040 \mu \mathrm{~g}$ of $\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}$ per mg,
-96.0 percent and not more than 102.0 percent of
$\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}$, ${ }_{\text {1S (USP28) }}$
calculated on the anhydrous basis.

## Change to read:

USP Reference standards $\langle 11\rangle —$ USP Clarithromycin $R S$. USP
Elarithromyein Related Compound A RS.

- USP Clarithromycin Identity $R S_{\text {.■ }}$ (USP28)


## Change to read:

Identification, Infrared-Absorption-(197S):
■Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.■1S (USP28)
1-in 20 solution in chloroform.
$\square_{\text {■1S (USP28) }}$

## Change to read:

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $89^{\circ}$ and $95^{\circ}$
■-94 ${ }^{\circ}$ and $-102^{\circ}$ ■1S (USP28)
( $t=20^{\circ}$ ).
Test solution: $\quad 10 \mathrm{mg}$ per mL , in ehloreform.
$\mathbf{■}_{\text {methylene chloride. }}$.1S (USP28)

## Change to read:

$\mathbf{p H}\langle 791\rangle$ : between 7.5

- $8.0_{15}$ (USP28)
and 10.0 , determined in a 1 in 500 suspension of it in a mixture of water and methanol (19:1).


## Change to read:

Residue on ignition $\langle 281\rangle$ : mot more than $0.3 \%$, the chatred residue being moistened with 2 mL of nitric acid and 5 drops of sulfuric acid.

- not more than $0.2 \%, 0.5 \mathrm{~g}$ of it being taken, the charred residue being moistened with 1 mL of sulfuric acid. ${ }^{1 S}$ (USP28)


## Change to read:

Heavy metals: $\Psi\langle z 34\rangle$
-1S (USP28)
not more than $0.002 \%$.
-Test solution-Dissolve 1.0 g of it in an $85 \%(\mathrm{v} / \mathrm{v})$ solution of dioxane in water, and dilute with the same diluent to 20 mL . Transfer 12 mL of this solution to a color-comparison tube.

Blank-Add 10 mL of an $85 \%(\mathrm{v} / \mathrm{v})$ solution of dioxane in water and 2 mL of the Test solution to a color-comparison tube.

Standard solution-Prepare using standard lead solution ( 1 ppm Pb ) obtained by diluting standard lead solution ( 100 ppm Pb ) with an $85 \%(\mathrm{v} / \mathrm{v})$ solution of dioxane in water. Add 10 mL of this solution ( 1 ppm Pb ) and 2 mL of the Test solution to a color-comparison tube. To each of the three tubes containing the Test solution, the Blank, and the Standard solution add 2 mL of pH 3.5 acetate buffer, mix, add 1.2 mL of thioacetamide-glycerin base TS, and mix. Compared to the Blank, the Standard solution shows a slight brown color. After 2 minutes, any brown color in the Test solution is not more intense than that in the Standard solution.■1S (USP28)

## Add the following:

-Related substances-
Solution A-Prepare a solution containing 4.76 g of monobasic potassium phosphate per L. Adjust to a pH of 4.4 with dilute phosphoric acid ( 1 in 10) or potassium hydroxide ( $45 \% \mathrm{w} / \mathrm{v}$ ). Pass this solution through a C18 filtration kit.

Solution B-Use acetonitrile.
Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed under Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Diluting solution-Prepare a mixture of acetonitrile and water (50:50).

Standard solution A-Transfer about 75 mg of USP Clarithromycin RS, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, and dissolve in 25 mL of acetonitrile. Dilute with water to volume, and mix.
Standard solution B-Transfer 5.0 mL of Standard solution $A$ to a $100-\mathrm{mL}$ volumetric flask, dilute with Diluting solution to volume, and mix.

Standard solution C-Transfer 1.0 mL of Standard solution $B$ to a $10-\mathrm{mL}$ volumetric flask, dilute with Diluting solution to volume, and mix. This solution contains about 0.0075 mg of USP Clarithromycin RS per mL.

Standard solution D—Transfer about 15 mg of USP Clarithromycin Identity RS, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in 5.0 mL of acetonitrile, dilute with water to volume, and mix.

Test solution-Transfer about 75 mg of Clarithromycin, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in 25 mL of acetonitrile, dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $205-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ column that contains packing L1 and is maintained at a constant temperature of about $40^{\circ}$. The flow rate is about 1.1 mL per minute. The chromatograph is programmed as follows.

Time $\quad$ Solution A $\quad$ Solution B

| (minutes) | $(\%)$ | $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0 \rightarrow 32$ | $75 \rightarrow 40$ | $25 \rightarrow 60$ | linear gradient |
| $32 \rightarrow 34$ | 40 | 60 | isocratic |
| $34 \rightarrow 36$ | $40 \rightarrow 75$ | $60 \rightarrow 25$ | linear gradient |
| $36 \rightarrow 42$ | 75 | 25 | isocratic |

Relative retention times with reference to clarithromycin (retention time $=$ about 11 minutes) include the following: impurity $\mathrm{I}=$ about 0.38 ; impurity $\mathrm{C}=$ about 0.89 ; impurity $\mathrm{F}=$ about 1.33 ; impurity $\mathrm{A}=$ about 0.42 ; impurity $\mathrm{D}=$ about 0.96 ; impurity $\mathrm{P}=$ about 1.35 ; impurity $\mathrm{J}=$ about 0.63 ; impurity $\mathrm{N}=$ about 1.15 ; impurity $\mathrm{K}=$ about 1.59 ; impurity L $=$ about 0.74 ; impurity $\mathrm{E}=$ about 1.27 ; impurity $\mathrm{G}=$ about 1.72 ; impurity $\mathrm{B}=$ about 0.79 ; impurity $0=$ about 1.38 ; impurity $\mathrm{H}=$ about 1.82 ; and mpurity $\mathrm{M}=$ about 0.81 .

System suitability-Chromatograph Standard solution B, and record the responses as directed for Procedure: the tailing factor for the main clarithromycin peak is not more than 1.7. Chromatograph Standard solution D, and record the responses as directed for Procedure: the peak-to-valley ratio ( $H_{P} / H_{V}$ ) of impurity D and clarithromycin is not less than 3.0, where $H_{P}$ is the height above the baseline of the peak due to impurity D ; and $H_{V}$ is the height above the baseline of the lowest point of the curve separating this peak from the peak due to clarithromycin.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Diluting solution, Standard solution B, Standard solution D, Standard solution C, and the Test solution into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the percentage of each impurity in the Clarithromycin taken by the formula:

$$
50\left(C_{C} / W\right)\left(r_{i} F / r_{C}\right) P
$$

in which $C_{C}$ is the concentration, in mg per mL, of USP Clarithromycin RS in Standard solution C; $W$ is the weight, in mg , of Clarithromycin taken to prepare the Test solution; $r_{i}$ is the peak area response for any individual impurity observed in the chromatogram obtained from the Test solution; $F$ is 1.0, or the correction factor of 0.27 , and 0.15 applied to the responses for peaks at relative retention times in relation to that of clarithromycin of about 1.72 , and 1.82 , corresponding to related compound G and related compound H , respectively; $r_{C}$ is the peak area response of the main clarithromycin peak in the chromatogram obtained from Standard solution $C$; and $P$ is the purity of USP Clarithromycin RS taken to prepare Standard solution A. Not more than $1.0 \%$ of any single related compound is found, not more than four related compounds exceed the limit of $0.4 \%$, and the total of all related compounds is not more than $3.5 \%$. ${ }^{1 S}$ (USP28)

## Change to read:

Assay-
Mobile phase-Prepare a mixture of methanel and- 0.067 M menobasic potassimm phosphate $(650: 350)$, adjust with phespherie acid to a pH of 4.0 , filter through a filter having a peresity of 0.5 Hmor finer, and degas. Make adjustments if neeessay (see System Suitability under Chromatography (621)).
Standard preparation- Bissolve an aceurately weighedquantity of USP Clarithromyein PS quantitatively in methanel, shaking and senieating if nee ssary to assure dissolution, to obtain a stock solut tion having a known concentration of about $625 \mu$ g of elarithremy ein $\left(\mathrm{G}_{38} \mathrm{H}_{69} \mathrm{NO}_{+7}\right)$ per mL, taking intorecm the stated potency, in Hg per mg, of USP Clarithremyein RS. Transfer 10.0 mL of this stock solution to a 50 mL volumetric flask, dilute with Mobile phase to volume, and mix. Filter through a filter having a perosity ef $0.5 \mathrm{\mu m}$ or finer, and use the filtrate as the Standed preparation. This solution contains about $125 \mu \mathrm{~g}$ of elarithromycin $\left(\mathrm{C}_{22} \mathrm{H}_{60} \mathrm{NO}_{+3}\right)$ per mL .

Resolution solution-Prepare a solution of USP Clarithromyein Related Compound A RS in methanolcontaining about $625 \mu \mathrm{~g}$ per mL. Transfer 10 mL of this solution and 10 mL of the stock soltt tion used to prepare the Standed preparation to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Assay preparation Transfer about 65 mg of Clarithromyein, aecurately weighed, to a 100 mL volumetric flask, add 80 mL of methanol to dissolve, shaking and sonieating if necessary to assure dissolution. Dilute with methanol to volume, and mix. Transfer 10.0 mL of this solution to a 50 mL volumetric flack, dilute with Mobile phase volume, mix, and filter through a filter having a peresity of $0.5 \mathrm{\mu m}$ or finer. Use the filtrate as the Assey prepara tion.

Chramagraphie syistem (see-Chromatography $\langle 624$ ) (The tiquid chrematograph is equipped with a 210 nm detector, an op tional guard column that eontains packing L1, a $4.6 \mathrm{~mm} \times 15 \mathrm{~cm}$ column that contains packing $L 1$, and is maintained at a constant
temperature of about $50^{\circ}$. The flow rate is about 1 mL per minute. Chromatograph the Resolution solution, and record the responses as directed for Procedure: the relative retention times are about 0.75 for clarithromyein and 1.0 for clarithremyein related com pernd $\Lambda$, and the resolution, $R$, between the clarithremyein peak and the elarithremyein related compernd $\Lambda$ peak is not less than 2.0. Chromatograph the Standard preparation, and record the respenses as directed under Precedtre: the coltmmeifficiency, deter mined from the clarithromycin peak, is not less than 750 theoreticat plates when caleulated by the formula:-

$$
5.545\left(t / H_{1 \sim 2}\right)^{2}
$$

the tailing factor is not less than 0.9 and not more than 2 , and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Preedure - [NOTE—Use peak areas where peak respenses are indiented.] Separately inject equal volumes (about 20 to-50 $\mu \mathrm{L}$ ) of the Standerd preparation and the Assay preparation into the ehromatograph, record the chromatograms, and meastre the responses for the major peaks. Caleulate the quatity, in $\mu \mathrm{S}$, of $\mathrm{G}_{28} \mathrm{H}_{69} \mathrm{NO}_{4}$ in each me of the Clarithromycin taken by the formula:

$$
500(C / M A)\left(r_{+}+r_{s}\right),
$$

in which $C$ is the concentration, in us per mb , of elarithromyein $\left(\mathrm{C}_{25} \mathrm{H}_{60} \mathrm{NO}_{4}\right)$ in the Standed preparation, $M$ is the quantity, in me, of Clarithromycin taken to prepare the Assay preparation, and $r_{t}$ andrs are the elarithromyein peak respenses obtained from the -As saly preparation and the Stenderd preparation, respectively.

■Solution A, Solution B, Diluting solution, and Standard solution D—Proceed as directed in the test for Related substances.

Standard preparation-Use Standard solution A, prepared as directed in the test for Related substances.

Assay preparation-Use the Test solution, prepared as directed in the test for Related substances.

Chromatographic system—Proceed as directed in the test for Related substances. In addition, the relative standard deviation for replicate injections of the Standard preparation is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L})$ of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak area responses for the major peaks. Calculate the percentage of $\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}$ in the portion of Clarithromycin taken by the formula:

$$
50\left(C_{S} / W\right)\left(r_{U} / r_{S}\right) P
$$

in which $C_{S}$ is the concentration, in mg per mL , of USP Clarithromycin RS in the Standard preparation; $W$ is the weight, in mg, of Clarithromycin taken to prepare the Assay preparation; $r_{U}$ and $r_{S}$ are the clarithromycin peak area responses obtained from the chromatograms of the Assay preparation and the Standard preparation, respectively; and $P$ is the purity of USP Clarithromycin RS taken to prepare the Standard preparation.■1S (USP28)

## BRIEFING

Clarithromycin Tablets, USP 27 page 463. Because of the proposed revision of the monograph for Clarithromycin, presented elsewhere in this issue of $P F$, to utilize a new liquid chromatographic test procedure for Related substances as a new Assay procedure, it is necessary to transfer to this monograph the details of the liquid chromatographic Assay that were previously included by reference. See also the briefing under Clarithromycin.
(PA7: W. Wright) RTS-40856-1

## Change to read:

Assay-
Mobile phase, Standard preparation, Resolution-solution, and Chromatographic syistem Proeeed as directed in the Assay under Clarithromacin.

- Mobile phase_Prepare a mixture of methanol and 0.067 M monobasic potassium phosphate ( $650: 350$ ), adjust with phosphoric acid to a pH of 4.0 , pass through a filter having a $0.5-\mu \mathrm{m}$ or finer porosity, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Quantitatively dissolve an accurately weighed quantity of USP Clarithromycin RS in methanol, shaking and sonicating if necessary to effect dissolution, to obtain a stock solution having a known concen-
tration of about $625 \mu$ g of clarithromycin $\left(\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}\right)$ per mL , taking into account the stated potency, in $\mu \mathrm{g}$ per mg , of USP Clarithromycin RS. Transfer 10.0 mL of this stock solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. Pass through a filter having a $0.5-\mu \mathrm{m}$ or finer porosity, and use the filtrate as the Standard preparation. This solution contains about $125 \mu \mathrm{~g}$ of clarithromycin $\left(\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}\right)$ per mL.

Resolution solution-Prepare a solution of USP Clarithromycin Related Compound A RS in methanol containing about $625 \mu \mathrm{~g}$ per mL . Transfer 10 mL of this solution and 10 mL of the stock solution used to prepare the Standard preparation to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. 1 (USP28)

Assay preparation-Finely powder an accurately counted number of Tablets, equivalent to about 2000 mg of clarithromycin, and with the aid of methanol quantitatively transfer the powder to a $500-\mathrm{mL}$ volumetric flask, add about 350 mL of methanol, and shake by mechanical means for 30 minutes. Dilute with methanol to volume, mix, and allow any insoluble matter to settle. Transfer 3.0 mL of the supernatant to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. Pass a portion of this solution through a filter having a $0.5-\mu \mathrm{m}$ or finer porosity, and use the filtrate as the Assay preparation.

## - Chromatographic system (see Chromatography

 $\langle 621\rangle$ )—The liquid chromatograph is equipped with a 210-nm detector, an optional guard column that contains packing L1, and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing LI. The chromatograph is maintained at a constant temperature of about $50^{\circ}$. The flow rate is about 1 mL per minute. Chromatograph the Resolution solution, and record the responses as directed for Procedure: the relative retention times are about 0.75 for clarithromycin and 1.0 for clarithromycin related compound A ; and the resolution, $R$, between the clarithromycin peak and the clarithromycin related compound A peak is not less than 2.0. Chromatograph the Standard preparation, and record the responses as directed for Procedure: the column efficiency, determined fromthe clarithromycin peak, is not less than 750 theoretical plates when calculated by the formula:

$$
5.545\left(t / W_{h_{2}}\right)^{2}
$$

the tailing factor is not less than 0.9 and not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$. ${ }^{1 S}$ (USP28)

Proedtre Proeed as directedfor Proedtrein the Assay un
der. Clarithromyiein. Caleulate the quantity, in mer, of $\mathrm{C}_{30} \mathrm{H}_{60} \mathrm{NO}_{43}$ in the pertion of Tablets taken by the formata:

$$
(50 / 3)(C / N)\left(x_{t}++_{s}\right)
$$

in which $N$ is the namber of Tablets taken, and the-other terms are as defined therein.

- Procedure-Separately inject equal volumes (about 20 to $50 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of clarithromycin $\left(\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}\right)$ in each Tablet taken by the formula:

$$
(50 / 3)(C / N)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of clarithromycin $\left(\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}\right)$ in the Standard preparation; $N$ is the number of Tablets taken; and $r_{U}$ and $r_{S}$ are the clarithromycin peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## Briefing

Clarithromycin Extended-Release Tablets, page 1861 of $P F$ 29(6) [Nov.-Dec. 2003]. Because of the proposed revision of the Assay in the monograph for Clarithromycin, presented elsewhere in this issue of $P F$, and the proposed transfer of the details of that Assay to the monograph for Clarithromycin Tablets, it is proposed
to refer in this new monograph to the Assay in the revised monograph for Clarithromycin Tablets. Details of a proposed test for Drug release are also presented. It is also proposed to revise the acceptance criteria in the Definition and the temperature conditions and weight-loss limit in the test for Loss on drying to be consistent with the NDA submission. See also the briefing under Clarithromycin.
(BPC: M. Marques; PA7: W. Wright) RTS—39803-2; 40856-2

## Add the following:

## ■Clarithromycin Extended-Release Tablets

» Clarithromycin Extended-Release Tablets contain not less than 90.0 percent and not more than 145.0110 .0 percent of the labeled amount of clarithromycin $\left(\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}\right)$.

Packaging and storage-Preserve in well-closed containers, protected from light. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Clarithromycin RS. USP Clarithromycin Related Compound A RS.

Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Drug release $\langle 724\rangle$ [Tome].
Medium: $\quad 0.3 \mathrm{M}$ phosphate buffer, pH 6.0 (prepared by dissolving 816.5 g of monobasic potassium phosphate and 48 g of sodium hydroxide in about 4 L of water, mixing,
and diluting with water to 20 L . Adjust with either concentrated phosphoric acid or 1 N sodium hydroxide to a pH of $6.0 \pm 0.05$ ); 900 mL .

Apparatus 2: 75 rpm .
Times: 30, 45, 60, and 120 minutes.
Procedure-Determine the percentages of the labeled amount of clarithromycin $\left(\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}\right)$ dissolved using the following method.
Standard solutions-Prepare five solutions of USP Clarithromycin RS dissolved in acetonitrile and diluted in Me dium, with known concentrations over the range of about 60 to $600 \mu \mathrm{~g}$ per mL .

Test solution-Use portions of the solution under test passed through a $35-\mu \mathrm{m}$ polyethylene filter.
Chromatographic system-Proceed as directed in the Assay.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the five Standard solutions and the Test solution into the chromatograph, and measure the responses for the major peaks. Perform a linear regression analysis to generate a standard curve using the peak area of each Standard solution versus its concentration. Determine the amount of clarithromycin $\left(\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}\right)$ dissolved at each specified time interval, using the peak area of each Test solution and the linear regression statistics for the Standard solutions.

Tolerances-The percentages of the labeled amounts of clarithromycin $\left(\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}\right)$ dissolved at the times specified conform to the following Acceptance Table.

| Level | Time (minutes) | Amount dissolved (individual limits) | Amount dissolved (average limits) |
| :---: | :---: | :---: | :---: |
| $\mathrm{L}_{1}$ | 30 | not more than 65\% | - |
|  | 45 | between 55 and 85\% | - |
|  | 60 | not less than 75\% | - |
|  | 120 | not less than $85 \%$ | - |
| $\mathrm{L}_{2}$ | 30 | not more than $75 \%$ | not more than $65 \%$ |
|  | 45 | between $45 \%$ and $95 \%$ | between $55 \%$ and $85 \%$ |
|  | 60 | not less than $65 \%$ | not less than $75 \%$ |
|  | 120 | not less than $75 \%$ | not less than $85 \%$ |
| $L_{3}$ | 30 | not more than 2 tablets release more than $75 \%$, and no individual tablet releases more than $85 \%$ | not more than $65 \%$ |
|  | 45 | not more than 2 tablets are outside the range of $45 \%$ to $95 \%$, and no individual tablet is outside the range of $35 \%$ to $105 \%$ | between $55 \%$ and $85 \%$ |
|  | 60 | not more than 2 tablets release less than $65 \%$, and no individual tablet releases less than 55\% | not less than $75 \%$ |
|  | 120 | not more than 2 tablets release less than $75 \%$, and no individual tablet releases less than $65 \%$ | not less than $85 \%$ |

Loss on drying $\langle 731\rangle$ —Dry a portion of powdered Tablets in vacuum at a pressure not exceeding 5 mm of mercury at $60^{\circ} 110^{\circ}$ for 3 hours: it loses not more than $6.0 \% 5.0 \%$ of its weight.
Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Assay-

Mobile phase, Resolution solution, and Chromatographic system-Proceed as directed in the Assay under Clathro myein Clarithromycin Tablets.

Standard preparation-Prepare as directed for Standard preparation in the Assay under Clatemern, exeept to dilute an aceurately meastred volume of the stock solution
quantitatively with Mobile phase tobain alution having a-known concentration of about 400 - g of clarithromyein $\left(\mathrm{G}_{38} \mathrm{H}_{69} \mathrm{NO}_{4}\right)$ per mb Clarithromycin Tablets.
Assay preparation-Finely powder an accurately counted number of Clarithromycin Extended-Release Tablets, equivalent to about 2000 mg of clarithromycin. With the aid of methanol quantitatively transfer the powder to a $500-\mathrm{mL}$ volumetric flask, add about 350 mL of methanol, and shake by mechanical means for 30 minutes. Dilute with methanol to volume, and mix. and allow any insoluble mat Sonicate for 30 minutes. Cool to room temperature, and allow to stand for at least 16 hours. Mix, and allow any insoluble matter to settle. Transfer 3.0 mL of the supernatant to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile
phase to volume, and mix. Pass a portion of this solution through a filter having a $0.5-\mu \mathrm{m}$ or finer porosity, and use the filtrate as the Assay preparation.

Procedure-Proceed as directed for Procedure in the Assay under Clarithromycin Tablets. Calculate the quantity, in mg, of clarithromycin $\left(\mathrm{C}_{38} \mathrm{H}_{69} \mathrm{NO}_{13}\right)$ in each Extended-Release Tablet taken by the formula:

$$
(50 / 3)(C / N)\left(r_{U} / r_{s}\right)
$$

in which $N$ is the number of Tablets taken, and the other terms are as defined therein. 1 (USP28)

## Briefing

Cyclophosphamide Tablets, USP 27 page 528. It is proposed to replace the Disintegration test with a Dissolution test. The Dissolution test was validated using a Nova-Pak C18 brand of L1 packing. The retention time is about 5.2 minutes for cyclophosphamide.
(BPC: M. Marques) RTS-40880-1

Delete the following:
■Bisintegration- $\langle 701\rangle$ : 30 mintes, determined as directedur der Uneoted Tablets.■1S (USP28)

## Add the following:

- Dissolution $\langle 711\rangle$ —

Medium: water; 900 mL , deaerated.
Apparatus: 1: 100 rpm .
Time: 45 minutes.

Determine the amount of $\mathrm{C}_{7} \mathrm{H}_{15} \mathrm{Cl}_{2} \mathrm{~N}_{2} \mathrm{O}_{2} \mathrm{P}$ dissolved by employing the following method.

Mobile phase-Prepare a suitable filtered and degassed mixture of water and acetonitrile (7:3). Make adjustments if necesary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Cyclophosphamide RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration corresponding to that of the solution under test.

Test solution-Use portions of the solution under test passed through a $0.8-\mu \mathrm{m}$ filter.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—
The liquid chromatograph is equipped with a $195-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 , and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peak. Calculate the amount of cyclophosphamide $\left(\mathrm{C}_{7} \mathrm{H}_{15} \mathrm{Cl}_{2} \mathrm{~N}_{2} \mathrm{O}_{2} \mathrm{P}\right)$ dissolved by the formula:

$$
900 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Cyclophosphamide RS in the Standard solution; and $r_{U}$ and $r_{S}$ are the peak responses for cyclophosphamide obtained from the Test solution and Standard solution, respectively.
Tolerances-Not less than $75 \%(Q)$ of the labeled amount of cyclophosphamide $\left(\mathrm{C}_{7} \mathrm{H}_{15} \mathrm{Cl}_{2} \mathrm{~N}_{2} \mathrm{O}_{2} \mathrm{P}\right)$ is dissolved in 45 minutes.■1S (USP28)

## BRIEFING

Desflurane, USP 27 page 549 and page 93 of PF 30(1) [Jan.Feb. 2004]. It is proposed to revise the preparation instructions for the Internal standard solution in the Assay to indicate the final concentration of USP Halothane RS, rather than specifying a volume to be used.
(PA1: K. Russo) RTS-41211-1

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers.
${ }^{\triangle}$ Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.
Replace the cap securely after each use. $\Delta U S P 28$

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Desflurane RS. USP Desflurane Related Compound $A R S$.
${ }^{\wedge}$ USP Halothane RS. $\triangle$ USP28
USP Sodium Fluoride RS.

## Change to read:

```
Assay-
    Internal standard solution Tramsfer 2.0 mL of halethane
*USP Halethame RS_USP28
toa-100 mL volumetric flask, dilute-with p-xylene-volume, and
mix.
```

-Dilute an accurately measured volume of USP Halothane RS with $p$-xylene, and dilute quantitatively, and stepwise if necessary, with $p$-xylene to obtain a solution having a
known concentration of about $20 \mu \mathrm{~L}$ per mL . 1 IS (USP28)
Standard preparation-Transfer 1.0 mL of Internal standard solution to a $2.0-\mathrm{mL}$ septum-capped vial, cap, seal, and weigh accurately. Using a cold syringe, inject about $25 \mu \mathrm{~L}$ of USP Desflurane RS, previously cooled to $0^{\circ}$ to $5^{\circ}$, into the vial. Allow the vial to come to ambient temperature, accurately weigh it, and calculate the quantity, in mg, of USP Desflurane RS added.
Assay preparation-Transfer 1.0 mL of Internal standard solution to a $2.0-\mathrm{mL}$ septum-capped vial, cap, seal, and weigh accurately. Using a cold syringe, inject about $25 \mu \mathrm{~L}$ of Desflurane, previously cooled to $0^{\circ}$ to $5^{\circ}$, into the vial. Allow the vial to come to ambient temperature, accurately weigh it, and calculate the quantity, in mg, of Desflurane added.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The gas chromatograph is equipped with a flame-ionization detector and a $2.4-\mathrm{mm} \times 3.7-\mathrm{m}$ stainless steel column coated with polytef and packed with $10 \%$ phase G31 and $15 \%$ phase G18 on 80 - to 100 -mesh support S1A. Helium is used as the carrier gas at a flow rate of about 24 mL per minute. The chromatograph is programmed as follows. Initially the temperature of the column is
maintained at about $80^{\circ}$ for 2.5 minutes, then increased at a rate of $2^{\circ}$ per minute, to $88^{\circ}$, maintained at $88^{\circ}$ for 3 minutes, then increased to $175^{\circ}$ at a rate of $70^{\circ}$ per minute, and maintained at $175^{\circ}$ for 4 minutes. The injection port temperature is maintained at about $200^{\circ}$, and the detector at about $250^{\circ}$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are 1.0 for desflurane and about 2.8 for halothane; the resolution, $R$, between the desflurane peak and the halothane peak is not less than 8 ; and the relative standard deviation for the ratios of the desflurane peak response to the halothane peak response obtained for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak area responses for the halothane and desflurane peaks. Calculate the percentage of $\mathrm{C}_{3} \mathrm{H}_{2} \mathrm{~F}_{6} \mathrm{O}$ in the Desflurane taken by the formula:

$$
100\left(W_{S} / W_{U}\right)\left(R_{U} / R_{S}\right)
$$

in which $W_{S}$ is the quantity, in mg, of USP Desflurane RS used to prepare the Standard preparation; $W_{U}$ is the quantity, in mg , of Desflurane used to prepare the Assay preparation; and $R_{U}$ and $R_{S}$ are the ratios of the peak area responses of desflurane to that of halothane obtained from the Assay preparation and the Standard preparation, respectively.

## BriEFING

Diethylstilbestrol Diphosphate Tablets, page 3385 of $P F$ 23(1) [Jan.-Feb. 1997]. This proposed new monograph, which previously appeared in Pharmacopeial Previews, is now being forwarded, with minor editorial revisions, to In-Process Revision.
(PA1: C. Anthony) RTS-41219-1

## Add the following:

## ■Diethylstilbestrol Diphosphate Tablets

» Diethylstilbestrol Diphosphate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of diethylstilbestrol diphosphate $\left(\mathrm{C}_{18} \mathrm{H}_{22} \mathrm{O}_{8} \mathrm{P}_{2}\right)$.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle$ —USP Diethylstilbestrol RS. USP Diethylstilbestrol Diphosphate RS.

Identification-Weigh and finely powder not less than 20 Tablets. Prepare a filtered test solution of the powder in alcohol having a concentration of about 2.0 mg of diethylstilbestrol diphosphate per mL . Separately apply $10 \mu \mathrm{~L}$ of this solution and $10 \mu \mathrm{~L}$ of a Standard solution of USP Diethylstilbestrol Diphosphate RS in alcohol containing 2.0 mg per mL to a thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ) coated with a $0.5-\mathrm{mm}$ layer of chromatographic silica gel mixture. [NOTE-Protect the plate from light.] Allow the applications to dry, and develop the chromatogram in a solvent system consisting of methanol and water ( $1: 1$ ) until the solvent front has moved about threefourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Examine the plate under short-wavelength UV light, then spray the plate with a mixture of sulfuric acid and methanol ( $1: 1$ ), and allow to dry in an oven at $105^{\circ}$ : the $R_{F}$ value of the principal spot obtained from the test solution corresponds to that of the principal spot obtained from the Standard solution.

Disintegration $\langle 701\rangle$ : 30 minutes.
Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

Procedure for content uniformity-Transfer 1 Tablet to a $100-\mathrm{mL}$ volumetric flask, add 15 mL of methanol and 3 mL of 0.5 N sodium hydroxide, and stir until the Tablet is completely disintegrated. Dissolve in and dilute with water to volume, and filter, discarding the first 15 mL of filtrate. Transfer 4.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, add 0.4 mL of 0.5 N sodium hydroxide, dilute with
water to volume, and mix to obtain the test solution. Transfer about 50 mg of USP Diethylstilbestrol Diphosphate RS, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask; add 5 mL of methanol and 2 mL of 0.5 N sodium hydroxide; dissolve in and dilute with water to volume; and mix. Transfer 5.0 mL of this solution to a $250-\mathrm{mL}$ volumetric flask, add 1 mL of 0.5 N sodium hydroxide, and dilute with water to volume to obtain the Standard solution. Concomitantly determine the absorbances of both solutions at the wavelength of maximum absorbance at about 241 nm , with a suitable spectrophotometer, using a mixture of 0.4 mL of 0.5 N sodium hydroxide in 100 mL of water as the blank. Calculate the quantity, in mg, of $\mathrm{C}_{18} \mathrm{H}_{22} \mathrm{O}_{8} \mathrm{P}_{2}$ in the Tablet taken by the formula:

$$
25 T C\left(A_{U} / A_{S}\right)
$$

in which T is the labeled quantity, in mg , of diethylstilbestrol diphosphate in the Tablet; $C$ is the concentration, in $\mu \mathrm{g}$ per mL, of USP Diethylstilbestrol Diphosphate RS in the Standard solution; and $A_{U}$ and $A_{S}$ are the absorbances of the test solution and the Standard solution, respectively.

## Limit of free diethylstilbestrol-

Vanadyl sulfate solution-Transfer about 100 mg of vanadyl sulfate to a $200-\mathrm{mL}$ volumetric flask, dissolve in 20 mL of sulfuric acid, dilute with glacial acetic acid to volume, and mix.
Standard solution-Dissolve an accurately weighed quantity of USP Diethylstilbestrol RS in alcohol to obtain a solution having a known concentration of about 0.1 mg per mL . Transfer 5.0 mL of this solution to a suitable container, evaporate to dryness over a steam bath, and dissolve the residue in 10 mL of Vanadyl sulfate solution.

Test solution-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of diethylstilbestrol diphos-
phate, to a suitable container; add 15 mL of water and 2.5 mL of 1 N sodium hydroxide; stir for 5 minutes; and adjust with phosphoric acid to a pH of 8.0. Transfer this solution to a separator, and extract with four $20-\mathrm{mL}$ portions of ether, combining the ether extracts. Filter the combined extracts through a pledget of glass wool, evaporate over a steam bath to dryness, and dissolve the residue in 10 mL of Vanadyl sulfate solution.

Procedure-Heat the Standard solution and the Test solution over a steam bath for 1 hour, and cool to room temperature. Concomitantly determine the absorbance of each solution at the wavelength of maximum absorbance at about 520 nm with a suitable spectrophotometer, using Vanadyl sulfate solution as the blank. Calculate the quantity, in mg , of free diethylstilbestrol in the portion of powder taken by the formula:

$$
0.005 C\left(A_{U} / A_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Diethylstilbestrol RS in the Standard solution, and $A_{U}$ and $A_{s}$ are the absorbances of the Test solution and the Standard solution, respectively: not more than $0.35 \%$ is found.

## Limit of diethylstilbestrol monophosphate-

Vanadyl sulfate solution and Standard solution-Proceed as directed in the test for Limit of free diethylstilbestrol.

Test solution-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of diethylstilbestrol diphosphate, to a suitable container; add 15 mL of water and 2.5 mL of 1 N sodium hydroxide; stir for 5 minutes; and adjust with phosphoric acid to a pH of 2.2. Transfer this solution to a separator, and extract with four $20-\mathrm{mL}$ portions of ether,
combining the ether extracts. Filter through a pledget of glass wool, evaporate over a steam bath to dryness, and dissolve the residue in 10 mL of Vanadyl sulfate solution.

Procedure-Heat the Standard solution and the Test solution over a steam bath for 1 hour, and cool to room temperature. Concomitantly determine the absorbance of each solution at the wavelength of maximum absorbance at about 520 nm with a suitable spectrophotometer, using Vanadyl sulfate solution as the blank. Calculate the quantity, in mg , of diethylstilbestrol monophosphate in the portion of powder taken by the formula:

$$
1.298\left\{\left[(0.005 C)\left(A_{U} / A_{S}\right)\right]-F\right\},
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Diethylstilbestrol RS in the Standard solution; $A_{U}$ and $A_{S}$ are the absorbances of the Test solution and the Standard solution, respectively; and $F$ is the amount, in mg , of free diethylstilbestrol found in the test for Limit of free diethylstilbestrol: not more than $2.0 \%$ is found.

Assay-Weigh and finely powder not less than 20 Tablets. Transfer a portion of the powder, equivalent to about 100 mg of diethylstilbestrol diphosphate, to a $250-\mathrm{mL}$ volumetric flask; add 25 mL of alcohol and 5 mL of 1 N sodium hydroxide; dilute with water to volume; mix; and filter. Transfer 5.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Similarly prepare a Standard solution of USP Diethylstilbestrol Diphosphate RS having a known concentration of about $20 \mu \mathrm{~g}$ per mL . Concomitantly determine the absorbances of both solutions at the wavelength of maximum absorbance at about 241 nm with a suitable spectrophotometer, using Vanadyl sulfate solution, prepared as directed in the test for Limit
of free diethylstilbestrol, as the blank. Calculate the quantity, in mg, of diethylstilbestrol diphosphate $\left(\mathrm{C}_{18} \mathrm{H}_{22} \mathrm{O}_{8} \mathrm{P}_{2}\right)$ in the Tablets taken by the formula:

$$
5 C\left(A_{U} / A_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Diethylstilbestrol RS in the Standard solution, and $A_{U}$ and $A_{s}$ are the absorbances of the solution from the Tablets and the Standard solution, respectively. $\quad$ 1S (USP28)

Dimenhydrinate Oral Solution, USP 27 page 629; Dimenhydrinate Syrup, $U S P 27$ page 630; Dimenhydrinate Tablets, $U S P$ 27 page 630. The revisions in these monographs are intended to clarify the calculation in the tests for Content of 8-chlorotheophylline.
(PA4: E. Gonikberg) RTS-41329-1

## Dimenhydrinate Oral Solution

(Monograph under this new title-to become official June 1, 2005)
(Current monograph title is Dimenhydrinate Syrup)

## Change to read:

## Content of 8-chlorotheophylline-

Ammonium bicarbonate solution, Diluent, Solution A, Solution B, Mobile phase, Internal standard solution, and Chromatographic system-Proceed as directed in the Assay under Dimenhydrinate Tablets.

Standard solution-Prepare as directed for Standard preparation in the Assay under Dimenhydrinate Tablets.

Test solution-Prepare as directed for Assay preparation in the Assay.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg per mL , of 8 -chlorotheophylline $\left(\mathrm{C}_{7} \mathrm{H}_{7} \mathrm{ClN}_{4} \mathrm{O}_{2}\right)$ in the portion of Oral Solution taken by the formula:

$$
(214.61 / 469.96)(0.05 W)\left(R_{U} / R_{S}\right)
$$

in which 214.61 and 469.96 are the molecular weights of 8 -chlorotheophylline and dimenhydrinate, respectively; $W$ is the weight, in mg, of USP Dimenhydrinate RS in the Standard solution; and $R_{U}$ and $R_{S}$ are peak area ratios of 8-chlorotheophylline to the internal standard obtained from the Test solution and the Standard solution, respectively. An amount of 8 -chlorotheophylline that is between $43.4 \%$ and $47.9 \%$ of the amount of dimenhydrinate

- $_{\text {obtained }}$ in the Assay $_{1 S}$ (USP28)
is found.


## BRIEFING

Dimenhydrinate Syrup, USP 27 page 630—See briefing under Dimenhydrinate Oral Solution.
(PA4: E. Gonikberg) RTS-41329-1

## Dimenhydrinate Syrup

(Current title—not to change until June 1, 2005)
Monograph title change-to become official June 1, 2005 See Dimenhydrinate Oral Solution

## Change to read:

Content of 8-chlorotheophylline-
Ammonium bicarbonate solution, Diluent, Solution A, Solution B, Mobile phase, Internal standard solution, and Chromatographic system-Proceed as directed in the Assay under Dimenhydrinate Tablets.

Standard solution-Prepare as directed for Standard preparation in the Assay under Dimenhydrinate Tablets.

Test solution-Prepare as directed for Assay preparation in the Assay.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major
peaks. Calculate the quantity, in mg per mL , of 8-chlorotheophylline $\left(\mathrm{C}_{7} \mathrm{H}_{7} \mathrm{ClN}_{4} \mathrm{O}_{2}\right)$ in the portion of Syrup taken by the formula:

$$
(214.61 / 469.96)(0.05 W)\left(R_{U} / R_{S}\right)
$$

in which 214.61 and 469.96 are the molecular weights of 8 -chlorotheophylline and dimenhydrinate, respectively; $W$ is the weight, in mg, of USP Dimenhydrinate RS in the Standard solution; and $R_{U}$ and $R_{S}$ are the peak area ratios of 8-chlorotheophylline to the internal standard obtained from the Test solution and the Standard solution, respectively. An amount of 8 -chlorotheophylline that is between $43.4 \%$ and $47.9 \%$ of the amount of dimenhydrinate
$\square_{\text {obtained }}$ in the Assay $\mathbf{m}_{1 S}$ (USP28)
is found.

## Briefing

Dimenhydrinate Tablets, USP 27 page 630-See briefing under Dimenhydrinate Oral Solution.
(PA4: E. Gonikberg) RTS-41329-2

## Change to read:

## Content of 8-chlorotheophylline-

Ammonium bicarbonate solution, Diluent, Solution A, Solution B, Mobile phase, Internal standard solution, and Chromatographic system-Prepare as directed in the Assay.

Standard solution-Prepare as directed for Standard preparation in the Assay.

Test solution-Prepare as directed for Assay preparation in the Assay.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg , of 8-chlorotheophylline $\left(\mathrm{C}_{7} \mathrm{H}_{7} \mathrm{ClN}_{4} \mathrm{O}_{2}\right)$ per Tablet taken by the formula:

$$
(214.61 / 469.96) W\left(R_{U} / R_{S}\right)
$$

in which 214.61 and 469.96 are the molecular weights of 8 -chlorotheophylline and dimenhydrinate, respectively; $W$ is the weight, in mg, of USP Dimenhydrinate RS in the Standard solution; and $R_{U}$ and $R_{S}$ are peak area ratios of 8 -chlorotheophylline to the internal standard obtained from the Test solution and the Standard solution, respectively. An amount of 8 -chlorotheophylline that is between $43.4 \%$ and $47.9 \%$ of the amount of dimenhydrinate
$\boldsymbol{m}_{\text {obtained }}$ in the Assay ${ }^{1 \text { 1S }}$ (USP28)
is found.

Briefing

Ensulizole, USP 27 page 706. It is proposed to revise the Assay to include the formula to be used in the calculation.
(BPC: M. Marques) RTS-41309-1

## Change to read:

Assay-Transfer about 1200 mg of Ensulizole, accurately weighed, to a $300-\mathrm{mL}$ iodine flask, and dissolve by stirring in 25 mL of 0.5 N sodium hydroxide. Add phenolphthalein TS, and titrate the excess with 0.5 N hydrochloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.5 N sodium hydroxide is equivalent to 137.15 mg of $\mathrm{C}_{13} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{~S}$.
${ }^{\square}$ Calculate the percentage of $\mathrm{C}_{13} \mathrm{H}_{10} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{~S}$ in the portion of Ensulizole taken by the formula:

$$
\frac{\left[\left(V_{\mathrm{NaOH}} \times T_{\mathrm{NaOH}}\right)-\left(V_{\mathrm{HCl}} \times T_{H C l}\right)\right] \times 0.5 \times 274.30 \times 100}{W \times L O D \times 10}
$$

in which $V_{\text {Naö }}$ is the volume, in mL , of 0.5 N sodium hydroxide added; $T_{\text {NaOH }}$ is the titer of the 0.5 N sodium hydroxide; $V_{H C I}$ is the volume, in mL , of 0.5 N hydrochloric acid used; $T_{H C l}$ is the titer of 0.5 N hydrochloric acid; $W$ is the weight, in g , of Ensulizole taken; and $L O D$ is the percentage of loss on drying, as determined in the test for Loss on drying.-1S (USP28)

Epinephrine Nasal Solution, USP 27 page 711; Epinephryl Borate Ophthalmic Solution, USP 27 page 714. It is proposed to revise the Assay to change the name of the iodine and potassium iodide TS to iodine and potassium iodide TS 1, a change proposed in the section Reagents, Indicators, and Solutions in this issue of $P F$.
(BPC: M. Marques) RTS-41175-4

## Change to read:

Assay-Pipet 30 mL of Nasal Solution into a $125-\mathrm{mL}$ separator, add 25 mL of chloroform, shake vigorously for 1 minute, allow the liquids to separate, and discard the chloroform. Wash twice more with chloroform, separating and discarding the lower layer as completely as possible each time. Rinse the stopper and mouth of the separator with a few drops of water. Add 0.2 mL of starch TS, then while swirling the separator add iodine and potassium iodide TS

## $\square^{-T S} 1_{1 S}$ (USP28)

dropwise until the blue color formed persists, and immediately add just sufficient 0.1 N sodium thiosulfate to discharge the blue color. [NOTE-Proceed with the assay from this point without delay.]

Add to the liquid in the separator 2.10 g of sodium bicarbonate, preventing it from coming in contact with the mouth of the separator, and swirl until most of the bicarbonate has dissolved. By means of a $1-\mathrm{mL}$ syringe that is not fitted with a needle, rapidly inject 1.0 mL of acetic anhydride directly into the contents of the separator. Immediately insert the stopper in the separator, and shake vigorously until the evolution of carbon dioxide has ceased ( 7 to 10 minutes), releasing the pressure as necessary through the stopcock. Allow to stand for 5 minutes, and extract the solution with six $25-\mathrm{mL}$ portions of chloroform, filtering each extract through a small pledget of cotton, previously washed with chloroform, into a beaker.

Evaporate the combined chloroform extracts on a steam bath in a current of air to about 3 mL , transfer the residue by means of small portions of chloroform to a tared $50-\mathrm{mL}$ beaker, and heat again to evaporate the solvent completely. Heat further at $105^{\circ}$ for $30 \mathrm{~min}-$ utes, cool in a desiccator, and weigh the residue of triacetylepinephrine. Add 5.0 mL of chloroform, cover the beaker, gently swirl the contents until the residue has completely dissolved, and determine the specific rotation, $R$, using a $200-\mathrm{mm}$ semimicro polarimeter tube.

Calculate the quantity, in mg , of $\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO}_{3}$ in the volume of Na sal Solution taken by the formula:

$$
(183.20 / 309.32)(W)(0.5+0.5 R / 93)
$$

in which 183.20 and 309.32 are the molecular weights of epinephrine and triacetylepinephrine, respectively; and $W$ is the weight, in mg , and $R$ is the specific rotation (in degrees, without regard to the sign), of the isolated triacetylepinephrine.

Briefing

Epinephryl Borate Ophthalmic Solution, USP 27 page 714See briefing under Epinephrine Nasal Solution.
(BPC: M. Marques) $\quad$ RTS $-41175-3$

## Change to read:

Assay-Transfer an accurately measured volume of Ophthalmic Solution, equivalent to about 100 mg of epinephrine, to a $250-$ mL separator. Dilute with water to 30 mL , and adjust with dilute hydrochloric acid ( 1 in 12 ) to a pH of $4.0 \pm 0.2$. Add 25 mL of carbon tetrachloride, shake vigorously for 1 minute, allow the phases to separate, and discard the carbon tetrachloride washing. In the same manner, wash with two additional $25-\mathrm{mL}$ portions of carbon tetrachloride, and discard the washings. Rinse the stopper and the mouth of the separator with 2 to 3 mL of water such that the rinsings enter the separator and combine with the solution under assay. Add 0.2 mL of starch TS, and, while swirling the separator, add iodine and potassium iodide TS
-TS 1n1S (USP28)
dropwise until the blue color persists. Immediately add a volume of 0.1 N sodium thiosulfate just sufficient to discharge the blue color. [NOTE-Proceed with the assay from this point without delay.]

Add 2.10 g of sodium bicarbonate through a dry powder funnel to prevent the powder from coming in contact with the mouth of the separator, and swirl to dissolve most of the solid. By means of a syringe fitted with a suitable pipet, rapidly inject 1.0 mL of acetic anhydride directly into the contents of the separator. Swirl the unstoppered separator gently for 3 minutes to allow carbon dioxide to escape. Insert the stopper, and shake gently until the evolution of carbon dioxide has ceased ( 7 to 10 minutes), releasing the pressure through the stopcock as necessary. Allow to stand for 5 minutes. Extract with six $25-\mathrm{mL}$ portions of chloroform, shaking for $1 \mathrm{~min}-$ ute each time, filtering each extract through a small pledget of chloroform-saturated cotton and collecting the extracts in a 400mL beaker. Add several glass beads, and evaporate on a steam bath to about 3 mL . With the aid of 15 to 20 mL of chloroform, transfer the residue to a tared $50-\mathrm{mL}$ beaker, and evaporate on the steam bath to dryness. Dry the residue at $105^{\circ}$ for 30 minutes, cool in a desiccator, and weigh the triacetylepinephrine so obtained. Transfer 10.0 mL of chloroform to the beaker, and gently swirl to dissolve the residue, dislodging the semisolid residue from the glass surface, if necessary, with a small metal spatula. Determine the angular rotation of the solution in a $100-\mathrm{mm}$ polarimeter tube.

Calculate the quantity, in mg, of epinephrine $\left(\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO}_{3}\right)$ in the volume of Ophthalmic Solution taken by the formula:

$$
(183.20 / 309.32)(W)(0.5+0.5 R / 93)
$$

in which 183.20 and 309.32 are the molecular weights of epinephrine and triacetylepinephrine, respectively; $W$ is the weight, in mg , of the isolated triacetylepinephrine; and $R$ is the specific rotation, in degrees, of the triacetylepinephrine solution.

## Briefing

Ergoloid Mesylates Tablets, USP 27 page 721, page 3056 of the First Supplement, and page 1477 of PF 29(5) [Sept.-Oct. 2003]; Ergoloid Mesylates Sublingual Tablets; Ergotamine Tartrate Tablets, USP 27 page 725; Ergotamine Tartrate Sublingual Tablets; Nitroglycerin Tablets, USP 27 page 1330; Nitroglycerin Sublingual Tablets. Revisions that are proposed are intended to subdivide the standards of the existing monograph on Ergoloid Mesylates Tablets by replacing the current monograph with two separate monographs, the titles of which are proposed by the Expert Committee on Nomenclature and Labeling to be Ergoloid Mesylates Tablets and Ergoloid Mesylates Sublingual Tablets. The standards of the revised Ergoloid Mesylates Tablets monograph would be those taken from the present monograph that are applicable to tablets that are to be swallowed intact. The "Tablets" term is used with the understanding that the article is an immediaterelease dosage form but, in accordance with existing nomenclature policy, the term "Immediate-Release" is not included in the name. The standards of the new Ergoloid Mesylates Sublingual Tablets monograph would be those taken from the present monograph that are applicable to tablets that are not to be swallowed intact but are meant to be administered for sublingual delivery of the drug, and the proposed title is in the general form [DRUG] [ROUTE OF ADMINISTRATION][DOSAGE FORM]. The Expert Committee on Nomenclature and Labeling considers that the term "Sublingual" appearing prominently in the product name will represent a significant improvement in that the consumer will be provided with the assurance that the product will be used properly to achieve the benefit of the medication. The standards encompassed within the two proposed monographs are the same as those currently combined within the single monograph on Ergoloid Mesylates Tablets.

The revisions are proposed for publication in the First Supplement to USP 28-NF 23, which is to become official April 1, 2005, but with October 1, 2006, designated as the official date for the name revisions. The 18 -month postponement of the official date for the name changes would be intended to allow for product label changes to be made and for health practitioners and consumers to become familiar with the revised terminology.

Revisions are similarly proposed in this number of $P F$, to replace the present monograph on Ergotamine Tartrate Tablets with separate monographs under the names Ergotamine Tartrate Tablets and Ergotamine Tartrate Sublingual Tablets, and to change the title of the monograph on Nitroglycerin Tablets to Nitroglycerin Sublingual Tablets.
(PA3: S. Salado; NL: C. Barnstein) RTS-40684-3

## Ergoloid Mesylates Tablets

(Monograph to be deleted as of October 1, 2006)

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers.

- Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.■1S (USP28)


## Change to read:

Dissolution $\langle 711\rangle$ (for Tablets intended to be swallowed)Medium: water; 500 mL .
Apparatus 2: 50 rpm , the distance between the paddle blade and the inside bottom of the vessel being maintained at $4.5 \pm 0.2$ cm during the test.
Time: 30 minutes.

- Determine the amount of ergoloid mesylates dissolved
using the following procedure. $\quad$ 2S (USP27)
Mobile phase-Prepare as directed in the Assay.
Standard solution-Dissolve an accurately weighed quantity of USP Ergoloid Mesylates RS in water to obtain a solution having a known concentration of about $50 \mu \mathrm{~g}$ per mL . Transfer 4 mL of this solution for every 0.5 mg of ergoloid mesylates contained in the Tablets to a $200-\mathrm{mL}$ volumetric flask, add 1 mL of 0.1 N hydrochloric acid and 100 mL of water, mix, and dilute with water to volume.

Test solution-Transfer a $20-\mathrm{mL}$ portion of the solution under test to a suitable container, add $100 \mu \mathrm{~L}$ of 0.1 N hydrochloric acid, and mix.

Chromatographic system-Proceed as directed in the Assay except that the sum of the relative standard deviation values for the four ergoloid mesylates peaks for replicate injections is not more than 3.0\%.

Procedure-Separately inject equal volumes (about $200-\mathrm{Ht}$

- $500 \mu \mathrm{~L})_{\text {m }}{ }^{\text {S (USP27) }}$
of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity of ergoloid mesylates as directed in the Assay.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of ergoloid mesylates is dissolved in 30 minutes.

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed solution containing a mixture of water, acetonitrile, and triethylamine (700:300:9). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard solution-Transfer about 113 mg of papaverine hydrochloride to a 1-L flask. Add a mixture of 0.01 M tartaric acid and acetonitrile ( $2: 1$ ) to volume, and mix.

Standard preparation-Transfer about 33 mg of USP Ergoloid Mesylates RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Internal standard solution to volume, and mix. Use a freshly prepared solution.

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg of Ergoloid Mesylates to a $50-\mathrm{mL}$ centrifuge tube. Add 15.0 mL of Internal standard solution, insert the stopper into the tube, and shake for about 15 minutes. Centrifuge, filter if necessary, and use the clear supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a 3.9 mm

$\times 15-\mathrm{cm}$ column that contains packing L1. - [NOTE-Use an L1 column capable of handling pH values greater than 11.] [1S (USP27) The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency determined for the dihydro-$\beta$-ergocryptine mesylate peak is not less than 1000 theoretical plates; the tailing factor for dihydro- $\beta$-ergocryptine mesylate is not more than 2.0 ; the resolution, $R$, between the dihydro- $\alpha$-ergocryptine mesylate and dihydroergocristine mesylate is not less than 2.0; the resolution, $R$, between dihydroergocristine and dihydro-$\beta$-ergocryptine is not less than 2.0 ; and the relative standard deviation of the ratio of the sum of the four peaks to the internal standard for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The order of elution is papaverine, dihydroergocornine, dihydro- $\alpha$-ergocryptine, dihydroergocristine, and dihy-dro- $\beta$-ergocryptine. Calculate the quantity, in mg , of ergoloid mesylates in the portion of Tablets taken by the formula:

$$
15 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Ergoloid Mesylates RS in the Standard preparation; and $R_{U}$ and $R_{S}$ are the sums of the ratios of responses of the four major peaks to the response of the internal standard peak obtained from the Assay preparation and the Standard preparation, respectively. Calculate the percentage of each of the individual alkaloids taken by the formula:

$$
100 R_{i}(M W) \mathrm{yi} / \Sigma\left[R_{i}(M W)_{i}\right]
$$

where $R_{i}$ is the peak response ratio of the individual alkaloid to the internal standard; $(M W)_{i}$ is the molecular weight of the individual alkaloid; and $\Sigma\left[R_{i}(M W)_{i}\right]$ is the summation of the products of peak response ratios and molecular weights for the four alkaloids.

BRIEFING

Ergoloid Mesylates Tablets—See briefing under Ergoloid Mesylates Tablets.
(PA3: S. Salado; NL: C. Barnstein) RTS-40684-3

## Add the following:

## ■Ergoloid Mesylates Tablets

(Monograph with nomenclature related changes-to become official October 1, 2006)
» Ergoloid Mesylates Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ergoloid mesylates, consisting of not less than 30.3 percent and not more then 36.3 percent of the methanesulfonate salt of each of the individual alkaloids (dihydroergocristine, dihydroergocornine, and dihydroergocryptine). The ratio of alpha- to beta-dihydroergocryptine mesylate is not less than 1.5:1.0 and not more than $2.5: 1.0$.

Packaging and storage-Preserve in tight, light-resistant containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-Label the Tablets to indicate that they are intended for swallowing intact.

USP Reference standards $\langle 11\rangle$ —USP Ergoloid Mesylates $R S$.

Identification-Mix a small amount of powdered Tablets, equivalent to about 5 mg of ergoloid mesylates, with 5 mL of water and 5 mL of a mixture of equal volumes of glacial acetic acid and sulfuric acid, and add 1 drop of freshly prepared ferric chloride solution (1 in 20): a violet-blue color develops within 5 minutes.

Dissolution $\langle 711\rangle$ -
Medium: water; 500 mL .
Apparatus 2: 50 rpm , the distance between the paddle
blade and the inside bottom of the vessel being maintained
at $4.5 \pm 0.2 \mathrm{~cm}$ during the test.
Time: 30 minutes.
Determine the amount of ergoloid mesylates dissolved using the following procedure.
Mobile phase-Prepare as directed in the Assay.

Standard solution-Dissolve an accurately weighed quantity of USP Ergoloid Mesylates RS in water to obtain a solution having a known concentration of about $50 \mu \mathrm{~g}$ per mL . Transfer 4 mL of this solution for every 0.5 mg of ergoloid mesylates contained in the Tablets to a $200-\mathrm{mL}$ volumetric flask, add 1 mL of 0.1 N hydrochloric acid and 100 mL of water, mix, and dilute with water to volume.

Test solution-Transfer a $20-\mathrm{mL}$ portion of the solution under test to a suitable container, add $100 \mu \mathrm{~L}$ of 0.1 N hydrochloric acid, and mix.

Chromatographic system-Proceed as directed in the $A s$ say except that the sum of the relative standard deviation values for the four ergoloid mesylates peaks for replicate injections is not more than $3.0 \%$.

Procedure-Separately inject equal volumes (about 500 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity of ergoloid mesylates as directed in the Assay.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of ergoloid mesylates is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Assay-

Mobile phase-Prepare a filtered and degassed solution containing a mixture of water, acetonitrile, and triethylamine (700:300:9). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard solution-Transfer about 113 mg of papaverine hydrochloride to a 1-L flask. Add a mixture of 0.01 M tartaric acid and acetonitrile $(2: 1)$ to volume, and mix.

Standard preparation-Transfer about 33 mg of USP Ergoloid Mesylates RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Internal standard solution to volume, and mix. Use a freshly prepared solution.

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg of ergoloid mesylates to a $50-\mathrm{mL}$ centrifuge tube. Add 15.0 mL of Internal standard solution, insert the stopper into the tube, and shake for about 15 minutes. Centrifuge, filter if necessary, and use the clear supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. [NOTE-Use an L1 column capable of handling pH values greater than 11.] The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency determined for the dihydro- $\beta$-ergocryptine mesylate peak is not less than 1000 theoretical plates; the tailing factor for dihydro- $\beta$-ergocryptine mesylate is not more than 2.0 ; the resolution, $R$, between dihydro- $\alpha$-ergocryptine mesylate and dihydroergocristine mesylate is not less than 2.0 ; the resolution, $R$, between dihydroergocristine and dihydro- $\beta$-ergocryptine is not less than 2.0 ; and the relative standard deviation of the ratio of the sum of the four peaks to the internal standard for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The order of elution is papaverine, dihydroergocornine, dihydro- $\alpha$-ergo-
cryptine, dihydroergocristine, and dihydro- $\beta$-ergocryptine. Calculate the quantity, in mg , of ergoloid mesylates in the portion of Tablets taken by the formula:

$$
15 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Ergoloid Mesylates RS in the Standard preparation; and $R_{U}$ and $R_{S}$ are the sums of the ratios of responses of the four major peaks to the response of the internal standard peak obtained from the Assay preparation and the Standard preparation, respectively. Calculate the percentage of each of the individual alkaloids taken by the formula:

$$
100 R_{i}(M W) \mathrm{yi} / \Sigma\left[R_{i}(M W)_{i}\right],
$$

in which $R_{i}$ is the peak response ratio of the individual alkaloid to the internal standard; $(M W)_{i}$ is the molecular weight of the individual alkaloid; and $\Sigma\left[R_{i}(M W)_{i}\right]$ is the summation of the products of peak response ratios and molecular weights for the four alkaloids.■1S (USP28)
(Official October 1, 2006)

Ergoloid Mesylates Sublingual Tablets—See briefing under Ergoloid Mesylates Tablets.
(PA3: S. Salado; NL: C. Barnstein) RTS-40684-1

## Add the following:

## Ergoloid Mesylates Sublingual Tablets <br> (Monograph under this new title-to become official October 1, 2006)

» Ergoloid Mesylates Sublingual Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ergoloid mesylates, consisting of not less than 30.3 percent and not more then 36.3 percent of the methanesulfonate salt of each of the individual alkaloids (dihydroergocristine, dihydroergocornine, and dihydroergocryptine). The ratio of alpha- to beta-dihydroergocryptine mesylate is not less than $1.5: 1.0$ and not more than $2.5: 1.0$.

Packaging and storage-Preserve in tight, light-resistant containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-Label the Tablets to indicate that they are intended for sublingual administration.

USP Reference standards $\langle 11\rangle$ —USP Ergoloid Mesylates RS.

Identification-Mix a small amount of powdered Sublingual Tablets, equivalent to about 5 mg of ergoloid mesylates, with 5 mL of water and 5 mL of a mixture of equal volumes of glacial acetic acid and sulfuric acid, and add 1 drop of freshly prepared ferric chloride solution (1 in 20): a violet-blue color develops within 5 minutes.

Disintegration $\langle 701\rangle$ : 15 minutes.
Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Assay-

Mobile phase—Prepare a filtered and degassed solution containing a mixture of water, acetonitrile, and triethylamine (700:300:9). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard solution-Transfer about 113 mg of papaverine hydrochloride to a $1-\mathrm{L}$ flask. Add a mixture of 0.01 M tartaric acid and acetonitrile $(2: 1)$ to volume, and mix.

Standard preparation-Transfer about 33 mg of USP Ergoloid Mesylates RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Internal standard solution to volume, and mix. Use a freshly prepared solution.

Assay preparation-Weigh and finely powder not fewer than 20 Sublingual Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg of ergoloid mesylates, to a $50-\mathrm{mL}$ centrifuge tube. Add 15.0 mL of In ternal standard solution, insert the stopper into the tube, and shake for about 15 minutes. Centrifuge, filter if necessary, and use the clear supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. [NOTE-Use an L1 column capable of handling pH values greater than 11.] The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency determined for the dihydro- $\beta$-ergocryptine mesylate peak is not less than 1000 theoretical plates; the tailing factor for dihydro- $\beta$-ergocryptine mesylate is not more than 2.0; the resolution, $R$, between the dihydro- $\alpha$-ergocryptine mesylate and dihydroergocristine mesylate is not less than
2.0 ; the resolution, $R$, between dihydroergocristine and di-hydro- $\beta$-ergocryptine is not less than 2.0 ; and the relative standard deviation of the ratio of the sum of the four peaks to the internal standard for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The order of elution is papaverine, dihydroergocornine, dihydro- $\alpha$-ergocryptine, dihydroergocristine, and dihydro- $\beta$-ergocryptine. Calculate the quantity, in mg , of ergoloid mesylates in the portion of Sublingual Tablets taken by the formula:

$$
15 C\left(R_{U} / R_{S}\right)
$$

where $C$ is the concentration, in mg per mL, of USP Ergoloid Mesylates RS in the Standard preparation; and $R_{U}$ and $R_{S}$ are the sums of the ratios of responses of the four major peaks to the response of the internal standard peak obtained from the Assay preparation and the Standard preparation, respectively. Calculate the percentage of each of the individual alkaloids taken by the formula:

$$
100 R_{i}(M W) \mathrm{yi} / \Sigma\left[R_{i}(M W)_{i}\right]
$$

in which $R_{i}$ is the peak response ratio of the individual alkaloid to the internal standard; $(M W)_{i}$ is the molecular weight of the individual alkaloid; and $\Sigma\left[R_{i}(M W)_{i}\right]$ is the summation of the products of peak response ratios and molecular weights for the four alkaloids.■1S (USP28)
(Official October 1, 2006)

## BRIEFING

Ergotamine Tartrate Tablets, USP 27 page 725—See briefing under Ergoloid Mesylates Tablets.
(PA3: S. Salado) RTS-41094-1

## Ergotamine Tartrate Tablets

(Monograph to be deleted as of October 1, 2006)
Change to read:
Packaging and storage-Preserve in well-closed, light-resistant containers.
${ }^{\square}$ Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ} \cdot$ ■1S (USP28)

## BRIEFING

Ergotamine Tartrate Tablets-See briefing under Ergoloid Mesylates Tablets.
(PA3: S. Salado; NL: C. Barnstein) RTS-41094-1

## Add the following:

## ■Ergotamine Tartrate Tablets

(Monograph with nomenclature related changes-to become official October 1, 2006)

## » Ergotamine Tartrate Tablets contain not less

 than 90.0 percent and not more than 110.0 percent of the labeled amount of $\left(\mathrm{C}_{33} \mathrm{H}_{35} \mathrm{~N}_{5} \mathrm{O}_{5}\right)_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$.Packaging and storage-Preserve in well-closed, light-resistant containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-Label the Tablets to indicate that they are intended for swallowing intact.

USP Reference standards $\langle 11\rangle$ —USP Ergotamine Tartrate $R S$.

Identification-Triturate a quantity of finely powdered Tablets, equivalent to about 5 mg of ergotamine tartrate, with 10 mL of solvent hexane for a few minutes, allow to settle, and discard the solvent hexane extract. Add to the residue 10 mL of chloroform saturated with ammonia (prepared by shaking chloroform with ammonium hydroxide, then drawing off the chloroform layer), triturate for a few minutes, filter, and evaporate the filtrate on a steam bath to dryness. Dissolve the residue in a mixture of 4 mL of glacial acetic acid and 4 mL of ethyl acetate. To 1 mL of this solution add slowly, with continuous agitation and cooling, 1 mL of sulfuric acid: a blue color with a red tinge develops. Add 0.1 mL of ferric chloride TS, previously diluted with an equal volume of water: the red tinge becomes less apparent and the blue color more pronounced.

## Dissolution $\langle 711\rangle$

Medium: $\quad$ tartaric acid solution (1 in 100); 1000 mL .
Apparatus 2: 75 rpm.
Time: 30 minutes.
Procedure-Determine the amount of $\left(\mathrm{C}_{33} \mathrm{H}_{35} \mathrm{~N}_{2} \mathrm{O}_{5}\right)_{2}$. $\mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$ dissolved from fluorescence intensities, using the maximum excitation wavelength at about 327 nm and the maximum emission wavelength at about 427 nm , of filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Ergotamine Tartrate RS in the same Medium.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\left(\mathrm{C}_{33} \mathrm{H}_{35} \mathrm{~N}_{2} \mathrm{O}_{5}\right)_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$ is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

Assay-
Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and 0.01 M monobasic potassium phosphate ( $55: 45$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard solution-Transfer about 40 mg of ergonovine maleate to a $250-\mathrm{mL}$ volumetric flask, add a mixture of acetonitrile and water $(55: 45)$ to volume, and mix.

Standard preparation-Transfer about 10 mg of USP Ergotamine Tartrate RS, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, add a mixture of acetonitrile and water ( $55: 45$ ) to volume, and mix. Transfer 5.0 mL of this solution to a $50-$ mL volumetric flask, add 5.0 mL of Internal standard solution, dilute with the mixture of acetonitrile and water ( $55: 45$ ) to volume, and mix to obtain a solution having a known concentration of about 0.02 mg of USP Ergotamine Tartrate RS per mL.

Assay preparation-Transfer a number of whole Tablets, equivalent to about 10 mg of ergotamine tartrate, to a $500-$ mL volumetric flask. Add 50.0 mL of Internal standard solution, 300 mL of a mixture of acetonitrile and water ( $55: 45$ ), and sonicate for about 10 minutes. Dilute with the mixture of acetonitrile and water $(55: 45)$ to volume, and mix. Filter through a $0.45-\mu \mathrm{m}$ membrane disk, discarding the first 25 mL of the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph
the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for ergonovine maleate and 1.0 for ergotamine tartrate; the resolution, $R$, between the analyte and internal standard peaks is not less than 3.0 ; the column efficiency determined from the analyte peak is not less than 3000 theoretical plates; the tailing factor for the analyte peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\left(\mathrm{C}_{33} \mathrm{H}_{35} \mathrm{~N}_{5} \mathrm{O}_{5}\right)_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$ in the portion of Ergotamine Tartrate Tablets taken by the formula:

$$
500 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Ergotamine Tartrate RS in the Standard preparation, and $R_{U}$ and $R_{S}$ are the peak response ratios obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)
(Official October 1, 2006)

## Briefing

Ergotamine Tartrate Sublingual Tablets—See briefing under Ergoloid Mesylates Tablets.
(PA3: S. Salado; NL: C. Barnstein) RTS-41094-2

## Add the following:

## ■Ergotamine Tartrate Sublingual Tablets <br> (Monograph under this new title-to become official October 1, 2006)

» Ergotamine Tartrate Sublingual Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $\left(\mathrm{C}_{33} \mathrm{H}_{35} \mathrm{~N}_{5} \mathrm{O}_{5}\right)_{2}$. $\mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$.

Packaging and storage-Preserve in well-closed, light-resistant containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-Label Tablets to indicate that they are intended for sublingual administration.

USP Reference standards $\langle 11\rangle$ —USP Ergotamine Tartrate RS.

Identification-Triturate a quantity of finely powdered Sublingual Tablets, equivalent to about 5 mg of ergotamine tartrate, with 10 mL of solvent hexane for a few minutes, allow to settle, and discard the solvent hexane extract. Add to the residue 10 mL of chloroform saturated with ammonia (prepared by shaking chloroform with ammonium hydroxide, then drawing off the chloroform layer), triturate for a few minutes, filter, and evaporate the filtrate on a steam bath to dryness. Dissolve the residue in a mixture of 4 mL of glacial acetic acid and 4 mL of ethyl acetate. To 1 mL of this solution add slowly, with continuous agitation and cooling, 1 mL of sulfuric acid: a blue color with a red tinge develops. Add 0.1 mL of ferric chloride TS, previously diluted with an equal volume of water: the red tinge becomes less apparent and the blue color more pronounced.

Disintegration $\langle 701\rangle$ : 5 minutes.
Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and 0.01 M monobasic potassium phosphate (55:45). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Internal standard solution-Transfer about 40 mg of ergonovine maleate to a $250-\mathrm{mL}$ volumetric flask, add a mixture of acetonitrile and water ( $55: 45$ ) to volume, and mix.
Standard preparation-Transfer about 10 mg of USP Ergotamine Tartrate RS, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, add a mixture of acetonitrile and water (55:45) to volume, and mix. Transfer 5.0 mL of this solution to a $50-$ mL volumetric flask, add 5.0 mL of Internal standard solution, dilute with the mixture of acetonitrile and water ( $55: 45$ ) to volume, and mix to obtain a solution having a known concentration of about 0.02 mg of USP Ergotamine Tartrate RS per mL.

Assay preparation-Transfer a number of whole Sublingual Tablets, equivalent to about 10 mg of ergotamine tartrate, to a $500-\mathrm{mL}$ volumetric flask. Add 50.0 mL of Internal standard solution, 300 mL of a mixture of acetonitrile and water (55:45), and sonicate for about 10 minutes. Dilute with the mixture of acetonitrile and water $(55: 45)$ to volume, and mix. Filter through a $0.45-\mu \mathrm{m}$ membrane disk, discarding the first 25 mL of the filtrate.
Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about
0.7 for ergonovine maleate and 1.0 for ergotamine tartrate; the resolution, $R$, between the analyte and internal standard peaks is not less than 3.0 ; the column efficiency determined from the analyte peak is not less than 3000 theoretical plates; the tailing factor for the analyte peak is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\left(\mathrm{C}_{33} \mathrm{H}_{35} \mathrm{~N}_{5} \mathrm{O}_{5}\right)_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$ in the portion of Sublingual Tablets taken by the formula:

$$
500 C\left(R_{U} / R_{S}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Ergotamine Tartrate RS in the Standard preparation, and $R_{U}$ and $R_{S}$ are the peak response ratios obtained from the Assay preparation and the Standard preparation, respectively

$$
\text { - } 1 \text { S (USP28) }
$$

(Official October 1, 2006)

## BRIEFING

Estradiol Transdermal System, page 9080 of $P F 25(6)$ [Nov.Dec. 1999]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded to In-Process Revision. In addition, minor editorial changes have been made.
(PA1: C. Anthony) RTS-40960-1

## Add the following:

## ■ Estradiol Transdermal System

» Estradiol Transdermal System contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of estradiol $\left(\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{O}_{2}\right)$.

Packaging and storage-Preserve in hermetic, light-resistant, unit-dose pouches.

USP Reference standards $\langle 11\rangle —$ USP Estradiol RS.
Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Drug release $\langle 724\rangle$ -
FOR PRODUCTS LABELED FOR DOSING EVERY 84 HOURS-
Medium: water; 900 mL .
Apparatus 5: 50 rpm .
Times: 24, 48, and 96 hours.
Determine the amount of $\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{O}_{2}$ released by employing the following method.
Mobile phase-Prepare a filtered and degassed mixture of water and acetonitrile ( $3: 2$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard solutions-Dissolve an accurately weighed quantity of USP Estradiol RS in dehydrated alcohol, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about $9 \mu \mathrm{~g}$ per mL . Dilute this solution with water to obtain additional solutions having known concentrations of about $0.9,0.45$, and $0.045 \mu \mathrm{~g}$ per mL .

Test solution-At each sampling time interval, withdraw a
$10-\mathrm{mL}$ aliquot of the solution under test.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a fluorometric detector, set at an excitation wavelength of 220 nm and an emission wavelength set at 270 nm , and a $4.6-\mathrm{mm} \times 3-\mathrm{cm}$ column that contains packing L1. The column temperature is maintained at $40^{\circ}$. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solutions, and record the peak responses as directed for Procedure: the tailing factor is between 0.9 and 2.5 ; and the relative standard deviation for replicate injections of the $0.45 \mu \mathrm{~g}$ per mL Standard solution is not more than $3.0 \%$.

Procedure—Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solutions and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Plot the peak responses of the Standard solutions versus concentration, in $\mu \mathrm{g}$ per mL , of estradiol. From the graph so obtained determine the amount, in $\mu \mathrm{g}$ per mL , of $\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{O}_{2}$ released.

Tolerances-The amounts of $\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{O}_{2}$ released, as percentages of the labeled amount of the dose absorbed in vivo at the times specified, conform to Acceptance Table 4.

| Time (hours) | Amount dissolved |
| :---: | :---: |
| 24 | between $2.4 \%$ and $26.4 \%$ |
| 48 | between $4.8 \%$ and $52.0 \%$ |
| 96 | between $10.0 \%$ and $85.0 \%$ |

Uniformity of dosage units $\langle 905\rangle$ : meets the requirements.

## Alcohol content-

Diluent-Prepare a mixture of acetonitrile and water (1:1).
Internal standard solution-Pipet 4.0 mL of dehydrated methanol into a $100-\mathrm{mL}$ volumetric flask. Dilute with water to volume, and mix.

Standard solution-Accurately weigh, by difference, about 1.6 mL of dehydrated alcohol into a tared $50-\mathrm{mL}$ volumetric flask containing about 15 mL of water. Dilute with Diluent to volume, and mix. Pipet 10.0 mL of this solution into a $50-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix. Pipet 25.0 mL of this solution into a $50-\mathrm{mL}$ volumetric flask, add 5.0 mL of Internal standard solution, dilute with water to volume, and mix.

Test solutions-Prepare as directed in the Assay for Assay preparations, with the following changes. Pipet 25.0 mL of each solution into individual $50-\mathrm{mL}$ volumetric flasks. Add 5.0 mL of Internal standard solution, dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ ) The gas chromatograph is equipped with a flame-ionization detector and a $2-\mathrm{mm} \times 2$-m glass column that contains support S2. The carrier gas is helium, flowing at a rate of 30 mL per minute. The column temperature is $100^{\circ}$. The injection port temperature and the detector temperature are maintained at $200^{\circ}$. Chromatograph the Standard solution, and record the peak areas as directed for Procedure: the relative retention times are about 0.4 for the internal standard and about 1.0 for alcohol; and the relative standard deviation for replicate injections, determined from the ratios of alcohol peak areas to those of the internal standard, is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of the Standard solution and each of the Test solutions into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the amount of alcohol, in mg, in each Transdermal System taken by the formula:

$$
160 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of dehydrated alcohol in the Standard solution; and $R_{U}$ and $R_{S}$ are the ratios of the peak responses of alcohol to the internal standard obtained from the Test solutions and the Standard solution, respectively. Calculate the average amount of alcohol in the Test solution taken: between $80 \%$ and $120 \%$ of the labeled amount of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$ is found.

## Assay-

Diluent-Prepare a mixture of acetonitrile and water (1:1).

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and water ( $55: 45$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Estradiol RS in Diluent. Dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparations-Cut 10 Transdermal Systems into pieces, keeping the pieces from each system separate. Remove the protective liners, if any, from the strips and discard. Transfer the pieces of each system into separate stoppered flasks of suitable size, and add an accurately measured volume of Diluent to each flask to obtain solutions having a concentration of about 0.1 mg of estradiol per mL . Shake by mechanical means for about 3 hours, and sonicate for 15 minutes.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The column temperature is maintained at $35^{\circ}$. The flow rate is about 1 mL per minute. Chromatograph the Standard
preparation, and record the peak responses as directed for Procedure: the tailing factor is between 0.9 and 1.6 ; and the relative standard deviation for replicate injections is not more than $2.5 \%$.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L})$ of the Standard preparation and the Assay preparations into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of estradiol $\left(\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{O}_{2}\right)$ in each Transdermal System taken by the formula:

$$
V C\left(r_{U} / r_{s}\right)
$$

in which $V$ is the volume, in mL , of Diluent used to prepare the Assay preparation; $C$ is the concentration, in mg per mL , of USP Estradiol RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. Calculate the average quantity, in mg , of estradiol in each Transdermal System. Use the individual assays to determine the Uniformity of dosage units. $\mathbf{I S}^{15}$ (USP28)

Briefing

Etodolac Extended-Release Tablets, page 320 of PF 29(1) [Jan.-Feb. 2003]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded to In-Process Revision.
(PA2: C. Anthony) RTS-40961-1

## Add the following:

## ■Etodolac Extended-Release Tablets

» Etodolac Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of etodolac $\left(\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO}_{3}\right)$.

Packaging and storage-Preserve in well-closed containers. Store at controlled room temperature, protected from light.

USP Reference standards $\langle 11\rangle$ —USP Etodolac RS. USP Etodolac Related Compound A RS.

Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, as obtained in the Assay.

Bissolution- $\langle 74\rangle$ : [Toceme.]
Drug release $\langle 724\rangle$ -
Medium: $\quad 0.05 \mathrm{M}$ phosphate buffer, $\mathrm{pH} 7.4 ; 1000 \mathrm{~mL}$.
Apparatus 2: 75 rpm , with sinker.
Times: $3,6,10$, and 16 hours.
Procedure-Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO}_{3}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 279 nm on filtered portions of the solution under test, suitably diluted with Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Etodolac RS in the same Medium. Use Medium as the blank.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO}_{3}$ dissolved at the times specified conform to $A c$ ceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :---: |
| 3 | between $15 \%$ and $40 \%$ |
| 6 | between $35 \%$ and $70 \%$ |
| 10 | between $60 \%$ and $95 \%$ |
| 16 | not less than $80 \%$ |

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Chromatographic purity-

Diluent, Mobile phase, and System suitability solutionProceed as directed in the Assay.
Test solution-Use the Assay preparation, prepared as directed in the Assay.

Chromatographic system-Prepare as directed in the Assay. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.8 for etodolac related compound A and 1.0 for etodolac; the resolution, $R$, between etodolac related compound A and etodolac is not less than 2.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Inject a volume (about $10 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure all of the peak areas. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:
in which $r_{i}$ is the peak area for each impurity; and $r_{s}$ is the sum of the areas of all the peaks: not more than $0.2 \%$ of any individual impurity is found; and not more $0.75 \%$ of total impurities is found.

## Assay-

## Diluent: acetonitrile.

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile, water, and phosphoric acid (500:500:0.25). Make adjustments if necessary (see System Suitability under Chromatography (621〉).

System suitability solution-Dissolve accurately weighed quantities of USP Etodolac RS and USP Etodolac Related Compound A RS in Diluent, and quantitatively dilute with Diluent to obtain a solution having known concentrations of about 0.48 mg per mL and 0.05 mg per mL , respectively.

Standard preparation-Dissolve an accurately weighed quantity of USP Etodolac RS in Diluent, and quantitatively dilute with Diluent to obtain a solution having a known concentration of about 0.6 mg per mL .

Assay preparation-[NOTE—Do not finely powder Tablets.] Weigh and powder not fewer than 20 Tablets, and transfer an accurately weighed portion of the powder, equivalent to about 600 mg of etodolac, to a $200-\mathrm{mL}$ volumetric flask. Add about 100 mL of Diluent, mix, and then shake for 40 minutes by mechanical means. Dilute with Diluent to volume, and mix. Pass through a filter having a $0.45-$ $\mu \mathrm{m}$ porosity, discarding the first 3 mL of the filtrate. Transfer 2.0 mL of the filtrate to a $10-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $274-\mathrm{nm}$ detector, a $4.0-\mathrm{mm} \times 4.0-\mathrm{cm}$ guard column that contains $5-\mu \mathrm{m}$ packing L1, and a $4.0-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains 5 $\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record
the peak responses as directed for Procedure: the relative retention times are about 0.8 for etodolac related compound A and 1.0 for etodolac; the resolution, $R$, between etodolac related compound A and etodolac is not less than 2.5; and the tailing factor is not more than 2.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of etodolac $\left(\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO}_{3}\right)$ in the portion of Tablets taken by the formula:

$$
1000 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Etodolac RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Fenbendazole. Because there is no existing $U S P-N F$ monograph for this article, a new monograph is being proposed. In the test for Related compounds, the liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The retention time for fenbendazole is about 19 minutes. USP has received data indicating that a Hewlett Packard Zorbax SB, C-18 column is suitable for use. The four USP Reference Standards specified in the monograph for use in the test for Related compounds are currently available through USP. In the Assay, a titrimetric procedure in which Fenbendazole is dissolved
in acetic acid and titrated with 0.1 N perchloric acid is used. Interested parties are encouraged to submit their comments to USP for evaluation.
(VET: I. DeVeau) RTS-41050-1

## Add the following:

## ■Fenbendazole


$\mathrm{C}_{15} \mathrm{H}_{13} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S} \quad 299.35$

Carbamic acid, [5-(phenylthio)-1 H -benzimidazol-2-yl]-, methyl ester.

Methyl 5-(phenylthio)-2-benzimidazolecarbamate [43210-67-9].
» Fenbendazole contains not less than 98.0 percent and not more than 101.0 percent of $\mathrm{C}_{15} \mathrm{H}_{13} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S}$, calculated on the dried basis.

Packaging and storage-Preserve in well-closed, light-resistant containers, and store at $25^{\circ}$; excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-Label it to indicate that it is for veterinary use only.

USP Reference standards $\langle 11\rangle$ —USP Fenbendazole $R S$. USP Fenbendazole Related Compound A RS. USP Fenbendazole Related Compound B RS. USP Mebendazole RS.

Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
Loss on drying $\langle 731\rangle$ —Dry it at $100^{\circ}$ to $105^{\circ}$ for 3 hours: it loses not more than $1.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.3 \%$.
Heavy metals, Method II $\langle 231\rangle$ : not more than $10 \mu \mathrm{~g}$ per g.

## Related compounds-

Solution A-Prepare a mixture of water, methanol, and acetic acid ( $70: 30: 1$ ).

Solution B-Prepare a mixture of methanol, water, and acetic acid ( $70: 30: 1$ ).

Mobile phase-Use variable mixtures of Solution A and Solution B as directed for Chromatographic system.

Hydrochloric methanol-Prepare a mixture of methanol and hydrochloric acid (99:1).

Standard solution 1-Dissolve an accurately weighed quantity of USP Fenbendazole RS in Hydrochloric methanol to obtain a solution having a known concentration of about 5 mg per mL . Dilute 1.0 mL of this solution with methanol to 200.0 mL . Dilute 5.0 mL of this solution with Hydrochloric methanol to 10.0 mL . This solution contains about 0.0125 mg of USP Fenbendazole RS per mL.

Standard solution 2-Dissolve an accurately weighed quantity of USP Fenbendazole Related Compound A RS in methanol to obtain a solution having a known concentration of about 0.1 mg per mL . Dilute 1.0 mL of this solution with Hydrochloric methanol to 10.0 mL , and mix.
Standard solution 3-Dissolve an accurately weighed quantity of USP Fenbendazole Related Compound B RS in methanol to obtain a solution having a known concentration of about 0.1 mg per mL . Dilute 1.0 mL of this solution with Hydrochloric methanol to 10.0 mL , and mix.

Resolution solution-Dissolve 10.0 mg of USP Fenbendazole RS and 10.0 mg of USP Mebendazole RS in 100.0 mL of methanol. Dilute 1.0 mL of this solution with Hydrochloric methanol to 10.0 mL , and mix.
Test solution-Dissolve 50.0 mg of Fenbendazole in 10.0 mL of Hydrochloric methanol.

Chromatographic system (see Chromatography $\langle 621\rangle$ The liquid chromatograph is equipped with a 280 -nm detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-10$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| $10-40$ | 0 | 100 | isocratic |
| $40-50$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |

Chromatograph the Resolution solution, and record the peak area responses as directed for Procedure: the retention time for fenbendazole is about 19 minutes; the relative retention time for mebendazole is about 0.85 and 1.0 for fenbendazole; and the resolution, $R$, between mebendazole and fenbendazole is not less than 1.5. Chromatograph Standard solution 2 and Standard solution 3, and record the peak area responses as directed for Procedure: the relative retention times are about 0.25 for fenbendazole related compound A and 0.65 for fenbendazole related compound B.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of Standard solution 1, Standard solution 2, Standard solution 3, and the Test solution into the chromatograph, record the chromatograms, and measure the area responses for all of the peaks. Calculate the percentages of fenbendazole related compound A and of fenbendazole related compound B in the portion of Fenbendazole taken by the formula:

$$
0.1(C / W)\left(r_{i} / r_{s i}\right),
$$

in which $C$ is the concentration, in mg per mL, of USP Fenbendazole Related Compound A RS or USP Fenbendazole Related Compound B RS in Standard solution 2 or Standard solution 3, as appropriate; $W$ is the weight, in mg, of Fenbendazole taken to prepare the Test solution; $r_{i}$ is the peak area response of the relevant related compound obtained from the Test solution; and $r_{S i}$ is the peak area response of the relevant related compound obtained from Standard solution 2 or Standard solution 3, as appropriate. Not more than $0.5 \%$ of either related compound is found. Calculate the percentage of any other impurity in the portion of Fenbendazole taken by the formula:

$$
0.1(C / W)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Fenbendazole RS in Standard solution 1; $W$ is as defined above; $r_{i}$ is the peak area response of any impurity other than fenbendazole related compound A or fenbendazole related compound B obtained from the Test solution; and $r_{s}$ is the peak area response of the main peak in the chromatogram obtained from Standard solution 1. Disregard any impurity peak with a response that is less than one-fifth that of $r_{s}$. Not more than $0.5 \%$ of any other impurity is found. The sum of all impurities found, including fenbendazole related compound A and fenbendazole related compound B , is not more than $1 \%$.

Assay—Dissolve about 200 mg of Fenbendazole, accurately weighed, in 30 mL of glacial acetic acid, warming if necessary to effect solution. Cool, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Each mL of 0.1 N perchloric acid is equivalent to 29.94 mg of $\mathrm{C}_{15} \mathrm{H}_{13} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S}$.■1S (USP28)

## Briefing

Fexofenadine Hydrochloride, page 841 of PF 30(3) [MayJune 2004]. It is proposed to revise the Packaging and storage statement by adding a recommended storage temperature. In addition, minor editorial style changes have been made.
(PA1: K. Russo; PSD: C. Okeke) RTS-41227-1

## Add the following:

## ■Fexofenadine Hydrochloride


$\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl} \quad 538.13538 .12$

Benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenyl-methyl)-1-piperidinyl]butyl]- $\alpha, \alpha$-dimethyl-, hydrochloride, $( \pm)$ -
( $\pm$ )-p-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)piperidi-no]butyl]- $\alpha$-methylhydratropic acid, hydrochloride [138452-21-8].
» Fexofenadine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in well-clesed, lightresistant containers. Preserve in tight well-closed, light-resistant containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle — U S P$ Fexofenadine Hydrochloride RS. USP Fexofenadine Related Compound A RS. USP Fexofenadine Related Compound B RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Bissolve 30 mg of Ferefenadine Hydrechloride in 2
mL of methanol, add 30 mL of water, and acidify with nitric acid: meets the requirements of the test for Chloride $\langle 194\rangle=$
The retention time of the fexofenadine peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

C: Differential scanning calorimetry $\langle 891\rangle$-Accurately weigh 2 to 6 mg of Fexofenadine Hydrochloride into an aluminum pan, and crimp the pan, using a suitable sample press. Analyze the sample from $25^{\circ}$ to $225^{\circ}$ at $10^{\circ}$ per minute. The sample exhibits a single endotherm $190^{\circ}$ between $193^{\circ}$ and $199^{\circ}$. [NOTE-The pan can be sealed hermetically, provided a pinhole is punched into the lid so that the sample can degas during heating.]
Water, Method Ic $\langle 921\rangle$ : not more than $0.5 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $0.002 \%$.
Specific surface area, Method II $\langle 846\rangle$-Outgas a portion of Fexofenadine Hydrochloride, 0.2 to 0.5 g , using helium flow for 1 hour at $100^{\circ}$ or vacuum for 1 hour at $100^{\circ}$. Test the sample, using gas sorption: between 2.5 and $5.0 \mathrm{~m}^{2}$ per g is found.

## Limit of fexofenadine related compound B-

Ammonium acetate buffer solution-Add 2.3 mL of glacial acetic acid to 2000 mL of water. Adjust with 6 N ammonium hydroxide to a pH of $4.0 \pm 0.1$.

Mobile phase-Prepare a filtered and degassed mixture of Ammonium acetate buffer solution and acetonitrile (80:20). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Add about 1.2 mg of USP Fexofenadine Related Compound B RS, accurately weighed, to a $5-\mathrm{mL}$ volumetric flask. Dilute with Mobile phase to volume, and mix. Transfer 2.0 mL of the solution so obtained into a $100-\mathrm{mL}$ volumetric flask; add about 25 mg of USP Fexofenadine Hydrochloride RS, accurately weighed; dilute with Mobile phase to volume; and mix.
Standard solution-Dilute the System suitability solution quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $2.5 \mu \mathrm{~g}$ of USP Fexofenadine Hydrochloride RS per mL.

Test solution-Dissolve an accurately weighed quantity of Fexofenadine Hydrochloride in Mobile phase to obtain a solution having a concentration of about 0.25 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 45-\mathrm{em} 25-\mathrm{cm}$ column that contains packing L45. The column is maintained at room temperature. The flow rate is about 0.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the retention time for fexofenadine is between 15 and 23 minutes; the relative retention times are about 0.7 for fexofenadine related compound B and 1.0 for fexofenadine; and the resolution, $R$, between fexofenadine and fexofenadine related compound $B$ is not less than 1.5 3.0.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Test solution and the Standard solution into the chromatograph, record the chromatograms, and measure the
peak areas. Calculate the percentage of fexofenadine related compound B in the portion of Fexofenadine Hydrochloride taken by the formula:

$$
1.25\left(r_{U} / r_{s}\right)
$$

in which 1.25 is the response factor for fexofenadine related compound B relative to fexofenadine, $r_{U}$ is the peak response for fexofenadine related compound B obtained from the Test solution, and $r_{s}$ is the peak response for fexofenadine obtained from the Standard solution: not more than $0.1 \%$ is found.

## Related compounds-

Phosphate-perchlorate buffer, Diluting solution, Mobile phase, fystem and Chromatographic system-Prepare as directed in the Assay.

Standard solution Dissolve an aceurately weighed quantity of USP Fexofenadine-Related Compound A RS in Diluting solution to obtain a selution having a known eencentration of about 0.5 mg per mL. Dilute with Mobite phase quantitatively, and stepwise if necessary, to obtain a solution having a known concentrat + ion of about 0.005 mg per mL.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Reference solution-Use the Assay preparation, prepared as directed in the Assay.
Test solution-Use the Assay stock preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Test solution, the Standard solution, the Reference solution, and Mobile phase (used as the blank) into the chromatograph; record the chromatograms; and measure the peak areas, excluding the peaks corresponding to those obtained from the Mobile phase. Calculate the entity, in
me, percentage of fexofenadine related compound A in the portion of Fexofenadine Hydrochloride taken by the formula:

$$
\begin{gathered}
50 C\left(r_{i} \not+r_{s}\right), \\
100\left(C_{S} / C_{T}\right)\left(r_{U} / r_{S}\right),
\end{gathered}
$$

in which $C_{S}$ is the concentration, in mg per mL, of USP Fexofenadine Related Compound A RS in the Standard solution; $C_{T}$ is the concentration, in mg per mL , of fexofenadine in the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses for fexofenadine related compound A obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of decarboxylated degradant [(+)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperi-dinyl]-butyl]-isopropylbenzene], with a relative retention time of 3.2, in the portion of Fexofenadine Hydrochloride taken by the formula:

$$
(100 / 1.1)\left(C_{S} / C_{T}\right)\left(r_{U} / r_{S}\right),
$$

in which $C_{S}$ is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the Standard solution; $C_{T}$ is the concentration, in mg per mL, of fexofenadine in the Test solution; $r_{U}$ is the peak response of the decarboxylated degradant obtained from the Test solution; $r_{s}$ is the peak response of fexofenadine obtained from the Standard solution; and 1.1 is the response factor for the decarboxylated degradant relative to fexofenadine. Galeulate the per eentage of other impurities in the portion of Fex efenadine Hydrochloride aken by the formmar-
in which + is the peak respense for each impurity obtained from the Test solution; and $x_{s}$ is the peak respense for fex ofenadine from the Test Calculate the percentage of other impurities in the portion of Fexofenadine Hydrochloride taken by the formula:

$$
100\left(C_{S} / C_{T}\right)\left(r_{i} / r_{S}\right)
$$

in which $C_{S}$ is the concentration, in mg per mL , of fexofenadine in the Reference solution; $C_{T}$ is the concentration, in mg per mL , of fexofenadine in the Test solution; $r_{i}$ is the peak response for any other impurity obtained from the Test solution; and $r_{s}$ is the peak response of fexofenadine obtained from the Reference solution: ferofenadine related compernd $\Lambda$ is found; and not more than $0.45 \%$ of impurities is fotment not more than $0.18 \%$ of fexofenadine related compound A is found, not more than $0.15 \%$ of decarboxylated degradant is found, not more than $0.1 \%$ of any other unknown impurity is found, not more than $0.2 \%$ total other unknown impurities is and not more than $0.3 \% 0.30 \%$ of total impurities is found.

Content of chloride—Dissolve about 300 mg of Fexofenadine Hydrochloride, accurately weighed, in 50 mL of methanol. Titrate with 0.1 N silver nitrate VS, and determine the endpoint potentiometrically (see Titrimetry $\langle 541\rangle$ ). Each mL of 0.1 N silver nitrate VS is equivalent to 3.545 mg of chloride: not less than $6.45 \%$ and not more than $6.75 \%$ of chloride is found, calculated on an anhydrous basis.

## Assay-

Phosphate-perchlorate buffer-Dissolve 6.64 g of monobasic sodium phosphate and 0.84 g of sodium perchlorate in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.0.

Diluting solution-Prepare a mixture of acetonitrile and Phosphate-perchlorate buffer (50:50).

Mobile phase-Prepare a filtered and degassed mixture of Phosphate-perchlorate buffer and acetonitrile (65:35). Add 3 mL of triethylamine per L , and mix. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Sysem suitability preard preparation-
Prepare a solution of USP Fexofenadine Hydrochloride RS and USP Fexofenadine Related Compound A RS in Mobile phase having known concentrations of about 0.06 mg per mL and 0.005 mg per mL , respectively.

Standard preparation Dissolve an aceurately weighed
quantity of USP Fexefenadine-Hydrechloride-RS in Dilut-
ing solution to obtain a solution having a known concentrat tion of about 0.5 mg per mL . Dilute quantitatively, and stepwise if necessary, with Mebile phase to-0btain aconcentration of 0.06 mg of USP Fexefenadine Hydrochloride RS per mE.
Assay stock preparation-Transfer about 50 mg of Fexofenadine Hydrochloride, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with Diluting solution to volume to obtain a solution having a concentration of about 1.0 mg of fexofenadine hydrochloride per mL .

Assay preparation-Transfer 3.0 mL of Assay stock preparation to a $50-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume to obtain a solution having a concentration of about 0.06 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L11. The column is maintained at room temperature. The flow rate is about 1.5 mL per minute. Chromatograph the Sys Standard preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between fexofenadine and fexofenadine related compound A is not less than 10 ; the tailing factor is
not more than 2.0 ; and the relative standard deviations for replicate injections determined from fexofenadine and fexofenadine related compound A are not more than $2.0 \%$ and $3.0 \%$, respectively.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}$ in the portion of Fexofenadine Hydrochloride taken by the formula:

$$
833.3 C\left(r_{U} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Fexofenadine Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses for fexofenadine obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

BRIEFING

Cryopreserved Human Fibroblast-Derived Dermal Substitute; Human Fibroblast-Derived Temporary Skin Substitute. Because there are no existing $U S P-N F$ monographs for these articles, new monographs are being proposed. Cryopreserved Human Fibroblast-Derived Dermal Substitute and Human Fibroblast-Derived Temporary Skin Substitute are monolayer biologically derived wound dressings, the cells of which are derived from neonatal foreskins. Cryopreserved Human Fibroblast-Derived Dermal Substitute is composed of material entirely of animal and human origin (except for the polyglactin matrix) and is metabolically active at the time of application. Human Fibroblast-Derived Temporary Skin Substitute includes nylon and silicone components in addition to the material of human and animal origin; it is metabolically inactive at the time of application. Six tests are proposed for both articles: Sterility, Bacterial endotoxins, Histological characterization, Metabolic activity assessment, DNA content, and Total collagen content. Histological characterization is divided into three subtests: general histology, collagen distribution, and fibronectin distribution; reference photomicrographs representing pas-
sing units are specified to assist the analyst in ascertaining quality. Interested parties are encouraged to submit their comments to USP for evaluation.
(GCT: I. DeVeau) RTS-40948-2; 41012-1

## Add the following:

## -Cryopreserved Human FibroblastDerived Dermal Substitute

» Cryopreserved Human Fibroblast-Derived Dermal Substitute is a living monolayer skin substitute derived from neonatal foreskins. It is composed of fibroblasts, an extracellular matrix, and a bioabsorbable scaffold. Human fibroblasts are seeded onto a bioabsorbable, nonantigenic and nonpyrogenic mesh scaffold composed of polyglactin, a copolymer of glycolide and lactide. The fibroblasts proliferate to fill the interstices of this scaffold to create a three-dimensional human dermal substitute that secretes human dermal collagen, matrix proteins, growth factors, and cytokines. Cryopreserved Human Fibroblast-Derived Dermal Substitute does not contain macrophages, lymphocytes, blood vessels, hair follicles, muscle fibers, or keratin. The fibroblast-cell banks, from which Cryopreserved Human Fibroblast-Derived Dermal Substitute is derived, test negative for human and animal viruses and retroviruses and are also tested for normal cell morphology, human karyology, and isoenzymes. Maternal blood sera are tested for evidence of infection with human
immunodeficiency virus types 1 and 2 , hepatitis $B$ and $C$ viruses, syphilis, and human T-lymphotropic virus type 1 and are found negative for the purpose of donor selection. Cryopreserved Human Fibroblast-Derived Dermal Substitute is manufactured with sterile components under aseptic conditions within the final package. Reagents used in the manufacture of Cryopreserved Human Fibroblast-Derived Dermal Substitute are tested and found free of viruses, retroviruses, endotoxins, and mycoplasma before use. All materials derived from bovine sources originate from countries free of bovine spongiform encephalopathy. During subsequent screening of the fibroblast cell strain at various stages in the manufacturing process, testing for these same viruses, as well as Epstein-Barr virus and human T-lymphotropic virus type 2 , is carried out and found to be negative. The final product tests negative for the presence of mycoplasma.

Packaging and storage-Cryopreserved Human Fibro-blast-Derived Dermal Substitute is aseptically packaged and supplied frozen in a clear ethyl vinyl acetate bag containing one piece of approximately $5 \mathrm{~cm} \times 7.5 \mathrm{~cm}$ for a single application. The solution within the bag is a salinebased cryoprotectant supplemented with $10 \%$ dimethyl sulfoxide and bovine serum to facilitate long-term storage. An aluminum-plastic foil envelope surrounds the bag for its protection. Cryopreserved Human Fibroblast-Derived Dermal Substitute should be stored at $-75 \pm 10^{\circ}$ for no longer than 6 months.

Labeling-The label indicates the dimensions of the Cryopreserved Human Fibroblast-Derived Dermal Substitute material enclosed. It contains the expiry date, required storage conditions, and the lot number. The label cautions that Cryopreserved Human Fibroblast-Derived Dermal Substitute is not to be used if the package shows signs of damage. Additional labeling requirements include instructions on the proper thawing and handling of Cryopreserved Human Fibroblast-Derived Dermal Substitute, the timeframe for use after package opening, and a statement that cytotoxic agents are not to be used.

USP Reference standards $\langle 11\rangle$ —USP Endotoxin $R S$.
USP Authentic Visual References $\langle 11\rangle$ —USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs. [NOTE-These three photomicrographs represent examples of passing units. They are specified to assist in ascertaining histological quality.]

Sterility $\langle 71\rangle$ : meets the requirements.
Test solution-Thaw Cryopreserved Human FibroblastDerived Dermal Substitute by placing the tissue, still in its ethyl vinyl acetate bag, in a water bath heated to a temperature of $34^{\circ}$ to $37^{\circ}$ for 2 to 3 minutes. The minimum amount of water in the water bath is 2 L per Cryopreserved Human Fibroblast-Derived Dermal Substitute unit. Perform the test on 20 mL of the cryopreservative.

Bacterial endotoxins $\langle 85\rangle$ —Thaw Cryopreserved Human Fibroblast-Derived Dermal Substitute by placing the tissue, still in its ethyl vinyl acetate bag, in a water bath heated to a temperature of $34^{\circ}$ to $37^{\circ}$ for 2 to 3 minutes. The minimum amount of water in the water bath is 2 L per Cryopreserved Human Fibroblast-Derived Dermal Substitute unit. Remove the unit from the ethyl vinyl acetate bag, and immerse in 25 mL of LAL Reagent Water. Extract for 60 minutes at $37^{\circ}$ with shaking on an orbital shaker set at 125 revolutions
per minute. Remove a 4-mL aliquot of the extract for testing: it contains not more than 0.5 USP Endotoxin Unit per mL .

## Histological characterization-

BUFFERED FORMALIN-Prepare a solution containing 10\% $(\mathrm{w} / \mathrm{v})$ formaldehyde solution and $1.0 \%$ to $1.5 \%$ methanol in a suitable buffer, adjusted to a pH of 6.8 to 7.2. ${ }^{1}$
PREPARATION OF TISSUE FOR STAINING-Cut Cryopreserved Human Fibroblast-Derived Dermal Substitute into $3-\mathrm{mm} \times 3-\mathrm{mm}$ sections. Place three sections into suitable histological tissue cassettes, ${ }^{2}$ and insert the cassettes into suitable histological cassette basket(s). ${ }^{3}$ At a temperature of $40^{\circ}$, sequentially immerse the histological cassette basket(s) in separate solutions of Buffered formalin (2 hours), two changes of $80 \%$ alcohol ( 30 minutes per step), alcohol ( 30 minutes), three changes of dehydrated alcohol ( 30 minutes per step), suitable histological xylene substitute (30 minutes), ${ }^{4}$ and two changes of suitable xylene substitute ( 30 minutes per step). Immerse the histological cassette bas$\operatorname{ket}(\mathrm{s})$ into molten paraffin ${ }^{5}$ that is at a temperature of $60^{\circ}$ for 30 minutes. Remove the cassette basket(s), and immerse in a fresh container of molten paraffin ( $60^{\circ}$ ) for 60 minutes. Remove the histological tissue cassette from the container and basket, and disassemble. Fill preheated embedding molds with molten paraffin heated to $56^{\circ}$ to $60^{\circ}$, and place on top of a preheated warming platform that is designed for histology work. Transfer Cryopreserved Human Fibroblast-

[^162]Derived Dermal Substitute specimens from the cassettes using forceps, and place specimens into individual molds. Orient the specimens in molds so as to cut cross sections. Cool the paraffin by sliding the mold down the platform to its cool side until the paraffin has solidified. Maintain specimen orientation with forceps during cooling, removing the forceps when the paraffin becomes translucent. Slide the paraffin block onto a histological cold plate to rapidly cool the block. Trim the paraffin block with a new single-edged razor blade to form a rectangle or slight trapezoid to within 5 mm of the tissue mass, if necessary. Cool the block at $4^{\circ}$ for 15 to 30 minutes. Clamp the tissue block into the block holder of the microtome. Fill a histological tissue flotation water bath with fresh water, add an appropriate amount of a suitable histological adhesive, ${ }^{6}$ and heat to $5^{\circ}$ less than the melting point of the paraffin. Properly mount and adjust the tissue and paraffin block into a microtome. Set the microtome to make cuts 5 microns thick with a blade angle of $5 \pm 2^{\circ}$. Insert a sharp stainless steel microtome knife that has been properly honed or a new disposable microtome knife into the knife holder. Cut a ribbon that contains 6 to 10 sections of Cryopreserved Human Fibroblast-Derived Dermal Substitute. Pick up the ribbon with forceps, and stretch it across the tissue flotation water bath. Separate 2 to 3 adjacent sections from the ribbon on the water bath. The selected sections should not be compressed, wrinkled, or scratched. Pick up the selected sections by dipping a microscope slide into the water bath under the floating sections, and gently lift the slide out of the water. For each staining procedure, prepare three slides from each of the three starting Cryopreserved Human Fibroblast-Derived

[^163]Dermal Substitute $3-\mathrm{mm} \times 3-\mathrm{mm}$ sections. Allow the mounted sections to air-dry completely, or dry the slide in a $60^{\circ}$ oven for 1 hour.

HEMATOXYLIN-EOSIN STAINING-
Hematoxylin-alcohol solution-Dissolve 2.5 g of hematoxylin in 25.0 mL of dehydrated alcohol with heating.

Potassium alum solution-Dissolve 50.0 g of potassium alum in 500 mL of water with heating.

Hematoxylin staining solution-Mix Hematoxylin-alcohol solution and Potassium alum solution. Bring to a boil as rapidly as possible with constant stirring. Do not heat for more than 1 minute. Slowly add 0.185 g of sodium iodate. Reheat to a simmer until the solution becomes a deep purple. Remove from heat, and quickly cool. Filter daily before use.
$10 \%$ Acid alcohol—Add 5.0 mL of hydrochloric acid to 495 mL of $70 \%$ alcohol.

Eosin solution-Dissolve 1 g of eosin Y in 100 mL of alcohol. Filter daily before use.

Procedure-The microscope slide with affixed tissue, as prepared in Preparation of tissue for staining, is sequentially immersed in three changes of a suitable histological, aliphatic xylene substitute ( 2 minutes per step), three changes of dehydrated alcohol ( 1 minute per step), alcohol (20 seconds), running tap water rinse ( 1 minute), Hematoxylin staining solution ( 4 to 5 minutes), running tap water rinse ( 1 minute), $10 \%$ Acid alcohol ( 15 seconds), running tap water rinse ( 1 minute), a suitable bluing reagent ${ }^{7}$ (20 to 30 seconds), running tap water rinse ( 1 minute), alcohol (20 seconds), Eosin solution (10 to 20 seconds, until a red-dish-brown color is obtained in the tissue), three changes of dehydrated alcohol ( 10 seconds per step), and three changes of a suitable histological xylene substitute ( 10 seconds per step). Adjust the above immersion times as needed to suit-

[^164]ably stain the tissue. Remove the slide from the last histological xylene substitute wash, and blot dry the back of the slide. Do not allow the tissue to dry. Affix a coverslip over the tissue using a coverslip mountant. Using USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrograph 1 for comparison, the test article shows a polyglactin scaffold mesh and a secreted col-lagen-based matrix; the tissue contains normal human fibroblast distributed throughout the secreted matrix and resembles normal human papillary dermis. Fibroblasts appear elongated and spindle-shaped. The tissue, which is about $100-$ to $300-\mu \mathrm{m}$ thick, contains about 106 cells per $\mathrm{cm}^{2}$.

## COLLAGEN STAINING-

Bouins's solution-Mix 75.0 mL of $1.22 \%$ picric acid solution, 25.0 L of dimethoxymethane, and 5.0 L of acetic acid.

Weigert's iron hematoxylin solution $A$-Dissolve 1.0 g of hematoxylin in 100.0 mL of alcohol.

Weigert's iron hematoxylin solution B—Mix 4.0 mL of $29 \%$ ferric chloride, 95.0 mL of water, and 1.0 mL of hydrochloric acid.

Weigert's iron hematoxylin working solution-Mix equal volumes of Weigert's iron hematoxylin solution $A$ and Weigert's iron hematoxylin solution $B$. Pass the solution through a filter having a porosity of $0.45-\mu \mathrm{m}$. Prepare fresh as needed.

Gomori's trichrome solution-Mix 1.0 mL of acetic acid and 100 mL of water. Dissolve 0.6 g of chromotrope 2R, 0.3 g of Fast Green FCF, and 0.6 g of phosphotungstic acid.
$1 \%$ Acetic acid—Mix 1.0 mL of acetic acid and 100 mL of water.

Procedure-The microscope slide with affixed tissue, as prepared in Preparation of tissue for staining is sequentially immersed in three changes of a suitable histological, alipha-
tic xylene substitute ( 2 minutes per step), three changes of dehydrated alcohol ( 1 minute per step), alcohol ( 20 seconds), and running tap water rinse ( 1 minute). Immerse the slide in Bouins's solution, and place in a $42^{\circ}$ water bath for 1 hour. Rinse the slide in water for 10 seconds. Sequentially immerse the slide in Weigert's iron hematoxylin working solution ( 10 minutes) and running tap water rinse (10 minutes). Rinse the slide in water for 10 seconds, and immerse in Gomori's trichrome solution ( 3 to 5 minutes). Rinse the slide in $1 \%$ Acetic acid for 20 seconds. Sequentially immerse the slide in three changes of alcohol ( 10 seconds per step) and three changes of a suitable histological, aliphatic xylene substitute ( 10 seconds per step). Affix a coverslip over the tissue using a suitable coverslip mountant. Nuclei will stain black; cytoplasm, keratin, and muscle fibers will stain red; and collagen and mucin will stain blue. Using USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrograph 2 for comparison, the tissue contains normal human fibroblast distributed throughout the secreted matrix and resembles normal human papillary; dermis, muscle fibers, and keratin are absent.

DISTRIBUTION OF FIBRONECTIN-
Tris-saline buffer-Prepare a solution containing 0.1 M tris(hydroxymethyl)aminomethane hydrochloride and 0.15 M sodium chloride, adjusted to a pH of 7.8 .
$3 \%$ Hydrogen peroxide-Mix 30 mL of hydrogen peroxide in water or methanol.

Diaminobenzidine solution-Use a suitable solution. ${ }^{8}$
Hematoxylin staining solution-Prepare as directed for Hematoxylin-eosin staining.

[^165]Procedure-The microscope slide with affixed tissue as prepared in Preparation of tissue for staining is dried either overnight at $37^{\circ}$ or for 1 hour at $60^{\circ}$. The microscope slide with affixed tissue as prepared in Preparation of tissue for staining is sequentially immersed in three changes of a suitable histological, aliphatic xylene substitute ( 2 minutes per step), three changes of dehydrated alcohol ( 1 minute per step), alcohol (20 seconds), and running tap water rinse (1 minute). Sequentially immerse the slide in Tris-saline buffer (10 minutes), $3 \%$ Hydrogen peroxide ( 30 minutes), three changes of Tris-saline buffer ( 1 minute per step), a suitable normal rabbit serum ${ }^{9}$ ( 30 minutes), water ( 5 minutes), and three changes of Tris-saline buffer ( 1 minute per step). Incubate the slide with a suitable solution of rabbit anti-human fibronectin antibody, ${ }^{10}$ diluted using a suitable antibody diluent ${ }^{11}$ to an antibody titer of $21.0 \pm 2.1 \mathrm{mg}$ per L for 1 (hour. Sequentially immerse the slide in water ( 5 minutes) and three changes of Tris-saline buffer (1 minute per step). Place enough drops of a biotinylated goat anti-rabbit antibody solution ${ }^{12}$ to cover the tissue section, and incubate for 30 minutes. Sequentially immerse the slide in water (5 minutes) and three changes of Tris-saline buffer (1 minute per step). Place enough drops of a streptavidin conjugated horseradish peroxidase solution ${ }^{13}$ to cover the tissue section, and incubate for 30 minutes. Sequentially immerse the slide in water ( 5 minutes) and three changes of Tris-saline buffer ( 1 minute per step). Incubate the slide with Dia-

[^166]minobenzidine solution for 1 to 5 minutes, until a suitable difference in staining is seen by comparison with a control in which the fibronectin (primary) antibody is omitted. Sequentially immerse the slide in water (1 minute), Hematoxylin staining solution ( 4 to 5 minutes), and water ( 1 minute). Do not allow the tissue to dry. Affix a coverslip over the tissue using a low-viscosity, aqueous, synthetic-resin coverslip mountant. Using USP Cryopreserved Human FibroblastDerived Dermal Substitute Reference Photomicrograph 3 for comparison, fibronectin is found colocalizing with the collagen fibers. The intensity of staining may vary from region to region of the slide.

## Metabolic activity assessment-

DPBS solution A-Dissolve 1.32 g of calcium chloride and 1.21 g of magnesium sulfate heptahydrate in 2 L of water.
DPBS solution B-Dissolve 80.0 g of sodium chloride; 2.0 g of potassium chloride; 11.5 g of dibasic sodium phosphate; 2.0 g of monobasic potassium phosphate; 10.0 g of glucose; 0.36 g of sodium phosphate; 0.5 g of streptomycin sulfate; and 1,000,000 USP Units of penicillin G sodium in 8 L water.

DPBS working solution-Mix DPBS solution B with DPBS solution $A(8: 2)$. Pass the solution through a filter having a porosity of $0.22 \mu \mathrm{~m}$.
Dulbecco's modified Eagle's tissue culture medium-Prepare a solution that contains the following components:

| Component | mg per L |
| :--- | :---: |
| Calcium chloride | 264.9 |
| Ferric nitrate nonahydrate | 0.10 |
| Potassium chloride | 400.0 |
| Magnesium sulfate heptahydrate | 200.0 |
| Sodium chloride | $6,400.0$ |
| Sodium bicarbonate | $3,700.0$ |


| Component | mg per L |
| :--- | :---: |
| Sodium phosphate, monobasic |  |
| (monohydrate) | 125.0 |
| Dextrose | $4,500.0$ |
| Phenol red | 15.0 |
| Sodium pyruvate | 110.0 |
| L-Arginine hydrochloride | 84.0 |
| L-Cystine | 48.0 |
| Aminoacetic acid | 30.0 |
| L-Histidine hydrochloride monohydrate | 42.0 |
| L-Isoleucine | 104.8 |
| L-Leucine | 104.8 |
| L-Lysine hydrochloride | 146.2 |
| L-Methionine | 30.0 |
| L-Phenylalanine | 66.0 |
| L-Serine | 42.0 |
| L-Threonine | 95.2 |
| L-Tryptophan | 16.0 |
| L-Tyrosine | 72.0 |
| L-Valine | 93.6 |
| D-Calcium pantothenate | 4.0 |
| Choline chloride | 4.0 |
| Folic acid | 4.0 |
| Inositol | 7.0 |
| Nicotinamide | 4.0 |
| Pyridoxine hydrochloride | 4.0 |
| Thiamine hydrochloride | 0.40 |
|  | 4.0 |

L-Glutamine solution-Prepare a $100-\mathrm{mL}$ solution containing 2.92 g of L -glutamine.

Sodium pyruvate solution-Prepare $100-\mathrm{mL}$ of a solution containing 1.10 g of sodium pyruvate.

Antibiotic-antimycotic solution-Prepare 100 mL of a solution containing 0.85 g of sodium chloride, 10,000 USP Units of penicillin G sodium, $10,000 \mu \mathrm{~g}$ of streptomycin (base), and $25 \mu \mathrm{~g}$ of amphotericin B.

Assay stock medium - Mix 1000 mL of Dulbecco's modified Eagle's tissue culture medium, 10 mL of $L$-Glutamine solution, 10 mL of Sodium pyruvate solution, 10 mL of Antibiotic-antimycotic solution, and 20 mL of fetal bovine serum. ${ }^{14}$

MTT-assay solution-Dissolve 0.50 g of 3 -(4,5-di-methylthiazol-2yl)-2,5-diphenyl tetrazolium bromide in 1 L of Assay stock medium, using constant stirring. Sterilize the solution by passing it through a suitable filter having a porosity of $0.2 \mu \mathrm{~m}$.
MTT formazan stock solution-Prepare a solution containing $100 \mu \mathrm{~g}$ of 1-(4,5-dimethylthiazol-2-yl)-3,5-diphenylformazan per mL of isopropyl alcohol.

MTT formazan calibration solutions-Prepare solutions containing the following five MTT formazan concentrations: $15 \mu \mathrm{~g}$ per $\mathrm{mL}, 30 \mu \mathrm{~g}$ per $\mathrm{mL}, 45 \mu \mathrm{~g}$ per $\mathrm{mL}, 60 \mu \mathrm{~g}$ per mL , and $75 \mu \mathrm{~g}$ per mL of MTT formazan, using MTT formazan stock solution and diluting with isopropyl alcohol.

Procedure-Thaw Cryopreserved Human Fibroblast-Derived Dermal Substitute by placing the tissue, still in its ethyl vinyl acetate bag, in a water bath heated to between $34^{\circ}$ and $37^{\circ}$ for 2 to 3 minutes. The minimum amount of water in the water bath is 2 L per Cryopreserved Human Fi-broblast-Derived Dermal Substitute unit. Cut three $11-\mathrm{mm}$ $\times 11-\mathrm{mm}$ sections of Cryopreserved Human Fibroblast-Derived Dermal Substitute, and immerse the sections into separate, $3.0-\mathrm{mL}$ portions of MTT-assay solution. Incubate for 2 hours at $37 \pm 2^{\circ}$ in a $3 \%$ to $7 \% \mathrm{CO}^{2}$-air environment with shaking on an orbital shaker at 150 to 200 rpm . After incu-

[^167]bation remove from the $37^{\circ}, 3 \%$ to $7 \% \mathrm{CO}^{2}$-air environment. Remove the MTT-assay solution, and rinse twice with DPBS working solution. Immerse the Cryopreserved Human Fibroblast-Derived Dermal Substitute in 2 mL of isopropyl alcohol, and incubate at ambient temperature for 1 hour with shaking on an orbital shaker at approximately 125 rpm . Transfer $200-\mu \mathrm{L}$ aliquots of the five MTT formazan calibration solutions, in triplicate, and $200-\mu \mathrm{L}$ aliquots of the three isopropyl alcohol extracts of Cryopreserved Human Fibroblast-Derived Dermal Substitute to a suitable 96well flat-bottom plate. Read the absorbance of each aliquot at 540 nm , using $200 \mu \mathrm{~L}$ of isopropyl alcohol as the blank. Plot the responses of the MTT formazan calibration solutions versus concentration, in $\mu \mathrm{g}$ of MTT formazan per mL , and calculate the regression line using the least-squares method; the test is considered valid if the regression line has a square of the correlation coefficient not less than 0.95 : the absorbance value of individual, thawed, Cryopreserved Human Fibroblast-Derived Dermal Substitute sections is between 0.30 and 0.86 .

## DNA content-

Cell culture water-Use sterile water containing not more than 0.005 USP Endotoxin Unit per mL.

DNA extraction buffer-Transfer about 850 mL of Cell culture water to a sterile, 1-L graduated container. Dissolve 12.110 g of 2-amino-2-hydroxymethyl-1,3-propanediol, 3.802 g of edetate disodium, 23.380 g of sodium chloride, and 0.080 g of sodium dodecyl sulfate, with stirring. Adjust with 1 N hydrochloric acid or 1 N sodium hydroxide to a pH of 7.0. Dilute with Cell culture water to 1 L .

Proteinase K solution-Prepare a solution of Tritirachium album proteinase K in 10 mM of 2-amino-2-hydroxy-methyl-1,3-propanediol, adjusted to a pH of 7.5 , having an activity of 600 units per $\mathrm{mL} .{ }^{15}$

Working DNA extraction buffer-Add 1.22 mL of Proteinase $K$ solution to 38.78 mL of DNA extraction buffer, and mix.

Dilution buffer-Transfer 850 mL of Cell culture water to a sterile, 1-L graduated container. Add 1.211 g of 2-amino-2-hydroxymethyl-1,3-propanediol, 3.802 g of edetate disodium, and 5.844 g of sodium chloride, with stirring. Adjust with 1 N hydrochloric acid or 1 N sodium hydroxide to a pH of 7.0. Dilute with Cell culture water to 1 L .

DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution-Prepare a solution containing 8.00 g of sodium chloride, 1.15 g of dibasic sodium phosphate (anhydrous), 0.20 g of potassium chloride, and 0.20 g of monobasic potassium phosphate per L .

Calf thymus DNA solution-Prepare a solution containing 1 mg of calf thymus DNA per mL of DPBS without $\mathrm{Ca}^{++}$, $\mathrm{Mg}^{++}$solution, mixing thoroughly for 12 to 24 hours at ambient temperature. Dilute the resulting solution with $D P B S$ without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution to prepare a solution containing $50 \mu \mathrm{~g}$ of calf thymus DNA per mL , mixing thoroughly on a vortex mixer for 10 minutes.

Calf thymus DNA calibration solutions-Prepare four calibration solutions containing $5 \mu \mathrm{~g}$ per $\mathrm{mL}, 10 \mu \mathrm{~g}$ per $\mathrm{mL}, 15$ $\mu \mathrm{g}$ per mL , and $20 \mu \mathrm{~g}$ per mL of calf thymus DNA, using Calf thymus DNA solution and diluting with DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution.
DNA staining solution—Prepare a solution containing 0.5 $\mu \mathrm{g}$ of 2'-(4-hydroxyphenyl)-5-(4-methyl-1-piperazinyl)-2,5'-bi-1H-benzimidazole trihydrochloride pentahydrate per mL of Dilution buffer. Store in low-actinic glassware.

[^168]Procedure-Thaw Cryopreserved Human Fibroblast-Derived Dermal Substitute by placing the tissue, still in its ethyl vinyl acetate bag, in a water bath heated to between $34^{\circ}$ and $37^{\circ}$ for 2 to 3 minutes. The minimum amount of water in the water bath is 2 L per Cryopreserved Human Fi-broblast-Derived Dermal Substitute unit. Cut three $11-\mathrm{mm}$ $\times 11-\mathrm{mm}$ sections of Cryopreserved Human Fibroblast-Derived Dermal Substitute. To each of three microcentrifuge tubes add 1 mL of DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution. Immerse a single Cryopreserved Human Fibroblast-Derived Dermal Substitute $11-\mathrm{mm} \times 11-\mathrm{mm}$ section into each microcentrifuge tube to remove the cryopreservative. Aspirate the DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution from each tube, and replace with 1 mL of Working DNA extraction buffer, making sure that each Cryopreserved Human Fibroblast-Derived Dermal Substitute is completely submerged in the extraction buffer. Incubate the samples in a $56^{\circ}$ to $60^{\circ}$ water bath for 4 to 18 hours. Sonicate for 10 to 15 seconds using an ultrasonic cell disrupter to achieve complete cellular disruption of the tissue and to mix the contents of the tube. Centrifuge the microcentrifuge tubes at 12,000 to 15,000 $\times g$ to pellet non-DNA material. Transfer three $50-\mu \mathrm{L}$ aliquots of each sample supernatant to individual wells of a 96well black plate suitable for performing fluorescent analysis.
Transfer triplicate $50-\mu \mathrm{L}$ aliquots of each of the Calf thymus DNA calibration solutions to the 96 -well plate, as well as a $50-\mu \mathrm{L}$ aliquot of DPBS working solution for the blank. Add $150 \mu \mathrm{~L}$ of $D N A$ staining solution to all wells containing the tissue samples, Calf thymus DNA calibration solutions, and the blank. Cover with aluminum foil, and place in a dark cabinet for 30 to 45 minutes at $15^{\circ}$ to $30^{\circ}$. Read the fluorescence of each well, using an excitation wavelength of 355 nm and an emission wavelength of 460 nm , blanking against the DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution well. Plot the responses of the Calf thymus DNA calibration solutions
versus concentration, in $\mu \mathrm{g}$ of calf thymus DNA per mL, and calculate the regression line using the least-squares method. The test is considered valid if the $\% C V$ of the replicate values is less than $15 \%$, the slope is between 4.48 and 6.27 , the $y$-intercept is between -2.04 and 3.65 , and the square of the correlation coefficient is not less than 0.990 . From the regression line so obtained, determine the amount of DNA, in $\mu \mathrm{g}$ per $11-\mathrm{mm} \times 11-\mathrm{mm}$ sample: the amount of DNA of individual Cryopreserved Human Fibroblast-Derived Dermal Substitute $11-\mathrm{mm} \times 11-\mathrm{mm}$ section is between 6 and $15 \mu \mathrm{~g}$.

## Total collagen content-

DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution-Proceed as directed for DNA content.

DPBS with $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution-Prepare a solution containing 8.00 g of sodium chloride, 1.15 g of dibasic sodium phosphate (anhydrous), 0.20 g of potassium chloride, 0.20 g of monobasic potassium phosphate, 0.10 g of magnesium chloride hexahydrate, and 0.10 g of calcium chloride (anhydrous) per L.

Collagenase extraction solution-Prepare a solution of Clostridium histolyticum collagenase, type 2, in DPBS with $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution having an activity of at least 250 units per mL .
$2 \%$ Acetic acid solution-Mix 10 mL of acetic acid with 490 mL of water.

Collagen stock standard solution-Prepare a solution having a concentration of 2 mg of collagen, type I , per mL of $2 \%$ Acetic acid solution.

Collagen calibration standards-Cut polyglactin mesh ${ }^{16}$ into seventeen $11-\mathrm{mm} \times 11-\mathrm{mm}$ squares, and place one square into 17 individual wells of a 24 -well plate. Each well of the 24 -well plate has a surface area of about $220 \mathrm{~mm}^{2}$ and

[^169]a volume of about 3.5 mL . In quadruplicate, prepare wells containing $0.050 \mathrm{mg}, 0.100 \mathrm{mg}, 0.200 \mathrm{mg}$, and 0.400 mg of collagen by adding $25 \mathrm{~mL}, 50 \mathrm{~mL}$, 100 mL , and 200 mL , respectively, of the Collagen stock standard solution. The remaining well to which no Collagen stock standard solution has been added is used as the blank. Allow the wells to air dry.

Sirius red solution-Dissolve 0.5 g of Direct Red 80 in 500 mL of saturated picric acid.

1\% (p-tert-Octylphenoxy)polyethoxyethanol solutionMix 10 mL of (p-tert-octylphenoxy)polyethoxyethanol in 990 mL of DPBS with $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution.

Procedure-Thaw Cryopreserved Human Fibroblast-Derived Dermal Substitute by placing the tissue, still in its ethyl vinyl acetate bag, in a water bath heated to between $34^{\circ}$ and $37^{\circ}$ for 2 to 3 minutes. The minimum amount of water in the water bath is 2 L per Cryopreserved Human Fi-broblast-Derived Dermal Substitute unit. Cut three $11-\mathrm{mm}$ $\times 11-\mathrm{mm}$ sections of Cryopreserved Human Fibroblast-Derived Dermal Substitute. Place each test section into separate wells of a 24 -well plate. Add $200 \mu \mathrm{~L}$ of $1 \%$ (p-tertOctylphenoxy)polyethoxyethanol solution to each sample. Shake on a rotating platform shaker at 100 to 150 rpm for 60 to 70 minutes at room temperature. Aspirate off the $1 \%$ (p-tert-Octylphenoxy)polyethoxyethanol solution, and rinse three times with 2 mL of DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution. Transfer each of the collagen standards to individual wells of the 24 -well plate. Add 0.5 mL of Sirius red solution to each test sample and collagen standards. Shake on a rotating platform shaker at 100 to 150 rpm for 60 minutes at room temperature. Aspirate off the Sirius red solution from each well. Rinse each well twice with 2 mL of $\operatorname{DPBS}$ without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution. Add an additional 2 mL of $D P B S$ without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution to each well, and allow to stand for 2 minutes. Aspirate off the DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$
solution, and rinse twice more with 2 mL of $D P B S$ without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution. Aspirate off all traces of DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution. Add 0.5 mL of Collagenase extraction solution to each well containing the Collagen calibration standards. Add 2.0 mL of Collagenase extraction solution to each well containing test samples. Rotate the plate on an orbital rotator at about 150 rpm for 90 minutes at $37^{\circ}$. Transfer $200 \mu \mathrm{~L}$ from each well, and transfer to a suitable 96 -well flat-bottom plate. Read the absorbance of each aliquot at 540 nm . Dilute the Cryopreserved Human Fibroblast-Derived Dermal Substitute sample preparation further with DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution if the absorbance is greater than the absorbance of the highest of the Collagen calibration standards. Plot the responses of the Collagen calibration standards versus the amount, in mg of collagen, and calculate the regression line using the least-squares method. The test is considered valid if the slope is between 3.00 and 5.00 and the square of the correlation coefficient is greater than or equal to 0.950 . Determine the mg of collagen per Cryopreserved Human Fibroblast-Derived Dermal Substitute section from the regression line and using the following equation:

$$
C C_{S R}=D f \times A \times S C_{S R},
$$

in which $C C_{S R}$ is the collagen content of the piece, in $\mathrm{mg} ; D f$ is the dilution factor (normally 4, unless the sample had to be further diluted); $A$ is the absorbance at 540 nm ; and $S C_{S R}$ is the slope of the regression line of the standards calculated above. The test is considered valid if the slope of the regression line is between 3.00 and 5.00 and has a square of the correlation coefficient greater than 0.950 : the amount of collagen in individual Cryopreserved Human Fibroblast-Derived Dermal Substitute $11-\mathrm{mm} \times 11-\mathrm{mm}$ samples is between 0.40 and $2.0 \mathrm{mg} \cdot \mathbf{1 S}$ (USP28)

## Briefing

Human Fibroblast-Derived Temporary Skin SubstituteSee briefing under Cryopreserved Human Fibroblast-Derived Dermal Substitute.

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(GCT: I. DeVeau) RTS-40948-1; 41012-2
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## Add the following:

## ©Human Fibroblast-Derived Temporary Skin Substitute

» Human Fibroblast-Derived Temporary Skin Substitute is a nonliving monolayer skin substitute derived from neonatal foreskins. It is composed of fibroblasts, an extracellular matrix, and a nylon mesh bonded to a transparent, semipermeable silicone membrane. Human fibroblasts are seeded onto the nylon mesh. The fibroblasts proliferate within the nylon mesh and secrete human dermal collagen, matrix proteins, growth factors, and cytokines. Following freezing, no cellular metabolic activity remains; however, the tissue matrix and bound growth factors remain. Human Fibroblast-Derived Temporary Skin Substitute does not contain macrophages, lymphocytes, blood vessels, hair follicles, muscle fibers, or keratin. The fibroblast-cell banks, from which Human Fibroblast-Derived Temporary Skin Substitute is derived, test negative for human and animal viruses and retroviruses and are also tested for normal cell morphology, human karyology,
and isoenzymes. Maternal blood sera are tested for evidence of infection with human immunodeficiency virus types 1 and 2 , hepatitis B and C viruses, syphilis, and human T-lymphotropic virus type 1 and is found negative for the purpose of donor selection. Reagents used in the manufacture of Human Fibroblast-Derived Temporary Skin Substitute are tested and found free from viruses, retroviruses, endotoxins, and mycoplasma before use. Human Fibroblast-Derived Temporary Skin Substitute is manufactured with sterile components under aseptic conditions within the final package. All materials derived from bovine sources originate from countries free of bovine spongiform encephalopathy. During subsequent screening of the fibroblast cell strain at various stages in the manufacturing process, testing for these same viruses, as well as Epstein-Barr virus and human T-lymphotropic virus type 2 , is carried out and found to be negative. The final product tests negative for the presence of mycoplasma.

Packaging and storage-Human Fibroblast-Derived Temporary Skin Substitute is aseptically packaged and supplied frozen in a clear plastic cassette containing two, approximately $12.5-\mathrm{cm} \times 19-\mathrm{cm}$, units. The solution within the cassette is a phosphate-buffered cryoprotectant solution used to facilitate long-term storage. A clear plastic bag surrounds the cassette for its protection. Human Fibroblast-Derived Temporary Skin Substitute should be stored at a temperature of $-70^{\circ}$ to $-20^{\circ}$ for no longer than 18 months. Labeling-The label indicates the dimensions of the Human Fibroblast-Derived Temporary Skin Substitute material enclosed. It contains the expiry date, required storage con-
ditions, and the lot number. The label cautions that Human Fibroblast-Derived Temporary Skin Substitute is not to be used if the package shows signs of damage. Additional labeling requirements include instructions on the proper thawing and handling of Human Fibroblast-Derived Temporary Skin Substitute and the time frame for use after package opening.

USP Reference standards $\langle 11\rangle$ —USP Endotoxin RS.
USP Authentic Visual References $\langle 11\rangle$ —USP Human Fi-broblast-Derived Skin Substitute Reference Photomicrographs. These three photomicrographs represent examples of passing units, prepared as directed in Hematoxylin-eosin staining, Collagen staining, and Distribution of fibronectin. They are specified to assist in ascertaining histological quality. The fibroblasts are embedded in an extracellular matrix that they have secreted (USP Human Fibroblast-Derived Skin Substitute Reference Photomicrograph 1). The collagen (USP Human Fibroblast-Derived Skin Substitute Reference Photomicrograph 2) and fibronectin (USP Human Fibroblast-Derived Skin Substitute Reference Photomicrograph 3) are to be found throughout the extracellular matrix. The nylon fibers (yellow in USP Human Fibro-blast-Derived Skin Substitute Reference Photomicrograph 1) and the silicone backing (grey in USP Human Fibro-blast-Derived Skin Substitute Reference Photomicrograph 1) are frequently visible although easily lost during processing. However, at this magnification, the presence of these components is the only visible difference between the Cryopreserved Human Fibroblast-Derived Dermal Substitute and the Human Fibroblast-Derived Temporary Skin Substitute. Sterility tests $\langle 71\rangle$ : meets the requirements.

Test solution-Thaw Human Fibroblast-Derived Temporary Skin Substitute by placing the tissue, still in its polycarbonate cassette contained in a plastic covering bag, in a water bath heated to a maximum of $37^{\circ}$ for 15 to 20 minutes
until no visible ice remains in the cassette. The minimum amount of water in the water bath is 2 L per Human Fibro-blast-Derived Temporary Skin Substitute unit. Perform the test on 20 mL of the cryopreservative.

Bacterial endotoxins $\langle 85\rangle$-Thaw Human Fibroblast-Derived Temporary Skin Substitute by placing the tissue, still in its polycarbonate cassette contained in a plastic covering bag, in a water bath heated to a maximum of $37^{\circ}$ for 15 to 20 minutes until no visible ice remains in the cassette. The minimum amount of water in the water bath is 2 L per Hu man Fibroblast-Derived Temporary Skin Substitute unit. Remove the unit from the polycarbonate cassette, and immerse in 25 mL of LAL Reagent Water. Extract for 60 min utes at $37^{\circ}$ with shaking on an orbital shaker set at 125 revolutions per minute. Remove a $4-\mathrm{mL}$ aliquot of the extract for testing: it contains not more than 0.5 USP Endotoxin Unit per mL.

## Histological characterization-

Buffered formalin and Preparation of tissue for stainingProceed as directed in the test for Histological characterization under Cryopreserved Human Fibroblast-Derived Dermal Substitute, substituting Human Fibroblast-Derived Temporary Skin Substitute for Cryopreserved Human Fi-broblast-Derived Dermal Substitute. The fibroblasts appear elongated and spindle shaped. The tissue contains about $10^{6}$ cells per $\mathrm{cm}^{2}$ and about 500 cells per mm along the section.

## HEMATOXYLIN-EOSIN STAINING-

Hematoxylin-alcohol solution, Hematoxylin staining solution, 10\% Acid alcohol, Eosin solution, and Proce-dure-Proceed as directed for Hematoxylin-eosin staining in the test for Histological characterization under Cryopreserved Human Fibroblast-Derived Dermal Substitute. Using USP Human Fibroblast-Derived Skin Substitute Reference Photomicrograph 1 (hematoxylin-eosin stained) for comparison, the nylon-scaffold mesh, silicone membrane,
and secreted collagen-based matrix are present and the tissue contains normal human fibroblast distributed throughout the secreted matrix and resembles normal human papillary dermis.

## COLLAGEN STAINING-

Bouins's solution, Weigert's iron hematoxylin working solution, Gomori's trichrome solution, 1\% Acetic acid, and Procedure-Proceed as directed for Collagen staining in the test for Histological characterization under Cryopreserved Human Fibroblast-Derived Dermal Substitute. Using USP Human Fibroblast-Derived Skin Reference Photomicrograph 2 for comparison, collagen is found throughout the extracellular matrix in a manner indistinguishable from Cryopreserved Human Fibroblast-Derived Dermal Substitute.

## DISTRIBUTION OF FIBRONECTIN-

Tris-saline buffer, 3\% Hydrogen peroxide, Diaminobenzidine solution, Hematoxylin staining solution, and Proce-dure-Proceed as directed for Distribution of fibronectin in the test for Histological characterization under Cryopreserved Human Fibroblast-Derived Dermal Substitute. Using USP Human Fibroblast-Derived Skin Substitute Reference Photomicrograph 3 (diaminobenzidine-hematoxylin stained) for comparison, fibronectin binds to collagen and is found throughout the extracellular matrix in a manner indistinguishable from Cryopreserved Human Fi-broblast-Derived Dermal Substitute.

## Metabolic activity assessment-

DPBS working solution, Assay stock medium, MTT-assay solution, MTT formazan calibration solutions, and Proce-dure-Proceed as directed in the test for Metabolic activity assessment under Cryopreserved Human Fibroblast-Derived Dermal Substitute, substituting Human Fibroblast-Derived Temporary Skin Substitute for Cryopreserved Human

Fibroblast-Derived Dermal Substitute: the absorbance value of individual Human Fibroblast-Derived Temporary Skin Substitute sections at 540 nm is less than 0.1 .

## DNA content-

Cell culture water, Working DNA extraction buffer, Dilution buffer, DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution, Calf thymus DNA calibration solutions, DNA staining solution, and Procedure-Proceed as directed in the test for DNA content under Cryopreserved Human Fibroblast-Derived Dermal Substitute, substituting Human Fibroblast-Derived Temporary Skin Substitute for Cryopreserved Human FibroblastDerived Dermal Substitute. The amount of DNA in individual Human Fibroblast-Derived Temporary Skin Substitute $11-\mathrm{mm} \times 11-\mathrm{mm}$ sections is between 6 and $14 \mu \mathrm{~g}$.

## Total collagen content-

DPBS without $\mathrm{Ca}^{++}, \mathrm{Mg}^{++}$solution, DPBS with $\mathrm{Ca}^{++}$, $\mathrm{Mg}^{++}$solution, Collagenase extraction solution, $2 \%$ Acetic acid solution, Collagen calibration standards, Sirius red solution, 1\% (p-tert-Octylphenoxy)polyethoxyethanol solution, and Procedure-Proceed as directed in the test for Total collagen content under Cryopreserved Human Fibroblast-Derived Dermal Substitute, substituting Human Fibroblast-Derived Temporary Skin Substitute for Cryopreserved Human Fibroblast-Derived Dermal Substitute: the amount of collagen in individual Human Fibroblast-Derived Temporary Skin Substitute $11-\mathrm{mm} \times 11-\mathrm{mm}$ samples is between 0.50 and 4.0 mg .■1S (USP28)

## Briefing

Flumazenil, page 1480 of $P F 29(5)$ [Sept.-Oct. 2003]. It is proposed to modify the Identification test $B$ by substituting an HPLC method for the TLC method, using the same data obtained in the Assay. Test 1 and Test 2 under Related compounds, and also the

Assay, are changed to include a validated method that uses just one reference standard and identifies a number of different products of synthesis. The validation work was performed using an Intersil ODS-2 brand of L1 packing. In a typical chromatogram, the retention time of Flumazenil is about 11 minutes. It is proposed to replace the test for Water, Method 1, with a test for Loss on drying, because this substance is not hygroscopic. It is also proposed to replace the test for Limit of alcohol and methylene chloride with a test for Organic volatile impurities, Method IV, which is more general in nature and not process-specific.
(PA3: S. Salado) RTS-40739-1

## Add the following:

## ■Flumazenil


$\mathrm{C}_{15} \mathrm{H}_{14} \mathrm{FN}_{3} \mathrm{O}_{3} \quad 303.3$

4H-Imidazo[1,5- $\alpha][1,4]$ benzodiazepine-3-carboxylic acid, 8-fluoro-5,6-dihydro-5-methyl-6-oxo-, ethyl ester.
Ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo $[1,5-\alpha][1,4]$ benzodiazepine-3-carboxylate [78755-81-4].
» Flumazenil contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{15} \mathrm{H}_{14} \mathrm{FN}_{3} \mathrm{O}_{3}$, calculated on the anhydrous dried basis.

Packaging and storage-Preserve in tight containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Flumazenil $R S$.
USP Flamtzenil Related Competnd A RS. USP Flantazenit
Related Compernd BRS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Thin Layer Chromatographic Identificaion Test $\langle z 01\rangle$ —

Biluent, Adsorbent, Test solution, Standerd solution 1, Application whane, and Developing solvent system-Proeeed as directed for Related commends Test 1.

B: The retention time of the major peak for flumazenil in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Melting range, Class Ia $\langle 741\rangle$ : between $198^{\circ}$ and $202^{\circ}$.
Bacterial endotoxins $\langle 85\rangle$ - It contains not more than 25.0 USP Endotoxin Units per mg of Flumazenil.

$$
\text { Water, Methed } I\langle 924\rangle \div \text { net mere than } 0.5 \%
$$

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 3 hours: it loses not more than $0.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $0.002 \%$.

## Related compounds-

TEST 1-
Ninhydrin solution-Dissolve 0.5 g of ninhydrin in 90 mL of alcohol, and add 10 mL of glacial acetic acid.

Diluent-Prepare a mixture of alcohol and chloroform (1:1).

Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture (see Chromatography $\langle 621\rangle$ ).

Test solution-Transfer about 250 mg of Flumazenil, accurately weighed, to a $5-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Diluent to volume, and mix.

Standated solution 1 Dissolve an aceurately weighed pertion of USP Flumazenil PS in Diltent, and dilute quantitatively, and stepwise if necessary, with Diltent to obtain a solution having a known concentration of about 50 mg per mL.

Standard solution $\geq 1$-Prepare a solution of USP Flumazenil RS USP Flumazenil Related Compound A RS, USP Flumazenil Related Compound B RS, and $N, N$-dimethylformamide diethyl acetal in Diluent having known concentrations of about 0.5 mg per $\mathrm{mL}-0.5 \mathrm{mg}$ per mL , abt 0.5 mg per mL , and about $0.6 \mu \mathrm{~L}$ per mL , respectively.

Standard solution 子2-Dilute 2.0 mL of Standard solution 1 with Diluent to 10.0 mL .
Stand solution- Dilute 1.0 mL of Stand solution
$z$ with Diltent to 10.0 mL .
Standard solution 5- Dilute 0.5 mL of Standard solution
2with Diluent to 10.0 mL .
Application volume: $10 \mu \mathrm{~L}$.
Developing solvent system: a mixture of chloroform, glacial acetic acid, alcohol, and water ( $75: 15: 7.5: 2.5$ ).

Procedure-Proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$. Dry the plate for 10 minutes in a current of cold air, and view under short-wavelength UV light. Spray the plate with Ninhydrin solution, and heat at $105^{\circ}$ for 15 minutes. The $R_{F}$ values of analytes are as follows.

| Compound | $R_{F}$ | Detection |
| :---: | :---: | :---: |
| Flumazenil | about 0.8 | UV |
| Flumazenil related eompound B | about 0.7 | UV |
| Flumazenil related eompound $A$ | about 0.1 | UV |
| $N, N$-Dimethylformamide diethyl acetal | about 0.04 | Ninhydrin |

Any spot at an $R_{F}$ value corresponding to $N, N$-dimethylformamide diethyl acetal in the chromatogram obtained from the Test solution is not more intense than the corresponding
spot in the chromatogram obtained from Standard solution 3 2: not more than $0.2 \%$ is found. Compare any unspecified spot in the chromatogram of the Test solution with the spet for flumazenil obtained in the chromatograms of Standard solution 3, Stallat solution 4, and Standerd solution-5, when riewed under UV light. Repert the approximate level of each of the unknown impurities: not more than $0.2 \%$ of any unknown impurity is found; and not more than 0.5\% of totalunknown impurities is found. [NOTE-Use the spots for flumazenill related compound $\Lambda$ and flumazenil relatedcompound B in the chromatograms of Standard solution - 3, Standend solution - and Standed solution 5 as references only. They are quantified in Test 2.3

TEST 2
Biluted phosphoric acid pH 2.0, Mobile phase, System suitability solution, and Chromatographic system-Proceed as directed in the Assay.
Standard solution Use the Standard preparation deseribed in the Assay.

Fest solution-Use the Assay preparation deseribed in the Assay.

Procedure Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Staldard solution and Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Caleulate the pereentage of any impurity in the pertion of Flumazenil taken by the formula:

$$
(10,000 F)(C / H)\left(r_{i},+s\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Flt mazenil $R S$ in the Stadeded soltion; $F$ is the relative response factor of the impurity according to the table below; Wis the weight, in mg, of Flumazenil, on the anhydrous bu sis, used to prepare theTest solution; ris the peak area for
any impurity in the Test solution; and s is the peak area for $^{\text {is }}$ flumazenil in the Standard solution: the impurities meet the requirements given in the table below.

| Compound name | Relative retention time | Relative <br> Respense <br> Factor | Limit (\%) |
| :---: | :---: | :---: | :---: |
| Flumazenil related eompernd $A$ | about 0.23 | Q.9 | 0.2 |
| Flumazenil related empernd B | about 0.45 | $\theta .9$ | 0.3 |
| Flumazenil | 1.0 | - | - |
| Unknown-impurities | - | 1.0 | $\theta .2$ |
| Totat | - | - | 0.5 |

TEST 2-
Diluted phosphoric acid, pH 2.0, Mobile phase, System suitability solution, Assay preparation, and Chromatographic system-Proceed as directed in the Assay.

Standard solution-Dissolve an accurately weighed quantity of USP Flumazenil RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $1 \mu \mathrm{~g}$ per mL .

Test solution-Transfer about 25.0 mg of Flumazenil, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Procedure-Separately inject equal volumes (about $5 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms for at least three times the retention time of flumazenil peak, and measure the areas for the major peaks. Calculate the percentage of any impurity in the portion of Flumazenil taken by the formula:

$$
2500(C / W)(1 / F)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Flumazenil RS in the Standard solution; $F$ is the relative response factor according to the Table below; $W$ is the weight, in mg , of Flumazenil, on the dried basis, used to prepare the Test solution; $r_{i}$ is the peak area for any impurity in the Test solution; and $r_{s}$ is the peak area for flumazenil in the Standard solution: the impurities meet the requirements given in the Table below.

| Compound name | Relative <br> retention <br> time | Relative <br> Response <br> Factor | Limit <br> (\%) |
| :---: | :---: | :---: | :---: |
| Flumazenil related compound A | about 0.4 | 1.1 | 0.2 |
| 7-Fluoro-4-methyl-3,4-dihydro-2,5H-1,4-benzodiazepine-2,5-dione | about 0.5 | 1.5 | 0.2 |
| Ethyl 5,6-dihydro-5-methyl-6-oxo-4H-imidazo- <br> $[1,5-\alpha][1,4]$ benzodiazepine-3-carboxilate | about 0.7 | 1.3 | 0.2 |
| Flumazenil related compound B | about 0.8 | 1.1 | 0.2 |
| Flumazenil | 1.0 | - | - |


|  | Relative | Relative |  |
| :--- | :---: | :---: | :---: |
| Compound | retention | Response | Limit |
| name | time | Factor | $(\%)$ |
| Ethyl 8-chloro-5,6-dihydro-5-methyl-6-oxo-4H- |  |  |  |
| imidazo-[1,5- $\alpha[1,4]$ benzodiazepine-3-carboxilate about 2.2 1.1 | 0.2 |  |  |
| Any individual unknown impurity | - | 1.0 | 0.1 |
| Total |  |  |  |

## Limit of aleohol and methylene chloride-

Standard solution Prepare a solution in dimethylsulfox ide containing $100 \mu \mathrm{~g}$ per mL of dehydrated alcohel and 4 Hg per mL of methylenechloride. Transfer 1 mL of this selution to a $20-\mathrm{mL}$ gas chrematographic headspace viat, and eap-immediately.

Fest solution Transfer about 100 mg of Flumazenil, aceurately weighed, to a $20-\mathrm{mL}$ gas chrematographic head space vial, add $1.0-\mathrm{mL}$ of dimethyl-sulfexide, eap immediately, and swirl.

Chromatographic system (see Chromatography $\langle 624$ ) The gas chromatograph is equipped with a headspace injec for and a flame ionization detector, a $0.32 \mathrm{~mm} \times 30 \mathrm{~m}$ fused siliea capillary column bonded with a 1.8 - $m$ layer of phase-G43, and a split injection system. The carrier gas is helium, flowing at a rate of about 1.7 mL per mintte, and the total flow rate is about 40 mL per minute. The chromato graph is programmed as follows. Initially the temperature of the coltmm is maintained at about $40^{\circ}$ for 20 mintutes, then the temperature is inereased at a rate of $35^{\circ}$ per mintete to $240^{\circ}$, and maintained at $240^{\circ}$ for 20 minutes. The injection pert temperature is maintained at about $140^{\circ}$, and the detec for is maintained at about $260^{\circ}$. The Standerd solttion and the Test solttion are maintained at about $90^{\circ}$, and the needle and transfer temperatures are maintained at about $140^{\circ}$. Chromatograph the Standard solttion, and record the peak
respenses as directed for Procedure: the elution order is at eohol and methylene chloride; the resolution, $R$, between at eohol and methylene chloride is not less than 3.0; and the relative-standard deviation of consecutive injections is net more that $10.0 \%$.

Procedure Using a heated, gas tight syringe, separately inject equal volumes (about 1 mL ) of the headspace of the Standerd solution and the Test solution into the chromategraph, record the ehromatograms, and measure the peak areas. Calculate the percentage of alcohol and methylene ehloride in the pertion of Flamazenil taken by the formmat:

$$
100(C / H)\left(r_{4}+\Psi_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of the relevant analyte in the Standeted solution; W is the weight, in mg, of Flumazenil taken to prepare the Test solution; and $f_{\&}$-and $x_{s}$ are the peak areas of the correspending analyte obtained from the Test solution and the Standard solution, respectively: not more than $0.1 \%$ of alcohel and not more than $0.001 \%$ of methylene chloride is found.

Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

Solvent: dimethyl sulfoxide.

Assay-
Piluted phosphoric acid, pH 2.0. Adjust 800-mL of Water with phespheric acid to pH $2.0 \pm 0.05$.

Mebile phase Prepare a filtered and degassed mixtare of Piltul phosphoric acid, pH 2.0 and acetonitrile (80:20). Make adjustments if neeessary (see-System Suitability under Chromatography $\langle 621$ ) .

Standard preparation Dissolve an aceurately weighed quantity of USP Flumazenil PS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known-concentration of about $\theta .1$ mg per mL .

Systen suitability solution- Dissolve appropriate quantities of USP Fltmazenil Related Compennd A RS and USP Flumazenil Related Compound B RS in the Standard prepafation, and dilute quantitatively, and stepwise if necessaty, with Standard preparation to obtain a solution having known concentrations of each of about $0.2 \mu$ 上 per mL . Assay preparation Transfer about 10.0 mg of Flumaze fil, aceurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobite phase to volume, and mix. Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chrematograph is equipped with a 230 -nm detec for and a $4.6-\mathrm{mm} \times 15$-m coltumn that contains packing E7. The flow rate is about 1.5 mL per minte. Chremategraph the System stuitability solution, and record the peak respenses as directed for Procedure: the relative retention times are about 0.23 for flumazenil related compound $A$, about 0.45 for flumazenil related compound $B$, and 1.0 for flumazenil; the resolution, $R$, between flumazenil related eompernd $B$ and flumazenil is net less than 3.0 ; and the tait ing factor is net more than 1.5 for the flumazenil peak. Chrematograph the Standard prepatiation, and record the peak respenses as directed for Procedure: the relative standard deviation for replieate injections is not more than $2.0 \%$.

Procdure Separately inject equal volumes (about 25 HL) of the Standard preparation and the 1 ssay preparation into the ehrematograph, record the chrematograms, and measure the area for the flumazenil peaks. Calculate the quantity, in mg, of $\mathrm{C}_{45} \mathrm{H}_{44} \mathrm{FN}_{3} \mathrm{O}_{3}$ in the pertion of Flumazenit taken by the formula:

$$
100 C\left(r_{4} \not 廾_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Flu mazenil RS in the Statedted preparation; and + and $\Psi_{s}$ are the peak areas obtained from the $A$ ssay preparation and the Standared preparation, respeetively.

Diluted phosphoric acid, pH 2.0—Adjust 800 mL of water with phosphoric acid to a pH of $2.0 \pm 0.05$.

Mobile phase—Prepare a filtered and degassed mixture of Diluted phosphoric acid, pH 2.0 , methanol, and tetrahydrofuran ( $80: 13: 7$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve appropriate quantities of chlordiazepoxide and USP Flumazenil RS in Mobile phase, and dilute stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $6.4 \mu \mathrm{~g}$ per mL of each compound.

Standard preparation-Dissolve an accurately weighed quantity of USP Flumazenil RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 1.0 mg per mL.

Assay preparation-Transfer about 25.0 mg of Flumazenil, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ ) The liquid chromatograph is equipped with a $230-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromato-
graph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.82 for chlordiazepoxide and 1.0 for flumazenil; the resolution, $R$, between chlordiazepoxide and flumazenil is not less than 2.0 ; the column efficiency is not less than 1500 theoretical plates for the flumazenil peak and the tailing factor is not more than 1.5 for the flumazenil peak. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about $5 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the flumazenil peaks. Calculate the quantity, in mg , of $\mathrm{C}_{15} \mathrm{H}_{14} \mathrm{FN}_{3} \mathrm{O}_{3}$ in the portion of Flumazenil taken by the formula:

$$
25 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Flumazenil RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively.■IS (USP28)

## BRIEFING

Flurazepam Hydrochloride, USP 27 page 833 and page 490 of PF 30(2) [Mar.-Apr. 2004]. It is proposed not to chromatograph replicate injections of the System suitability solution in Chromatographic system in the test for Related compounds. No relative standard deviation is required for the System suitability solution.

## Change to read:

» Flurazepam Hydrochloride contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{21} \mathrm{H}_{23} \mathrm{ClFN}_{3} \mathrm{O} \cdot 2 \mathrm{HCl}$, calculated on the tried
$\boldsymbol{\Delta}^{\text {anhhydrous }}{ }_{\triangle U S P 28}$
basis.

## Change to read:

## Related compounds-

Mobile phase-Prepare a filtered and degassed mixture of methanol and $1 \%$ ammonium acetate ( $80: 20$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve accurately weighed quantities of USP Flurazepam Related Compound C RS and USP Flurazepam Related Compound F RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about $2 \mu \mathrm{~g}$ per mL for each component. Prepare fresh daily.

Test solution-Transfer about 50 mg of Flurazepam Hydrochloride, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, add methanol to volume, and mix. [NOTE-Prepare this solution just prior to use.]

System suitability solution-Dissolve accurately weighed quantities of USP Flurazepam Hydrochloride RS and 2-amino-5-chlorobenzophenone in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration in each mL of about $150 \mu \mathrm{~g}$ of USP Flurazepam Hydrochloride RS and about $60 \mu \mathrm{~g}$ of 2-amino-5-chlorobenzophenone.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $239-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph of

## ■11S (USP28)

the System suitability solution, and record the peak responses as directed under Procedure: the resolution, $R$, between 2-amino-5chlorobenzophenone and flurazepam is not less than 2. Chromatograph replicate injections of the Standard solution, and record the peak responses as directed under Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in percentage, of flurazepam related compound C and flurazepam related compound F in the portion of Flurazepam Hydrochloride taken by the formula:

$$
2.5(C / W)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Flurazepam Related Compound C RS or USP Flurazepam Related Compound F RS in the Standard solution; $W$ is the weight, in mg, of Flurazepam Hydrochloride taken; and $r_{U}$ and $r_{S}$ are the peak responses for the related compounds obtained from the Test solution and the Standard solution, respectively. The limit is not more than $0.1 \%$ of flurazepam related compound C and not more than $0.1 \%$ of flurazepam related compound $F$.

## Briefing

Fluticasone Propionate. Because there is no existing USP monograph for this drug substance, the following new monograph is being proposed. The liquid chromatographic procedures in the test for Related compounds and in the Assay are based on analyses performed with the Spherisorb ODSI brand of L1 column.
(AER: K. Zaidi) RTS-40414-1

## Add the following:

## ■Fluticasone Propionate


$\mathrm{C}_{25} \mathrm{H}_{31} \mathrm{~F}_{3} \mathrm{O}_{5} \mathrm{~S} \quad 500.57$

Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy-, ( $6 \alpha$, $11 \beta, 16 \alpha, 17 \alpha$ )-S-(fluoromethyl) ester.
$S$-(Fluoromethyl) $6 \alpha, 9$-difluoro-11 $\beta, 17$-dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$-carbothioate, 17-
propionate [80474-14-2].
» Fluticasone Propionate contains not less than 98.0 percent and not more than 100.5 percent of $\mathrm{C}_{25} \mathrm{H}_{31} \mathrm{~F}_{3} \mathrm{O}_{5} \mathrm{~S}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight, light-resistant containers, and store at a temperature not exceeding $30^{\circ}$.

Labeling-Fluticasone Propionate in the form of microcrystals is so labeled.

USP Reference standards $\langle 11\rangle$ —USP Fluticasone Propionate RS. USP Fluticasone Propionate System Suitability Mixture RS. USP Fluticasone Propionate Resolution Mixture RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, as obtained in the Assay.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $+32^{\circ}$ and $+36^{\circ}(t=$ $20^{\circ}$ ), calculated on the anhydrous, solvent-free basis.

Test solution: $0.5 \%(\mathrm{w} / \mathrm{v})$ of Fluticasone Propionate in dichloromethane ( 0.5 g in 100 mL ).

Water, Method I $\langle 921\rangle$ : not more than $0.2 \%(\mathrm{w} / \mathrm{w})$.

## Related compounds-

Solution A-Mix 0.5 mL of phosphoric acid in 1000 mL of acetonitrile.

Solution B-Mix 0.5 mL of phosphoric acid in 1000 mL of methanol.

Solution C-Mix 0.5 mL of phosphoric acid in 1000 mL of water.

Mobile phase-Use variable mixtures of Solution A, Solution B, and Solution C, as directed under Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Transfer approximately 2.0 mg of USP Fluticasone Propionate System Suitability Mixture RS to 5 mL of Solution $A$, and sonicate to dissolve. Add 5 mL of Solution $C$, and mix.

Test solution-Transfer approximately 2.0 mg of Fluticasone Propionate to 5 mL of Solution $A$, and sonicate to dissolve. Add 5 mL of Solution $C$, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $239-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at $40^{\circ}$. The chromatograph is programmed as follows: Chromatograph the

System suitability solution, and measure the peak responses as directed for Procedure: the resolution, $R$, between fluticasone propionate related compound $B$ and fluticasone propionate related compound $C$ is not less than 0.6 ; the resolution between fluticasone propionate related compound D and fluticasone propionate is not less than 1.5 ; the relative retention times and limits are as provided in Ta ble 1.

| Time | Solution $A$ | Solution $B$ | Solution $C$ |  |
| :---: | :---: | :---: | :---: | :--- |
| (minutes) | $(\mathrm{v})$ | $(\mathrm{v})$ | $(\mathrm{v})$ | Elution |
| 0 | 42 | 3 | 55 | equilibrium |
| $0-40$ | $42 \rightarrow 53$ | 3 | $55 \rightarrow 44$ | linear gradient |
| $40-60$ | $53 \rightarrow 87$ | 3 | $44 \rightarrow 10$ | linear gradient |
| $60-70$ | 87 | 3 | 10 | isocratic |
| $70-75$ | $87 \rightarrow 42$ | 3 | $10 \rightarrow 55$ | re-equilibration |

Procedure-Separately inject a volume (about $50 \mu \mathrm{~L}$ ) of the System suitability solution and the Test solution into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Fluticasone Propionate taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for each impurity; and $r_{s}$ is the sum of the responses of all the peaks.

Table 1

|  | Approximate <br> Relative <br> Compound | Limit <br> Retention Time |
| :---: | :---: | :---: |
| Fluticasone propionate | 0.5 | 0.2 |
| related compound A | 0.75 | 0.1 |
| Fluticasone propionate <br> related compound B | 0.8 | 0.1 |
| Fluticasone propionate <br> related compound C | 0.95 | 0.3 |
| Fluticasone propionate |  |  |
| related compound D | 1.0 | - |

Table 1 (Continued)

|  | Approximate <br> Relative <br> Compound | Limit <br> Retention Time <br> $(\%)$ |
| :--- | :---: | :---: |
| Fluticasone propionate <br> related compound E | 1.3 | 0.3 |
| Other impurities |  |  |
| Total impurities * | - | 0.1 |
| * Calculate the total impurities from the sum of all impurity |  |  |
| peaks greater than or equal to $0.05 \%$ |  |  |

## Bromofluoromethane content-

Standard stock solution-Transfer about $20 \mu \mathrm{~L}$ of bromofluoromethane to 10 mL of dimethylformamide, and mix. Dilute $10 \mu \mathrm{~L}$ of this solution with 1 mL of dimethylformamide ( $0.002 \% \mathrm{v} / \mathrm{v}$ ).

Standard solution-Dilute $10 \mu$ L of Standard stock solution with 1 mL of dimethylformamide, and mix ( $0.00002 \%$ $\mathrm{v} / \mathrm{v})$.

Test solution-Dissolve 200 mg of Fluticasone Propionate in 1.0 mL of dimethylformamide.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with an electron-capture detector, a $0.32-\mathrm{mm} \times 25-\mathrm{m}$ capillary column coated with a $5-\mu \mathrm{m}$ film of phase G27, and a split injection system. The carrier gas is nitrogen, flowing at a rate of about 2.8 mL per minute. The make-up gas is nitrogen, flowing at a rate of 30 mL per minute. The column temperature is programmed as follows. Initially the temperature of the column is equilibrated at $40^{\circ}$ for 3.5 minutes, then the temperature is increased at the rate of $30^{\circ}$ per minute to $200^{\circ}$, and maintained at $200^{\circ}$ for 10 minutes. The split injector ( $70: 1$ ) is maintained at a temperature of $85^{\circ}$, and the detec-
tor temperature is maintained at $250^{\circ}$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure.

Procedure-Separately inject equal volumes (about $5 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, and measure the responses for the bromofluoromethane peaks. The intensity of bromofluoromethane peak in the chromatogram of the Test solution is less than the intensity of bromofluoromethane peak in the chromatogram of the Standard solution.

## Acetone content-

Internal standard solution-Prepare a $0.05 \%$ (v/v) solution of tetrahydrofuran in dimethylformamide.

Standard solution-Prepare $0.05 \%(\mathrm{v} / \mathrm{v})$ of acetone in Internal standard solution.

Test solution-Dissolve an accurately weighed quantity of Fluticasone Propionate in Internal standard solution to obtain a solution having a known concentration of about 50 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector and a $0.53-\mathrm{mm} \times 25-\mathrm{m}$ column coated with a 2 $\mu \mathrm{m}$ film of phase G15. The carrier gas is nitrogen or helium, flowing at a rate of about 5.5 mL per minute. The column temperature is programmed as follows. Initially the temperature of the column is equilibrated at $60^{\circ}$ for 3.5 minutes, then the temperature is increased at the rate of $30^{\circ}$ per minute to $180^{\circ}$, and maintained at $180^{\circ}$ for 3 minutes. The splitless injector temperature is maintained at $150^{\circ}$, and the detector temperature is maintained at $250^{\circ}$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $5.0 \%$.

Procedure-Separately inject equal volumes (about 0.1 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, and record the peak responses. Calculate the percentage of acetone $(\% \mathrm{w} / \mathrm{w})$ in the portion of Fluticasone Propionate taken by the formula:

$$
0.05 \mathrm{D} / C\left(R_{U} / R_{S}\right)
$$

in which $D$ is the density of acetone at $20^{\circ}$; $C$ is the concentration, in g per mL , of fluticasone propionate in the Test solution; and $R_{U}$ and $R_{S}$ are the ratios of the acetone peak response to the tetrahydrofuran peak response obtained from the Test solution and the Standard solution, respectively: not more than $1.0(\% \mathrm{w} / \mathrm{w})$ is found.

## Assay-

0.01 M Monobasic ammonium phosphate buffer, pH 3.5Dissolve 11.5 g of monobasic ammonium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of $3.5 \pm 0.05$, and mix.

Mobile phase-Prepare a filtered and degassed mixture of methanol, 0.01 M Monobasic ammonium phosphate buffer, pH 3.5, and acetonitrile ( $50: 35: 15$ ). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).
Resolution solution-Dissolve approximately 2.0 mg of USP Fluticasone Propionate Resolution Mixture RS in 50 mL of Mobile phase.

Standard preparation-Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.04 mg per mL .

Assay preparation-Dissolve an accurately weighed quantity of Fluticasone Propionate in Mobile phase, and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentration of about 0.04 mg per mL.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $239-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Resolution solution and the Standard preparation, and record the peak areas as directed for Procedure: the relative retention times are about 1.10 for fluticasone propionate related compound D and 1.0 for fluticasone propionate; the resolution, $R$, between fluticasone propionate and fluticasone propionate related compound D is not less than 1.5 ; and the relative standard deviation for replicate injections is not more than $2 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L})$ of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{25} \mathrm{H}_{31} \mathrm{~F}_{3} \mathrm{O}_{5} \mathrm{~S}$ in the portion of Fluticasone Propionate taken by the formula:

$$
C V\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration of USP Fluticasone Propionate RS, in mg per mL, in the Standard preparation; $V$ is the volume, in mL, of the Assay preparation, and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## Briefing

Fluvastatin Sodium, page 8420 of $P F$ 25(4) [July-Aug. 1999]; Fluvastatin Capsules, page 8423 of $P F$ 25(4) [July-Aug. 1999]. These new monographs, which previously appeared in Pharmacopeial Previews, are now forwarded with major changes to In-Process Revision. The previously proposed tests for Chromatographic purity and the Assay are being cancelled and replaced with updated methods. The separate test for Limit of 3-hydroxy-5-keto-fluvastatin is also being cancelled; this test is now performed as a part of the test for Chromatographic purity. The liquid chromatographic procedures in the tests for Chromatographic purity and the Assay are based on analyses performed with the Keystone Hypersil ODS brand of L1 column. The typical retention time for the fluvastatin peak is about 5.3 minutes for the Fluvastatin Sodium procedure and 5.4 minutes for the Fluvastatin Capsules. It is proposed to add a storage statement to the Packaging and storage section, to revise the Reference standards section, and to add a clarification to Identification test $C$.
(PA4: E. Gonikberg; PSD: C. Okeke) RTS-41110-1

## Add the following:

## Fluvastatin Sodium

$\mathrm{C}_{24} \mathrm{H}_{25} \mathrm{FNNaO}_{4} \quad 433.46$

6-Heptenoic acid, 7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-, monosodium salt, $\left[R^{*}, S^{*}-(E)\right]-( \pm)$.

Sodium ( $\pm$ )-( $3 R^{*}, 5 S^{*}, 6 E$ )-7-[3-( $p$-fluorophenyl)-1-isopro-pylindol-2-yl]-3,5-dihydroxy-6-heptenoate
[93957-55-2].
» Fluvastatin Sodium contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{24} \mathrm{H}_{25} \mathrm{FNNaO}_{4}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight, light-resistant containers, protected from moisture. Store between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Fluvastatin Sodium RS. USP Fhavastan Soditm Anti-Isomer RS. USP Fluvastatin Related Compound A RS. USP Fluvastatin Related Compound B RS. USP Fluvastatin for System Suitability RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$.
C: A solution ( 0.2 in 1 ) meets the requirements of the flame test for Sodium $\langle 191\rangle$.
$\mathbf{p H}\langle 791\rangle$ : between 8.0 and 10.0, in a solution ( 1 in 100), the test being performed immediately after preparation.

Water, Method $I\langle 921\rangle$ : not more than $4.0 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.002 \%$.
Chromatographic purity-[NOTE-Protect all solutions from light, and use amber autosampler vials and low-actinic glassware.]
Solution A, Solution B, and Mobile phase-Proceed as directed in the Assay.
System suitability stock solution-Prepare a solution in a mixture of methanol and acetonitrile $(3: 2)$ containing about 0.1 mg of USP Fluvastatin Related Compound A RS and about 0.1 mg of USP Fluvastatin Related Compound B RS per mL.

System suitability solution-Transfer about 50 mg of USP
Fluvastatin for System Suitability RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, and dissolve in 35 mL of Solution B. Add 5.0 mL of System suitability stock solution into the flask, dilute with Solution $A$ to volume, and mix. [NOTE-The System suitability stock solution and the System suitability solution are stable for up to 6 months if stored in refrigerator.]
Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Chromatographic system-Proceed as directed in the Assay, except use the liquid chromatograph equipped with either a programmable variable wavelength detector or two separate detectors capable of monitoring at 305 nm and at 365 nm . Chromatograph the System suitability solution, and record the peak responses at 305 nm as directed for Procedure. Identify the peaks corresponding to fluvastatin, fluvastatin anti-isomer, fluvastatin hydroxydiene, and fluvastatin $t$-butyl ester. The resolution, $R$, between the fluvastatin anti-isomer peak and the fluvastatin peak is not less than 1.6 ; the column efficiency is not less than 700 theoretical plates for the fluvastatin peak; and the tailing factor is not more than 3.0. Chromatograph the Standard solution, and record the peak responses at 305 nm as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms at 305 nm and 365 nm , identify the impurities listed in Table 1, and mea-
sure the peak responses. [NOTE-3-Hydroxy-5-keto fluvastatin is monitored using a wavelength of 365 nm , and all other compounds are monitored at 305 nm .] Calculate the percentage of each impurity, except for 3-hydroxy-5-keto fluvastatin, in the portion of Fluvastatin Sodium taken by the formula:

$$
100 F\left(C_{S} / C_{T}\right)\left(r_{i(305)} / r_{S(305)}\right)
$$

in which $F$ is the relative response factor as listed in Table 1 [NOTE-Use $F$ equal to 1.0 for unknown impurities]; $C_{S}$ is the concentration, in mg per mL , of USP Fluvastatin Sodium RS in the Standard solution; $C_{T}$ is the concentration, in mg per mL , of Fluvastatin Sodium in the Test solution; $r_{i(305)}$ is the peak response at 305 nm for each impurity obtained from the Test solution; and $r_{s(305)}$ is the peak response at 305 nm for the fluvastatin peak, obtained from the Standard solution.
Calculate the percentage of 3-hydroxy-5-keto fluvastatin in the portion of Fluvastatin Sodium taken by the formula:

$$
100 F\left(C_{S} / C_{T}\right)\left(r_{i(365)} / r_{S(365)}\right)
$$

in which $F, C_{S}$, and $C_{T}$ are defined above; $r_{i(365)}$ is the peak response at 365 nm for 3-hydroxy-5-keto fluvastatin, obtained from the Test solution; and $r_{s(365)}$ is the peak response at 365 nm for the fluvastatin peak, obtained from the Standard solution. In addition to not exceeding the limits for each impurity in Table 1, not more than $0.1 \%$ of any other individual impurity is found; and not more than $1.0 \%$ of total impurities is found.

Table 1

|  | Relative | Relative |  |
| :---: | :---: | :---: | :---: |
| Name | Retention <br> Response | Resp | Factor (F) | Limit (\%)

${ }_{2}$ At 365 nm
2 Fluvastatin related compound A
${ }^{3}$ Fluvastatin related compound B

## Assay-

Solution A-Add 20 mL of $25 \%$ aqueous tetramethylammonium hydroxide solution to 880 mL of water. Adjust with about 2.3 mL of phosphoric acid to a pH of $7.2 \pm 0.2$. Add 100 mL of a mixture of methanol and acetonitrile (3:2), mix, and filter.

Solution B—Add 20 mL of $25 \%$ aqueous tetramethylammonium hydroxide solution and 80 mL of water to 900 mL of a mixture of methanol and acetonitrile ( $3: 2$ ). Adjust with about 2.3 mL of phosphoric acid to a pH of $7.2 \pm 0.2$, mix, and filter. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system.

System suitability preparation-Transfer an accurately weighed quantity of USP Fluvastatin for System Suitability RS to a suitable volumetric flask, dissolve first in Solution B, using $40 \%$ of the final volume, then dilute with Solution $A$ to volume, and mix to obtain a solution having a known concentration of about 0.5 mg of fluvastatin sodium per mL .
Standard preparation-Transfer an accurately weighed quantity of USP Fluvastatin Sodium RS to a suitable volumetric flask, dissolve first in Solution B, using 40\% of the final volume, then dilute with Solution $A$ to volume, and mix to obtain a solution having a known concentration of about 0.5 mg of fluvastatin sodium per mL .
Assay preparation-Transfer about 25 mg of Fluvastatin Sodium, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask. Dissolve in 20 mL of Solution B, dilute with Solution $A$ to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $305-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 5-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 3.0 mL per minute, and the column temperature is maintained at $35^{\circ}$. The chromatograph is programmed as follows. [NOTE-Adjust the start time of the gradient step and the equilibration time for each instrument.]

Time $\quad$ Solution A Solution B

| (minutes) | $(\%)$ | $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0--6$ | 60 | 40 | isocratic |
| $6-20$ | $60 \rightarrow 18$ | $40 \rightarrow 82$ | linear gradient |
| $20-20.1$ | $18 \rightarrow 60$ | $82 \rightarrow 40$ | linear gradient |
| $20.1-25.1$ | 60 | 40 | equilibration |

Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the relative retention times are about 1.0 for fluvastatin and 1.2 for fluvastatin anti-isomer; the resolution, $R$, between the flu-
vastatin anti-isomer peak and the fluvastatin peak is not less than 1.6 ; the column efficiency is not less than 700 theoretical plates for the fluvastatin peak; and the tailing factor is not more than 3.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the fluvastatin peaks. Calculate the quantity, in mg, of $\mathrm{C}_{24} \mathrm{H}_{25} \mathrm{FNNaO}_{4}$ in the portion of Fluvastatin Sodium taken by the formula:

$$
50 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Fluvastatin Sodium RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the fluvastatin peak responses obtained from the Assay preparation and the Standard preparation, respectively..1S (USP28)

## Add the following:

## ■ Fluvastatin Capsules

## » Fluvastatin Capsules contain an amount of Flu-

 vastatin Sodium equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fluvastatin $\left(\mathrm{C}_{24} \mathrm{H}_{25} \mathrm{FN} \Theta_{4}\right)$ $\mathrm{C}_{24} \mathrm{H}_{26} \mathrm{FNO}_{4}$.Packaging and storage-Preserve in tight, light-resistant containers, protected from moisture and from light. Store in a cool place or at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Fluvastatin Sodium RS. USP Flu In As USP Fluvastatin for System Suitability RS. USP Fluvastatin Related Compound A RS.

## Identification-

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

B: A solution ( 0.2 in 1 ) meets the requirements of the flame test for Sodium $\langle 191\rangle$.

Dissolution $\langle 711\rangle$ -
Medium: water; 500 mL .
Apparatus 2: 50 rpm , sinkers not used.
Time: 30 minutes.
Determine the amount of $\epsilon_{24} \mathrm{H}_{26} \mathrm{FNO}_{4} \mathrm{C}_{24} \mathrm{H}_{26} \mathrm{FNO}_{4}$ dissolved by employing the following method.

Buffer solution-Dissolve about 1.534 g of monobasic ammonium phosphate in about 800 mL of water, and adjust with phosphoric acid or ammonium hydroxide to a pH of 3.5.

Mobile phase-Prepare a filtered and degassed mixture of methanol and Buffer solution (7:3).
Standard solution-[NOTE-A volume of methanol, not exceeding $2 \%$ of the final volume of solution, may be used to aid in dissolving the USP Reference Standard.] Dissolve an accurately weighed quantity of USP Fluvastatin Sodium RS in Medium to obtain a solution having a known concentration of fluvastatin corresponding to that obtained when 1 Capsule is dissolved in 500 mL of solvent.

Test solution-Withdraw $20-\mathrm{mL}$ portions of liquid under test from each vessel, and pass through a suitable filter, discarding the first 2 mL of the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $235-\mathrm{nm}$ detector, a suitable $7-\mu \mathrm{m}$ guard column that contains packing L1, and a $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \% 1.5 \%$.
Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the fluvastatin peaks. From the measured peak areas, calculate the quantity of $\epsilon_{24} \mathrm{H}_{25} \mathrm{FNO}_{4} \mathrm{C}_{24} \mathrm{H}_{26} \mathrm{FNO}_{4}$ dissolved.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\epsilon_{26} \mathrm{H}_{25} \mathrm{FNO}_{4} \mathrm{C}_{24} \mathrm{H}_{26} \mathrm{FNO}_{4}$ is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements, the Chromatographic system being prepared as directed for the Dissolution test.

Chromatographic purity-[NOTE-Protect all solutions from light, and use amber autosampler vials and low-actinic glassware.]

Solution A, Solution B, Mobile phase, and Diluent-Proceed as directed in the Assay.

System suitability stock solution-Prepare a solution in methanol containing about 0.1 mg of USP Fluvastatin Related Compound A RS per mL.
System suitability solution-Transfer about 50 mg of USP Fluvastatin for System Suitability RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, and dissolve in 35 mL of methanol. Add 5.0 mL of System suitability stock solution into the flask, dilute with Diluent to volume, and mix. [NOTE-The System suitability stock solution and the System suitability solution are stable for up to 6 months if stored in refrigerator.]

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Chromatographic system-Proceed as directed in the Assay, except use the liquid chromatograph equipped with either a programmable variable wavelength detector or two separate detectors capable of monitoring at 305 nm and at 365 nm . Chromatograph the System suitability solution, and record the peak responses at 305 nm as directed for Procedure. Identify the peaks corresponding to fluvastatin, fluvastatin anti-isomer, and fluvastatin hydroxydiene. Chromatograph the System suitability solution, and record the peak responses at 305 nm as directed for Procedure: the resolution, $R$, between the fluvastatin anti-isomer peak and the fluvastatin peak is not less than 1.4; and the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms at 305 nm and 365 nm , identify the impurities listed in Table 1, and measure the peak responses. [NOTE-3-Hydroxy-5-keto fluvastatin is monitored using a wavelength of 365 nm , and all
other compounds are monitored at 305 nm .] Calculate the percentage of each impurity, except for 3-hydroxy-5-keto fluvastatin, in the portion of Capsules taken by the formula:

$$
100 F(411.48 / 433.46)\left(C_{S} / C_{T}\right)\left(r_{i(305)} / r_{S(305)}\right)
$$

in which $F$ is the relative response factor as listed in Table 1 [NOTE-Use $F$ equal to 1.0 for unknown impurities]; 411.48 and 433.46 are the molecular weights of fluvastatin and fluvastatin sodium, respectively; $C_{S}$ is the concentration, in mg per mL, of USP Fluvastatin Sodium RS in the Standard solution; $C_{T}$ is the concentration, in mg per mL , of fluvastatin in the Test solution, based on the label claim; $r_{i(305)}$ is the peak response at 305 nm for each impurity obtained from the Test solution; and $r_{S(305)}$ is the peak response at 305 nm for the fluvastatin peak, obtained from the Standard solution.

Calculate the percentage of 3-hydroxy-5-keto fluvastatin in the portion of Capsules taken by the formula:

$$
100 F(411.48 / 433.46)\left(C_{S} / C_{T}\right)\left(r_{i(365)} / r_{S(365)}\right)
$$

in which $F, C_{S}$, and $C_{T}$ are defined above; $r_{i(365)}$ is the peak response at 365 nm for 3-hydroxy-5-keto fluvastatin, obtained from the Test solution; and $r_{S(365)}$ is the peak response at 365 nm for the fluvastatin peak, obtained from the Standard solution. In addition to not exceeding the limits for each impurity in Table 1, not more than $0.5 \%$ of any unknown impurity is found; not more than $1.5 \%$ of total unknown impurities is found; and not more than $4.0 \%$ of total impurities is found.

Table 1

|  | Relative <br> Retention <br> Name | Relative <br> Response |  |
| :---: | :---: | :---: | :---: |
| Fluvastatin anti- <br> isomer | 1.2 | 1.0 | 1.5 |
| Factor $(F)$ | Limit (\%) |  |  |
| 3-Hydroxy-5-keto <br> fluvastatin | 1.6 | $0.037^{1}$ | 1.0 |
| Fluvastatin hydroxy- <br> diene |  |  |  |
| Fluvastatin short <br> chain aldehyde | 2.2 | 1.1 | 1.0 |

${ }^{1}$ At 365 nm
${ }^{2}$ Fluvastatin related compound A

## Assay-

pH 7.2 Buffer—Prepare a solution containing 40 mL of $25 \%$ aqueous tetramethylammonium hydroxide in 1 L of water, and adjust with approximately 4.5 mL of phosphoric acid to a pH of $7.2 \pm 0.2$.

Methanol-acetonitrile mixture-Prepare a mixture of methanol and acetonitrile $(3: 2)$.

Solution A-Prepare a filtered and degassed mixture of pH 7.2 Buffer and Methanol-acetonitrile mixture (87.5: 12.5).

Solution B-Prepare a filtered and degassed mixture of Methanol-acetonitrile mixture and pH 7.2 Buffer (87.5 : 12.5).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system.
Diluent-Prepare a mixture of $p H$ 7.2 Buffer and Metha-nol-acetonitrile mixture (54:46).

System suitability preparation-Dissolve an accurately weighed quantity of USP Fluvastatin for System Suitability RS in Diluent to obtain a solution having a known concentration of about 0.42 mg of fluvastatin sodium per mL .

Standard preparation-Dissolve an accurately weighed quantity of USP Fluvastatin Sodium RS in Diluent to obtain a solution having a known concentration of about 0.42 mg of fluvastatin sodium per mL.

Assay stock preparation-Transfer the contents and the empty shells of 10 Capsules to a $200-\mathrm{mL}$ glass-stoppered flask. Add 100.0 mL of methanol, and stir with magnetic or mechanical stirrer for 45 minutes. Centrifuge a portion of this solution at 4000 rpm for 20 minutes.

Assay preparation-Quantitatively transfer an amount of the Assay stock preparation, containing 20.0 mg of fluvastatin based on the label claim, to a $50-\mathrm{mL}$ volumetric flask, and dilute with Diluent to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $305-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 5-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing Ll. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows. [NOTE-Adjust the start time of the gradient step and the equilibration time for each instrument.]

Time $\quad$ Solution $A$ Solution $B$

| (minutes) | $(\%)$ | $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0-6$ | 54 | 46 | isocratic |
| $6-17$ | $54 \rightarrow 17$ | $46 \rightarrow 83$ | linear gradient |
| $17-20$ | 17 | 83 | isocratic |
| $20-20.1$ | $17 \rightarrow 54$ | $83 \rightarrow 46$ | linear gradient |
| $20.1-26.1$ | 54 | 46 | equilibration |

Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the retention time of the fluvastatin peak is about 5.4 minutes; the
relative retention times are about 1.0 for fluvastatin and 1.2 for fluvastatin anti-isomer; the resolution, $R$, between the fluvastatin anti-isomer peak and the fluvastatin peak is not less than 1.4 ; and the relative standard deviation for replicate injections is not more than $1.5 \%$. [NOTE-If the retention time of the fluvastatin peak exceeds 5.7 minutes, adjust the isocratic step accordingly, so that both fluvastatin peak and anti-isomer peak elute within the isocratic region.]
Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the fluvastatin peaks. Calculate the quantity, in mg , of fluvastatin $\left(\mathrm{C}_{24} \mathrm{H}_{26} \mathrm{FNO}_{4}\right)$ in the portion of Capsules taken by the formula:

$$
5000(411.48 / 433.46)(C / V)\left(r_{U} / r_{s}\right)
$$

in which 411.48 and 433.46 are the molecular weights of fluvastatin and fluvastatin sodium, respectively; $V$ is the volume, in mL, of the Assay stock preparation taken to prepare the Assay preparation; $C$ is the concentration, in mg per mL , of USP Fluvastatin Sodium RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the fluvastatin peak responses obtained from the Assay preparation and the Standard preparation, respectively. 1 (USP28)

## BRIEFING

Fluvoxamine Maleate; Fluvoxamine Maleate Tablets. Because there are no existing USP monographs for this drug substance and dosage form, new monographs are being presented. The liquid chromatographic procedure in the test for Chromato-
graphic purity and in the Assay is based on analyses performed with a Waters Symmetry column. The typical retention time for fluvoxamine maleate is about 8 minutes.
(PA3: S. Salado) RTS-40316-5

## Add the following:

## ■Fluvoxamine Maleate


» Fluvoxamine Maleate contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$, calculated on the dried basis.

Packaging and storage-Preserve in well-closed, light-resistant containers. Store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Fluvoxamine Maleate $R S$.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Melting temperature $\langle 741\rangle$ : between $121^{\circ}$ and $123^{\circ}$.
Loss on drying $\langle 731\rangle$ —Dry it in vacuum at $80^{\circ}$ for 2 hours: it loses not more than $0.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Maleic acid—Transfer about 800.0 mg of Fluvoxamine Maleate, accurately weighed, to a $250-\mathrm{mL}$ conical flask containing 50 mL of water. Titrate with 0.1 N sodium hydroxide VS, using 0.5 mL of phenolphthalein TS as the indicator. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Each mL of 0.1 N sodium hydroxide VS is equivalent to 5.805 mg of maleic acid $\left(\mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right)$. Between $26.0 \%$ and $27.5 \%$ of maleic acid is found.

Heavy metals, Method II 〈231〉: 0.001\%.

## Related compounds-

Buffer solution, Mobile phase, Resolution solution, and Chromatographic system-Proceed as directed in the Assay.

Identification solution-Dissolve a quantity of maleic acid in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.35 mg per mL .

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay stock preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution, Test solution, and the Identification solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of impurities in the portion of Fluvoxamine Maleate taken by the formula:

$$
5000(C / W) F\left(r_{i} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Fluvoxamine Maleate RS in the Standard solution; $W$ is the weight, in mg , of fluvoxamine maleate used to prepare the Test solution; $F$ is the response factor of each impurity as given in Table 1; $r_{i}$ is the individual peak area of each im-
purity in the Test solution; and $r_{s}$ is the peak area of fluvoxamine maleate in the Standard solution. The limits of impurities are specified in Table 1. [NOTE-Disregard any peak due to maleic acid or the reagent blank.]

Table 1

| Compound name | Relative retention time | Response <br> Factor | Limit <br> (\%) |
| :---: | :---: | :---: | :---: |
| Maleic acid | about 0.19 | - | - |
| 5-Methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(E)-O-[2-[(2-succinyl)amino]ethyl]oxime | about 0.50 | 1.0 | 0.3 |
| 5-Methoxy-4'-(trifluoromethyl) valerophenone ( $E$ )-O-(2-aminoethyl)aminoethyl oxime maleate | about 0.67 | 1.4 | 0.2 |
| $Z$-isomer | about 0.79 | 1.0 | 0.5 |
| Fluvoxamine | 1.0 | - | - |
| 4'-(Trifluoromethyl)valerophenone $(E)$ - $O$ - 2-(2-amino ethyl)aminoethyl oxime maleate | about 1.18 | 1.0 | 0.2 |
| (E)-O-2-(2-Aminoethyl)-4-(trifluoromethyl)- $\alpha$-phenylacetophenone oxime maleate | about 1.74 | 1.0 | 0.2 |
| 4'-(Trifluoromethyl)valerophenone $(E)-O$-(2-aminoethyl) oxime maleate | about 2.00 | 1.0 | 0.2 |
| 5-Methoxy-4'-(trifluoromethyl) valerophenone oxime | about 3.45 | 0.6 | 0.2 |
| 5-Methoxy-4'-(trifluoromethyl) valerophenone ketone | about 4.2 | 0.3 | 0.2 |
| Unknown impurities | - | 1.0 | 0.1 |
| Total | - | - | 1.5 |

Organic volatile impurities, Method $I\langle 467\rangle$ : meets the requirements.

Assay-
Buffer solution-Dissolve about 5 g of 1-pentanesulfonic acid sodium salt and 0.7 g of monobasic potassium phosphate in 620 mL of water. Adjust with phosphoric acid to a pH of $3.00 \pm 0.05$.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (62:38). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Resolution solution-Transfer about 6 mg of Fluvoxamine Maleate to a $50-\mathrm{mL}$ volumetric flask. Heat the sample at $120^{\circ}$ for 10 minutes. Cool down to room temperature, and add 3.0 mL of 0.1 N hydrochloric acid. Heat the solution in a water bath for 10 minutes. Cool down to room temperature,
add 50 mg of Fluvoxamine Maleate, and dissolve in 25 mL of Mobile phase. Dilute with Mobile phase to volume, and mix.

Standard preparation-Dissolve an accurately weighed quantity of USP Fluvoxamine Maleate RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.05 mg per mL .
Assay stock preparation-Transfer an accurately weighed quantity of about 50 mg of Fluvoxamine Maleate to a $50-$ mL volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Assay preparation—Transfer 5.0 mL of the Assay stock preparation to a $100-\mathrm{mL}$ volumetric flask. Dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $234-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L7. The flow rate is about 1.7 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.2 for maleic acid, 0.5 for 5-methoxy-1-[4-(trifluoromethyl)phe-nyl]-1-pentanone-(E)-O-[2-[(2-succinyl)amino]ethyl]oxime, 0.8 for the $Z$-isomer, and 1.0 for fluvoxamine maleate; the resolution, $R$, between the $Z$-isomer and fluvoxamine maleate is not less than 3.0 and not less than 5.0 between 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-( $E$ )-$O$-[2-[(2-succinyl)amino]ethyl]oxime and the $Z$-isomer. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the fluvoxamine maleate peaks. Calculate the quantity, in mg, of $\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$ in the portion of Fluvoxamine Maleate taken by the formula:

$$
1000 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Fluvoxamine Maleate RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively. $\quad$ IS (USP28)

## Briefing

Fluvoxamine Maleate Tablets-See briefing under Fluvoxamine Maleate.
(PA3: S. Salado) RTS-40316-1

## Add the following:

## ■ Fluvoxamine Maleate Tablets

» Fluvoxamine Maleate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fluvoxamine maleate $\left(\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right)$.

Packaging and storage-Preserve in tight containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Fluvoxamine Maleate $R S$.

Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Dissolution $\langle 711\rangle$ - [To come].
Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Related compounds-

Buffer solution, Mobile phase, Resolution solution, and Chromatographic system-Proceed as directed in the Assay.

Identification solution-Dissolve a quantity of maleic acid in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a concentration of about 0.35 mg per mL .

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay stock preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution, the Test solution, and the Identification solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of impurities in the portion of Tablets taken by the formula:

$$
100(C / D) F\left(r_{i} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Fluvoxamine Maleate RS in the Standard solution; $D$ is the expected concentration, in mg per mL , of fluvoxamine maleate taking into account the labeled amount and the amount of sample taken to prepare the Test solution; $F$ is the response factor of each impurity as given in Table $1 ; r_{i}$ is the individual peak area of each impurity in the Test solution; and $r_{s}$ is the peak area of fluvoxamine maleate in the Standard solution. The limits of impurities are specified in Table 1. [NOTE-Disregard any peak due to maleic acid or to the reagent blank.]

Table 1

| Compound name | Relative retention time | Response <br> Factor | Limit \% |
| :---: | :---: | :---: | :---: |
| Maleic acid | about 0.19 | - | - |
| 5-Methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone( $E$ )-O-[2-[(2-succinyl)amino]ethyl]oxime | about 0.50 | 1.0 | 0.8 |
| 5-Methoxy-4'-(trifluoromethyl)valerophenone ( $E$ )-O-(2-aminoethyl)aminoethyl oxime maleate | about 0.67 | 1.4 | 0.2 |
| $Z$-isomer | about 0.79 | 1.0 | 0.5 |
| Fluvoxamine | 1.0 | - | - |
| 4'-(Trifluoromethyl)valerophenone( $E$ )-O-2-(2-aminoethyl)aminoethyl oxime maleate | about 1.18 | 1.0 | 0.2 |

Table 1 (Continued)

| Compound name | Relative retention time | Response Factor | Limit <br> \% |
| :---: | :---: | :---: | :---: |
| (E)-O-2-(2-Aminoethyl)-4-(trifluoromethyl)- $\alpha$-phenylacetophenone oxime maleate | about 1.74 | 1.0 | 0.2 |
| 4'-(Trifluoromethyl)valerophenone $(E)$-O-(2-aminoethyl) oxime maleate | about 2.00 | 1.0 | 0.2 |
| 5-Methoxy-4'-(trifluoromethyl)valerophenone oxime | about 3.45 | 0.6 | 0.2 |
| 5-Methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(E)-O-(2-aminoethyl] oxime maleic acid monoamide | about 4.3 | 1.0 | 0.2 |
| 5-Methoxy-4'-(trifluoromethyl)valerophenone ketone | about 4.2 | 0.3 | 0.2 |
| Unknown impurities | - | 1.0 | 0.1 |
| Total | - | - | 1.8 |

## Assay-

Buffer solution-Dissolve approximately 5 g of 1-pentanesulfonic acid sodium salt and 0.7 g of monobasic potassium phosphate in 620 mL of water. Adjust with phosphoric acid to a pH of $3.00 \pm 0.05$.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $62: 38$ ). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).
Resolution solution-Transfer approximately 6 mg of fluvoxamine maleate to a $50-\mathrm{mL}$ volumetric flask. Heat the sample at $120^{\circ}$ for 10 minutes. Cool down to room temperature, and add 3.0 mL of 0.1 N hydrochloric acid. Heat the solution in a water bath for 10 minutes. Cool down to room temperature, add 50 mg of fluvoxamine maleate, and dissolve in 25 mL Mobile phase. Dilute with Mobile phase to volume, and mix.

Standard preparation-Dissolve an accurately weighed quantity of USP Fluvoxamine Maleate RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.05 mg per mL .
Assay stock preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg of fluvoxamine maleate, to a $500-\mathrm{mL}$ volumetric flask, add about 250 mL of Mobile phase, sonicate for about 15 minutes, shake by mechanical means for about 15 minutes, dilute with Mobile phase to volume, and mix. Centrifuge a portion of this solution for 10 minutes.

Assay preparation-Transfer 5.0 mL of the supernatant from the Assay stock preparation to a $100-\mathrm{mL}$ volumetric flask. Pass a portion of this solution through a filter having a $45-\mu \mathrm{m}$ or finer porosity, and use the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $234-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L7. The flow rate is about 1.7 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.19 for maleic acid, 0.5 for 5-methoxy-1-[4-(trifluoromethyl)phe-nyl]-1-pentanone-(E)-O-[2-[(2-succinyl)amino]ethyl]oxime, 0.79 for the $Z$-isomer, and 1.0 for fluvoxamine maleate; and the resolution, $R$, between the $Z$-isomer and fluvoxamine maleate is not less than 2.0 and not less that 5.0 between 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone- $(E)-O-[2-[(2$-succinyl)amino]ethyl]oxime and the $Z$-isomer. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than 2.0\%.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the fluvoxamine maleate peaks. Calculate the quantity, in mg , of fluvoxamine maleate $\left(\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right)$ in the portion of Tablets taken by the formula:

$$
10,000 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Fluvoxamine Maleate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Gemcitabine for Injection, page 3061 of the First Supplement. A revision is proposed in the test for Clarity of solution to replace $\tau$, tau with NTU to describe the turbidity measurement.
(PA6: L. Evans) RTS-41353-1

## Change to read:

Clarity of solution-Dissolve it in the solvent and at the concentration recommended in the labeling: not more than $10 \tau$
$\mathbf{- 1 0}_{10} \mathrm{NTU}_{1 \mathrm{~S}}$ (USP28)
(see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ), determined by ratio turbidimetry within 15 minutes of reconstitution, corrected for a diluent blank.

## BRIEFING

Gemfibrozil Capsules, USP 27 page 858. It is proposed to clarify the instructions for the preparation of the Medium in the test for Dissolution.
(BPC: M. Marques) RTS-41150-1

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: $\quad 0.2 \mathrm{M} \mathrm{pH} 7.5$ phosphate buffer prepared as direed under Solutions in the section Reagents, Indicator's, and Solutions, exeept that 0.8 M menobasic petassitm phesphate-solution and 0.8 M sodium hydroxide solution are used;
-by dissolving 545 g of monobasic potassium phosphate in 5 L of water, adding 131 g of sodium hydroxide, diluting with water to about 19.5 L , and mixing well. Adjust with either 1 N phosphoric acid or 1 N sodium hydroxide to a pH of 7.5 , and dilute with water to 20 L ; ${ }_{\text {1S }}$ (USP28) 900 mL .

Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-Determine the amount of $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{O}_{3}$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solution under test, suitably diluted with 1 N sodium hydroxide, in comparison with a Standard solution obtained as follows. Prepare a Standard stock
solution of USP Gemfibrozil RS having a known concentration of about 0.33 mg per mL in Dissolution Medium. [NOTE-Initially dissolve the USP Reference Standard in an amount of methanol not to exceed $1 \%$ of the volume of the Standard stock solution.] Quantitatively dilute the Standard stock solution with 1 N sodium hydroxide to obtain a Standard solution having a concentration estimated to correspond to that of the filtered and diluted solution under test.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{O}_{3}$ is dissolved in 45 minutes.

## BRIEFING

Gemfibrozil Tablets, USP 27 page 859. On the basis of comments received, it is proposed to clarify the instructions for the preparation of the Medium in the test for Dissolution.
(BPC: M. Marques) RTS-41143-1

## Change to read:

## Dissolution $\langle 711\rangle$ -

Medium: $\quad 0.2 \mathrm{M} \mathrm{pH} 7.5$ phosphate buffer prepared as direet under Buffer Solutions in the seetion Reagents, Indicutors, and So tutions, exeept that 0.8 M menobasie petassium phesphate selution and 0.8 M sodium hydroxide solution are used;
-by dissolving 545 g of monobasic potassium phosphate in 5 L of water, adding 131 g of sodium hydroxide, diluting with water to about 19.5 L , and mixing well. Adjust with either 1 N phosphoric acid or 1 N sodium hydroxide to a pH of 7.5 , and dilute with water to 20 L ; ${ }_{1 S}$ (USP28) 900 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
Procedure-Determine the amount of $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{O}_{3}$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solution under test, suitably diluted with 1 N sodium hydroxide, in comparison with a Standard solution obtained as follows. Prepare a Standard stock solution of USP Gemfibrozil RS having a known concentration of about 0.33 mg per mL in Dissolution Medium. [nOTE-Initially dissolve the USP Reference Standard in an amount of methanol not to exceed $1 \%$ of the volume of the Standard stock solution.] Quantitatively dilute the Standard stock solution with 1 N sodium hydroxide to obtain a Standard solution having a concentration estimated to correspond to that of the filtered and diluted solution under test.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{O}_{3}$ is dissolved in 30 minutes.

## Briefing

Glimepiride, page 1891 of PF 29(6) [Nov.-Dec. 2003]. On the basis of comments received, this monograph is being revised. It is proposed to change acceptance criteria in the Definition in compliance with an FDA-approved submission. It is proposed to replace the gas chromatographic procedure in the test for Water with a titrimetric Karl Fisher procedure. Several alternative columns are being proposed for the liquid chromatographic procedure in the test for Limit of cis-isomer. The analyses could also be performed with $4.6-\mathrm{mm} \times 15-\mathrm{cm}, 4.6-\mathrm{mm} \times 25-\mathrm{cm}, 4-\mathrm{mm} \times 12.5-\mathrm{cm}$, or $4-\mathrm{mm}$ $\times 25-\mathrm{cm}$ LiChrospher Diol or LiChrosorb Diol columns containing packing L20; it may be necessary to adjust the flow rate accordingly. Some changes are also being proposed for Related compounds and the Assay. In addition, minor editorial changes have been made.
(PA4: E. Gonikberg) RTS-41258-1

## Add the following:

## Glimepiride


$\mathrm{C}_{24} \mathrm{H}_{34} \mathrm{~N}_{4} \mathrm{O}_{5} \mathrm{~S} \quad 490.62$

1 H -Pyrrole-1-carboxamide, 3-ethyl-2,5-dihydro-4-methyl-$N-[2-[4-[[[[(4-$ methylcyclohexyl)amino]carbonyl]ami-no]sulfonyl]phenyl]ethyl]-2-oxo-, trans-.

1-[[p-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxa-mido)ethyl]phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea [93479-97-1].
» Glimepiride contains not less than 97.098 .0 percent and not more than 102.0 percent of $\mathrm{C}_{24} \mathrm{H}_{34} \mathrm{~N}_{4} \mathrm{O}_{5} \mathrm{~S}$, calculated on the anhydrous basis.

Packaging and storage-Store in well-closed containers, at a temperature not exceeding $25^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Glimepiride $R S$. USP Glimepiride Related Compound A RS. USP Glimepiride Related Compound B RS. USP Glimepiride Related Compound C RS. USP Glimepiride Related Compound D $R S$.

Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
Water, Method Ic $\langle 921\rangle$ -
Diluent Use dimethylformamide dried over a molecular sieve ( 2 mm ; pere-size: 0.4 nm ).

Standerd solution Transfer about 100.0 mg of water, aceurately weighed, inte a -100 mL volumetric flask containing the Diltent, dilute with Diltent to volume, and mix.

Blank solution Use the Diluent.
Fest solution Dissolve about 50 mg of Glimepiride, aceurately weighed, in 1.0 -ml of Diluent.

Chrematographic system (see Chromatography $\langle 624\rangle$ ) -
The ges chromatograph is equipped with a thermal condtetivity detector, a $0.32 \mathrm{~mm} \times 30 \mathrm{~m}$ fused silicacoltmment fainimg bended phase G43-in a $1.8 \mathrm{\mu m}$ film thickness, and a splitless injection system. The carrier ges is helitm flowing at a rate of about 2.2 mL per mintute. The temperature of the coltumn is maintained at $80^{\circ}$, the injection port temperature is maintained at $200^{\circ}$, and the detector is maintained at $250^{\circ}$. Ghrematograph the Standard solution, and record the peak respenses as directed for Procedtre: the resolution, $R$, beween the water peak and the air peak is not less than 2.0; and the relative standard deviation for replieate injections is net more than 10\%. [NOTE-The appreximate-retention times for air, water, and dimethylformamide are about 1.6, 1.8 , and 5.5 minutes, respectively.

Procedure Separately inject equal volumes (about $1 \mu \mathrm{H}$ ) of the Blank solution, the Standard solution, and the Test solution int the gas chromatograph, record the chromate-
grams, and measure the peak respenses. Caleulate the pereentage of water in the pertion of Glimepiride taken by the fermata:

$$
\left(r_{f}-r_{B}\right)\left(\left(r_{s}-r_{b}\right)\left(H_{s}+H_{t}\right)\right.
$$

in which $r_{B}, r_{7}$, and $r_{s}$ are the peak respenses obtained from the Blank solution, the Test solution, and the Standurd soltution, respectively; $H_{s}$ is the weight, in mg, of water taken to prepare the Standetrd solution; and $-W_{t}$ is the weight, in me, ef Glimepiride taken to prepare the Test solution. The water eentent is not mere than $0.5 \%$ Dissolve about 0.25 g of Glimepiride, accurately weighed, in dimethylformamide previously dried over a molecular sieve ( 2 mm , pore size 0.4 nm ), and dilute with the same solvent to 5.0 mL . Use 1.0 mL of the solution. Perform a blank determination, using 1.0 mL of the solvent.

Residue on ignition $\langle 281\rangle$ : not more than $0.2 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $0.001 \%$.
Limit of cis-isomer (glimepiride related compound A)-
Mobile phase-Transfer 100 mL of isopropyl alcohol into a 1 -L volumetric flask, add 1 mL of glacial acetic acid, dilute with hexane to volume, filter, and degas.

System suitability stock solution—Dissolve about 1 mg of USP Glimepiride Related Compound A RS in 1 mL of methylene chloride. Add 3 mL of Mobile phase, and mix.

System suitability solution-Transfer about 10 mg of USP Glimepiride RS to a $20-\mathrm{mL}$ volumetric flask, and dissolve in 5 mL of methylene chloride. Dilute with Mobile phase to volume, and mix. Transfer 5 mL of this solution to a separate flask, add $50 \mu \mathrm{~L}$ of the System suitability stock solution, and mix.

Test solution-Transfer about 10 mg of Glimepiride to a $20-\mathrm{mL}$ volumetric flask, and dissolve in 5 mL of methylene chloride. Dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $228-\mathrm{nm}$ detector and a $3-\mathrm{mm} \times 15-\mathrm{cm}$ column containing $5-\mu \mathrm{m}$ packing L20. The flow rate is about 0.5 mL per minute. [NOTE-The analyses could also be performed with $4.6-\mathrm{mm} \times 15-\mathrm{cm}$, $4.6-\mathrm{mm} \times 25-\mathrm{cm}, 4-\mathrm{mm} \times 12.5-\mathrm{cm}$, or $4-\mathrm{mm} \times 25-\mathrm{cm}$ columns containing packing L20. It is recommended that the flow rate be adjusted to about 1.1 mL per minute for a $4.6-\mathrm{mm}$ column and to about 0.8 mL per minute for a 4.0 mm column.] Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are 1.0 for glimepiride and not more than 0.9 for the glimepiride cis-isomer, and the signal-to-noise ratio of the glimepiride $c i s$-isomer peak is not less than 15 .

Procedure-Inject about $10 \mu \mathrm{~L}$ of the Test solution into the chromatograph, and measure the peak areas for the glimepiride $c i s$-isomer and glimepiride. Calculate the percentage of glimepiride $c i s$-isomer in the portion of Glimepiride taken by the formula:

$$
100 r_{c i s} /\left(r_{c i s}+r_{G}\right),
$$

in which $r_{c i s}$ and $r_{G}$ are the peak areas for the glimepiride cisisomer and glimepiride, respectively: not more than $0.8 \%$ of the glimepiride $c i s$-isomer is found.

## Related compounds-

Mobile phase, Diluent, System suitability solution, and Chromatographic system—Prepare as directed in the Assay. Test solution-Use the Assay preparation.
Diluted test solution 1-Dilute 5.0 mL of the Test solution with Diluent to 100.0 mL . Dilute 5.0 mL of the solution obtained with Diluent to 50.0 mL . This solution contains about 0.001 mg of glimepiride per mL .

Diluted test solution 2-Dilute 1.0 mL of Diluted test solution 1 with Diluent to 10.0 mL .

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Test solution and Diluted test solutions 1 and 2 into the chromatograph, record the chromatograms, and measure the peak response for glimepiride obtained from Diluted test solution 1 and the responses for all other peaks, except the glimepiride peak, obtained from the Test solution. Disregard any peak with an area less than that of the glimepiride peak in the chromatogram obtained from Diluted test solution 2. Continue the elution for 2.5 times the retention time of the glimepiride peak. Calculate the percentage of each related compound (see Table 1) and any unknown impurity in the portion of Glimepiride taken by the formula:

$$
100\left(C_{S} / C_{T}\right)\left(r_{i} / r_{s}\right)
$$

in which $C_{S}$ is the concentration, in mg per mL , of glimepiride in Diluted test solution 1; $C_{T}$ is the concentration, in mg per mL, of glimepiride in the Test solution; $r_{i}$ is the peak response for each individual peak obtained from the Test solution; and $r_{s}$ is the glimepiride peak obtained from Diluted test solution 1. In addition to not exceeding the limits for each impurity in Table 1, not more than $0.1 \%$ of any ether unspecified individual impurity is found; and not more than $0.5 \%$ of total impurities, excluding glimepiride related compound $B$, is found.

## Table 1

| Name | Relative |  |
| :---: | :---: | :---: |
|  | Retention <br> Time | Limit <br> $(\%)$ |
| ${\text { Glimepiride related compound } \mathrm{B}^{1}}$ | 0.2 | 0.4 |
| Glimepiride related compound $\mathrm{C}^{2}$ | 0.3 | 0.1 |
| Glimepiride related compound $\mathrm{D}^{3}$ | 1.1 | 0.2 |

${ }_{2}^{1}$ Glimepiride-sulfonamide
${ }_{3}$ Glimepiride-urethane

Assay-
Mobile phase—Dissolve 0.5 g of monobasic sodium phosphate in 500 mL of water. Adjust with phosphoric acid to a pH of 2.1 to 2.7 , and add in mixtare of 500 mL of wand 500 mL of acetonitrile. Adjust with phesphorie acidte a pH Of 2.5 to 3.5.

Diluent-Prepare a mixture of acetonitrile and water (4:1).

Standard preparation-Dissolve an accurately weighed quantity of USP Glimepiride RS in Diluent to obtain a solution having a known concentration of about 0.2 mg per mL . System suitability solution-Prepare a solution in Diluent containing 0.1 mg each of USP Glimepiride Related Compound B RS, USP Glimepiride Related Compound C RS, and USP Glimepiride Related Compound D RS per mL. Dilute 1 mL of this solution with the Standard preparation to 50 mL .
Assay preparation-Transfer about 20.0 mg of Glimepiride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix. [NOTE-Keep the Assay preparation at a temperature not exceeding $12^{\circ}$, and store it no longer than 15 hours.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $228-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and identify the glimepiride peak and the peaks due to the related compounds listed in Table 1. Record the peak responses as directed for Procedure: the resolution, $R$, between glimepiride related compound B and glimepiride related compound C is not less than 4.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas of the major peaks. Calculate the percentage of $\mathrm{C}_{24} \mathrm{H}_{34} \mathrm{~N}_{4} \mathrm{O}_{5} \mathrm{~S}$ in the portion of Glimepiride taken by the formula:

$$
10,000(C / W)[100 /(100-L)]\left(r_{U} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Glimepiride RS in the Standard preparation; $W$ is the weight, in mg, of Glimepiride taken to prepare the Assay preparation; $L$ is the percentage of water as determined in the test for Water; and $r_{U}$ and $r_{S}$ are the peak responses for the glimepiride obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Gonadorelin Acetate. Because there is no existing $U S P-N F$ monograph for this article, a new monograph is being proposed. The Related compounds test consists of two HPLC methods to ensure that all impurities are resolved from the main peak of the article: in System 1, the liquid chromatograph is equipped with a 220 nm detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. In System 2, the liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. USP has received data indicating that YMC ODS-A, C-18 columns are suitable for use in both System 1 and System 2. The Assay is based on an amino acid analysis procedure. Interested parties are encouraged to submit their comments to USP for evaluation.
(BNT: I. DeVeau) RTS-40507-1; 40682-1

## Add the following:

## ■Gonadorelin Acetate

5-0XOP H W S Y GLR P G $\cdot x \mathrm{CH}_{3} \mathrm{COOH} \quad \cdot y \mathrm{H}_{2} \mathrm{O}$
$\mathrm{C}_{55} \mathrm{H}_{75} \mathrm{~N}_{17} \mathrm{O}_{13} \cdot x \mathrm{C}_{2} \mathrm{H}_{4} \mathrm{O}_{2} \cdot y \mathrm{H}_{2} \mathrm{O} \quad 1182.3$

Luteinizing hormone-releasing factor acetate (salt) hydrate.

$$
\begin{aligned}
& \text { Glp-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH2 } \\
& x \mathrm{NH}_{3} \mathrm{COOH} \quad[52699-48-6 ; 33515-09-2] .
\end{aligned}
$$

» Gonadorelin Acetate is a synthetic polypeptide hormone having the property of stimulating the release of the luteinizing hormone from the hypothalamus. It contains not less than 80 percent by weight of $\mathrm{C}_{55} \mathrm{H}_{75} \mathrm{~N}_{17} \mathrm{O}_{13}$, the remainder being acetic acid and water.

NOTE-Gonadorelin Acetate is extremely hygroscopic. Protect from exposure to moisture, and store in a desiccator.

Packaging and storage-Preserve in tight, well-sealed containers, protected from moisture. Store between $-25^{\circ}$ and $-10^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Gonadorelin Acetate RS. USP Gonadorelin Acetate Related Compound A RS.

## Identification-

A: The monoisotopic mass by Mass Spectrometry $\langle 736\rangle$ is $1181.6 \pm 1$ mass units.

B: The retention time of the major peak in the chromatogram of the Test solution corresponds to that in the chromatogram of the Standard solution, as obtained in the test for Related compounds.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $-54^{\circ}$ and $-66^{\circ}$, at $20^{\circ}$, calculated with reference to the peptide content determined in the Assay.

Test solution: 10 mg per mL , in $1 \%(\mathrm{v} / \mathrm{v})$ acetic acid.
Water, Method Ic $\langle 921\rangle$ : not more than $7.0 \%$, determined by directly introducing not less than 2 mg of the solid substance into the titrator.

Limit of fluoride-[NOTE-Use polypropylene vessels for preparation of solutions and standards.]

Standard solutions-Prepare a series of calibration standards containing $10,1,0.1$, and 0.05 ppm fluoride dissolved in an ionic strength adjustment buffer suitable for the electrode in use ( pH about 5).
Test solution-Dissolve between 3 and 5 mg of Gonadorelin Acetate in 1.375 mL of the same buffer as that used for the preparation of the Standard solutions.
Procedure-Using a fluoride ion-selective electrode connected to a $\mathrm{pH} /$ ion meter, measure the potential of each Standard solution, and plot the response versus the logarithm of the concentration. Determine the regression line using the least squares method. The test is considered valid if the slope of the curve is in the range of -54 to -60 mV per decade and the regression curve has a square of the correlation coefficient, $r^{2}$, not less than 0.995 . From the calibration curve and the concentration of the Test solution, determine the amount of fluoride in the sample: not more than $0.1 \%$ (w/w) is found.

## Acetic acid and trifluoroacetic acid-

Solution A-To 900 mL of water add 7.0 mL of phosphoric acid and 5.0 mL of concentrated ammonia. Mix, and dilute with water to 1000 mL , pass through a $0.45-\mu \mathrm{m}$ filter, and degas. Add 20 mL of methanol, mix, and degas for an additional 2 minutes.

Solution B-Prepare a degassed mixture of acetonitrile and water $(1: 1)$.

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Dilute 5.0 mL of phosphoric acid with water to 1000 mL , and mix thoroughly.

Trifluoroacetic acid stock solution-Add about 50 mL of water to a $100-\mathrm{mL}$ volumetric flask with a stopper. Tare the stoppered flask on an analytical balance until there is no further significant drift in the reading. Carefully add 670 $\mu \mathrm{L}$ of trifluoroacetic acid to the flask, stopper immediately, and weigh. Dilute with water to volume.

Standard solutions-Accurately weigh out 150, 75, and 10 mg of sodium acetate trihydrate into three separate $100-\mathrm{mL}$ volumetric flasks. Add $10 \mathrm{~mL}, 2 \mathrm{~mL}$, and 100 $\mu \mathrm{L}$, respectively, of the Trifluoroacetic acid stock solution to the flasks, and dilute each with Diluent to the $100-\mathrm{mL}$ mark. Calculate the concentration, in mg per mL , of acetic acid in each Standard solution using the following equation:

$$
0.00434 W_{A},
$$

in which $W_{A}$ is the weight, in mg , of sodium acetate trihydrate taken. Calculate the concentration, in mg per mL, of trifluoroacetic acid in each Standard solution using the following equation:

$$
0.0001\left(W_{T} V\right)
$$

in which $W_{T}$ is the weight, in mg , of trifluoroacetic acid used for preparation of the Trifluoroacetic acid stock solution; and $V$ is the volume, in mL , of Trifluoroacetic acid stock solution used to prepare the Standard solution.

Test solution-Prepare duplicate samples by accurately weighing out two separate aliquots of about 4.0 mg of Gonadorelin Acetate and dissolving each with 1 mL of the Diluent.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column containing $5-\mu \mathrm{m}$ packing L1. The flow rate is approximately 1.5 mL per minute. The chromatograph is programmed as follows.

| Time | Solution A | Solution B |  |
| :---: | :---: | :---: | :--- |
| (minutes) | $\%$ | $\%$ | Elution |
| $0-5$ | 100 | 0 | isocratic |
| $5-6$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear |
| $6-14$ | 0 | 100 | isocratic |
| $14-15$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | return to initial |
| $15-25$ | 100 | 0 | re-equilibration |

Chromatograph the Standard solutions, and record the peak responses as directed for Procedure: the column efficiency is not less than 2000 theoretical plates for the trifluoroacetic acid peak and not less than 10,000 for the acetic acid peak; and the relative standard deviation for six replicate injections of the most concentrated Standard solution is not more than $2.0 \%$.

Procedure-Inject in duplicate equal volumes (about 20 $\mu \mathrm{L}$ ) of each of the Standard solutions followed by the duplicate Test solutions. Plot the peak areas of each of the components in the Standard solutions versus concentration, in mg per mL , and determine the regression line using the least squares method. The test is considered valid if the regression curves for both acetic acid and trifluoroacetic acid have a square of the correlation coefficient, $r^{2}$, not less than 0.995 . From the resulting graph, determine the percentages of acetic acid and trifluoroacetic acid in the Test solution: between $8 \%$ and $12.5 \%$ of acetic acid is found, and not more than $0.25 \%$ of trifluoroacetic acid is found.

## Related compounds-

Standard solution-Dissolve an accurately weighed quantity of USP Gonadorelin Acetate RS in water to obtain a solution having a known concentration of about 0.5 mg per mL .

System suitability solution—Dissolve an accurately weighed quantity of USP Gonadorelin Acetate Related Compound A RS in water to obtain a solution having a known concentration of about 0.5 mg per mL . Mix equal volumes of this solution and the Standard solution.

Test solution-Dissolve an accurately weighed quantity of Gonadorelin Acetate in water to obtain a solution having a known concentration of about 0.5 mg per mL .

## SYSTEM 1-

Solvent 1 -Mix 1 mL of trifluoroacetic acid with 1 L of water. Pass through a $0.45-\mu \mathrm{m}$ filter, and degas.

Solvent 2-Mix 1 mL of trifluoroacetic acid with 1 L of acetonitrile.
Solution A-Prepare a mixture of Solvent 1 and Solvent 2 (95:5).
Solution B-Prepare a mixture of Solvent 2 and Solvent 1 ( $60: 40$ ).

Chromatographic system (see Chromatography $\langle 621\rangle$ )The HPLC is equipped with a $220-\mathrm{nm}$ detector and a 4.6 $\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is approximately 1.5 mL per minute. The chromatograph is programmed as follows.

| Time | Solution A | Solution B |  |
| :---: | :---: | :---: | :--- |
| (minutes) | $(\%)$ | $(\%)$ | Elution |
| 0 | 91 | 9 | initial |
| $0-25$ | $91 \rightarrow 45$ | $9 \rightarrow 55$ | linear |
| 25 | $45 \rightarrow 91$ | $55 \rightarrow 9$ | return to initial |
| $25-30$ | 91 | 9 | re-equilibrium |

SYSTEM 2-
Mobile phase—Add 47 mL of phosphoric acid and 55 mL of triethylamine to 4 L of water, and adjust with phosphoric acid or triethylamine to a pH of 2.5 , as appropriate. Pass through a $0.45-\mu \mathrm{m}$ filter, and degas. Add acetonitrile to obtain a $13 \%(\mathrm{v} / \mathrm{v})$ concentration of acetonitrile.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The HPLC is equipped with a $215-\mathrm{nm}$ detector and a 4.6 $\mathrm{mm} \times 10-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is approximately 1.5 mL per minute using isocratic elution and having a run time of 50 minutes.
Using both System 1 and System 2 chromatograph the Standard solution, and record the peak responses as directed for Procedure. The Standard solution is used only to identify the gonadorelin acetate peak. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between gonadorelin acetate and gonadorelin acetate related compound A is not less than 2.0 ; the column efficiency is not less than 75,000 theoretical plates for System 1 and not less than 3000 theoretical plates for System 2; the tailing factor is not more than 2.0 for both System 1 and System 2; and the relative standard deviation for five replicate injections is not more than $2.0 \%$.

Procedure-Inject equal volumes (about $20 \mu \mathrm{~L}$ ) of each of the Standard solution, the System suitability solution, and the Test solution, followed by a co-injection of the Test solution with the Standard solution, into both System 1 and System 2. Include blank injections between the different solutions. Integrate all peaks in order to obtain a baseline similar to that in the blank chromatograms, disregarding any peaks due to the solvent, counter-ion, and baseline artifacts. Using peak areas, and including all peaks greater than $0.05 \%$, calculate the percentage of each impurity in the por-
tion of Gonadorelin Acetate taken: not more than 1\% of any single impurity is found, and not more than $2 \%$ of total impurities is found.

Amino acid analysis-Proceed as directed in the Assay. Express the content of each amino acid in $\mu$ moles, and calculate the total number of $\mu$ moles of Gonadorelin Acetate in the test sample as directed in the Assay. By dividing the number of $\mu$ moles of each amino acid by the total number of $\mu$ moles of Gonadorelin Acetate in the test sample, the relative proportions of amino acids are found: serine, 0.7 to 1.05; glutamic acid, 0.95 to 1.05 ; proline, 0.95 to 1.05 ; glycine, 1.9 to 2.1 ; leucine, 0.9 to 1.1 ; tyrosine, 0.7 to 1.05 ; histidine, 0.95 to 1.05 ; and arginine, 0.95 to 1.05 . Isoleucine and lysine are absent; not more than traces of other amino acids except tryptophan are detected.

Assay-Examine by means of an amino acid analyzer using Method 1-Postcolumn Ninhydrin Detection under Biotech-nology-Derived Articles-Tests $\langle 1047\rangle$. Standardize the instrument with a mixture containing equal molar per volume amounts (except for L-cystine which is half the molar amount) of glycine and the L-form of the following amino acids: lysine, threonine, alanine, leucine, histidine, serine, valine, tyrosine, arginine, glutamic acid, methionine, phenylalanine, aspartic acid, proline, isoleucine, tryptophan, and cystine.
Assay preparation (see Protein Hydrolysis, Method 1 $\langle 1047\rangle$ )—Accurately weigh out between 0.4 and 1.0 mg of Gonadorelin Acetate in glass ampuls. Add a minimum of 1.0 mL of Hydrolysis Solution containing $4 \%$ phenol, freeze the sample ampul, and flame seal under vacuum. Hydrolyze at $110^{\circ}$ for about 22 hours. After hydrolysis, dry the test sample under vacuum to remove any residual acid. To the ampul add 2 mL of a buffer solution that is suitable for the amino acid analyzer, and pass through a filter having a $0.45-\mu \mathrm{m}$ porosity.

Procedure-Prepare a co-injection of the Standard solution and the test sample. Inject a suitable volume into the amino acid analyzer, and record and measure the responses for each amino acid peak. Express the content of each amino acid in $\mu$ moles. The total number of $\mu$ moles of gonadorelin acetate in the test sample is calculated by summing the number of $\mu$ moles for glutamic acid, proline, glycine, leucine, tyrosine, histidine, and arginine, and dividing by eight. Calculate the percentage of $\mathrm{C}_{55} \mathrm{H}_{75} \mathrm{~N}_{17} \mathrm{O}_{13}$ in the portion of Gonadorelin Acetate taken by the formula:
118.23(N/W),
in which $N$ is the total number of $\mu$ moles of gonadorelin acetate; and $W$ is the weight of the sample in mg. $\quad$ IS (USP28)

## BRIEFING

Hydromorphone Hydrochloride, USP 27 page 935 and page 1900 of $P F 29(6)$ [Nov.-Dec. 2003]. It is proposed to revise the test for Ordinary impurities to include the word "immediate" in the Visualization section to emphasize the importance of timely exposure of the TLC plate to iodine vapors.
(PA2: C. Anthony) RTS-41349-1

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers.
-Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$. 2 (USP27)

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. ${ }^{15}$ (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle$ -
■USP Endotoxin RS. ${ }^{\text {1S (USP28) }}$
USP Hydromorphone Hydrochloride RS.

## Change to read:

Ordinary impurities $\langle 466\rangle$ -
Test solution: water.
Standard solution: water.
Eluant: a mixture of methylene chloride, methanol, and ammonium hydroxide ( $80: 20: 1$ ).
Visualization: 3, followed by overspraying with hydrogen peroxide TS and

■immediate $_{\text {■1S (USP28) }}$
exposure of the plate to iodine vapors for about 30 minutes.

## Add the following:

■Other requirements-Where the label states that Hydromorphone Hydrochloride is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Hydromorphone Hydrochloride Injection. Where the label states that Hydromorphone Hydrochloride must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Hydromorphone Hydrochloride Injection.■1S (USP28)

BRIEFING

Isoflurane, USP 27 page 1030 and page 1912 of $P F$ 29(6) [Nov.-Dec. 2003]. It is proposed to expand the Note in the Related compounds test to cover the analysis of multiple samples using this procedure. In addition, editorial style changes have been made.
(PA1: K. Russo) RTS-41104-1

## Change to read:

Packaging and storage-Preserve in tight containers.
${ }^{\square}$ Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ} \cdot$ [2S (USP27)

## Change to read:

## Related compounds-

$\square_{\text {NOTE-The Internal standard solution }}$ and the Standard solution are prepared using the same Isoflurane that is under test. ■If multiple lots or samples of Isoflurane are under test, one sample may be selected for the Internal standard solution and the Standard solution. An appropriate blank correction should be made when determining the percentages of impurities in the other lots or samples. $\quad 1 \mathrm{SS}$ (USP28) $\mathbf{m}^{2 S}$ (USP27)
Internal standard solution-Transfer about 1 g of normal butyl acetate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dilute with Isoflurane to volume, and mix.
Standard solution-To 95 mL of Isoflurane in a $100-\mathrm{mL}$ volumetric flask, add $10.0 \mu \mathrm{~L}$ of USP Isoflurane Related Compound A RS, $7.0 \mu \mathrm{~L}$ of USP Isoflurane Related Compound B RS, $10.0 \mu \mathrm{~L}$ of acetone, and $250 \mu$ L of Internal standard solution, dilute with Isoflurane to volume, and mix. It contains $0.01 \%$ of isoflurane related compound A, $0.007 \%$ of isoflurane related compound B, and $0.01 \%$ of acetone.
Test solution-To 20.0 mL of Isoflurane add $50.0 \mu \mathrm{~L}$ of Internal standard solution, and mix. It contains about $0.0025 \%(\mathrm{w} / \mathrm{v})$ of normal butyl acetate.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—The gas chromatograph is equipped with a flame-ionization detector and a $2.4-\mathrm{mm} \times 3.7-\mathrm{m}$ nickel or stainless steel column packed with $10 \%$ phase G31 and $15 \%$ phase G18 on 60 - to 80 -mesh sodium hydroxide-washed support S1C. Helium is used as the carrier gas at a flow rate of about 25 mL per minute. The column temperature is programmed for 7 minutes at $65^{\circ}$, then increases to $110^{\circ}$ at a rate of $4{ }^{\circ}$ per minute. The injection port temperature is maintained at about $150^{\circ}$ and the detector temperature is maintained at about $200^{\circ}$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor for the normal butyl acetate peak is not more than 1.5 ; and the relative standard deviation of the ratio of the response of the acetone peak to the response of the normal butyl acetate peak for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $3 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms for 40 minutes, and measure the responses for all the peaks. Separately calculate the percentages of acetone, isoflurane related compound A , and isoflurane related compound B in the portion of Isoflurane taken by the formula:

$$
P\left[R_{U} /\left(R_{S}-R_{U}\right)\right]
$$

in which $P$ is the percentage of the relevant analyte in the Standard solution; and $R_{U}$ and $R_{S}$ are the peak response ratios obtained from the Test solution and the Standard solution, respectively: not more than $0.01 \%$ of acetone, not more than $0.01 \%$ of isoflurane related compound A , and not more than $0.007 \%$ of isoflurane related compound $B$ are found. Calculate the percentage of any other individual impurity by the formula:

$$
P\left[R_{i} /\left(R_{S}-R_{i}\right)\right]
$$

in which $P$ is the percentage of isoflurane related compound B in the Standard solution; $R_{i}$ is the peak response ratio of any individual impurity to the internal standard obtained from the Test solution; and $R_{S}$ is the peak response ratio of isoflurane related compound B to the internal standard obtained from the Standard solution: not more than $0.003 \%$ of any other individual impurity is found.

## BRIEFING

Ketoconazole Tablets, USP 27 page 1057. It is proposed to delete the test for Disintegration and to replace it with a test for Dissolution.
(BPC: M. Marques) RTS-41228-1

## Delete the following:

- Disintegration- $\langle 704\rangle$ : 10 minutes.■1S (USP28)


## Add the following:

■Dissolution $\langle 711\rangle$ -
Medium: $\quad 0.1 \mathrm{~N}$ hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm.
Time: 30 minutes.
Procedure-Determine the amount of $\mathrm{C}_{26} \mathrm{H}_{28} \mathrm{Cl}_{2} \mathrm{~N}_{4} \mathrm{O}_{4}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 270 nm on portions of the solution under test passed through a $0.45-\mu \mathrm{m}$ filter and
suitably diluted with Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Ketoconazole RS in the same Medium.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{26} \mathrm{H}_{28} \mathrm{Cl}_{2} \mathrm{~N}_{4} \mathrm{O}_{4}$ is dissolved in 30 minutes. $\quad$ 1S (USP28)

## BRIEFING

Lidocaine Hydrochloride, USP 27 page 1087. It is proposed to revise the Chromatographic system in the Assay to clarify that the temperature of the column, and not the entire HPLC system, is controlled. Minor editorial revisions are also made.
(PA1: K. Russo) RTS-41279-2

## Change to read:

## Assay-

Mobile phase-Mix 50 mL of glacial acetic acid and 930 mL of water, and adjust with 1 N sodium hydroxide to a pH of 3.40 . Mix about 4 volumes of this solution with 1 volume of acetonitrile, such that the retention time of lidocaine is about 4 to 6 minutes. Pass through a membrane filter having a $1-\mu \mathrm{m}$ or finer porosity, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve about 85 mg of USP Lidocaine RS, accurately weighed, with warming if necessary, in 0.5 mL of 1 N hydrochloric acid in a $50-\mathrm{mL}$ volumetric flask, dilute with Mo bile phase to volume, and mix to obtain a Standard preparation having a known concentration of about 1.7 mg of lidocaine per mL .

Assay preparation-Transfer about 100 mg of Lidocaine Hydrochloride, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.
Resolution preparation-Prepare a solution of methylparaben in Mobile phase containing about $220 \mu \mathrm{~g}$ per mL . Mix 2 mL of this solution and 20 mL of the Standard preparation.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. is oper ated at a emperature between $20^{\circ}$ and $25^{\circ}$, maintained at $\pm 1.0^{\circ}$ of the selected temperature.
-The column temperature is maintained between $20^{\circ}$ and
$25^{\circ}, \pm 1.0^{\circ}$ of the selected temperature. $\quad 1$ (USP28)
The flow rate is about 1.5 mL per minute. Chromatograph about 20 $\mu \mathrm{L}$ of the Resolution preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between the lidocaine and methylparaben peaks is not less than 3.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Assay preparation and the Standard preparation into the chromatograph. Record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{14} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{O} \cdot \mathrm{HCl}$ in the portion of Lidocaine Hydrochloride taken by the formula:

$$
(270.80 / 234.34)(50 C)\left(r_{U} / r_{S}\right)
$$

in which 270.80 and 234.34 are the molecular weights of lidocaine hydrochloride and lidocaine, respectively; $C$ is the concentration, in mg per mL , of USP Lidocaine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the lidocaine peak responses obtained from the Assay preparation and the Standard preparation, respectively.

BriEfing

Lidocaine Hydrochloride and Epinephrine Injection, USP 27 page 1089. It is proposed to revise the Chromatographic system in the Assay for lidocaine hydrochloride and the Assay for epinephrine to clarify that the temperature of the column, and not the entire HPLC system, is controlled.
(PA1: K. Russo) RTS-41279-3

## Change to read:

## Assay for lidocaine hydrochloride-

Mobile phase-Mix 50 mL of glacial acetic acid and 930 mL of water, and adjust with 1 N sodium hydroxide to a pH of 3.40 . Mix about 4 volumes of this solution with 1 volume of acetonitrile, such that the retention time of lidocaine is about 4 to 6 minutes. Pass through a membrane filter having a $1-\mu \mathrm{m}$ or finer porosity, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve about 85 mg of USP Lidocaine RS, accurately weighed, with warming if necessary, in 0.5 mL of 1 N hydrochloric acid in a $50-\mathrm{mL}$ volumetric flask, dilute with Mo bile phase to volume, and mix to obtain a Standard preparation having a known concentration of about 1.7 mg of lidocaine per mL .

Assay preparation-Transfer an accurately measured volume of Injection, equivalent to about 100 mg of lidocaine hydrochloride, to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Resolution preparation-Prepare a solution of methylparaben in Mobile phase containing about $220 \mu \mathrm{~g}$ per mL . Mix 2 mL of this solution and 20 mL of the Standard preparation.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. and is oper ated at a temperare berween $20^{\circ}$ and $25^{\circ}$ maintained at $\pm 1.0^{\circ}$ of the selected temperature.
-The column temperature is maintained between $20^{\circ}$ and
$25^{\circ}, \pm 1.0^{\circ}$ of the selected temperature. $\quad$ IS (USP28)

The flow rate is about 1.5 mL per minute. Chromatograph about 20 $\mu \mathrm{L}$ of the Resolution preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between lidocaine and methylparaben is not less than 3.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Assay preparation and the Standard preparation into the chromatograph. Record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of lidocaine hydrochloride $\left(\mathrm{C}_{14} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{O} \cdot \mathrm{HCl}\right)$ in each mL of the Injection taken by the formula:

$$
(270.80 / 234.34)(50)(C / V)\left(r_{U} / r_{S}\right)
$$

in which 270.80 and 234.34 are the molecular weights of lidocaine hydrochloride and lidocaine, respectively; $C$ is the concentration, in mg per mL , of USP Lidocaine RS in the Standard preparation; $V$ is the volume, in mL , of Injection taken; and $r_{U}$ and $r_{S}$ are the lidocaine peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Change to read:

## Assay for epinephrine-

Mobile phase-Mix 50 mL of glacial acetic acid and 930 mL of water, and adjust with 1 N sodium hydroxide to a pH of 3.40 . Dissolve 1.1 g of sodium 1-heptanesulfonate in this solution, add 1.0 mL of 0.1 M edetate disodium, and mix. Mix about 9 volumes of this solution with 1 volume of methanol, such that the retention time of epinephrine is about 4 to 6 minutes. Pass through a membrane filter having a $1-\mu \mathrm{m}$ or finer porosity, and degas.

Standard preparation-Dissolve an accurately weighed quantity of USP Epinephrine Bitartrate RS in Mobile phase to obtain a solution having a known concentration of about $9 \mu \mathrm{~g}$ of epinephrine bitartrate per mL . Pipet 10 mL of this solution into a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix to obtain a Standard preparation having a known concentration of about 1.8 $\mu \mathrm{g}$ of epinephrine bitartrate per mL .

Assay preparation-Transfer an accurately measured volume of Injection, equivalent to about $50 \mu \mathrm{~g}$ of epinephrine, to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is fitted with a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ stainless steel column packed with packing L1 and is equipped with an electrochemical detector held at a potential of +650 mV , a controller capable of regulating the background current, and a suitable recorder. and it is operated at a temperature between $20^{\circ}$ and $25^{\circ}$ maintained at $\pm 1.0^{\circ}$ of the selected temperattre.
-The column temperature is maintained between $20^{\circ}$ and
$25^{\circ}, \pm 1.0^{\circ}$ of the selected temperature. 1 IS (USP28)
The flow rate is about 1 mL per minute. Chromatograph the Standard preparation as directed for Procedure: the relative standard deviation of the peak responses of successive injections of the Standard preparation is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Assay preparation and the Standard preparation into the chromatograph by means of a suitable microsyringe or sampling valve, adjusting the specimen size and other operating parameters such that satisfactory chromatography and peak responses are obtained. Record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in $\mu \mathrm{g}$, of epinephrine $\left(\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO}_{3}\right)$ in each mL of the Injection taken by the formula:
$(183.21 / 333.30)(50)(C / V)\left(r_{U} / r_{S}\right)$,
in which 183.21 and 333.30 are the molecular weights of epinephrine and epinephrine bitartrate, respectively; $C$ is the concentration,
in $\mu \mathrm{g}$ per mL , of USP Epinephrine Bitartrate RS in the Standard preparation; $V$ is the volume, in mL , of Injection taken; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Loratadine Oral Solution, page 3066 of the First Supplement. It is proposed to change the particle size of the packing used in the Assay from $5 \mu \mathrm{~m}$ to $10 \mu \mathrm{~m}$. The reverse phase HPLC procedure was validated using a $10-\mu \mathrm{m} \mu$ Bondapak brand of L11 column. It is proposed to implement this revision via the Sixth Interim Revision Announcement pertaining to USP 27-NF 22, with an official date of December 1, 2004.
(PA1: K. Russo) RTS-41163-1

## Change to read:

## Assay-

0.05 M Monobasic potassium phosphate solution-Transfer about 6.8 g of monobasic potassium phosphate, accurately weighed, to a $1-\mathrm{L}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Adjust with phosphoric acid to a pH of $3.0 \pm 0.1$.

Mobile phase-Prepare a filtered and degassed mixture of 0.05 M Monobasic potassium phosphate solution and acetonitrile (7:3). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard preparation-Dissolve an accurately weighed quantity of butylparaben in a mixture of water and acetonitrile (7:3), and dilute quantitatively, and stepwise if necessary, with a mixture of water and acetonitrile $(7: 3)$ to obtain a solution having a concentration of about 0.3 mg per mL .

Standard stock peparation-Dissolve an accurately weighed quantity of USP Loratadine RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 1.0 mg per mL .

Standard preparation-Transfer 5.0 mL of Internal standard preparation, 5.0 mL of Standard stock preparation, and 12 mL of water into a $50-\mathrm{mL}$ volumetric flask. Dilute with a mixture of water and acetonitrile (7:3), and mix.

Assay preparation-Transfer an accurately measured quantity of Oral Solution, equivalent to 5 mg of loratadine, into a $50-\mathrm{mL}$ volumetric flask. Pipet 5.0 mL of Internal standard preparation into the flask, dilute with a mixture of water and acetonitrile $(7: 3)$ to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a 254-nm detector and a $4-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains $5 \mu \mathrm{~m}$

## ${ }^{\bullet} 10-\mu \mathrm{m}$.

packing ${ }^{\text {L }} 11$. The flow rate is about 2 mL per minute. The column temperature is maintained between $20^{\circ}$ and $30^{\circ}$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.78 for
butylparaben and 1.0 for loratadine; the resolution, $R$, between loratadine and butylparaben is not less than 1.9 ; the tailing factor is not more than 1.6 for the loratadine and butylparaben peaks; and the relative standard deviation for replicate injections is not more than $2 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg of loratadine $\left(\mathrm{C}_{22} \mathrm{H}_{23} \mathrm{ClN}_{2} \mathrm{O}_{2}\right)$ in the portion of Oral Solution taken by the formula:

$$
50 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Loratadine RS in the Standard preparation; and $R_{U}$ and $R_{S}$ are the ratios of loratadine to the internal standard peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Mafenide Acetate, USP 27 page 1113; Mafenide Acetate for Topical Solution, $U S P 27$ page 1114. In accordance with the implemented name change for the Reference Standard, it is proposed to change USP 4-Formylbenzenesulfonamide RS to USP Mafenide Related Compound A RS. The test for Chromatographic purity, which has been editorially restyled, is also affected by this revision.
(PA7b: B. Davani) RTS-41315-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Mafenide Acetate RS. USP 4 Formylbenzenesulfonamide $R S$


## Change to read:

## Chromatographic purity-

Standard solutions-Dissolve USP Mafenide Acetate RS in methanol, mix to obtain Standard solution $A$ having a known concentration of $500 \mu \mathrm{~g}$ per mL , dissolve USP 4 Fermylbenzenesulfonamide RS

- USP Mafenide Related Compound $\mathrm{A} \mathrm{RS}_{\mathbf{n S S}_{\text {(USP28) }}}$ in methanol, and mix to obtain Standard solution $D$ having a known concentration of $500 \mu \mathrm{~g}$ per mL .
- [NOTE-USP Mafenide Related Compound A RS is 4-formylbenzenesulfonamide.] $\boldsymbol{\square}^{1 S}$ (USP28)

Quantitatively dilute portions of these solutions with methanol to obtain Standard solutions having the following compositions:

| Standard <br> solution | Dilution | Concentration <br> ( $\mu \mathrm{g}$ RS per mL ) | Percentage <br> (\%, for comparison <br> with test specimen) |
| :---: | :---: | :---: | :---: |
| $A$ | (undiluted) | 500 | 1.0 |
| $B$ | 5 in 10 | 250 | 0.5 |
| $C$ | 1 in 5 | 100 | 0.2 |
| $D$ | (undiluted) | 500 | 1.0 |
| $E$ | 5 in 10 | 250 | 0.5 |
| $F$ | 1 in 5 | 100 | 0.2 |

Test solution-Dissolve an accurately weighed quantity of Mafenide Acetate in methanol to obtain a solution containing 50 mg per mL .

Identification solution-Quantitatively dilute a portion of the Test solution with methanol to obtain a solution containing 500 $\mu \mathrm{g}$ per mL .

Ninhydrin solution-Dissolve 300 mg of ninhydrin in 100 mL of butyl alcohol, add 3 mL of glacial acetic acid, and mix.

Procedure-Apply separately $5 \mu \mathrm{~L}$ of the Test solution, $5 \mu \mathrm{~L}$ of the Identification solution, and $5 \mu \mathrm{~L}$ of each Standard solution to a suitable thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ) coated with a $0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture. Position the plate in a chromatographic chamber, and develop the chromatograms in a solvent system consisting of a mixture of ethyl acetate, methanol, and isopropylamine ( $77: 20: 3$ ) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate in warm, circulating air. Examine the plate under short-wavelength UV light, and compare the intensities of any secondary spots observed in the chromatogram of the Test solution at the $R_{F}$ value corresponding to those of the principal spots in the chromatograms of Standard solutions D, E, and F. Spray the plate with the Ninhydrin solution, heat the plate at $105^{\circ}$ for 5 minutes, and examine the plate. Compare the intensities of any secondary spots observed in the chromatogram of the Test solution to those of the principal spots in the chromatograms of Standard solutions $A, B$, and $C$. No secondary spot, observed by both visualizations, from the chromatogram of the Test solution is larger or more intense than the principal spots obtained from Standard solution B (0.5\%) and Standard solution $E(0.5 \%)$, and the sum of the intensities of all secondary spots obtained from the Test solution corresponds to not more than $1.0 \%$.

Mafenide Acetate for Topical Solution, USP 27 page 1114 See briefing under Mafenide Acetate.
(PA7b: B. Davani) RTS-41316-1

## Change to read:

USP Reference standards $\langle 11\rangle$ _ USP Mafenide Acetate RS. USP
4 FOrmylbenzenesulfonamide RS.
■USP Mafenide Related Compound $A R S_{\square_{1 S}}{ }_{\text {(USP28) }}$

## Change to read:

## Chromatographic purity-

Ion-pairing solution and Mobile phase-Proceed as directed in the Assay.

Concentrated standard solution-Prepare a solution of USP - 4 Fermylbenzenesulfonamide RS

■USP Mafenide Related Compound A RS. ${ }^{15}$ (USP28) in Mobile phase having a known concentration of about $25 \mu \mathrm{~g}$ per mL .

- [NOTE-USP Mafenide Related Compound A RS is 4-for-
mylbenzenesulfonamide.] $]_{1 S}$ (USP28)
Working standard solution-Pipet 10.0 mL of Concentrated standard solution into a $50-\mathrm{mL}$ volumetric flask, dilute with Mo bile phase to volume, and mix.
System suitability solution-Transfer about 10 mg of USP Mafenide Acetate RS, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, and dissolve by sonication in about 2 mL of Mobile phase. Pipet 4.0 mL of Concentrated standard solution into the same flask, dilute with Mobile phase to volume, and mix.

Standard solution-Pipet 10.0 mL of Working standard solution into a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Test solution-Use the Assay preparation.
Chromatographic system-Prepare as directed in the Assay. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between mafenide acetate and 4-9rmylbenzenesulfonamide
${ }^{-}$USP Mafenide Related Compound $\mathrm{A} \mathrm{RS}_{\text {(1S (USP28) }}$ is not less than 3.0; and the tailing factor is not more than 2.0. Chromatograph the Working standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: adjust the integration parameters so that the response is between $5 \%$ and $15 \%$ of full-scale deflection.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Mobile phase, the Working standard solution, and the Test solution into the chromatograph, allowing the Test solution to elute for a period of not less than three times the retention time of mafenide acetate; record the chromatograms, and measure the responses for the major peaks, disregarding the peaks corresponding to those obtained from the Mobile phase. Calculate the percentage of each impurity in the portion of the constituted Topical Solution taken by the formula:

$$
100 C\left(r_{i} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP 4 Fermybenzenesulfenamide $\operatorname{RS}$
${ }^{\text {■USP Mafenide Related Compound }} \mathrm{A} \mathrm{RS}_{\mathbf{■ 1 S}^{(U S P 28)}}$
in the Working standard solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the peak response of 4 -formylbenzenesulfonamide
$\boldsymbol{■}_{\text {mafenide related compound }} \mathrm{A}_{\boldsymbol{\square} 1 \mathrm{~S}}$ (USP28)
obtained from the Working standard solution: not more than $0.5 \%$ of any individual impurity is found; and not more than $1.0 \%$ of total impurities is found.

## BRIEFING

Mefloquine Hydrochloride, page 1527 of $P F$ 29(5) [Sept.-Oct. 2003]. On the basis of comments received, the following revisions in the test for Related compounds are proposed: the concentrations of the components in the System suitability solution are adjusted to obtain the same concentrations as the corresponding components in the Test solution; a new resolution requirement for column qualification in the Chromatographic system is specified; in the Procedure, the flow rate is adjusted to be consistent with that used in the Chromatographic system, and an impurity previously identified by relative retention time is now identified by its chemical name. In addition, the description for this drug substance, in Description and Solubility in the Reference Tables, is modified to include its existence in the polymorphic forms.
(PA7b: B. Davani) RTS-408661-1

## Add the following:

## ■Mefloquine Hydrochloride

$\mathrm{C}_{17} \mathrm{H}_{16} \mathrm{~F}_{6} \mathrm{~N}_{2} \mathrm{O} \cdot \mathrm{HCl} \quad 414.77$

4-Quinolinemethanol, $\alpha$-2-piperidinyl-2,8-bis(trifluoro-methyl)-, monohydrochloride, $\left(R^{*}, S^{*}\right)-( \pm)$ -

DL-erythro- $\alpha$-2-Piperidyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol monohydrochloride [51773-92-3].
» Mefloquine Hydrochloride contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{17} \mathrm{H}_{16} \mathrm{~F}_{6} \mathrm{~N}_{2} \mathrm{O} \cdot \mathrm{HCl}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight, light-resistant containers. Store between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$-USP Mefloquine Hydrochloride RS. USP Mefloquine Related Compound A RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: It responds to the tests for Chloride $\langle 191\rangle$.
Specific rotation $\langle 781\rangle$ : between $-0.2^{\circ}$ and $+0.2^{\circ}$. Use a solution prepared by dissolving about 2.5 g in methanol, and dilute with methanol to 50.0 mL .

Water, Method $I\langle 921\rangle$ : not more than $3.0 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.002 \%$.

## Related compounds-

Mobile phase-Dissolve 1 g of tetraheptylammonium bromide in a mixture of methanol, 1.5 g per L solution of sodium hydrogen sulfate, and acetonitrile ( $1: 2: 2$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
System suitability solution-Transfer about 8 mg of USP Mefloquine Hydrochloride RS and 8 mg 4 mg of quiUSP Mefloquine Related Compound A RS to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix. [NOTE-Mefloquine related compound A is threo-mefloquine.] Transfer 5.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Test solution-Transfer about 0.10 g of Mefloquine Hydrochloride, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Diluted test solution-Transfer 1.0 mL of the Test solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. Transfer 1.0 mL of this solution to a $20-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector, a $4-\mathrm{mm} \times 2.5-\mathrm{cm}$ precolumn, and a $4.0-\mathrm{mm} \times 25-\mathrm{cm}$ column, both containing $5-\mu \mathrm{m}$ packing L1. The flow rate is about 0.8 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.5 for quinidine and 1.0 for mefloquine; the resolution, $R$, between the quinidine mefloquine related compound A peak and the mefloquine peak is not less than $8.5 ; 2.0$; and the relative standard deviation for replicate injections is not more than 3\%. 2.0\%.

Procedure-Equilibrate the column with Mobile phase at a flow rate of about 2 mL 0.8 mL per minute for about 30 minutes. Inject $20 \mu \mathrm{~L}$ of Diluted test solution. Adjust the sensitivity of the system so that the height of the major peak is at least $50 \%$ of the full scale of the recorder. Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Test solution and Diluted test solution into the chromatograph, record the chromatogram for a time that is 10 times the retention time of the main peak, and measure the responses of all peaks, excluding the main peak and any other peak producing a response of less than 0.2 times $(0.02 \%)$ of the main peak in chromatogram of the Diluted test solution. The response of the mefloquine related compound A peak in the Test solution with a relative retention time of about 0.7 ,
with reference to the main peak, is not more than twice the area of the main peak in the chromatogram of the Diluted test solution $(0.2 \%)$. The response of any other individual peak, other than the main peak in the chromatogram of the Test solution, is not greater than that of the main peak in the chromatogram of the Diluted test solution (0.1\%); and the sum of the responses of any such peaks in the chromatogram of the Test solution is not greater than five times the response of the main peak in the chromatogram of the Diluted test solution ( $0.5 \%$ ).

Assay-Dissolve about 0.35 g , accurately weighed, in 15 mL of anhydrous formic acid, and add 40 mL of acetic anhydride. Titrate with 0.1 N perchloric acid VS, and determine the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 41.48 mg of $\mathrm{C}_{17} \mathrm{H}_{16} \mathrm{~F}_{6} \mathrm{~N}_{2} \mathrm{O} \cdot \mathrm{HCl}_{\text {. }}$ (US (USP28)

## BRIEFING

Mercaptopurine Tablets, USP 27 page 1169 and page 1049 of PF 29(4) [July-Aug. 2003]. It is proposed to add a Dissolution Test 2 to this monograph because FDA recently approved a new generic version of this product that is bioequivalent to the Reference Listed Drug but requires different Tolerances.
(BPC: M. Marques) RTS-41273-1

## Add the following:

-Labeling-When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used. 1 (USP28)

## Delete the following:

${ }^{\mathbf{A}}$ Pisintegration- $\langle 704\rangle \div 30$ minutes._USP28

## Add the following:

${ }^{4}$ Dissolution $\langle 711\rangle$ -
$\mathbf{■}_{\text {TEST 1-■1S (USP28) }}$
Medium: $\quad 0.1 \mathrm{~N}$ hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm.
Time: 60 minutes.
Determine the amount of mercaptopurine $\left(\mathrm{C}_{5} \mathrm{H}_{4} \mathrm{~N}_{4} \mathrm{~S}\right)$ dissolved by employing the following method.

Mobile phase_Prepare a filtered and degassed solution of $0.1 \%$ acetic acid in water. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $230-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2.5 mL per minute. Chromatograph replicate injections of the Standard solution prepared as described below for Procedure, and record the peak responses as directed for Procedure: the retention time for mercaptopurine is not less than 4 minutes, and the relative standard deviation is not more than $2.0 \%$.

Procedure—Inject a volume (about $10 \mu \mathrm{~L}$ ) of a filtered portion of the solution under test into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $\mathrm{C}_{5} \mathrm{H}_{4} \mathrm{~N}_{4} \mathrm{~S}$ dissolved in comparison with a Standard solution having a known concentration of USP Mercaptopurine RS in the same Medium and similarly chromatographed.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{5} \mathrm{H}_{4} \mathrm{~N}_{4} \mathrm{~S}$ is dissolved in 60 minutes.
$\mathbf{■}_{\text {TEST }}$ 2—If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium, Apparatus, Chromatographic system, and Procedure—Proceed as directed for Test 1.

Time: 120 minutes.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{5} \mathrm{H}_{4} \mathrm{~N}_{4} \mathrm{~S}$ is dissolved in 120 minutes.■1S (USP28) $\triangle$ USP28

## BRIEFING

Mesoridazine Besylate, USP 27 page 1176 and page 1925 of PF 29(6) [Nov.-Dec. 2003]. It is proposed to modify the Visualization procedure in the test for Ordinary impurities to enhance the detection of the lowest standard concentration and the possible impurities found.
(PA3: S. Salado) RTS-40172-1

## Add the following:

${ }^{\boldsymbol{\Delta}}$ Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. $\Delta$ USP28

## Change to read:

USP Reference standards $\langle 11\rangle-$
${ }^{\Delta}$ USP Endotoxin RS. $\mathbf{\Delta U S P 2 8}$
USP Mesoridazine Besylate RS.

## Change to read:

Ordinary impurities $\langle 466\rangle$ -
Test solution: a solution in methanol having a known concentration of 14.1 mg per mL equivalent to 10 mg of mesoridazine per mL .

Standard solution: methanol.
Eluant: a mixture of chloroform, isopropyl alcohol, and ammonium hydroxide ( $87: 12: 1$ ).

Visualization: 3,

- followed by spraying with $3 \%(\mathrm{v} / \mathrm{v})$ aqueous hydrogen

```
peroxide.m1S (USP28)
    Application volume: }10\mu\textrm{L}
    Limit: 3.0%.
```


## Add the following:

${ }^{\Delta}$ Other requirements-Where the label states that Mesoridazine Besylate is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Mesoridazine Besylate Injection. Where the label states that Mesoridazine Besylate must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Mesoridazine Besylate Injection. $\mathbf{\Delta U S P 2 8}$

## BRIEFING

Methylphenidate Hydrochloride Extended-Release Tablets, USP 27 page 1218. It is proposed to specify the appropriate filter to be used in the Drug release test. Glass fiber filters should not be used because of drug absorption.
(BPC: M. Marques) RTS-41184-1

## Change to read:

Drug release $\langle 724\rangle$ -
Medium: water; 500 mL .
Apparatus 2: 50 rpm .
Times: 1 hour; 2 hours; 3.5 hours; 5 hours; 7 hours.
■ Test solution-Use portions of the solution under test passed through a $0.45-\mu \mathrm{m}$ polypropylene filter. [NOTE-

## Do not use glass fiber filters.] $]_{115}$ (USP28)

Procedure-Determine the amount of $\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ dissolved, employing the procedure set forth in the Assay, making any necessary volumetric adjustments.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{14} \mathrm{H}_{19} \mathrm{NO}_{2} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $25 \%$ and $45 \%$ |
| 2 | between $40 \%$ and $65 \%$ |
| 3.5 | between $55 \%$ and $80 \%$ |
| 5 | between $70 \%$ and $90 \%$ |
| 7 | not less than $80 \%$ |

## BRIEFING

Metoprolol Succinate, USP 27 page 1229. It is proposed to update the USP Reference standards section, to revise the temperature conditions in the test for Loss on drying, and to correct the formula in Related compounds Test 2.
(PA5: A.Wilk) RTS-40872-1

## Change to read:

USP Reference standards $\langle 11\rangle-U S P$ Metoprolol Succinate RS.

- USP Metoprolol Related Compound A RS. USP Metopro-
lol Related Compound B RS. USP Metoprolol Related Compound C RS. USP Metoprolol Related Compound D $R$.■1S (USP28)


## Change to read:

Loss on drying $\langle 731\rangle$ - Dry it in vacuum at $100^{\circ} 105^{\circ}$
$-60^{\circ}$
for 4 1S (USP28)
for 4 hours: it loses not more than $0.2 \%$ of its weight.

## Change to read:

## Related compounds-

TEST 1-
Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture.
Test solution-Dissolve an accurately weighed quantity of Metoprolol Succinate in methanol to obtain a solution containing 50 mg per mL .
Standard solution-Dilute the Test solution quantitatively, and stepwise if necessary, with methanol to obtain a solution having a concentration of 0.1 mg per mL .

Application volume: $\quad 10 \mu \mathrm{~L}$.
Developing solvent system: a mixture of ethyl acetate and methanol ( $80: 20$ ).
Procedure-Proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$. Place two $50-\mathrm{mL}$ beakers, each containing 30 mL of ammonium hydroxide, on the bottom of a chromatographic chamber that is lined with filter paper and contains the Developing solvent system, and allow to equilibrate for 1 hour. Position the plate in the chromatographic chamber, and develop the chromatogram until the solvent front has moved about two-thirds of the length of the plate. Remove the plate from the chamber, mark the solvent front, and dry the plate for 3 hours in a current of warm air. Place the plate in a chamber containing iodine vapor, and allow to react for at least 15 hours. Compare the intensities of the brown spots appearing on the chromatogram: any secondary spot obtained from the Test solution is not more intense than the corresponding spot obtained from the Standard solution. Not more than $0.2 \%$ is found.

TEST 2-
Sodium dodecyl sulfate solution, Mobile phase, and Resolution solution-Prepare as directed in the Assay.

Standard solution-Dissolve an accurately weighed quantity of USP Metoprolol Succinate RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $1.0 \mu \mathrm{~g}$ per mL .

Test solution-Transfer about 50 mg of Metoprolol Succinate, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—Prepare as directed in the Assay. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between metoprolol related compound A and metoprolol related compound B is not less than 1.5; and the resolution, $R$, between metoprolol related compound B and metoprolol related compound C is not less than 2.5. [NOTE-The relative retention times are about 0.6 for metoprolol related compound $\mathrm{C}, 0.7$ for metoprolol related compound $\mathrm{B}, 0.8$ for metoprolol related compound A, 1.0 for metoprolol, and 5.0 and 5.2 for the two diastereomers of metoprolol related compound D.] Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $5.0 \%$.

Procedure-Inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Metoprolol Succinate taken by the formula:

$$
\begin{gathered}
\left(G_{s}+\epsilon_{q}\right)\left(r_{i}+r_{s}\right), \\
-100\left(C_{S} / C_{T}\right)\left(r_{i} / r_{S}\right),,_{\text {1S }} \text { (USP28) }
\end{gathered}
$$

in which $C_{S}$ is the concentration, in mg per mL , of USP Metoprolol Succinate RS in the Standard solution; $C_{T}$ is the concentration of metoprolol succinate in the Test solution; $r_{i}$ is the individual peak response of related impurities; and $r_{S}$ is the peak response obtained from the Standard solution: not more than $0.1 \%$ of any single impurity is found, and not more than $0.5 \%$ of total impurities is found. [NOTE-The sum of the peak responses for the two diastereomers of metoprolol related compound D is used in the above calculation to report the amount of metoprolol related compound D.]

Naproxen Delayed-Release Tablets. Because there is no existing $U S P$ monograph for this dosage form, a new monograph is being proposed. The stability-indicating liquid chromatographic procedure in the Assay is based on analyses performed with the Beckman Ultrasphere ODS C18 brand of L1 column. The typical retention time for naproxen is about 9.0 minutes.
(PA2: C. Anthony) RTS-38696-1

## Add the following:

## Naproxen Delayed-Release Tablets

## » Naproxen Delayed-Release Tablets contain not

less than 90.0 percent and not more than 110.0 percent of the labeled amount of naproxen $\left(\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{O}_{3}\right)$.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle$ —USP Naproxen $R S$.

## Identification-

A: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ -
Test solution-Use the solution under test as obtained in the Buffer stage of the Drug release test.
Standard solution-Use the Standard solution prepared as directed in the Buffer stage of the Drug release test.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Drug release, Method $B\langle 724\rangle$ -
ACID STAGE-
Acid stage medium: $\quad 0.1 \mathrm{~N}$ hydrochloric acid; 1000 mL .
Apparatus 2: 50 rpm.
Time: 2 hours.
Procedure-Determine the amount of $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{O}_{3}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 332 nm on filtered portions of the solution under test, suitably diluted with Acid stage medium, if necessary, in comparison with a Standard solution having a known concentration of USP Naproxen RS in the same Medium.

Tolerances-Not more than $10 \%$ of the labeled amount of $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{O}_{3}$ is dissolved in 2 hours.

## BUFFER STAGE-

Buffer stage medium: $\quad 0.2 \mathrm{M}$ phosphate buffer, pH 6.8 ; 1000 mL .

Apparatus 2: 50 rpm.
Time: 45 minutes.
Procedure-Determine the amount of $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{O}_{3}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 332 nm on filtered portions of the solution under test, suitably diluted with Buffer stage medium, if necessary, in comparison with a Standard solution having a known concentration of USP Naproxen RS in the same Medium.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{O}_{3}$ is dissolved in 45 minutes.

Uniformity of dosage units $\langle\mathbf{9 0 5}\rangle$ : meets the requirements.

## PROCEDURE FOR CONTENT UNIFORMITY-

Mobile phase, Diluent A, Diluent B, and Chromatographic system-Proceed as directed in the Assay.
Standard solution-Transfer about 12.5 mg of USP Naproxen RS, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dilute with Diluent $A$ to volume, and mix well. Transfer $10-\mathrm{mL}$ of this solution to a $25-\mathrm{mL}$ volumetric flask, dilute with Diluent $B$ to volume, and mix

Test solution-Transfer 1 Tablet to a $200-\mathrm{mL}$ volumetric flask, and add about 140 mL of Diluent B. Shake by mechanical means for 15 minutes, sonicate for 15 minutes, dilute with Diluent $B$ to volume, and mix. Pass a portion of this solution through a $0.45-\mu \mathrm{m}$ filter, pipet 2.0 mL of the filtrate for a $500-\mathrm{mg}$ tablet and $2.5-\mathrm{mL}$ for a $375-\mathrm{mg}$ tablet into a $50-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume.

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of $1 \%$ acetic acid solution and acetonitrile (11:9).

Diluent $A$-Use acetonitrile and water (9:1).
Diluent $B$-Use acetonitrile and water ( $1: 1$ ).
Standard stock preparation-Transfer about 12.5 mg of USP Naproxen RS, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Diluent $A$ to volume, and mix.

Standard preparation-Accurately transfer 10.0 mL of the Standard stock preparation into a $50-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume.

Assay preparation-Weigh and powder 20 Tablets. Accurately weigh an amount of the powder, equivalent to about 250 mg of naproxen, into a $100-\mathrm{mL}$ volumetric flask, and add about 70 mL of Diluent $B$. Shake by mechanical means for 15 minutes, sonicate for 15 minutes, dilute with Diluent $B$ to volume, and mix. Pass this solution through a $0.45-\mu \mathrm{m}$ filter, transfer 2.0 mL of the filtrate into a $50-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor of the naproxen peak is not more than 1.5 , and the relative standard deviation for replicate injections of the Standard preparation is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the naproxen peak. Calculate
the quantity, in mg , of naproxen $\left(\mathrm{C}_{14} \mathrm{H}_{14} \mathrm{O}_{3}\right)$ in the portion of Tablets taken by the formula:

$$
2500 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Naproxen RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the

Standard preparation, respectively.■1S (USP28)

## Briefing

Naratriptan Hydrochloride, page 3071 of the First Supplement; Naratriptan Tablets, page 3072 of the First Supplement and page 1540 of $P F 29(5)$ [Sept.-Oct. 2003]. The following changes are proposed: replacing USP Naratriptan Related Compound A RS and USP Naratriptan Related Compound B RS by USP Naratriptan Resolution Mixture RS; an adjustment in the gradient profile under Chromatographic system in the Chromatographic purity test; and listing the names of impurities that are currently referred to only by relative retention times in the table under Procedure in the Chromatographic purity test.
(PA3: S. Salado) RTS-41134-1

## Change to read:

USP Reference standards $\langle 11\rangle$-USP Naratriptan Hydrochloride RS. USP Naratriptan Related Compound A RS. USP Nar atriptar Related Compond B-RS.
${ }^{-}$USP Naratriptan Resolution Mixture $R S$.■1S (USP28)

## Change to read:

## Chromatographic purity-

0.05 M Ammonium phosphate buffer-Dissolve 5.75 g of monobasic ammonium phosphate in 1000 mL of water, and adjust with phosphoric acid to a pH of $3.00 \pm 0.05$.

Solution A-Prepare a filtered and degassed mixture of 0.05 M Ammonium phosphate buffer and acetonitrile (97:3).

Solution B-Prepare a filtered and degassed mixture of 0.05 M Ammonium phosphate buffer and acetonitrile (4:1).

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Resolution solution-Dissolve an accurately weighed quantity of USP Nantriptan-Hydrechloride-RS and USP Naraiptane tated Compernd B-RS

■USP Naratriptan Resolution Mixture $\mathrm{RS}_{\mathbf{n}_{1 S} \text { (USP28) }}$ in water to obtain a solution having a known concentration of about 0.11 mg per mL . and 0.11 Hg per mL , respectively.

## ■1S (USP28)

Test solution-Dissolve an accurately weighed quantity of Naratriptan Hydrochloride in water to obtain a solution having a known concentration of about 0.11 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $225-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $4-\mu \mathrm{m}$ packing L1. The column temperature is maintained at $40^{\circ}$. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

| $\begin{gathered} \text { Time } \\ \text { (minutes) } \\ \hline \end{gathered}$ | Solution A (\%) | Solution B (\%) | Elution |
| :---: | :---: | :---: | :---: |
| 0-35.0 | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| 35.0-40.0 | 0 | 100 | isocratic |
| 40.0-40.4 | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $\begin{array}{r} \mathbf{m}_{1.0}^{\mathbf{n S S}_{1 S}(U S P 28)} \\ 40.150 .0 \end{array}$ | 100 | 0 | re-equilibration |
|  |  |  |  |

Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.04 for maratripan relatempemed $B$

■2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1 H -indol-5-yl]ethanesulfonic acid methylamide (naratriptan related
compound B$)_{\mathbf{m}_{1 S}(U S P 28)}$
and 1.0 for naratriptan; and the resolution, $R$, between naratriptan and naratriptan related compound $B$ is not less than 1.5 .

Procedure-Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the areas for all of the peaks. Calculate the percentage of each impurity in the portion of Naratriptan Hydrochloride taken by the formula:

$$
100\left(r_{i} / F\right) /\left[r_{N}+\Sigma\left(r_{i} / F\right)\right],
$$

in which $F$ is the relative response factor (see the accompanying table for values) for each impurity; $r_{i}$ is the peak response for each impurity; and $r_{N}$ is the naratriptan peak response (see the accompanying table for limits).

| Relative retention time | Relative respense factor ( $F$ ) | Limit (\%) |
| :---: | :---: | :---: |
| 0.93 | 1.0 | 0.2 |
| 4.04 | 0.6 | 0.4 |
| 1.18 | 0.6 | 0.2 |
| 1.25 | 0.4 | 0.2 |
| 4.36 | $\theta \cdot 6$ | 0.3 |
| 1.44 | 0.5 | $\theta .4$ |
| 1.48 | 1.0 | 0.2 |
| 1.90 | 1.00 | 0.2 |

In addition to not exceeding the limits listed in the accompanying table, not more than $0.1 \%$ of any other individual impurity is found; and not more than $1.5 \%$ of total impurities is found.
$\left.\begin{array}{llcc}\hline \text { Compound Name } & \text { Relative } & \text { Relative Response } \\ \text { Retention Time }\end{array}\right)$

## Change to read:

## Assay-

0.01 M Triethylamine phosphate buffer-Dilute 0.6 mL of phosphoric acid with water to 900 mL , and adjust with triethylamine to a pH of 2.5 .

Mobile phase-Prepare a filtered and degassed mixture of 0.01 M Triethylamine phosphate buffer and isopropyl alcohol (9:1). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Resolution solution-Dissolve accurately weighed quantities of USP Naratriptan Hydrochloride RS and USP Naratriptan Related Gempeund A RS, and USP Naratriptan Related Compound B RS
-USP Naratriptan Resolution Mixture $^{\text {RS }_{\text {■1S (USP28) }}}$
in Mobile phase to obtain a solution having known concentrations of about 0.11 mg per $\mathrm{mL}, 0.14 \mu \mathrm{~g}$ per mL ,

■ 1 (USP28)
and $0.11 \mu \mathrm{~g}$ per mL , respectively.

Standard preparation-Dissolve an accurately weighed quantity of USP Naratriptan Hydrochloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.11 mg per mL .

Assay preparation-Transfer about 11 mg of Naratriptan Hydrochloride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $282-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $3-\mu \mathrm{m}$ packing L11. The column temperature is maintained at $35^{\circ}$. The flow rate is about 1.5 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for naratrip relatempound $A$
-3-(1-methylpiperidin-4-yl)-1H-indole (naratriptan related

## compound A), ${ }_{1 S}$ (USP28)

1.0 for naratriptan, and 1.1 for naratriptan related compound $B$; and the resolution, $R$, between naratriptan related compound A and naraptriptan and between naratriptan related compound B and naratriptan is not less than 1.5. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{17} \mathrm{H}_{25} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S} \cdot \mathrm{HCl}$ in the portion of Naratriptan Hydrochloride taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Naratriptan Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Naratriptan Tablets, page 3072 of the First Supplement and page 1540 of $P F 29(5)$ [Sept.-Oct. 2003]-See briefing under Naratriptan Hydrochloride.
(PA3: S. Salado) RTS-41134-2

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Naratriptan Hydrochloride RS. USP Naratriptan Related Compand A RS. USP Nar atriptan Related Compound B-RS.

■USP Naratriptan Resolution Mixture $R$.■ IS (USP28) $^{\text {■ }}$

## Change to read:

## Chromatographic purity-

0.05 M Ammonium phosphate buffer and Resolution solutionPrepare as directed in the test for Chromatographic purity under Naratriptan Hydrochloride.

Solution A-Use filtered and degassed 0.05 M Ammonium phosphate buffer.

Solution B-Use filtered and degassed acetonitrile.
Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Test solution-Transfer 5 Tablets into a suitable amber flask. Add 20.0 mL of 0.1 N sodium hydroxide, and allow to stand for 10 minutes. Sonicate for 10 minutes with regular vigorous swirling of the flask. Add 30.0 mL of 0.05 M Ammonium phosphate buffer,
and mix well. Centrifuge a portion of this solution at 3500 rpm for about 10 minutes, and pass through a suitable filter having a 0.2 \#\#
$\square_{0.45-\mu m_{12 S}}$ (USP27)
porosity, discarding the first 3 mL of the filtrate.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $225-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $4 \mu \mathrm{~m}$
$\square_{\text {ne2s (USP27) }}$
packing L1. The column temperature is maintained at $40^{\circ}$. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

| $\begin{gathered} \text { Time } \\ \text { (minutes) } \\ \hline \end{gathered}$ | Solution A (\%) | Solution B (\%) | Elution |
| :---: | :---: | :---: | :---: |
| 0-35.0 | $97 \rightarrow 80$ | $3 \rightarrow 20$ | linear gradient |
| 35.0-40.0 | 80 | 20 | isocratic |
| 40.0-40.4 | $80 \rightarrow 97$ | $20 \rightarrow 3$ | linear gradient |
| $\begin{array}{r} \mathbf{m}_{41.0}^{1 \mathrm{~m}} \mathrm{mS}_{4}(\mathrm{USP28)} \\ 40.4 \end{array}$ | 97 | 3 | re-equilibration |
| $\mathbf{\square}_{41.0-51.0}^{\mathbf{1}_{\text {1S }}}$ (USP28) |  |  |  |

Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.07 for matripan related compeund $B$
-2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1 H -indol-
$5-\mathrm{yl}]$ ethanesulfonic acid methylamide (naratriptan related
compound B) ${ }_{1 \mathrm{IS}(U S P 28)}$
and 1.0 for naratriptan; and the resolution, $R$, between naratriptan and naratriptan related compound B is not less than 1.5 .

Procedure-Inject a volume (equivalent to about $5 \mu \mathrm{~g}$ of naratriptan hydrochloride) of the Test solution into the chromatograph, record the chromatogram, and measure the areas for all of the peaks. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$
100\left(r_{i} / F\right) /\left[r_{N}+\Sigma\left(r_{i} / F\right)\right]
$$

in which $F$ is the relative response factor (see the accompanying table for values) for each impurity; $r_{i}$ is the peak response for each impurity; and $r_{N}$ is the naratriptan peak response (see the accompanying table for limits).

| Relativeretention <br> time | Relative respense- <br> factor $(F)$ | Limit $(\%)$ |
| :---: | :---: | :---: |
| 1.07 | 0.6 | $\theta .2$ |
| 1.26 | 0.6 | 0.2 |
| 1.33 | 0.4 | $\theta .3$ |
| 1.44 | 0.6 | $\theta .2$ |
| 1.62 | 0.5 | $\theta .2$ |

In addition to not exceeding the limits listed in the accompanying table, not more than $0.2 \%$ of any other individual impurity is found; and not more than $1.5 \%$ of total impurities is found.

| Compound Name | Relative <br> Retention Time | Relative Response <br> Factor $(F)$ | Limit (\%) |
| :---: | :---: | :---: | :---: |
| 2-[3-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-1 H -indol- <br> 5-yl]ethanesulphonic acid methylamide | About 1.07 | 0.6 | 0.2 |
| 2,2-Bis-[3-(1-methylpiperidin-4-yl)-1 H -indol-5-yl] ethanesulphonic acid methylamide | About 1.26 | 0.6 | 0.2 |
| 1-Methyl-4-[5-(2-methylsulphamoyl-ethyl)-1 H -indol-3-yl]-pyridinium chloride | About 1.33 | 0.4 | 0.3 |
| 2-[3-(1-methylpiperidin-4-yl)-5-(2-methylsulphamoyl-ethyl)-indol-1-yl]ethanesulphonic acid methylamide | About 1.44 | 0.6 | 0.2 |
| 4-[1,5-Bis-(2-methylsulphamoyl-ethyl)-1 H -indol-3-yl]-1methylpyridinium chloride | About 1.62 | 0.5 | 0.2 |

## Change to read:

## Assay-

0.01 M Triethylamine phosphate buffer, Mobile phase, and Resolution solution-Prepare as directed in the Assay under Naratriptan Hydrochloride.

Standard preparation-Dissolve an accurately weighed quantity of USP Naratriptan Hydrochloride RS in 0.1 N sodium hydroxide to obtain a solution having a known concentration of about 0.2 mg per mL . Dilute an accurately measured volume of this solution in 0.01 M Triethylamine phosphate buffer to obtain a solution having a known concentration of about $20 \mu \mathrm{~g}$ per mL .

Assay preparation-Transfer 5 Tablets into an amber $250-\mathrm{mL}$ volumetric flask, add 30 mL of 0.1 N sodium hydroxide, and shake on a wrist-action shaker for at least 30 minutes. Sonicate for 10 minutes with regular vigorous swirling of the flask. Add about 170 mL of 0.01 M Triethylamine phosphate buffer, and mix well. Allow to cool to room temperature, dilute with 0.01 M Triethylamine phosphate buffer to volume, and mix. Centrifuge a portion of this solution at 3500 rpm for about 10 minutes, and pass through a suitable filter having a $0.2 \mu \mathrm{~m}$
${ }^{\bullet} 0.45-\mu \mathrm{m}_{\text {■2S (USP27) }}$
porosity, discarding the first 3 mL of the filtrate.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $224-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $3-\mu \mathrm{m}$
$\mathrm{m}^{5-\mu \mathrm{m}_{\text {2S }}}$ (USP27)
packing L11. The flow rate is about 1.3 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for naratriptan related compernd $A$,

■3-(1-methylpiperidin-4-yl)-1 H -indole (naratriptan related compound A), ■1S (USP28)
1.0 for naratriptan, and 1.1 for naratriptan related compound $B$; and the resolution, $R$, between naratriptan related compound A and naratriptan and between naratriptan related compound $B$ and naratrip-
tan is not less than 1.5. Chromatograph the Standard preparation, record the chromatogram, and measure the peak response as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (equivalent to about $1 \mu \mathrm{~g}$ of naratriptan hydrochloride) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of naratriptan $\left(\mathrm{C}_{17} \mathrm{H}_{25} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S}\right)$ in the portion of Tablets taken by the formula:

$$
(335.47 / 371.93) 100(C / D)\left(r_{U} / r_{S}\right)
$$

in which 335.47 and 371.93 are the molecular weights of naratrip$\tan$ and naratriptan hydrochloride, respectively; $C$ is the concentration, in mg per mL , of USP Naratriptan Hydrochloride RS in the Standard preparation; $D$ is the concentration, in mg per mL , of naratriptan in the Assay preparation, based upon the labeled quantity of naratriptan in the portion of Tablets taken and the extent of dilution; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Briefing

Nifedipine Extended-Release Tablets, USP 27 page 1321 and page 1542 of $P F 29(5)$ [Sept.-Oct. 2003]. It is proposed to revise Drug release Test 1 to clarify the instructions for performing the
test. It is also proposed to specify the volume of the Medium to be used in Phase 1 of Drug release Test 3. In addition, minor editorial style changes have been made.
(BPC: M. Marques) RTS-41015-1

## Change to read:

Drug release $\langle 724\rangle$ -
Test 1: If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 1.

Medium: water; 50 mL .
Apparatus 7:
$\square 15$ to 30 cycles per minute. $\mathbf{m}_{1 S}$ (USP28)
Do not use the reciprocating disk, but use a $25-\mathrm{cm}$ plexiglas rod, the perimeter of the Tablets being affixed to the rod with a waterinsoluble glue. The solution containers are $25-\mathrm{mm}$ test tubes, 150 to 200 mm in length, and the water bath is maintained at $37 \pm 0.5^{\circ}$.

- At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50

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mL of fresh Medium. 1 l (USP28)
Times: \(\quad 4,12\),and 24 hetris.
Times: 4, 12, and 24 hours.
```

$\mathbf{\square}$ 8, 12, 16, 20, and 24 hours.■1S (USP28)
Diluting solution 1: a mixture of methanol and acetonitrile (1:1).

Piluting solution 2. a mixture of Diluting solution 1 and water (1:1).

- Diluting solution: a mixture of methanol and water (1:1).n1S (USP28)

Standard solutions-Transfer about 50 mg of USP Nifedipine RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in 50 mL of Pill,
$\boldsymbol{m}_{\text {methanol, }} \mathbf{■ 1 S}_{\text {(USP28) }}$
dilute with water to volume, and mix to obtain a Standard stock solution. Quantitatively dilute this Standard stock solution with $\mathrm{Bi}_{\mathrm{i}}$ tuting solution 2 to obtain solutions having known concentrations ef 0.01 mg per $\mathrm{mL}, 0.05 \mathrm{mg}$ per mL , and 0.20 mg per mL that are used at 4 hours, 12 heurs, and 24 hours, respectively.
known concentrations.
Test solution-Use portions of the solution under test, passed through a $0.4-\mu \mathrm{m}$ filter, suitably diluted with methanol, and stepwise, if necessary, with Diluting solution to obtain a final mixture consisting of equal parts of methanol and water.■1S (USP28)

Procedure- [NOTE-For the 4 hour time period, filter, determine the absorbance at 456 nm , and use this determination to correct for excipient interference at the other time periods.] Determine the amount of $\mathrm{C}_{4} \mathrm{H}_{48} \mathrm{~N}_{2} \mathrm{O}_{6}$ released at ach 4 hour interval by employ ing UV absorption at the wavelength of maximman abserbance at about 338 mm , in 0.5 cm cells. Use test solutions that are suitably diluted, if neeessary, with Diluting solution 1 and water to obtain a final mixture of water, methanol, and acetonitrile ( $2: 1: 1$ ) in eomparison with the appropriate Standard solution, using Diluting solu 2 as the blank.
-Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}$ released in the Test solution at each 4-hour interval by employing UV absorption at the wavelength of maximum absorbance at about 338 nm , in $0.5-\mathrm{cm}$ cells. [NOTE-For the 4 -hour time period, determine the absorbance at 456 nm , and use this determination to correct for excipient interference.] $\mathbf{1 I S}_{\text {(USP28) }}$

Tolerances-The cumulative percentages of the labeled amount of nifedipine $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}\right)$, released in vivo and dissolved at the times specified, conform to Acceptance Table 1.

| Fime (hours) | Amount dissolved |
| :---: | :--- |
| 4 | betw $5 \%$ and $17 \%$ |
| 12 | ben $43 \%$ and $80 \%$ |
| 24 |  |

- 

| Time (hours) | Amount dissolved ${ }^{*}$ |
| :---: | :---: |
| 4 | between $5 \%$ and $17 \%$ |
| 8 | - |
| 12 | between $43 \%$ and $80 \%$ |
| 16 | - |
| 20 | not less than $80 \%$ |

* The amount dissolved is expressed in terms of the labeled tablet strength
rather than in terms of the labeled total contents. 1 S (USP28)

Test 2: If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 2.

Buffer concentrate-Transfer 330.9 g of dibasic sodium phosphate and 38 g of citric acid to a 1-L volumetric flask, add water to dissolve, add 10 mL of phosphoric acid, dilute with water to volume, and mix.

Medium-Mix 125.0 mL of Buffer concentrate and 1 L of $10 \%$ sodium lauryl sulfate solution, and dilute to 10 L . Adjust if necessary to a pH of $6.8 ; 900 \mathrm{~mL}$.

Apparatus 2: 50 rpm ,
$\boldsymbol{m}_{\text {with }}$ sinkers (see Figure 1).■2S (USP27)


Fig. 1 (printed with permission of the Japanese Pharmacopoeia)
Times: 3, 6, and 12 hours.
Determine the amount of nifedipine $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}\right)$ dissolved by employing the following method.

Mobile phase - Prepare a filtered and degassed mixture of acetonitrile and water ( $70: 30$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Nifedipine RS in methanol to obtain a solution having a known concentration of about 1.11 mg per mL . Dilute quantitatively and stepwise with Medium to obtain a solution having a known concentration of 0.1 mg per mL .

Chromatographic system-The liquid chromatograph is equipped with a $350-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 125-\mathrm{mm}$ column that contains $3-\mu \mathrm{m}$ packing L 1 . The flow rate is about 1.5 mL per minute. The column is maintained at about $40^{\circ}$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of filtered portions of the Standard solution and the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount of nifedipine $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}\right)$ dissolved.

Tolerances-The percentages of the labeled amount of nifedipine $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}\right)$ released in vivo and dissolved at the times specified conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 3 | between $10 \%$ and $30 \%$ |
| 6 | between $40 \%$ and $65 \%$ |
| 12 | not less than $80 \%$ |

Test 3: If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 3.
FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE-
Phase 1:
Medium: $\quad 0.05 \mathrm{M}$ phosphate buffer, pH 7.5 ;
■00 mL.■1S (USP28)
Apparatus 2: 100
Apparatus 2: 100 rpm .
Time: 1 hour.
Standard solution-Prepare a solution in Medium having an accurately known concentration of about 0.034 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding $10 \%$ of the final volume, can be used to help solubilize nifedipine.

Procedure-[NOTE-After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the Medium for Phase
2.] Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}$ released in Phase 1 from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the Standard solution, using the Medium as the blank.

Phase 2:
Medium: $\quad 0.5 \%$ sodium lauryl sulfate in simulated gastric fluid without enzyme, $\mathrm{pH} 1.2 ; 900 \mathrm{~mL}$.

Apparatus 2: 100 rpm.
Times: 1, 4, 8, and 12 hours.
Standard solution-Prepare a solution in Medium having an accurately known concentration of about 0.034 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding $10 \%$ of the final volume, can be used to help solubilize nifedipine.

Procedure-Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}$ released in Phase 2 from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the Standard solution, using Medium as the blank.

Tolerances-The cumulative percentages of the labeled amount of nifedipine $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}\right)$, released in vivo and dissolved at the times specified, conform to Acceptance Table 1.

| Time (hours) | Amount dissolved $^{*}$ |
| :---: | :--- |
| 1 | not more than $30 \%$ |
| 4 | between $30 \%$ and $55 \%$ |
| 8 | not less than $60 \%$ |
| 12 | not less than $80 \%$ |

* For each dosage unit, add the amount dissolved in phosphate buffer, pH 7.5 from Phase 1 to the amount dissolved at each time point in Phase 2.

FOR TABLETS LABELED TO CONTAIN 60 MG OF NIFEDIPINE-
Phase 1:
Medium: $\quad 0.05 \mathrm{M}$ phosphate buffer, pH 7.5 ;
■ 900 mL . ${ }^{1 \mathrm{~S}}$ (USP28)
Apparatus 2: 100 rpm .
Time: 25 minutes.
Standard solution-Prepare a solution in Medium having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding $10 \%$ of the final volume, can be used to help solubilize nifedipine.

Procedure-[NOTE-After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the Medium for Phase 2.] Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}$ released in Phase 1 from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the Standard solution, using the Medium as the blank.

Phase 2:
Medium: $\quad 0.5 \%$ sodium lauryl sulfate in simulated gastric fluid without enzyme, $\mathrm{pH} 1.2 ; 900 \mathrm{~mL}$.

Apparatus 2: 100 rpm .
Times: $1,4,8$, and 12 hours.
Standard solution-Prepare a solution in Medium having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding $10 \%$ of the final volume, can be used to help solubilize nifedipine.

Procedure-Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}$ released in Phase 2 from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the Standard solution, using Medium as the blank.

Tolerances-The cumulative percentages of the labeled amount of nifedipine $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}\right)$, released in vivo and dissolved at the times specified, conform to Acceptance Table 1.

| Time (hours) | Amount dissolved $^{*}$ |
| :---: | :--- |
| 1 | not more than $30 \%$ |
| 4 | between $40 \%$ and $70 \%$ |
| 8 | not less than $70 \%$ |
| 12 | not less than $80 \%$ |

* For each dosage unit, add the amount dissolved in phosphate buffer, pH 7.5 from Phase 1 to the amount dissolved at each time point in Phase 2.

Test 4: If the product complies with this test, the labeling indicates that the product meets USP Drug Release Test 4.

Medium: $\quad 0.5 \%$ sodium lauryl sulfate in simulated gastric fluid without enzyme, $\mathrm{pH} 1.2 ; 900 \mathrm{~mL}$.

Apparatus 2: 100 rpm .
Times: 1, 4, and 12 hours.
Standard solution-Prepare a solution in Medium having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL for Tablets labeled to contain 60 mg , and of about 0.034 mg of USP Nifedipine RS per mL for Tablets labeled to contain 30 mg . If necessary, a volume of methanol, not exceeding $10 \%$ of the final volume, can be used to help solubilize nifedipine.

Procedure-Determine the amount of $\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}$ released from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the Standard solution, using the Medium as the blank.

Tolerances-The cumulative percentages of the labeled amount of nifedipine $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{6}\right)$, released at the times specified, conform to Acceptance Table 1.

FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $12 \%$ and $35 \%$ |
| 4 | between $44 \%$ and $67 \%$ |
| 12 | not less than $80 \%$ |

FOR TABLETS LABELED TO CONTAIN 60 MG OF NIFEDIPINE

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $10 \%$ and $30 \%$ |
| 4 | between $40 \%$ and $63 \%$ |
| 12 | not less than $80 \%$ |

$\qquad$
$\rightarrow+$
posed is in the general form [DRUG][ROUTE OF ADMINISTRATION][DOSAGE FORM] to indicate by the title that the tablets are intended for sublingual use. The Expert Committee on Nomenclature and Labeling considers that the term "Sublingual" appearing prominently in the product name will represent a significant improvement in that the consumer will be provided with the assurance that, along with the labeling statement indicating that the tablets are for sublingual use, the product will be used properly to achieve the benefit of the medication.

The revisions are proposed for publication in the First Supplement to USP 28-NF 23, which is to become official April 1, 2005, but with October 1, 2006, designated as the official date for the name change. The eighteen-month postponement of the official date for the name change would be intended to allow for product label changes to be made and for health practitioners and consumers to become familiar with the revised terminology.
(NL: C. Barnstein) RTS-41140-1

## Nitroglycerin Tablets

(Current title-not to change until October 1, 2006)
Monograph title change-to become official October 1, 2006
(see Official Title Changes on the first page of In-Process Revision):
See Nitroglycerin Sublingual Tablets

## Briefing

Nitroglycerin Sublingual Tablets-See briefing under Nitroglycerin Tablets.
(NL: C. Barnstein) RTS-41140-1

## Add the following:

## ■ Nitroglycerin Sublingual Tablets

## (Monograph under this new title-to become official October 1, 2006) <br> (Current monograph title is Nitroglycerin Tablets)

BRIEFING

Nitroglycerin Tablets, USP 27 page 1330; Nitroglycerin Sublingual Tablets. A revision is proposed by the Expert Committee on Nomenclature and Labeling to change the title of this monograph to Nitroglycerin Sublingual Tablets. The title that is pro-
» Nitroglycerin Sublingual Tablets contain not less than 90.0 percent and not more than 115.0 percent of the labeled amount of nitroglycerin $\left(\mathrm{C}_{3} \mathrm{H}_{5} \mathrm{~N}_{3} \mathrm{O}_{9}\right)$.

Packaging and storage-Preserve in tight containers, preferably of glass, at controlled room temperature. Each container holds not more than 100 Sublingual Tablets.

Labeling-The labeling indicates that the Sublingual Tablets are for sublingual use, and the label directs that the Sublingual Tablets be dispensed in the original, unopened container, labeled with the following statement directed to the patient. "Warning: To prevent loss of potency, keep these tablets in the original container or in a supplemental nitroglycerin container specifically labeled as being suitable for Nitroglycerin Sublingual Tablets. Close tightly immediately after each use."

USP Reference standards $\langle 11\rangle$ —USP Diluted Nitroglycerin $R S$.

## Identification-

## A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ —

Test solution-Transfer an amount of finely powdered Sublingual Tablets, equivalent to about 1 mg of nitroglycerin, to a glass-stoppered vessel, add 1 mL of acetone, shake by mechanical means for 30 minutes, and filter.

Standard solution: 1 mg per mL , in acetone.
Developing solvent system: a mixture of toluene, ethyl acetate, and glacial acetic acid ( $16: 4: 1$ ).

Procedure-Proceed as directed in the chapter. Spray with a solution of diphenylamine in methanol (1 in 100), and irradiate the plate with short- and long-wavelength UV light for about 10 minutes.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Disintegration $\langle 701\rangle$ : 2 minutes, determined as set forth for Sublingual Tablets.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY-
Mobile phase, Standard preparation, and Chromatographic system-Proceed as directed in the Assay under Diluted Nitroglycerin.

Test preparation-Transfer 1 Sublingual Tablet to a suitable container, and dissolve in and dilute with Mobile phase to obtain a solution containing about 0.075 mg of nitroglycerin per mL .
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Test preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of nitroglycerin $\left(\mathrm{C}_{3} \mathrm{H}_{5} \mathrm{~N}_{3} \mathrm{O}_{9}\right)$ in the portion of Sublingual Tablets taken by the formula:

$$
V C\left(r_{U} / r_{s}\right)
$$

in which $V$ is the volume, in mL, of Mobile phase used to prepare the Test preparation; $C$ is the concentration, in mg per mL, of USP Diluted Nitroglycerin RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses for nitroglycerin obtained from the Test preparation and the Standard preparation, respectively. The content of each of the 10 Sublingual Tablets is within the range of $75.0 \%$ and $135.0 \%$ of the labeled claim. If the content of not more than 1 Sublingual Tablet is outside the range of $75.0 \%$ and
$135.0 \%$ and if the content of none of the Sublingual Tablets is outside the range of $60.0 \%$ and $150.0 \%$, test 20 additional units. The requirements are met if the content of each of the additional 20 units falls within the range of $75.0 \%$ and $135.0 \%$ of the labeled claim.

## Assay-

Mobile phase, Standard preparation, and Chromatographic system-Prepare as directed in the Assay under Di-

## luted Nitroglycerin.

Assay preparation-Dissolve not fewer than 20 Sublingual Tablets in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution containing about 0.075 mg per mL of nitroglycerin.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of nitroglycerin $\left(\mathrm{C}_{3} \mathrm{H}_{5} \mathrm{~N}_{3} \mathrm{O}_{9}\right)$ per Sublingual Tablet taken by the formula:

$$
100 /(T D C)\left(r_{U} / r_{s}\right)
$$

in which $T$ is the number of Sublingual Tablets taken; $D$ is the dilution factor of the Assay preparation; $C$ is the concentration, in mg per mL, of USP Diluted Nitroglycerin RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses for nitroglycerin obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)
(Official October 1, 2006)

## BRIEFING

Ofloxacin, USP 27 page 1355 and page 1940 of PF 29(6) [Nov.-Dec. 2003]. On the basis of new information and supporting data received, it is proposed to specify the HPLC column temperature and to modify the precision of the procedure in the test for Related compounds.
(PA7b: B. Davani) RTS-40955-1

## Change to read:

Packaging and storage-Preserve in well-closed containers, protected from light.
-Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and
$30^{\circ}$. 2 (USP27)

## Add the following:

${ }^{\boldsymbol{4}}$ Labeling-Where it is intended for use in preparing injectable dosage forms or other sterile dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. $\triangle$ USP28

## Change to read:

USP Reference standards $\langle 11\rangle$-USP Ofloxacin RS.


## Delete the following:

-Chromatographic purity-
Mobile phase Dissolve 27.2 g of menebasic petassium phesphate in 1000 mL of water, adjust with phosphoric aeid to a pH of 2.4, and mix. Prepare a fitered and degassed mixture-of this solution and acetonitrile (90:10). Make adjustments if neeessary (see System-Suitability under Chromatography $\langle 624\rangle$ ).

Systemt suitability standard soltution Dissolve an aceurately weighed quantity of USP Ofloxacin PS in methanel to obtain a solution having a known concentration of about $1.0 \mu$ g per mL .

Fest selution Quantitatively dissolve an aceurately weighed quantity of Oflexacin in methanel to obtain a selation containings abeut 1.0 mg per mL.

Chrematographic syistem (see-Chrematography $\langle 621\rangle$ ) The tiquid chromatograph is equipped with a 294 mm detector and a $4.6 \mathrm{~mm} \times 10 \mathrm{em}$ column that contains packing L 1 . The flow rate is about 2 ml per minute. Chrematograph the System suitability standard solution, and record the peak responses as directed for Procedtre: the evlumm effeieney, determined from the ofloxacin peak, is net less than 1400 theoretical plates when ealeulated by the formula:

$$
5.545\left(t_{\mu}+H_{12}\right)^{2}
$$

and the relative-standard deviation for replieate-injections is net mere than $2.0 \%$

Procedure Inject a volume (about $10 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram for a period of time that is 2.5 times the retention time of the main ofloxacin peak, and measure the areas for all the peaks, exeept to disregard the sot rent peak. Caleulate the pereentage of desfluoroofloxacin in the pertion of Ofloxain taken by the formula:-

$$
100\left(1.13 x_{4}+7\right)
$$

in whieh 1.13-is the respense facter of desflureofloxacin relative to that of ofloxacin; ris the area for the desfltoroofloxacin peak, if $^{\text {is }}$ present, at a retention time of about 0.56 relative to that of oflox rein; and $r$ is the total area of the peaks, except for the solvent peak: not more than $0.2 \%$ is found. Caleulate the percentage of each other impurity with an area greater than that of the ofloxacin peak in the chromatogram of the System suitability standard sotut tien-obtained under. Chromatographic system, by the formata:-
$100(+\div+7)$,
in which $r$,is the peak area for an-individualimpurity; and $x$ is the tetal area of the peaks in the ehremategram obtained frem the Test solution, exeept for the solvent peak: not more than $0.3 \%$ of any individual impurity is found; and the sum-of allimpurities found is net mere than $0.5 \%$. 1 S (USP28)

## Add the following:

-Related compounds-
Diluent-Prepare a mixture of water and acetonitrile (6:1).

Mobile phase-Dissolve 4.0 g of ammonium acetate and 7.0 g of sodium perchlorate in 1300 mL of water, adjust with phosphoric acid to a pH of 2.2 , and mix. Prepare a filtered and degassed mixture of this solution and 240 mL of acetonitrile. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Transfer 10.0 mg of USP Ofloxacin Related Compound A RS and 10.0 mg of USP Ofloxacin RS to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix. Dilute 10.0 mL of this solution with Diluent to 50.0 mL . Dilute 1.0 mL of this solution with Diluent to 50.0 mL .

Standard solution-Quantitatively dissolve an accurately weighed quantity of USP Ofloxacin RS in Diluent to obtain a solution that contains 0.0004 mg per mL of ofloxacin.

Test solution-Quantitatively dissolve an accurately weighed quantity of Ofloxacin in Diluent to obtain a solution containing about 0.2 mg per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a 294 -nm detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The column temperature is maintained at $45^{\circ}$. The flow rate is about 0.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution between ofloxacin and ofloxacin related compound A is not less than 2.0; and the relative standard deviation for replicate injections is not more than 5.0\%. 3.0\%.

Procedure-Inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Test solution and the Standard solution into the chromatograph, record the chromatogram for a period of time that is about 2.5 times the retention time of the ofloxacin peak, and measure the areas for all of the peaks except the solvent peak. Calculate the percentage of each impurity with an area greater than 0.1 times the average area of the ofloxacin peak obtained from the Standard solution by the formula:

$$
100\left(C / C_{T}\right)\left(r_{i} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Ofloxacin RS in the Standard solution; $C_{T}$ is the concentration, in mg per mL , of ofloxacin in the Test solution; $r_{i}$ is the peak area for an individual impurity; and $r_{s}$ is the average area of the ofloxacin peak obtained from the Standard solution: not more than $0.3 \%$ of any individual impurity is found; and the sum of all impurities found is not more than $0.5 \%$. 1 S (USP28)

## Add the following:

${ }^{\Delta}$ Other requirements-Where the label states that Ofloxacin is sterile, it meets the requirements under Sterility Tests
$\langle 71\rangle . \mathbf{\Delta U S P 2 8}$

## BRIEFING

Oxybutynin Chloride Extended-Release Tablets, page 525 of PF 30(2) [Mar.-Apr. 2004]. It is proposed to add a test for Drug release to this new monograph. In addition, minor editorial style changes have been made.
(BPC: M. Marques; PA4: E. Gonikberg) RTS-40034-1

## Add the following:

## ©Oxybutynin Chloride ExtendedRelease Tablets

» Oxybutynin Chloride Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of oxybutynin chloride $\left(\mathrm{C}_{22} \mathrm{H}_{31} \mathrm{NO}_{3} \cdot \mathrm{HCl}\right)$.

Packaging and storage-Preserve in tight containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$. USP Reference standards $\langle 11\rangle$ —USP Oxybutynin Chloride RS. USP Oxybutynin Related Compound $A R S$.

## Identification-

A: Infrared Absorption $\langle 197\rangle$ -
Test specimen-Add a quantity of finely powdered Tablets, equivalent to about 15 mg of oxybutynin chloride, to 5 mL of water per Tablet. Mix for 1 minute. Adjust with 0.1 N sodium hydroxide to a pH between 7 and 8 . Extract the solution twice with 10 mL of ether. Combine and evaporate the ether extract, and dry under vacuum over silica gel for at least 30 minutes. Redissolve the dried residue in a small amount of acetone, transfer the solution to an IR salt plate, and evaporate to cast a thin film.

Standard specimen-Dissolve 15 mg of USP Oxybutynin Chloride RS in 5 mL of water. Proceed as directed for the Test specimen, beginning with "Adjust with".
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Drug release $\langle 724\rangle$ -
Medium: simulated gastric fluid without enzymes; 50 mL .

Apparatus 7: 30 cycles per minute; 2 to 3 cm amplitude.

Times: 4,10 , and 24 hours.
Determine the amount of $\mathrm{C}_{22} \mathrm{H}_{31} \mathrm{NO}_{3} \cdot \mathrm{HCl}$ dissolved by employing the following method.
0.035 M Phosphate buffer, pH 2.2-Dissolve about 4.83 g of monobasic sodium phosphate in 1000 mL of water, add 2.3 mL of triethylamine, and adjust with phosphoric acid to a pH of $2.2 \pm 0.2$.

Acidified water-To 1 L of water add phosphoric acid dropwise to a pH of 3.5 , and mix well.
Standard stock solutions-Dissolve accurately weighed quantities of USP Oxybutynin RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain solutions having known concentrations of about 250, 300 , and $350 \mu \mathrm{~g}$ per mL .
Standard solutions-Prepare a series of dilutions of the Standard stock solutions in acidified water having final concentrations similar to those expected in the Test solution.

Test solution-Use portions of the solution under test. If the solution is cloudy, centrifuge at 2000 rpm for 10 minutes, and use the supernatant.

Mobile phase-Prepare a suitable filtered and degassed mixture of 0.035 M Phosphate buffer, pH 2.2 and acetonitrile ( $65: 35$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Use a medium range standard solution of USP Oxybutynin Chloride RS.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $230-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 5-\mathrm{cm}$ column that contains packing L11. The flow rate is about 1.5 mL per minute. The column temperature is maintained at about $35^{\circ}$. Chromatograph the System suitability solution, and record the chromatogram as directed for Procedure: the tailing factor is greater than 0.5 and less than 2.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solutions and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Construct a calibration curve by plotting the peak response versus concentration of the Standard solutions. A weighing factor, $1 / \mathrm{x}$, is applied to the regression line of the calibration curve to enhance the accuracy of the low standard concentrations. Determine the amount of $\mathrm{C}_{22} \mathrm{H}_{31} \mathrm{NO}_{3} \cdot \mathrm{HCl}$ dissolved in each interval from a linear regression analysis of the calibration curve.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{22} \mathrm{H}_{31} \mathrm{NO}_{3} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Acceptance Table 1.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 4 | not more than $20 \%$ |
| 10 | between $34.5 \%$ and $59.5 \%$ |
| 24 | not less than $80 \%$ |

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Related compounds-

Mobile phase, Diluent, Preparation medium, Impurity stock solution, and System suitability solution-Proceed as directed in the Assay.

Impurity standard solution-Dilute the Impurity stock solution with Diluent to obtain a solution having a known concentration of about $1 \mu \mathrm{~g}$ of phenylcyclohexylglycolic acid (oxybutynin related compound A) per mL .

Test solution- Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a 220 -nm detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L11. The flow rate is about 1.5 mL per minute. Chromatograph the Impurity standard solution, and record the peak responses as directed for Procedure: the tailing factor is greater than 0.75 and not more than 2.5 for the phenylcyclohexylglycolic acid peak. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.0 for oxybutynin and about 1.6 for phenylcyclohexylglycolic acid; the resolution, $R$, between oxybutynin and phenylcyclohexylglycolic acid is not less than 1.5; and the relative standard deviation of peak area responses for six replicate injections of System suitability solution is not more than $3 \%$ for each compound.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Impurity standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$
C\left(r_{U} / r_{s}\right),
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of phenylcyclohexylglycolic acid in the Impurity standard solution; and $r_{U}$ and $r_{S}$ are the peak responses for each impurity obtained
from the Test solution and the Impurity standard solution, respectively. Disregard any peak less than $0.1 \%$ : not more than $1 \%$ of phenylcyclohexylglycolic acid is found, and not more than $2 \%$ of total impurities is found.

## Assay-

Mobile phase_Prepare a mixture of water, acetonitrile, and triethylamine (65:35:0.15). Adjust with phosphoric acid to a pH of 3.9 , degas, and filter.

Diluent-Use water adjusted with phosphoric acid to a pH of 3.5 .

Preparation medium—Prepare a solution of methanol and acetonitrile (1:1).

Impurity stock solution-Dissolve an accurately weighed quantity of USP Oxybutynin Related Compound A RS in acetonitrile to obtain a solution having a known concentration of about 0.11 mg of phenylcyclohexylglycolic acid per mL . [NOTE-Oxybutynin related compound A is phenylcyclohexylglycolic acid.]

Standard stock preparation-Dissolve an accurately weighed quantity of USP Oxybutynin Chloride RS in acetonitrile to obtain a solution having a known concentration of about 0.37 mg per mL .

System suitability solution-Transfer 10 mL of the Standard stock preparation and 1 mL of the Impurity stock solution into a $100-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.

Standard preparation-Dilute the Standard stock preparation with Diluent to obtain a solution having a known concentration of about 0.1 mg per mL .

## Assay preparation-

FOR TABLETS THAT CONTAIN 5 MG OF OXYBUTYNIN CHLO-RIDE-Place 10 Tablets in a $500-\mathrm{mL}$ volumetric flask, add 150 mL of Preparation medium, and stir overnight or until dissolved. Dilute with Diluent to volume. Mix thoroughly, centrifuge, and use the clear supernatant.

FOR TABLETS THAT CONTAIN 10 MG OF OXYBUTYNIN CHLORIDE OR MORE—Place 10 Tablets in a $1000-\mathrm{mL}$ volumetric flask, add 300 mL of Preparation medium, and stir overnight or until dissolved. Dilute with Diluent to volume. If necessary, make a further dilution with Diluent to obtain a solution having a final concentration equivalent to 0.1 mg per mL of oxybutynin chloride. Mix thoroughly, centrifuge, and use the clear supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L11. The flow rate is about 1.5 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the tailing factor is greater than 0.75 and not more than 2.5. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.0 for oxybutynin and about 1.6 for phenylcyclohexylglycolic acid; the resolution, $R$, between oxybutynin and phenylcyclohexylglycolic acid is not less than 1.5 ; and the relative standard deviation of peak area responses for six replicate injections of System suitability solution is not more than $3 \%$ for each compound.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L})$ of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of oxybutynin chloride $\left(\mathrm{C}_{22} \mathrm{H}_{31} \mathrm{NO}_{3} \cdot \mathrm{HCl}\right)$ in the portion of Tablets taken by the formula:

$$
C V D\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of oxybutynin chloride in the Standard preparation; $V$ is the volume, in mL , of the Assay preparation; $D$ is the dilution factor; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## BRIEFING

Paclitaxel, USP 27 page 1394 and page 1947 of $P F$ 29(6) [Nov.-Dec. 2003]. It is proposed to revise the test for Related compounds to add two new impurities under Test 1, paclitaxel C and N methylpaclitaxel C, at limits of not more than $0.1 \%$ each, and to add Test 3 for materials produced by fermentation. Materials meeting this specification will require labeling to indicate it meets the requirements for USP Related compounds Test 3, which will also require a new reference standard, USP Paclitaxel Related Compound C. Thus it is also proposed to revise the USP Reference standards section to add USP Paclitaxel Related Compound C. The liquid chromatographic procedure described in Test 3 is based on analyses performed with a YMC brand of L1 column. The proposed revision published in PF 29(6) under Test 1 to increase the combined limits of celphalomannine and $2^{\prime \prime}, 3^{\prime \prime}$-dihydrocephalomannine from $0.5 \%$ to $0.8 \%$ is being canceled.
(PA6: L. Evans) RTS—39513-2; 39513-4; 39513-5; 41147-1

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers, and store $20^{\circ}$ and $25^{\circ}$.
$\mathbf{m}_{\text {at }}$ controlled room temperature. $\mathbf{m}^{2 S}$ (USP27)

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Endotoxin RS. USP Paclitaxel RS. USP Paclitaxel Related Compound A RS. USP Paclitaxel Related Compound B RS.


## Change to read:

## Related compounds-

TEST 1 (for material labeled as isolated from natural sources)-If the material complies with this test, the labeling indicates that it meets USP Related compounds Test 1.

Diluent-Prepare as directed in the Assay.
Solution A-Prepare filtered and degassed acetonitrile.
Solution B-Prepare filtered and degassed water.
Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve accurately weighed quantities of USP Paclitaxel Related Compound A RS and USP Paclitaxel Related Compound B RS in methanol to obtain a solution
having known concentrations of about $10 \mu \mathrm{~g}$ of each per mL . Transfer 5.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.
Standard solution-Dissolve, with the aid of sonication, an accurately weighed quantity of USP Paclitaxel RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about $5 \mu \mathrm{~g}$ per mL .

Test solution-Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $227-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L43. The flow rate is about 2.6 mL per minute. The column temperature is maintained at $30^{\circ}$. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0-35$ | 35 | 65 | isocratic |
| $35-60$ | $35 \rightarrow 80$ | $65 \rightarrow 20$ | linear gradient |
| $60-70$ | $80 \rightarrow 35$ | $20 \rightarrow 65$ | linear gradient |
| $70-80$ | 35 | 65 | isocratic |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.78 for paclitaxel related compound A and 0.86 for paclitaxel related compound B (relative to the retention time for paclitaxel obtained from the Test solution); and the resolution, $R$, between paclitaxel related compound A and paclitaxel related compound B is not less than 1.0. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than 2.0\%.

Procedure-Inject a volume (about $15 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the areas for the major peaks. Calculate the percentage of each impurity in the portion of Paclitaxel taken by the formula:

$$
100 F\left(r_{i} / r_{U}\right)
$$

in which $F$ is the relative response factor for each impurity peak (see Table 1 for values); $r_{i}$ is the peak area for each individual impurity; and $r_{U}$ is the peak area for paclitaxel. In addition to not exceeding the limits for paclitaxel related impurities in Table 1, not more than $0.1 \%$ of any other single impurity is found; and not more than $2.0 \%$ of total impurities is found.

Table 1

| Name | Relative Retention Time | Relative Response Factor (F) | Limit (\%) |
| :---: | :---: | :---: | :---: |
| Baccatin III | 0.24 | 1.29 | 0.2 |
| 10-Deacetylpaclitaxel | 0.53 | 1.00 | 0.5 |
| 7-Xylosylpaclitaxel | 0.57 | 1.00 | 0.2 |
| Cephalomannine (paclitaxel related compound A) | 0.78 | 1.26 | $\mathrm{a}_{1}{ }^{1}$ |
| $2^{\prime \prime}, 3^{\prime \prime}$-Dihydrocephalo- | 0.78 | 1.26 | $\mathrm{a}_{2}{ }^{1}$ |
| 10-Deacetyl-7-epipaclitaxel (paclitaxel related compound B) | 0.86 | 1.00 | 0.5 |
| Benzyl analog ${ }^{3}$ | 1.10 | 1.00 | $\mathrm{b}_{1}{ }^{2}$ |
| ■(paclitaxel related |  |  |  |
| compound C) $\mathbf{\| 1 S ~}^{\text {(USP28) }}$ |  |  |  |

Table 1 (Continued)

| Name | Relative Retention Time | Relative Response Factor (F) | Limit (\%) |
| :---: | :---: | :---: | :---: |
| 3",4"-Dehydropaclitaxel C | 1.10 | 1.00 | $\mathrm{b}_{2}{ }^{2}$ |
| -Paclitaxel C | 1.27 | 1.67 | 0.1 [1S (USP28) |
| 7-Epicephalomannine | 1.40 | 1.00 | 0.3 |
| 7-Epipaclitaxel | 1.85 | 1.00 | 0.5 |
| - $N$-Methylpaclitaxel C | 2.36 | 1.67 | 0.1 ■1S (USP28) |

${ }^{1}$ Resolution may be incomplete for these peaks depending upon the relative amounts present; the sum of $\mathrm{a}_{1}$ and $\mathrm{a}_{2}$ is not more than $0.5 \%$.
${ }_{2}$ Resolution may be incomplete for these peaks depending upon the relative amounts present; the sum of $b_{1}$ and $b_{2}$ is not more than $0.5 \%$.
${ }^{3}$ The following chemical name is assigned to the related compound, benzyl analog: Baccatin III 13 -ester with ( $2 R, 3 S$ )-2-hydroxy-3-phenyl-3-(2-phenylacetylamino)propanoic acid.

TEST 2 (for material labeled as produced by a semi-synthetic pro-cess)-If the material complies with this test, the labeling indicates that it meets USP Related compounds Test 2.

Diluent-Use acetonitrile.
Solution A-Use a filtered and degassed mixture of water and acetonitrile $(3: 2)$.
Solution B-Use filtered and degassed acetonitrile.
Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve accurately weighed quantities of USP Paclitaxel RS and USP Paclitaxel Related Compound B RS in Diluent, using shaking and sonication if necessary, to obtain a solution having known concentrations of about 0.96 mg and 0.008 mg per mL , respectively.

Test solution-Transfer about 10 mg of Paclitaxel, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, using shaking and sonication if necessary, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $227-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $3-\mu \mathrm{m}$ packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at $35^{\circ}$. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0-20$ | 100 | 0 | isocratic |
| $20-60$ | $100 \rightarrow 10$ | $0 \rightarrow 90$ | linear gradient |
| $60-62$ | $10 \rightarrow 100$ | $90 \rightarrow 0$ | linear gradient |
| $62-70$ | 100 | 0 | isocratic |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.94 for paclitaxel related compound B and 1.0 for paclitaxel ; the resolution, $R$, between paclitaxel related compound B and paclitaxel is not less than 1.2; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $15 \mu \mathrm{~L}$ ) of the Diluent and the Test solution into the chromatograph, record the chromatograms, and measure the areas for all of the peaks. Disregard any peaks due to the Diluent. Calculate the percentage of each impurity in the portion of Paclitaxel taken by the formula:

$$
100 F\left(r_{i} / r_{s}\right)
$$

in which $F$ is the relative response factor for each impurity (see Table 2 for values); $r_{i}$ is the peak area for each impurity obtained from the Test solution; and $r_{s}$ is the sum of the areas of all the peaks obtained from the Test solution. In addition to not exceeding the limits for paclitaxel related impurities in Table 2, not more than $0.1 \%$ of any other single impurity is found; and not more than $2.0 \%$ of total impurities is found.

Table 2

| Name | Relative Retention Time | Relative <br> Response <br> factor (F) | $\begin{gathered} \text { Limit } \\ (\%) \\ \hline \end{gathered}$ |
| :---: | :---: | :---: | :---: |
| 10-Deacetylbaccatin III | 0.11 | 1.24 | 0.1 |
| Baccatin III | 0.20 | 1.29 | 0.2 |
| Photodegradant ${ }^{2}$ | 0.42 | 1.39 | 0.1 |
| 10-Deacetylpaclitaxel | 0.47 | 1.00 | 0.5 |
| 2-Debenzoylpaclitaxel 2-pentenoate | 0.80 | 1.00 | 0.7 |
| Oxetane ring opened, acetyl and benzoyl ${ }^{2}$ | $0.92{ }^{1}$ | 1.00 | $x_{1}$ |
| 10-Acetoacetylpaclitaxel | $0.92{ }^{1}$ | 1.00 | $x_{2}$ |
| 10-Deacetyl-7-epipaclitaxel (paclitaxel related compound B) | $0.94{ }^{1}$ | 1.00 | $x_{3}$ |
| 7-Epipaclitaxel | 1.37 | 1.00 | 0.4 |
| 10,13-Bissidechainpaclitaxel ${ }^{2}$ | 1.45 | 1.00 | 0.5 |
| 7-Acetylpaclitaxel | 1.54 | 1.00 | 0.6 |
| 13-Tes-baccatin III | 1.80 | 1.75 | 0.1 |
| 7-Tes-paclitaxel | 2.14 | 1.00 | 0.3 |

${ }^{1}$ Resolution may be incomplete for these peaks depending upon the relative amounts present; the sum of $x_{1}, x_{2}$, and $x_{3}$ is not more than $0.4 \%$.
${ }^{2}$ The following chemical names are assigned to the related compounds Photodegradant, Oxetane ring opened, acetyl and benzoyl, and 10,13-Bissidechainpaclitaxel:

Photodegradant
$\frac{(1 R, 2 R, 4 S, 5 S, 7 R, 10 S, 11 R, 12 S, 13 S, 15 S, 16 S)-2,10-d i a c e t y l o x y-5,13-d i-~}{\text { P }}$ hydroxy-4,16,17,17-tetramethyl-8-oxa-3-oxo-12-phenylcarbonyloxypentacyclo[11.3.1.0 $\left.0^{1,11} \cdot 0^{4,11} \cdot 0^{7,10}\right]$ heptadec-15-yl
( $2 R, 3 S$ )-2-hydroxy-3-phenyl-3-(phenylcarbonylamino)propanoate
Oxetane ring opened, acetyl and benzoyl migrated
$(1 S, 2 S, 3 R, 4 S, 5 S, 7 S, 8 S, 10 R, 13 S)$-5,10-diacetyloxy-1,2,4,7-tetrahydroxy-
8,12,15,15-tetramethyl-9-oxo-4-(phenylcarbonyloxymethyl)tricyclo[9.3.1.0 ${ }^{3,8}$ ]pentadec-11-en-13-yl
( $2 R, 3 S$ )-2-hydroxy-3-phenyl-3-(phenylcarbonylamino)propanoate
10,13-bissidechainpaclitaxel
Baccatin III 13-ester with ( $2 R, 3 S$ )-2-hydroxy-3-phenyl-3-(phenylcarbonylamino)propanoic acid, 10 -ester with ( $2 S, 3 S$ )-2-hydroxy-3-phenyl-3(phenylcarbonylamino)propanoic acid

- TEST 3 (for material labeled as produced by a plant fermentation process)-If the material complies with this test, the labeling indicates that it meets USP Related compounds
Test 3.

Solution A-Prepare a filtered and degassed mixture of water and acetonitrile ( $3: 2$ ).

Solution B-Prepare filtered and degassed acetonitrile.
Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve an accurately weighed quantity of USP Paclitaxel RS and USP Paclitaxel Related Compound C RS in acetonitrile to obtain a solution having known concentrations for each Reference Standard of about 1 mg per mL . Sonicate if necessary.
Standard solution-Dissolve an accurately weighed quantity of USP Paclitaxel RS in acetonitrile to obtain a solution having a known concentration of about 1 mg per mL .

Test solution-Transfer about 10 mg of Paclitaxel, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask. Dissolve in acetonitrile, using sonication if necessary, dilute with acetonitrile to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $227-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L 1 . The flow rate is about 1.2 mL per minute. The column temperature is maintained at $35^{\circ}$. The chromatograph is programmed as follows.

| Time | Solution A |  |  |
| :---: | :---: | :---: | :--- |
| (minutes) | $(\%)$ | Solution B <br> $(\%)$ | Elution |
| $0-28$ | 100 | 0 | isocratic |
| $28-33$ | $100 \rightarrow 98$ | $0 \rightarrow 2$ | linear |
| $33-58$ | $98 \rightarrow 10$ | $2 \rightarrow 90$ | linear |
| $58-60$ | 10 | 90 | isocratic |
| $60-63$ | $10 \rightarrow 100$ | $90 \rightarrow 0$ | linear |
| $63-70$ | 100 | 0 | isocratic |

Chromatograph the System suitability solution, and record the peak responses as directed for the Procedure: the resolution, $R$, between paclitaxel and paclitaxel related compound C is not less than 1.8. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Inject a volume (about $12 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, and measure the areas for the major peaks. Calculate the percentage of each impurity in the portion of Paclitaxel taken by the formula:

$$
100 F\left(r_{i} / r_{s}\right),
$$

in which $F$ is the relative response factor for each impurity; $r_{\mathrm{i}}$ is the peak area for each impurity; and $r_{\mathrm{s}}$ is the sum of the areas of all the peaks obtained from the Test solution. In addition to not exceeding the limits for paclitaxel related impurities in Table 3, not more than $0.1 \%$ of any other single impurity is found, and not more than $2.0 \%$ of total impurities is found.

Table 3

|  |  | Relative |  |
| :--- | :---: | :---: | :---: |
|  | Relative | Response |  |
|  | Retention | Factor | Limit |
| Name | Time | $(F)$ | $(\%)$ |
| Propyl analog ${ }^{1}$ | 0.54 | 1.00 | 0.2 |
| Cephalomannine $^{\text {sec-Butyl analog }}{ }^{1}$ | 0.76 | 1.00 | 0.5 |
| $n$-Butyl analog ${ }^{1}$ | 0.81 | 1.00 | 0.2 |
| Benzyl analog (pacli- | 0.89 | 1.00 | 0.1 |
| taxel related <br> compound C) |  | 1.00 | 0.4 |

Table 3 (Continued)

|  | Relative |  |  |
| :--- | :---: | :---: | :---: |
|  | Relative | Response |  |
|  | Retention | Factor | Limit |
| Name | Time | $(F)$ | $(\%)$ |
| Baccatin VI | 1.23 | 1.00 | 0.2 |
| Pentyl analog1 | 1.31 | 1.00 | 0.2 |
| 7-Epipaclitaxel | 1.41 | 1.00 | 0.4 |

${ }^{1}$ The following chemical names are assigned to the related compounds Propyl analog, sec-Butyl analog, $n$-Butyl analog, and Pentyl analog:

## Propyl analog

Baccatin III 13-ester with ( $2 R, 3 S$ )-2-hydroxy-3-phenyl-3(propanoylamino)propanoic acid.

## sec-Butyl analog

Baccatin III 13-ester with ( $2 S, 3 S$ )-2-hydroxy-3-(2-methylbutanoylamino)-3-phenylpropanoic acid.
$n$-Butyl analog
Baccatin III 13-ester with ( $2 S, 3 S$ )-3-(butanoylamino)-2-hydroxy-3-phenylpropanoic acid.

## Pentyl analog

Baccatin III 13-ester with ( $2 R, 3 S$ )-2-hydroxy-3-(penta-noylamino)-3-phenylpropanoic acid. 1 IS (USP28)

Paroxetine Hydrochloride, page 911 of $P F$ 30(3) [May-June 2004]. On the basis of experimental data received, it is proposed to change the tailing factor for paroxetine related compound C in the test for Limit of related compound C. Because absolute alcohol is the grade of reagent used, it is also proposed to specify its use in the preparation of Mobile phase and Diluent.
(PA3: S. Salado) RTS-41164-1

## Add the following:

■ Paroxetine Hydrochloride

$\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3} \cdot \mathrm{HCl} \quad 365.83$
Piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-
fluorophenyl)-, hydrochloride, (3S-trans)-.
(-)-(3S,4R)-4-(p-Fluorophenyl)-3-[(3,4-methylenedioxy)phenoxy]methyl]piperidine hydrochloride
[78246-49-8].
Hemihydrate 374.83 [GAS
" Paroxetine Hydrochloride is anhydrous or contains one-half molecule of water of hydration. It contains not less than 98.5 percent and not more than 102.0 percent of $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3} \cdot \mathrm{HCl}$, calculated on the anhydrous and solvent-free basis.

## Change to read:

Packaging and storage-Preserve the anhydrous form in tight containers. Preserve the hemihydrate form in wellclosed containers. Store ben $15^{\circ}$ and $30^{\circ}-$ Store at controlled room temperature. 1 IS (USP28)

Labeling-Label it to indicate whether it is the anhydrous or the hemihydrate form. Label it to indicate with which impurity tests the article complies.

USP Reference standards $\langle 11\rangle$ —USP Paroxetine Hydrochloride RS. USP Paroxetine Related Compound A RS. USP Paroxetine Related Compound B RS. USP Paroxetine Related Compound C RS. USP Parane Related Com D RS. USP Paroxetine Related Compound E RS. USP Paroxetine Related Compound F RS. USP Paroxetine Related Compound G RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$ -
Test specimen-Dissolve a suitable portion of Paroxetine Hydrochloride in a solution of water in isopropyl alcohol (1 in 10), heat to $70^{\circ}$ to dissolve, recrystallize, enduse the residee. and dry the residue under vacuum at $50^{\circ}$ for 3 hours.

Standard specimen: a similar preparation of USP Paroxetine Hydrochloride RS.

B: A solution (1 in 100) in a mixture of methanol and water ( $1: 1$ ) meets the requirements of the test for Chloride $\langle 191\rangle$.

Melting range, Class $I\langle 741\rangle \div$ between $115^{\circ}$ and $126^{\circ}$ for the anhydrous form; [T0 come for the anhydrous form] be tween $141^{\circ}$ and $145^{\circ}$ for the hemihydrate form.

## Change to read:

Water, Method I $\langle 921\rangle$ : not more than $1.5 \%$ $1.0 \%{ }^{-1.5 \%}{ }_{\text {IS }}$ (USP28) for the anhydrous form and between z.0\% $2.2 \%$ and $3.0 \% 2.8 \%$ for the hemihydrate form.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.002 \%$.

## Change to read:

Limil of stereoisomers Limit of related compound C-
Mobile phase Prepare a flltered and degassed mixture of 0.5 M sodium chloride and methanol ( $4: 1$ ). Make adjust ments if neeessayy (see System Suitability under Chwoma -graphy (621) ).
0.05M Phesplate buffer solution Dissolve 8.7 g of dibasic petassium phosphate in 1000 mL of water, and adjust with phosphorie acid to a pH of 6.5 .

Mebile phate Prepare a filtered and degassed mixtare of 6.05 M Phesphate buffer solution and acetonitrile (92:8). Make adjustments if neeessary (see-System-Suitability under Chremategraphy (624)-.

Systen suitability solution Transfer about 5-mg of USP
Paroxetine Hydrochloride Related Compound C RS and about 5 mg of USP Paroxetine-Hydrochloride-RS, ac etrately weighed, to a $10-\mathrm{mL}$ volumetric flack. Dissolve in 1 mL of methand, dilate with Mobile phase to volume, and mix.

Standardsolution- Dissolve an aceurately weighed quantity of USP Paroxetine-Related Compound C RS and USP Paroxetine Hydrechloride RS in methanol, the voltume of the solvent not exceeding $20 \%$ of the final solution vol tume, and dilute quantitatively with 0.5 M - sodium chloride to obtain a solution having a known concentration of about Q.01 mg of each USP Reference Standard per mL. If stepwise dilution is necessary, diltte with Mobile phase instead.

Fest solution Transfer about 100 mg of Parozetine Hydrochloride, aceurately weighed, to a $100-\mathrm{mL}$ volumetrie flask, dissolve in $20-\mathrm{mL}$ of methanol, dilute with $0.5 \mathrm{M}-\mathrm{se}-$ ditum chleride to velume, and mix.

Chromatographie system (see-Chromatography $\langle 624\rangle$ )
The liquid chromatograph is equipped with a 295 -nm detecfor and a 4 mm $\times 10$ em column that contains packing L41. The flow rate is about 0.5 mL per minute. Chrematograph the-Standtad Systen suitability solution, and record the peak respenses as directed for Procedure: the relative retention times are about 0.56 for paroxetine related compound $G$ and 1.0 for parexetine; the reselution, $R$, between parexetine related compennd $C$ and paroxetine is not less than 1.8; the column efficiency determined from the related compound $G$
peak is not less than 230 theoretical plates; the tailing factor for the paroxetine related compeund $C$ peak is not more than 1.6; and the relative standard deviation for replieate injec tions is net more than $2.0 \%$.

Procedtre Separately inject equal volumes Inject a vol ume (about $10 \mu \mathrm{~L})$ of the Standard solution and the Test solution into the chromatograph, record the chromatogram, and measure all of the peak responses. Caleulate the per eentage of paroxetine related compound $C$ in the pertion ef Paroxetine Hydrochloride taken by the formula:

$$
10(C / H)\left(r_{4}+r_{s}\right),
$$

$$
100(+\neq+
$$

in which $C$ is the concentration, in $\mu$ g per mL , of USP Par exetine-Related Compound C RS in the Standard solution; Wis the quantity, in mg, of Parexetine Hydrochloride in the Fest solution; and $r_{\text {}}$-and $r_{\text {s }}$ are the peak respenses for par oxetine related compound Cobtained from the Test solution and the Standard solution, respectively. in which-i; is the peak response for paroxetine related compound $C$, and $r$, is the sum of the respenses of all of the peaks: not more that $0.1 \%$ is found.

LMMIT OF RELATED-COMPOUND-D-
Phesphate buffer Prepare a 0.05 M menobasic sodium phesphate solution in water, adjust with phespheric acid to a pH Of 3.0 , and mix.

Mebile phase Prepare a filtered and degassed mixtare of Phesphate buffer and acetonitrile (3:2). Make adjustments if neeessary (see System Stuitability under Chrematography $\langle 624\rangle$.
Standard solution- Dissolve aceurately weighed quantities of USP Paroxetine Related Compound D-RS and USP

Paroxetine Hydrochloride-RS in water, and dilute quantita-
tively, and stepwise if necessary, with water to obtain a solut tion having known concentrations of about 0.1 and 1.0 mg per mL , respectively.

Fest solution Transfer about 100 mg of Parozetine Hydrechleride, aceurately weighed, to a $50-\mathrm{mL}$ voltmetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )_ The liquid chromatograph is equipped with a 295 nm- detec for and a $4.6-\mathrm{mm} \times 25-\mathrm{em}$ coltumn that contains packing Ł13. The flow rate is about 1 mL per minute. Chremategraph the Standerd solution, and record the peak respenses as directed for Procedtre: the relative retention times are about 1.2 for paroxetine related compound $D$ and 1.0 for paroxetine; the resolution, $R$, between paroxetine related eompound $D$-and paroxetine is not less than 2.2; the columm efficieney determined frem the parexetine related compeund D peak is not less than- 4000 theoretical plates; the tailing factor for the related compound $D$ peak is not more than 1.8 ; and the relative standard deviation for replicate in jections is net more than $2.5 \%$.

Proecdure Separately inject equal volumes (about 10 HL) of the Standard solution and the Test solution into the ehromatograph, record the chromatograms, and measure the respenses for the major peaks. Caleulate the pereentage of paroxetine related compound $D$ in the portion of Paroxetine Hydrechloride taken by the formula:-

$$
5(C / H)\left(r_{t}+F_{s}\right)
$$

in which $C$ is the concentration, in $\mu$ g per mL, of USP Paroxetine Related Compound D-RS in the Standard solution; $W$ is the quantity, in mg, of Paroxetine Hydrochloride in the Test solution; and $r_{\text {}}$-and $r_{s}$ are the peak respenses for par exetine related compeund D-obtained from the Test solution
and the Standard solttion, respectively: the sum of the per
eentages found in the Limit of related eompound $C$ and the Limit of related eomapent $D$ tests is not more than $0.1 \%$.

Mobile phase-Prepare a mixture of $n$-hexane, $\square_{\text {abso- }}$ lute $_{1 S}$ (USP28) alcohol, water, and trifluoroacetic acid ( $900: 100: 2: 2$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent: $\quad$ a mixture of $\mathbf{m a b s o l u t e}^{\mathbf{1 S ~}_{\text {(USP28) }}}$ alcohol and $n$ hexane ( $1: 1$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Paroxetine Related Compound C RS, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 1 mg per mL.

Test solution-Transfer about 125 mg of Paroxetine Hydrochloride, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.

System suitability solution-Dilute known volumes of the Test solution and the Standard solution with Diluent to obtain a solution having known concentrations of about 0.1 mg per mL of each of USP Paroxetine Hydrechloride RS Paroxetine Hydrochloride and of USP Paroxetine Related Compound C RS.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $295-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing E49. L51. The flow rate is about 1.0 mL per minute, and the column temperature is maintained at $30^{\circ}$. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times for paroxetine and paroxetine related compound C are 1.0 and about 0.6 , respectively; the resolution, $R$, between paroxetine and paroxetine related compound C is not less than 2.0; and the tailing factor for paroxetine related
compound C is not greater than $2.0 \cdot \mathbf{m}^{2.5}$. 1 IS (USP28) Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$ for the paroxetine related compound C .

Procedure-Separately inject equal volumes (about $5 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of paroxetine related compound C in the portion of Paroxetine Hydrochloride taken by the formula:

$$
10,000(C / H)\left(+,+f_{s}\right)
$$

$$
2500(C / W)\left(r_{i} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Paroxetine Related Compound C RS in the Standard solution, $W$ is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the Test solution; and $r_{i}$ and $r_{s}$ are the peak areas for paroxetine related compound C in the Test solution and the Standard solution, respectively: not more than of $0.1 \%$ of paroxetine related compound C is found.

## Change to read:

Limit of 1-methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydro-pyridine-

Solution A-Prepare a filtered and degassed mixture of acetonitrile and trifluoroacetic acid (1000:1).

Solution B-Prepare a filtered and degassed mixture of water and trifluoroacetic acid (1000:1).

Mobile phase-Use variable mixtures of Solution A and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Paroxetine Related Compound E RS in a mixture of Solution $B$ and Solution $A(7: 3)$, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of 1-methyl-4-( $p$-fluorophenyl)-1,2,3,6-tetrahydropyridine of about 0.2100 ng per mL. $\mathbf{D O}_{2} 20$ ng per mL. 1 (USP28)

Test solution-Transfer about 20 mg of Paroxetine Hydrochloride, accurately weighed, to a suitable flask, add 1.0 mL of a mixture of Solution $B$ and Solution $A(7: 3)$, and shake to dissolve.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a tandem mass spectrophotometric detector, monitoring the mass-to-charge ratio of 44 arising from the fragmentation of mass-to-charge ratio of 192 , and a $2.0-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains base-deactivated packing L1. The flow rate is about 0.15 mL per minute. The collision-induced disassociation sector is filled with sufficient argon gas to produce -20 eV collisions. Adjust the argon gas pressure as necessary. The chromatograph is programmed as follows.

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the signal-to-noise ratio for the analyte response at a mass-to-charge ratio of 44 is not less than 5 ; and the relative standard deviation for replicate injections is not more than $5.0 \%$. [NOTE-A large peak due to paroxetine is observed at about 10 minutes in this system. Divert the flow of eluate from the mass spectrometer at about 10 minutes after injection.]
Procedure-Separately inject equal volumes (about 100 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in pg ng, of 1-methyl-4-( $p$-fluorophenyl)-1,2,3,6-tetrahydropyridine in the portion of Paroxetine Hydrochloride taken by the formula:

$$
C I\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Paroxetine Related Compound E RS in the Standard solution; I is the amount, in ng, of 1-methyl-4-( $p$-fluorophenyl)-1,2,3,6-tetrahydropyridine in each mg of USP Paroxetine Related Compound E RS in the Standard solution; and $r_{U}$ and $r_{s}$ are the peak responses for 1-methyl-4-( $p$-fluorophe-nyl)-1,2,3,6-tetrahydropyridine obtained from the Test solution and the Standard solution, respectively: not more than 200 pg 100 ng 20 ng is found ( $0.0001 \%$ ).

Chromatographic purity-[NOTE-Perform all related impurities methods unless the manufacturer has assurance, based on knowledge of the manufacturing process, that one of the tests is not relevant to their material.]

TEST 1-
Solution A—Prepare a filtered and degassed mixture of water, tetrahydrofuran, and trifluoroacetic acid (180:20:1).

Solution B-Prepare a filtered and degassed mixture of acetonitrile, tetrahydrofuran, and trifluoroacetic acid (180:20:1).
Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent: a mixture of water and tetrahydrofuran ( $9: 1$ ). Standard solution-Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about $1 \mu \mathrm{~g}$ per mL.

System suitability solution-Dissolve, by sonication if necessary, suitable quantities of USP Paroxetine Related Compound A RS and USP Paroxetine Related Compound B RS in a mixture of water and tetrahydroftran ( $9: 1$ ) Diluent to obtain a solution having known concentrations of about 0.01 mg of each USP Reference Standard per mL.

Test solution-Transfer about 25 mg of Paroxetine Hydrochloride, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in 20 mL of mixttre of water and tetrahydroftran $(9: 1)$, Diluent, sonicate, dilute with a mixture of and etrahydrefan (9:1) Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $285-\mathrm{nm}$ detector eapable of menitering at 263 and 295 mm and a $4.6-\mathrm{mm}$ $\times 25-\mathrm{cm}$ column that contains packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at $40^{\circ}$. The chromatograph is programmed as follows.

| Time (minutes) | Solution 4 <br> (\%) | Solution $B$ <br> (\%) | Elution |
| :---: | :---: | :---: | :---: |
| $\theta$ | 80 | 20 | equilibration (for |
|  |  |  | 10 minutes) |
| -0-30 | 80 | 20 | iseratie |
| 30-50 | $80 \rightarrow 20$ | $20 \rightarrow 80$ | linear gradient |
| -50-nd | 20 | 80 | isocratic |

Chromatograph the System sulitability solution, and reeord the peak responses as directed for Procedtre: the resolution, $R$, between paroxetine related eompound $\Lambda$ and paroxetine related compound $B$ is not less than 1.5 ; the column effir eieney determined from the parovetine related compound A peak is not less than 10,000 theoretient plates; the tailing factor for the paroxetine related compound $\Lambda$ peak is not more than 1.2 ; and the relative standard deviation for replieate injections is not more than $1.0 \%$.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 80 | 20 | equilibration |
| $0-30$ | 80 | 20 | isocratic |
| $30-50$ | $80 \rightarrow 20$ | $20 \rightarrow 80$ | linear gradient |
| $50-60$ | 20 | 80 | isocratic |
| $60-70$ | $20 \rightarrow 80$ | $80 \rightarrow 20$ | linear gradient |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.1 for paroxetine related compound B , and 1.0 for paroxetine related compound A ; the resolution, $R$, between paroxetine related compound A and paroxetine related compound $B$ is not less than 2.0 ; the tailing factor of the paroxetine related compound A peak is between 0.8 and 2.0; Ghromatograph the Stated solt tion, and record the peak respenses as directed for Proce-
dute: and the relative standard deviation for replicate injections is not more than $2.0 \%$ for paroxetine related compound A.

Procedure Inject a volume (about 20- 2 L ) of the Test seltion inte the chromatograph, recerd the chromategram, and meastre all of the peak respenses at beth 263 and 295 nm. Caleulate the percentage of each impurity in the pertion of Paroxetine Hydrochloride taken by the formula:

$$
100\left(r_{i}+r_{4}\right)
$$

in whieh $r$ is the peak respense for each impurity; andris the-stm of the respenses of all of the peaks: net mere-that $0.1 \% 0$ of any individualimpurity is found, and not more than

## $0.5 \%$ of totalimpurities is fount.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution, Test solution, and Diluent into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Paroxetine Hydrochloride taken by the formula:

$$
2500(C / W)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Paroxetine Hydrochloride RS in the Standard solution; $W$ is the weight, in mg , of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the Test solution; $r_{U}$ is the peak area of each impurity in the Test solution, excluding the peaks obtained in the chromatogram of the Diluent; and $r_{s}$ is the peak area of paroxetine obtained in the Standard solution: not more than of $0.5 \% 0.3 \%$ of any peak at a retention time of paroxetine related compound $B$ is found; not more that $0.1 \%$ of any other individual impurity is found; and not more than $1.0 \%$ of total impurities is found.

TEST 2-
Phosphate buffer-Dissolve 3.4 g of monobasic potassium phosphate and 3.4 g of tetrabutylammonium hydrogen sulfate in 1.0 L of water.

Solution A—Prepare a filtered and degassed mixture of Phosphate buffer and acetonitrile (98:2).
Solution B—Prepare a filtered and degassed mixture of Phosphate buffer and acetonitrile (6:4).

Mobile phase-Use variable mixtures of Solution A and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent: a mixture of Phosphate buffer and acetonitrile (9:1).
Standard solution-Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS, USP Paroxetine Related Compound B RS, USP Paroxetine Related Compound F RS, and USP Paroxetine Related Compound G RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having known concentrations of about $4 \mu \mathrm{~g}$ per $\mathrm{mL}, 10 \mu \mathrm{~g}$ per $\mathrm{mL}, 10 \mu \mathrm{~g}$ per mL , and $4 \mu \mathrm{~g}$ per mL , respectively.

Identification solution-Dissolve an accurately weighed quantity of Paroxetine Hydrochloride, USP Paroxetine Related Compound B RS, USP Paroxetine Related Compound F RS, and USP Paroxetine Related Compound G RS in Diluent to obtain a solution having known concentrations of about 2 mg per $\mathrm{mL}, 10 \mu \mathrm{~g}$ per $\mathrm{mL}, 10 \mu \mathrm{~g}$ per mL , and 4 $\mu \mathrm{g}$ per mL , respectively.

Test solution-Transfer about 25 mg of Paroxetine Hydrochloride, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-5$ | 100 | 0 | isocratic |
| $5-70$ | $100 \rightarrow 40$ | $0 \rightarrow 60$ | linear gradient |
| $70-90$ | $40 \rightarrow 0$ | $60 \rightarrow 100$ | linear gradient |
| $90-95$ | 0 | 100 | isocratic |
| $95-95.1$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $95.1-110$ | 100 | 0 | re-equilibration |

Chromatograph the Identification solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.91 for paroxetine related compound $B$, about 0.96 for paroxetine related compound $\mathrm{F}, 1.0$ for paroxetine, and about 1.34 for paroxetine related compound G. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $10.0 \%$ for the paroxetine related compound B , paroxetine related compound F , paroxetine hydrochloride, and paroxetine related compound G peaks.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of paroxetine related compound B, paroxetine related compound F , and paroxetine related compound G in the portion of Paroxetine Hydrochloride taken by the formula:

$$
5000(C / W)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of the appropriate USP Reference Standard in the Standard solution; $W$ is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the Test solution; and $r_{i}$ and $r_{s}$ are the peak areas for the corresponding impurity in the Test solution and the Standard solution, respectively: not more than of $0.5 \%$ of paroxetine related compound B is found; not more than $0.2 \%$ of paroxetine related compound F is found; and not more than $0.2 \%$ of paroxetine related compound G is found. Calculate the percentage of any unknown impurity in the portion of Paroxetine Hydrochloride taken by the formula:

$$
5000(C / W)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of the USP Paroxetine Hydrochloride RS in the Standard solution; $W$ is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the Test solution; $r_{i}$ is the peak area for any unknown impurity in the Test solution; and $r_{S}$ is the peak area of paroxetine in the Standard solution: not more than of $0.1 \%$ of any single unknown impurity is found, and not more than $1.0 \%$ of total impurities is found.

Organic volatile impurities, Method $V\langle 467\rangle$ : meets the requirements.

## Assay-

Acetate buffer-Prepare a 0.05 M solution of ammonium acetate in water, adjust with glacial acetic acid to a pH of 4.5, mix, and filter.

Mobile phase—Prepare a filtered and degassed mixture of Acetate buffer, acetonitrile, and triethylamine ( $60: 40: 1$ ). Adjust with glacial acetic acid to a pH of 5.5. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve suitable quantities of USP Paroxetine Related Compound B RS and USP Paroxetine Hydrochloride RS in water to obtain a solution having known concentrations of about 0.5 mg of each USP Reference Standard per mL.
Standard preparation-Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.5 mg per mL .

Assay preparation-Transfer about 50 mg of Paroxetine Hydrochloride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $295-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L13. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for paroxetine related compound B and 1.0 for paroxetine; the resolution, $R$, between paroxetine related compound $B$ and paroxetine is not less than 2.0 ; the column efficiency determined from the paroxetine peak is not less than 3000 theoretical plates; the tailing factor for the paroxetine peak is not more than 1.6; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the
quantity, in mg, of $\mathrm{C}_{19} \mathrm{H}_{20} \mathrm{FNO}_{3} \cdot \mathrm{HCl}$ in the portion of Paroxetine Hydrochloride taken by the formula:

$$
100 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Paroxetine Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP27)

## Briefing

Phenylethyl Alcohol, USP 27 page 1474. On the basis of comments received regarding the performance of the current Identification test, specifically that it is tedious, nonspecific, and outdated, it is proposed to delete the current test and replace it with a spectrophotometric identification test employing Infrared Absorption〈197F〉. It is also proposed to add a new Reference Standard, USP Phenylethyl Alcohol RS, to be used in the Identification test.
(EMC: C. Sheehan) RTS-40996-1

## Add the following:

-USP Reference standards $\langle 11\rangle$ —USP Phenylethyl Alcohol RS.■1S (USP28)

## Change to read:

Identification-[Caution Phenyl isocyanate is a strong lacrimam:] Transfer $1-\mathrm{mL}$ to a dry test tube, add $500-\mu \mathrm{L}$ of phenyl isoeyanate, and heat on a stem bath for 5 minntes. Cool, using iee if neessary, and indure crystallization by seratehing the walls of the tube with a glass rod. After erystals have formed, add about 10 mL ef solvent hewane, heat to beiling for a few mintutes, and filter the solution into a warm, dry test tube. Colleet the erystals that formon a filter, and wash them with cool solvent hexane: the crystals of phenethyl carbanilate so obtained melt between $78^{\circ}$ and $80^{\circ}$ (see Melting Range or Temperature $\langle 744$ ) .

- Infrared Absorption $\langle 197 \mathrm{~F}\rangle$.■ ${ }^{1 S}$ (USP28)

Briefing

Phenyltoloxamine Citrate, page 162 of $P F$ 30(1) [Jan.-Feb. 2004]. It is proposed to revise the Packaging and storage statement to indicate storage at room temperature.
(PA1: K. Russo; PSD: C. Okeke) RTS-40503-2

## Add the following:

## ©Phenyltoloxamine Dihydrogen Citrate


$\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7} \quad 447.47$
$N, N$-Dimethyl-2-( $\alpha$-phenyl-o-tolyloxy)ethylamine, citrate ( $1: 1$ ) salt.

2-(2-Dimethylaminoethoxy)diphenylmethane, citrate (1:1) salt Phenyltoloxamine dihydrogen citrate [1176-08-5].
» Phenyltoloxamine Bihydrogen Citrate contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7}$, calculated on the dried basis.

## Change to read:

Packaging and storage-Preserve in well-closed coniners store closed containers. ■Store at room temperature.■1S (USP28)

USP Reference standards $\langle 11\rangle$ —USP Phenyltoloxamine Pilhydren Citrate RS. USP Phenyltoloxamine Bilyy Eitrate Related Compound A RS.

## Identification,

A: Infrafed Absorption- $\langle 197 \mathrm{~K}\rangle$ :
B: Ultravidet Absorption- $\langle 197 U\rangle$ -
Solution: 100 нg per mL.
Meditm: 0.1 N hydrechleric acid.
C: Dissolve 0.5 g of Phenyltoloxamine-Dihydrogen
Gitrate in 15 mL of het water, add a slight excess of 5 M sedium hydroxide, filter, and add 2 N hydrechloric acid untill the filtrate is neutral to litmus paper: the solution meets the-requirements of the test for Citrate $\langle 194\rangle$ : Infrared $A b$ sorption $\langle 197 \mathrm{~K}\rangle$.

Melting range, Class $1 a\langle 741\rangle$ : between $137^{\circ}$ and $143^{\circ}$. $\mathbf{p H}\langle 791\rangle$ : between 3.2 and 4.2, in a solution (1 in 100).

Loss on drying $\langle 731\rangle$ ——Dry it in vacuum at $80^{\circ}$ for 3 hours: it loses not more than $0.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method $I\langle 231\rangle: \quad 20 \mu \mathrm{~g}$ per g .

## Related compounds-

Resolution solution-In a separatory funnel dissolve about 10 mg each of USP Phenyltoloxamine Pihydregen Citrate RS and USP Phenyltoloxamine Dihydrogen Citrate Related Compound A RS, accurately weighed, in 50 mL of water. Add 5 mL of ammonium hydroxide, and extract with three $10-\mathrm{mL}$ portions of ethylether methylene chloride. Combine the extracts, dry the solution over anhydrous sodium sulfate, and gently evaporate to dryness. Dissolve the residue in 20 mL of ehloreform methylene chloride.

Test solution-In a separatory funnel dissolve about 800 mg 400 mg of Phenyltoloxamine Pihydrogen Citrate, accurately weighed, in 50 mL of water. Proceed as directed for Resolution solution, beginning with "Add 5 mL of ammonium hydroxide."

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The gas chromatograph is equipped with a split injection system, a flame-ionization detector, and a $0.32-\mathrm{mm} \times 25-\mathrm{m}$
column coated with a $0.45-\mu \mathrm{m}$ film of phase G27. The carrier gas is helium, flowing at a rate of about 29 cm per second, with a split flow rate of about 25 mL per minute. The column temperature is programmed as follows. Initially the temperature of the column is equilibrated at $190^{\circ}$ for 3 minutes, then the temperature is increased at a rate of $4^{\circ}$ per minute to $240^{\circ}$ and maintained at $240^{\circ}$ for 8 minutes. The injection port and the detector temperatures are maintained at $280^{\circ}$. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution,
$R$, between phenyltoloxamine and phenyltoloxamine dihydrege related compound A is not less than 2.0 1.5.

Procedure-Inject a volume (about $1 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Phenyltoloxamine Pihydregen Citrate taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response of each impurity; and $r_{s}$ is the sum of the responses of all the peaks, excluding the solvent peaks: not more than $0.2 \%$ of phenyltoloxamine dihy droge related compound A , not more than $0.1 \%$ of any other individual impurity, is fomd; and not more than $1.0 \%$ of total impurities is found.

Organic volatile impurities, Method $1\langle 467\rangle$ : meets the requirements.

Assay-Dissolve about 0.5 g of Phenyltoloxamine Dihy droen Citrate, accurately weighed, in 80 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Each mL of 0.1 N perchloric acid is equivalent to 44.75 mg of $\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \cdot \mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7} \cdot \mathbf{\Delta U S P 2 8}$

## BRIEFING

Povidone, USP 27 page 1529, page 3078 of the First Supplement, and page 1968 of PF 29(6) [Nov.-Dec. 2003]. On the basis of comments received indicating difficulties in obtaining columns with the dimensions specified in the liquid chromatographic procedure in the test for Vinylpyrrolidinone, it is proposed to include a note suggesting several alternative columns. The analysis can also be performed with a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ Waters Symmetry Shield RP8 analytical column and with $4.0-\mathrm{mm} \times 30-\mathrm{mm}$ Nucleosil $120-5-\mathrm{C} 8$ and $4.6-\mathrm{mm} \times 30-\mathrm{mm}$ Zorbax Ace C-8 guard columns. In addition, minor editorial style changes have been made.
(EMC: C. Sheehan) RTS-41321-1

## Change to read:

Vinylpyrrolidinone- Dissolve-10.0g of Povidene-in $80-\mathrm{mL}$ of water, add 1.0 g of sodium reetate, and titrate with -0.10 N iodine until the coler of iodine no lenger fales. Add an additional 3.0 mL of 0.10 N iodine, allow to stand for 10 minntes, and titrate the exeess iodine with 0.10 N sodium thiosulfate, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination (see-Residual Titrations under Titrintry (544)), using the same total volume of 0.10 N iodine, aceurately measured, as was used for titrating the specimen: not more tham 3.6 mL of 0.10 N iodine is consumed, correspending to not more than $0.2 \%$ of vinylpyrretidinene.

- Mobile phase-Prepare a mixture of water and methanol ( $80: 20$ ).

Resolution solution-Transfer 10 mg of vinylpyrrolidinone and 500 mg of vinyl acetate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with methanol to volume. Transfer 1.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Standard solution-Transfer an accurately weighed quantity of 50 mg of vinylpyrrolidinone to a $100-\mathrm{mL}$ volumetric flask, dilute with methanol to volume, and mix. Transfer $1.0-\mathrm{mL}$ of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with methanol to volume, and mix. Transfer 5.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.
Test solution-Transfer an accurately weighed quantity of about 250 mg of Povidone to a $10-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $235-\mathrm{nm}$ detector, a $4.0-\mathrm{mm} \times 2.5-\mathrm{cm}$ guard column containing packing L7, and a $4.0-\mathrm{mm} \times 25-\mathrm{cm}$ analytical column containing 5$\mu \mathrm{m}$ packing L7. - [NOTE-The analysis can also be performed with $4.0-\mathrm{mm} \times 30-\mathrm{mm}$ and $4.6-\mathrm{mm} \times 30-\mathrm{mm}$ guard columns containing packing L7 and with a $4.6-\mathrm{mm}$ $\times 25-\mathrm{cm}$ analytical column containing $5-\mu \mathrm{m}$ packing L7.] 1S (USP28) The column temperature is maintained at about $40^{\circ}$. Adjust the flow rate so that the retention time of vinylpyrrolidinone is about 10 minutes. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between vinylpyrrolidinone and vinyl acetate is not less than 2.0. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separetely inject equal volumes (about 50 $\mu \mathrm{L}$ ) each of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the vinylpyrrolidinone peak. [NOTE-If necessary, after each injection of the Test solution, wash the polymeric material of Povidone from the guard column by passing the Mobile phase through the column backwards for about 30 minutes at the same flow rate.] Calculate the percentage of vinylpyrrolidinone in the sample taken by the formula:

$$
1000(C / W)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of vinylpyrrolidinone in the Standard solution; $W$ is the weight, in mg, of Povidone taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses for vinylpyrrolidinone obtained from the Test solution and Standard solution, respectively: not more than $0.001 \%$ is found. ${ }^{2 S}$ (USP27)

BRIEFING

Ringer's and Dextrose Injection, USP 27 page 1657. It is proposed to revise the Labeling statement by removing the warning regarding lactic acidosis because this product does not contain a source of lactate.
(PA1: K. Russo; NL: C. Barnstein) RTS-41099-1

## Change to read:

Labeling-The label states the total osmolar concentration in mOsmol per L. Where the contents are less than 100 mL , the label alternatively may state the total osmolar concentration in mOsmol per mL . The label includes alse the warning "Not for use in the treatment of lactic acidosis.".

■1S (USP28)

Briefing

Simethicone, USP 27 page 1689 and page 184 of PF 30(1) [Jan.-Feb. 2004]. It is proposed to replace the Infrared Absorption $\langle 197 \mathrm{~S}\rangle$ test under Identification with the Infrared Absorption $\langle 197 \mathrm{~F}\rangle$ test, which is based on a comparison of the IR spectra of Simethicone and USP Simethicone $R S$ as neat films between salt plates. The addition of the Note proposed in a previous $P F$ is now being canceled.
(PA4: E. Gonikberg) RTS-41124-1

## Change to read:

Identification, Infrared Absorption $\langle 1978\rangle$
${ }^{-}\langle 197 \mathrm{~F}\rangle \cdot \square 1 \mathrm{~S}$ (USP28) Fest sotation Prepare as directed for Assay prepatation in the Assely.

Standard solttion Prepare as directed for Standard preparit tion in the Asinty:


■1S (USP28)

## Briefing

Simethicone Capsules, USP 27 page 1690; Simethicone Oral Suspension, USP 27 page 1691; Simethicone Tablets, USP 27 page 1691. The proposed revision in the Identification test is necessary to eliminate the invalid cross-reference caused by a change in the monograph for Simethicone.
(PA4: E. Gonikberg) RTS-41124-2

## Change to read:

Identification, -Capsules respond to the Identification test under Simethicone.
-Infrared Absorption $\langle 197 \mathrm{~S}\rangle$ - [NOTE-Use the procedural blank, prepared as directed in the Assay, to set the instrument.]

Test solution-Prepare as directed for the Assay preparation in the Assay.

Standard solution-Prepare as directed for the Standard preparation in the Assay.

Cell size: $\quad 0.5 \mathrm{~mm} .{ }^{\text {1s }}$ (USP28)

## BRIEFING

Simethicone Emulsion, USP 27 page 1690 and page 184 of $P F$ 30(1) [Jan.-Feb. 2004]. Comments were received that for the Identification test, the addition of the dilute hydrochloric acid may, in some cases, help in breaking the emulsion and obtaining good separation of the toluene. On the basis of these comments, it is proposed to revise the statement regarding the omission of the dilute hydrochloric acid in the Identification test.
(PA4: E. Gonikberg) RTS-41124-5

## Change to read:

Identification-The IR absorption spectrum, determined in a 0.5 mm cell, of the solution of Emulsion prepared as directed in the Assay, the dilute hydrechloric acid being omitted,
-1S (USP28)
exhibits maxima only at the same wavelengths as that of a similar preparation of USP Polydimethylsiloxane RS.
-If necessary, the dilute hydrochloric acid may be omitted to improve separation.■1S (USP28)
${ }^{\boldsymbol{4}}$ [nOTE-Prepare a procedural blank by similarly treating 25.0 mL of toluene, and use this blank to set the instrument.] $\mathbf{\Lambda U S P 2 8}$

## BRIEFING

Simethicone Oral Suspension, USP 27 page 1691—See briefing under Simethicone Capsules.
(PA4: E. Gonikberg) RTS-41124-3

## Change to read:

Identification, It respends to the Identifeation test under Simethicone.

- Infrared Absorption $\langle 197 \mathrm{~S}\rangle$ - [NOTE-Use the procedural blank, prepared as directed in the Assay, to set the instrument.]

Test solution-Prepare as directed for the Assay preparation in the Assay.

Standard solution-Prepare as directed for the Standard preparation in the Assay.

Cell size: $\quad 0.5 \mathrm{~mm}$.■1s (USP28)

Briefing

Simethicone Tablets, USP 27 page 1691—See briefing under Simethicone Capsules.
(PA4: E. Gonikberg) RTS-41124-4

## Change to read:

Identification, - Tablets respend to the Ithentifien test under Simethicue
-Infrared absorption $\langle 197 \mathrm{~S}\rangle$ - [NOTE-Use the procedural blank, prepared as directed in the Assay, to set the instrument.]

Test solution-Prepare as directed for the Assay preparation in the Assay.

Standard solution-Prepare as directed for the Standard preparation in the Assay.

Cell size: $\quad 0.5 \mathrm{~mm} . \mathbf{1 S}^{1 \mathrm{~S}}$ (USP28)

## BRIEFING

Somatropin, page 1978 of $P F$ 29(6) [Nov.-Dec. 2003]. On the basis of comments received, it is proposed to perform the Bioidentity test on either the bulk lot or the finished product lots. In the Assay, it is also proposed to modify slightly the preparation of the Phosphate buffer used to prepare the Mobile phase to correspond to the Mobile phase used in the European Pharmacopoeia. The equation in the Assay used to calculate potency is revised to be more flexible and consistent with the labeling of the reference standard. Several editorial changes have also been made.
(BNT: L. Callahan) RTS-41180-1

## Add the following:

## ■Somatropin

| FPTIPLSRLF | DNAMLRAHRL | HQLAFDTYQE | FEEAYIPKEQ | KYSFLQNPQT |
| ---: | :--- | :--- | :--- | :--- |
| SLCFSESIPT | PSNREETQQK | SNLELLRISL | LLIQSWLEPV | QFLRSVFANS |
| LVYGASDSNV | YDLLKDLEEG | IQTLMGRLED | GSPRTGQIFK | QTYSKFDTNS |
| HNDDALLKNY | GLLYCFRKDM | DKVETFLRIV | QCRSVEGSGG | F |
| $\mathrm{C}_{990} \mathrm{H}_{1528} \mathrm{~N}_{262} \mathrm{O}_{300} \mathrm{~S}_{7}$ | 22,125 | $[12629-01-5]$. |  |  |

» Somatropin is a protein hormone consisting of 191 amino acid residues, and its structure corresponds to the major component of the growth hormone extracted from human pituitary glands. It is produced as a lyophilized powder or bulk solution by methods based on recombinant DNA technology. When prepared as a lyophilized powder, it contains not less than $910 \mu \mathrm{~g}$ of somatropin per mg , calculated on the anhydrous basis. When prepared as a bulk solution, it contains not less than $910 \mu \mathrm{~g}$ of somatropin per mg of total protein. The presence of host-cell DNA and host-cell protein impurities in Somatropin is process specificthe limits of these impurities are determined by validated methods. Manufacturers must demonstrate a correlation between the Assay and a validated and approved growth-promotion based bioassay. It may contain excipients. [NOTE-One mg of anhydrous Somatropin is equivalent to 3.0 USP Somatropin Units.]

Packaging and storage-Preserve in tight containers, and store between $-10^{\circ}$ and $-25^{\circ}$.

Labeling-The labeling states that the material is of recombinant DNA origin.

USP Reference standards $\langle 11\rangle$ —USP Endotoxin RS. USP Somatropin RS.

## Identification-

A: Proceed as directed in the test for Chromatographic purity, except to prepare a Standard solution by reconstituting a vial of USP Somatropin RS with the Diluent to obtain a solution having a known concentration of about 2.0 mg per mL. Chromatograph the Standard solution and the Test solution as directed for Procedure: the retention time of the somatropin peak in the chromatogram of the Test solution corresponds to that in the chromatogram of the Standard solution.

B: Peptide Mapping (see Biotechnology-Derived Articles—Tests $\langle 1047\rangle$ )-
Solution A-Prepare a filtered and degassed solution of trifluoroacetic acid in water ( 1 in $1000, \mathrm{v} / \mathrm{v}$ ).

Solution B-Transfer 100 mL of water to a $1000-\mathrm{mL}$ volumetric flask, add 1 mL of trifluoroacetic acid, dilute with acetonitrile to volume, and mix.

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments to either solution as necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Tris buffer-Prepare a 0.05 M solution of tris(hydroxymethyl)aminomethane (Tris), and adjust with hydrochloric acid to a pH of 7.5.

Trypsin solution-Prepare a solution containing 1 mg of trypsin per mL of Tris buffer, and mix. Store in a freezer, if necessary.

Standard solution-Prepare a solution containing 2.0 mg of USP Somatropin RS per mL of the Tris buffer, and mix. Add 1 mL of this solution to a suitable tube, and add $30 \mu \mathrm{~L}$
of Trypsin solution. Cap the tube, and place it in a water bath at $37^{\circ}$ for 4 hours. [NOTE-If this solution is not injected immediately, store it in a freezer.]

Test solution-Prepare a solution containing 2.0 mg of Somatropin per mL of Tris buffer, and mix. Add 1 mL of this solution to a suitable tube, and add $30 \mu \mathrm{~L}$ of Trypsin solution. Cap the tube, and place it in a water bath at $37^{\circ}$ for 4 hours. [NOTE-If this solution is not injected immediately, store it in a freezer.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $214-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L7. The flow rate is 1 mL per minute, and the column temperature is maintained at $30^{\circ}$. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0 \rightarrow 20$ | $100 \rightarrow 80$ | $0 \rightarrow 20$ | linear gradient |
| $20 \rightarrow 40$ | $80 \rightarrow 75$ | $20 \rightarrow 25$ | linear gradient |
| $40 \rightarrow 65$ | $75 \rightarrow 50$ | $25 \rightarrow 50$ | linear gradient |
| $65 \rightarrow 70$ | $50 \rightarrow 20$ | $50 \rightarrow 80$ | linear gradient |
| $70 \rightarrow 71$ | $20 \rightarrow 100$ | $80 \rightarrow 0$ | linear gradient |
| $71 \rightarrow 86$ | 100 | 0 | isocratic, re-equili- |
|  |  |  | bration |

Procedure-[NOTE-Condition the chromatographic system by running a blank gradient program prior to injecting the digests.] Separately inject equal volumes (about $100 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution, and record the chromatograms: the chromatographic profile of the Test solution is similar to that of the Standard solution.

Bioidentity-[NOTE-The Bioidentity test may be performed either on the Somatropin bulk drug substance or on the finished pharmaceutical product.]

Buffer solution-Prepare a solution of 0.1 M ammonium bicarbonate, and adjust with sodium hydroxide to a pH of 8.0.

Standard solutions - Transfer aceurately weighed quantiReconstitute the USP Somatropin RS, and dissolve in and dilute quantitatively with Buffer solution to obtain solutions having known concentrations between 10 and $100 \mu \mathrm{~g}$ per mL .
Test solutions-Transfer aceurately weighed amounts of
Semern, Prepare a solution of Somatropin, and dissolve in and dilute quantitatively with Buffer solution to obtain solutions having concentrations similar to those of the Standard solutions. [NOTE-Do not agitate while mixing; swirl gently.]

## Control solution-Use the Buffer solution.

Test animals-Select an appropriate number of only female or only male Sprague Dawley rats hypophysectomized at 25 to 30 days of age. After hypophysectomization, feed the rats on rat chow and $5 \%$ dextrose water for at least 72 hours. After 72 hours, feed the rats on rat chow and filtered and deionized water adjusted with 1 N hydrochloric acid to a pH of $3.0 \pm 0.25$. Weigh the rats when they are 37 to 44 days old, and retain only healthy rats. Reweigh the remaining rats 7 days later, and use only those rats that are in good health and have not gained or lost more than $10 \%$ of their body weight in the previous 7 -day period.

Procedure - Randomly divide the rats into control, standard, and test groups, each group containing approximately 10 rats. Each day for 10 days inject subcutaneously 0.1 mL of the Control solution, Standard solutions, and Test solutions to the control, standard, and test groups, respectively. Record the body weight of each animal at the start of the test and at approximately 18 hours following the $10^{\text {th }}$ injection. Determine the change in body weight for each rat during the 10-day period, and compute the potency of the Test solution
relative to that of the Standard solution using appropriate statistical analysis. Calculate the mean potency in USP Somatropin Units per mg: not less than 2 USP Somatropin Units per mg is found. Using appropriate statistical methods, calculate the width, $L$, of a $95 \%$ confidence interval for the estimated logarithm of the relative potency: $L$ is not more than 0.40 , which corresponds to confidence limits between $63 \%$ and $158 \%$ of the calculated potency. If $L$ is more than 0.40 , repeat the test until the results from two or more tests, combined by appropriate statistical methods, meet this criterion.
Microbial limits $\langle 61\rangle$ —The total aerobic microbial count does not exceed 300 cfu per g , the test being performed on about 0.2 to 0.3 g of powder, accurately weighed.

Bacterial endotoxins $\langle 85\rangle$-It contains not more than 10 USP Endotoxin Units per mg.

Water, Method Ic $\langle 921\rangle$ : not more than $10 \%$, when prepared as a lyophilized powder.

## Chromatographic purity-

Diluent-Prepare a solution of 0.05 M Tris in water, and adjust with hydrochloric acid to a pH of 7.5 .

Mobile phase-Degas the Diluent, mix with n-propyl alcohol ( $71: 29, \mathrm{v} / \mathrm{v}$ ), and filter. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Resolution solution-Prepare a solution of 2.0 mg of Somatropin per mL of the Diluent, pass through a filter to sterilize or add sodium azide to a final concentration of $0.01 \%$, and allow to stand at room temperature for 24 hours. [NOTE--Use within 48 hours after preparation, or store the solution in a refrigerator until ready to use.]
Test solution-Prepare a solution of 2.0 mg of Somatropin per mL of the Diluent immediately before use. [NOTEMaintain the solutions between $2^{\circ}$ and $8^{\circ}$, and use within 24 hours. If an automatic injector is used, maintain the temperature between $2^{\circ}$ and $8^{\circ}$.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L26 and is maintained at $45^{\circ}$. The flow rate is about 0.5 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the tailing factor of the somatropin peak (major peak) is between 0.9 and 1.8 ; and the resolution, $R$, between somatropin and its adjacent peak is not less than 1.0.

Procedure Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Test solution, record the chromatograms, and
meactre the are the major peak. Inject about $20 \mu \mathrm{~L}$ of the Test solution, record the chromatograms, and measure the peak responses. Calculate the percentage of impurities in the portion of Somatropin taken by the formula:

$$
100 A_{I} /\left(A_{I}+A_{S}\right)
$$

in which $A_{I}$ is the sum of the responses of all peaks other than the somatropin peak (major peak) and disregarding any peak due to the solvent; and $A_{S}$ is the response of the somatropin peak: not more than $6.0 \%$ of total impurities is found.

## Limit of high molecular weight proteins-

Phosphate buffer, Mobile phase, Diluent, Resolution solution, and Chromatographic system-Proceed as directed in the Assay.

Test solution-Prepare as directed for the Assay preparation in the Assay.

Procedure-Inject about $20 \mu \mathrm{~L}$ of the Test solution, record the chromatogram, and measure the areas of the main peak and of the peaks eluting prior to the main peak, excluding the solvent peaks. Calculate the percentage of high mo-
lecular weight proteins in the portion of Somatropin taken by the formula:

$$
100 A_{H} /\left(A_{H}+A_{M}\right),
$$

in which $A_{H}$ is the sum of the areas of the high molecular weight peaks, and $A_{M}$ is the area of the monomer peak in the chromatogram of the Test solution: not more than $4 \%$ of high molecular weight proteins is found.

Total protein (see Spectrophotometry and Light-Scattering〈851〉)-

Phosphate buffer-Prepare a 0.025 M solution of monobasic potassium phosphate in water, and adjust with sodium hydroxide to a pH of 7.0.

Test solution-Dissolve an accurately weighed quantity of Somatropin in Phosphate buffer to obtain a solution having an absorbance value between 0.5 and 1.0 at the wavelength of maximum absorbance at about 280 nm .

Procedure-Determine the absorbance of the Test solution using a spectrophotometric cell of path length $1-\mathrm{cm}$, at the wavelength of maximum absorbance at around 280 nm and at 320 nm , using Phosphate buffer as the blank. Calculate the protein content, in mg , in the portion of Somatropin taken by the formula:

$$
V\left(A_{\max }-A_{320}\right) / 0.82
$$

in which $V$ is the volume of the Test solution; and $A_{\text {max }}$ and $A_{320}$ are the absorbance values of the Test solution at the wavelength of maximum absorbance and at 320 nm , respectively.

## Assay-

Phosphate buffer - Prepare a 0.063 M solution of menebasic petassimm phesphate in water, and adjust with sodium hydroxide Dissolve 5.18 g of dibasic sodium phosphate and
3.65 g of monobasic sodium phosphate in 950 mL of water, adjust with phosphoric acid to a pH of 7.0 , and dilute with water to 1000 mL .

Mobile phase-Prepare a filtered and degassed mixture of the Phosphate buffer and isopropyl alcohol (97:3, v/v). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare 0.025 M solution by dissolving monebasie potassium phosphate in water and adjusting with so dium hydroxide pH of 7.0. Prepare a mixture of water and Phosphate buffer (1.5:1).
Resolution solution-Place 1 vial of USP Somatropin RS in an oven at $50^{\circ}$ for 12 to 24 hours. Remove from the oven, and dissolve the contents of the vial in Diluent to obtain a solution having a known concentration of about 1 mg per mL with the content of the dimer between $1 \%$ and $2 \%$.

## Standard preparation-Reconstitute a vial of USP Soma-

 tropin RS with the Diluent to obtain a solution having a known concentration of about 1.0 mg per mL .Assay preparation-Dissolve an accurately weighed quantity of Somatropin in Diluent, or dilute a bulk solution of Somatropin with Diluent, to obtain a solution having a concentration of about 1 mg per mL . [NOTE-If necessary, the amount of protein in solution can be determined by the test for Total protein.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $214-\mathrm{nm}$ detector and a $7.8-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L33 and is maintained at ambient temperature. The flow rate is 0.6 mL per minute. Chromatograph the Resolution solution as directed for Procedure: the resolution, $R$, (determined as the ratio of the valley height, between the dimer and the monomer, and the dimer peak height) is not more than 0.4 ; and the tailing factor of the monomer peak (major peak) is not more than 1.7.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the the Standard preparation and the Assay preparation, record the chromatograms for not less than twice the retention time of the somatropin monomer peak (major peak), and measure the peak responses for the monomer. Calculate the quantity of somatropin, in $\mu \mathrm{g}$ per mg, of totat protein, by the formula:-

$$
P\left(G_{s}+\mathrm{C}_{\downarrow}\right)\left(r_{\llcorner }+r_{s}\right),
$$

in which $P$ is the quantity of somatropin, in $\mu$ per mg, of USP Somatropin RS; $G_{s}$ and $G_{t}$ are the total protein concen trations, in mg per mL, of the Standard preparation and the Assy prepatan, respectively; concentration, in mg per mL , of somatropin in the Assay preparation by the formula:

$$
C_{S}\left(r_{U} / r_{S}\right)
$$

in which $C_{S}$ is the concentration, in mg per mL , of USP Somatropin RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses of the monomer in the Assay preparation and the Standard preparation, respectively.nis (USP28)

## Briefing

Somatropin for Injection, page 1983 of $P F 29(6)$ [Nov.-Dec. 2003]. It is proposed to add a test for Bioidentity to provide flexibility in testing and potentially to reduce the extent of animal testing. The test for Bioidentity need not be performed if the bulk substance used was tested and meets the requirements. It is also proposed to modify the Assay to take into account the labeling of the USP Somatropin RS.
(BNT: L. Callahan) $\quad$ RTS-41180-2

## Add the following:

## ■Somatropin for Injection

» Somatropin for Injection is a sterile, lyophilized mixture of Somatropin with one or more suitable buffering and stabilizing agents. It contains not less than 89.0 percent and not more than 110.0 percent of the amount of somatropin stated on the label. [NOTE-One mg of anhydrous Somatropin is equivalent to 3.0 USP Somatropin Units.]

Packaging and storage-Preserve in tight containers, and store between $2^{\circ}$ and $8^{\circ}$.

Labeling-The labeling states that the material is of recombinant DNA origin.

USP Reference standards $\langle 11\rangle —$ USP Endotoxin RS. USP Somatropin RS.

Identification-It meets the requirements for Identification test $A$ under Somatropin.

Bioidentity-[NOTE-If the bulk material is used to prepare Somatropin for Injection was tested and meets the requirements, it is not necessary to perform this test.] It meets the requirements for Bioidentity under Somatropin.

Bacterial endotoxins $\langle 85\rangle$-It contains not more than 20 USP Endotoxin Units per mg of somatropin.

Sterility $\langle 71\rangle$-It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.

Chromatographic purity-Proceed as directed for the Chromatographic purity test under Somatropin: not more than $12 \%$ of total impurities is found.

Limit of high molecular weight proteins-Proceed as directed in the test for Limit of high molecular weight proteins under Somatropin, except to use the Assay preparation as the Test solution: not more than $6 \%$ of high molecular weight proteins is found.

## Assay-

Phosphate buffer, Mobile phase, Diluent, Resolution solution, Standard preparation, and Chromatographic systemProceed as directed in the Assay under Somatropin.

Assay preparation-Dissolve the contents of a suitable number of containers in Diluent to obtain a concentration of 1 mg of somatropin per mL .

Procedure-Proceed as directed under Somatropin. Calculate the quantity of somatropin, in mg of somatropin per wial container, by the formula:

$$
\left(P G_{s}+1000\right)(N / N)\left(r_{t}+r_{s}\right)
$$

$$
C(V / N)\left(r_{U} / r_{s}\right)
$$

in which $P$ is the quantity of somatropin, in ug per me, of USP Somatropin PS; $\epsilon_{S}$ is the concentration, in mg per mL, of the-Stated prepatiation; in which $C$ is the concentration, in mg per mL , of USP Somatropin RS in the Standard preparation; $V$ is the total volume of the Assay preparation; $N$ is the number of viats containers used to obtain the Assay preparation; and $r_{U}$ and $r_{S}$ are the peak responses of the monomer in the Assay preparation and the Standard preparation, respectively.mis (USP28)

## BRIEFING

Sulfisoxazole, USP 27 page 1755. It is proposed to revise the Assay to specify the solvent used to prepare the titrant.
(HDQ: M. Marques) RTS-41337-1

## Change to read:

Assay_Place about 800 mg of Sulfisoxazole, accurately weighed, in a $250-\mathrm{mL}$ conical flask, add 50 mL of dimethylformamide, shake thoroughly to dissolve the solid, add 5 drops of a 1 in 100 solution of thymol blue in dimethylformamide, and titrate with 0.1 N lithium methoxide
$\boldsymbol{m}_{\text {in }}$ toluene $_{\mathbf{m}_{1 S} \text { (USP28) }}$
VS to a blue endpoint, taking precautions against absorption of atmospheric carbon dioxide. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N lithium methoxide is equivalent to 26.73 mg of $\mathrm{C}_{11} \mathrm{H}_{13} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}$.

BRIEFING

Titanium Dioxide, USP 27 page 1854. It is proposed to revise this monograph by dividing it into two separate monographs, as recommended by the USP Excipient Monograph Content Expert Committee, and IPEC Americas: Titanium Dioxide monograph for color-additive grade material and a proposed new USP Titanium Dioxide monograph (nomenclature title change to come) for UV-attenuation grade material. The current official USP monograph allows both color-additive grade and UV-attenuation grade titanium dioxide, which have quite different applications and requirements. The issues pertaining to the two materials can be more appropriately addressed in two separate monographs. See also briefing under Titanium Dioxide [N\&L to come] under General Monographs in this number of $P F$.

This will also facilitate the process of international harmonization of the color additive grade monograph, the Japanese Pharmacopoeia being the coordinating pharmacopoeia for Titanium Dioxide.

This proposed USP monograph for the color-additive grade is very similar to the older $U S P$ version before the UV-attenuation grade was allowed. This proposal also takes into consideration the U.S. FDA 21 CFR and FCC standards regarding Titanium Dioxide and also allows both anatase and rutile crystal structures. Also included are the Assay and the limit tests for Lead, Antimony, and Mercury, based on the harmonization draft proposal. Interested parties are urged to comment. Proposed changes from the current USP monograph include the following:

1. Definition-A change to the upper acceptance criterion is based on the harmonization draft proposal. Limit for added substances has been included. Reference to attenuation grade
material is deleted. The [NOTE] has been deleted and tests have been included for Lead, Antimony, and Mercury, based on the harmonization draft proposal.
2. Packaging and storage-A storage statement to include the phrase "No storage requirements specified" is added.
3. Labeling-Additional information is presented as to crystalline structure. Reference to attenuation grade material is deleted.
4. Identification-No change.
5. Loss on drying - No change.
6. Loss on ignition-Reference to attenuation grade material is deleted.
7. Water-soluble substances-A platinum crucible is specified for final heating. "A dull red heat" is replaced with " 650 " for the ignition temperature.
8. Acid-soluble substances-A platinum crucible is specified for final heating.. "A dull red heat" is replaced with " 650 " for the ignition temperature.
9. Arsenic-No change.
10. Organic volatile impurities-Deleted, based on information that no organic solvents are used in the manufacture of the article of commerce.
11. Limit of lead-Test is added, based on the harmonization draft proposal.
12. Limit of antimony - Test is added, based on the harmonization draft proposal.
13. Limit of mercury-Test is added, based on the harmonization draft proposal.
14. Assay-The current reduction/titration (Jones-Reductor) test is problematic and outdated. A new test is proposed, based on the harmonization draft proposal.
(EMC: C. Sheehan) RTS-41222-1

## Change to read:

H-Titanium Diexide contains not less than 99.0 pereent and not more than 100.5 percent of $\mathrm{TiO}_{z}$, calculated on the dried basis. If labeled as attemuation grade, then Ti tanium Diexide contains net less than 99.0 percent and not more than 100.5 percent of $\mathrm{TiO}_{2}$, ealeulated on the ignited basis. Attentation grade material may contain suitable-coatings, stabilizers, and treatments to assist formalation.

NOTE-If labeled as attentration grade, then all tests and assays are-condurted on uncoated, untreated material. For UV attentation grade, the test for Losf on drying does not apply. The FDA requires the content of lead to be not mere than 10 ppm , that of antimeny to be not more than 2 ppm , and that of mereury to be net mere than 1 ppm (21 CFR 73.1575).

■» Titanium Dioxide contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{TiO}_{2}$, calculated on the dried basis, after correcting for any suitable additives present in the $\mathrm{TiO}_{2}$. It may contain up to 2.0 percent (either sin-
gly or combined) of suitable additives, whether a diluent, dispersant, particle coating, stabilizer, or treatment to assist formulation. ${ }^{1 S}$ (USP28)

## Change to read:

Packaging and storage-Preserve in well-closed containers.
$\boldsymbol{m}^{\text {n }}$ No storage requirements specified.■1S (USP28)

## Change to read:

Labeling-If intended for UV attentation, the material must be la beled as attentation grade. If intended for UV attentation, and any added eoatings, stabilizers, of treatments are used, the labeling shall inelude the name and amount of the additives.

■Label as to crystalline structure (anatase or rutile). The labeling indicates the name and percentage, to at least one decimal place (w/w), of added substances present.■1s (USP28)

## Change to read:

Loss on ignition $\langle 733\rangle$-Ignite 2 g , previously dried and accurately weighed, at $800 \pm 25^{\circ}$ to constant weight: it loses not more than $0.5 \%$ of its weight. If tabeled as antention grade, ignite 4 g of tituium dioxide, aceurately weighed, at $800 \pm 25^{\circ}$ to eon stant weight: it loses not more than $13 \%$ of its weight.

$\boldsymbol{m}_{\text {■ }}$ (USP28)

## Change to read:

Water-soluble substances-Suspend 4.0 g in 50 mL of water, mix, and allow to stand overnight. Transfer to a $200-\mathrm{mL}$ volumetric flask, add 2 mL of ammonium chloride TS, and mix. If the Titanium Dioxide does not settle, add another $2-\mathrm{mL}$ portion of ammonium chloride TS. Allow the suspension to settle, dilute with water to volume, mix, and filter through a double thickness of fine-porosity filter paper, discarding the first 10 mL of the filtrate. Collect 100 mL of the clear filtrate, transfer to a tared platinum dish, evaporate on a hot plate to dryness, and ignite at a dull red hat
$\square_{\text {in }}$ a platinum crucible at $650^{\circ}$ (US (USP28)
to constant weight: the residue weighs not more than 5 mg (0.25\%).

## Change to read:

Acid-soluble substances-Suspend 5.0 g in 100 mL of 0.5 N hydrochloric acid, and heat on a steam bath for 30 minutes, with occasional stirring. Filter through an appropriate filter medium until clear. Wash with three $10-\mathrm{mL}$ portions of 0.5 N hydrochloric acid. Evaporate the combined filtrate and washings to dryness, and ignite at addll red heat
$\square_{\text {in }}$ a platinum crucible at $650^{\circ}$ (US (USP28)
to constant weight: the residue weighs not more than 25 mg (0.5\%).

## Add the following:

## -Limit of lead-

Blank solution-Place 10 mL of the dilute hydrochloric acid (1 in 20) in a $100-\mathrm{mL}$ beaker. Add 2 mL of dilute acetic acid (1 in 20), dilute with water to 50 mL , and mix.

Standard solution-Pipet 2.0 mL of Standard Lead Solution, (see Special Reagents section under Heavy Metals $\langle 231\rangle$ ) into a $100-\mathrm{mL}$ beaker, add 2 mL of dilute acetic acid (1 in 20), dilute with water to 50 mL , and mix.

Test stock solution-Transfer about 10 g of Titanium Dioxide, accurately weighed, into a $250-\mathrm{mL}$ beaker, and add 50 mL of dilute hydrochloric acid (1 in 20). Cover the beaker with a watch glass, boil gently for 15 minutes, and centrifuge to precipitate the insoluble residue. Pass through a filter, and collect the filtrate. Wash the beaker used and the residue three times with $10-\mathrm{mL}$ portions of boiling water, passing each washing through the original filter paper and combining these washings with the above filtrate. Wash the filter paper with a 10 - to $15-\mathrm{mL}$ portion of boiling water, combine these washings with the previous washings and filtrate, cool, dilute with water to 100 mL , and mix to obtain the Test stock solution. [NOTE-Save portions of this Test stock solution for use in the tests for Limit of antimony and Limit of mercury.]

Test solution-Transfer 20 mL of the Test stock solution to a $100-\mathrm{mL}$ beaker, add 1 drop of phenolphthalein TS, and add dropwise, ammonia TS until the solution becomes slightly pink. Add 2 mL of dilute acetic acid ( 1 in 20 ), dilute with water to 50 mL , and mix.

Procedure-Concomitantly determine the absorbances of the Standard solution and the Test solution at the lead emission line of 283.3 nm with an atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) equipped with a lead hallow-cathode lamp and an air-acetylene flame, using the Blank solution to set the in-
strument to zero. The absorbance of the Test solution is not greater than that of the Standard solution (not more than 10 ppm).■1S (USP28)

## Add the following:

-Limit of antimony-
Standard antimony stock solution-Transfer 1.874 g of antimony trichloride, accurately weighed, into a $1000-\mathrm{mL}$ volumetric flask, dissolve in and dilute with 0.3 N hydrochloric acid to volume, and mix.

Standard antimony solution-[NOTE-Prepare this solution immediately before use.] Pipet 1 mL of Standard antimony stock solution into a $100-\mathrm{mL}$ volumetric flask, dilute with 0.3 N hydrochloric acid to volume, and mix.

Standard solution-Transfer 2.0 mL of the Standard antimony solution into a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 1 in 20) to volume, and mix. This solution contains the equivalent of $0.2 \mu \mathrm{~g}$ of antimony per mL .

Blank solution-Use dilute hydrochloric acid (1 in 20).
Test solution-Use the Test stock solution, obtained as directed in the test for Limit of lead.

Procedure-Concomitantly determine the absorbance of equal volumes (about 20 mL ) of the Standard solution and the Test solution at the antimony emission line of 283.3 nm , with a suitable graphite furnace atomic absorption spectrophotometer (see Spectrophotometry and LightScattering $\langle 851\rangle$ ) equipped with an antimony hallow-cathode lamp, using the Blank solution to set the instrument to zero and maintaining the drying temperature of the furnace at $110^{\circ}$, the ashing temperature at $600^{\circ}$, and the atomization temperature at $2100^{\circ}$. The absorbance of the Test solution is not greater than that of the Standard solution (not more than 2 ppm ).■1S (USP28)

## Add the following:

## -Limit of mercury-

Mercury stock solution-Transfer 135.4 mg of mercuric chloride, previously dried in a desiccator over silica gel for 6 hours and accurately weighed, to a $1000-\mathrm{mL}$ volumetric flask, add 10 mL of diluted nitric acid, swirl to dissolve, dilute with water to volume, and mix.

Standard mercury solution-[NOTE-Prepare immediately before use.] Transfer $10-\mathrm{mL}$ of the Mercury stock solution to a $100-\mathrm{mL}$ volumetric flask, add 1 mL of diluted nitric acid, dilute with water to volume, and mix. Transfer 10 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, add 1 mL of diluted nitric acid, dilute with water to volume, and mix. This Standard mercury solution contains the equivalent of $1.0 \mu \mathrm{~g}$ of mercury per mL.
Stannous chloride-sulfuric acid solution-Dissolve 10 g of stannous chloride in diluted sulfuric acid (3 in 200) to make 100 mL .

Blank solution-Use dilute hydrochloric acid (1 in 40).
Standard solution-Transfer 5.0 mL of the Standard mercury solution into a $50-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 1 in 40) to volume, and mix.

Test solution-Use the Test stock solution, obtained as directed in the test for Limit of lead.
Procedure-Treat the Standard solution and the Test solution similarly as follows. Place 20 mL of the solution in an atomic absorption spectrophotometer sample bottle, add 10 mL of Stannous chloride-sulfuric acid solution, and immediately connect the sample bottle to an atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) equipped with a mercury hallow-cathode lamp. Circulate air through the system to introduce any vaporized mercury into the absorption cell, and determine the absorbance of the solution under test at mercury emission line of 253.7 nm after the recorder reading has risen rapidly
and becomes constant. Use the Blank solution to set the instrument to zero. The absorbance of the Test solution is not greater than that of the Standard solution (not more than 1 $\mathrm{ppm})$.■1S (USP28)

## Delete the following:

Earganic volatile imptrities, Meth $H$, 467 ): meets the requirements.als (USP28)

## Change to read:

Assay-Acetrately weigh abeut 300 me of Titanitm Dioxide, transfer to a 250 mL beaker, and add 20 mL of sulfuric acid and 7 to 8 g of ammonium sulfate. Mix, heat on a hot plate until fumes of sulfur trioxide appear, and continue heating over a strong flame until solution is complete or it is apparent that the undissolved resi due is siliceous matter. Cool, cautiously dilute with 100 mL of water, stir, heat carefully to boiling while-stimring, and allow the insoluble matter to settle. Filter, transfer the entire residue to the filter, and wash thereughly with cold 2 N sulfurie acid. Dilute the filtrate with water $10-200 \mathrm{~mL}$, and eatiously add about 10 mL of ammonitm hydroxide.

Prepare a zine amalgam column in a 25 cm Jones reductor tube, placing a pledge of glass wool in the bettom of the tube, and filling the constricted pertion of the tube with zine amalgam prepared as follows. Add 20 -to 30 mesh zine to mereuric chloride solution. ( 1 in 50), using about 100 mL of the solution for each 100 g of zine, and after about 10 minutes, deean the solution from the zine, then wash the zine by deeantation. Wash the zine amalgameolumm with 100 mL pertions of 2 N sulfuric acid until 100 mL of the washing does not decolorize 1 drop of 0.1 N petassimm permanganate.

Place 50 mL of ferric ammenitm sulfate TS in a 1000 mL sue tion flask, and add 0.1 N potassium permanganate untilla a faint pink coler persists for 5 minutes. Attach the Jones reductor tube to the neek of the flask, and pass 50 mL of 2 N sulfurie acid through the reductor at a rate of about 30 mL per mintute. Pass the prepared titanimm solution through the reductor at the same rate, and follow with 100 mL each of 2 N sulfuric acid and of water. During these eperations, keep the reductor filled with solution or water above the upper level of the amalgam. Taking preeations against the admis sion of atmospheric oxygen, gradually release the-suetion, wash down the outlet tube of the reductor and the sides of the receiver, and titrate immediately with 0.1 N potassimm permanganate VS. Perform ablank detemination, substifuting 200 mL of 2 N sulfurie acid for the assay solution, and make any necessary correction. Each mL of 0.1 N potassitm permanganate-is equivalent to 7.988 mg of $\mathrm{TiO}_{2}=$

- Accurately weigh about 150 mg of previously dried Titanium Dioxide, transfer to a $500-\mathrm{mL}$ conical flask, add 5 mL of water, and shake until a homogeneous, milky suspension is obtained. Add 30 mL of sulfuric acid and 12 g of ammonium sulfate, and mix. Initially heat gently, then heat strongly until a clear solution is obtained. Cool, cautiously add 120 mL of water and 40 mL of hydrochloric acid, and shake. Add 3 g of aluminum metal, and immediately insert a rubber stopper fitted with a U-shaped glass tube while im-
mersing the other end of the U-tube into a saturated solution of sodium bicarbonate contained in a $500-\mathrm{mL}$ wide-mouth bottle, and generate hydrogen. Allow to stand for a few minutes after the aluminum metal has dissolved completely to produce a transparent purple solution. Cool to below $50^{\circ}$ in running water, and remove the rubber stopper carrying the U-tube. Add 3 mL of a saturated potassium thiocyanate solution as an indicator, and immediately titrate with 0.2 N ferric ammonium sulfate VS until a faint brown color that persists for 30 seconds is obtained. Perform a blank determination (see Titrimetry $\langle 541\rangle$ ), and make any necessary correction. Each mL of 0.2 N ferric ammonium sulfate is equivalent to 7.988 mg of $\mathrm{TiO}_{2} \cdot \mathbf{1 S}$ (USP28)


## Briefing

Titanium Dioxide.This new USP monograph, with a nomenclature title proposal forthcoming, is being proposed for UV-attenuation grade Titanium Dioxide to support the proposed division of the current USP monograph into two separate monographs: a USP monograph for color-additive grade material and a USP monograph for UV-attenuation grade material. See also the briefing under Titanium Dioxide. Interested parties are urged to submit comments.

The proposed new monograph for the attenuation-grade material includes the following changes from the current official monograph:

1. Definition-Limits of added substances have been included. The [NOTE] has been deleted and tests have been included for Lead, Antimony, and Mercury.
2. Packaging and storage-Change to tight containers.
3. Labeling - Reference to UV attenuation and attenuation grade removed. Additional information is presented as to crystalline structure.
4. Identification-No change.
5. Loss on drying - This test does not apply.
6. Loss on ignition - No change. Reference to color grade is deleted.
7. Water-soluble substances-A platinum crucible is specified for final heating. "A dull red heat" is replaced with " $650^{\circ}$ " for the ignition temperature.
8. Acid-soluble substances-A platinum crucible is specified for final heating. "A dull red heat" is replaced with " $650^{\circ}$ " for the ignition temperature.
9. Arsenic-No change.
10. Organic volatile impurities-No change.
11. Limit of lead-Test is added to monitor this impurity.
12. Limit of antimony-Test is added to monitor this impurity.
13. Limit of mercury-Test is added to monitor this impurity.
14. Assay-The current reduction/titration (Jones-Reductor) test is problematic and outdated. A new test is proposed.
(PA6: L. Evans; NL: W.L. Paul) RTS-41223-1

## Add the following:

## ■Titanium Dioxide*

## *Nomenclature title change to come.

$\mathrm{TiO}_{2} \quad 79.87$

Titanium oxide $\left(\mathrm{TiO}_{2}\right)$.

Titanium oxide $\left(\mathrm{TiO}_{2}\right)$ [13463-67-7].
» Titanium Dioxide ${ }^{*}$ contains not less than 99.0 percent and not more than 100.5 percent of $\mathrm{TiO}_{2}$, calculated on the ignited basis, after correcting for any additives remaining. It may contain up to 13.0 percent (singly or combined) of suitable additives, whether a diluent, dispersant, particle coating, stabilizer, or treatment to assist formulation.

Packaging and storage-Preserve in tight containers.
Labeling-Label as to crystalline structure (anatase or rutile). The labeling indicates the name and percentage, to at least one decimal place ( $\mathrm{w} / \mathrm{w}$ ), of added substances present. Identification-Add 5 mL of sulfuric acid to 500 mg , and heat gently. After fumes of sulfur trioxide appear, continue heating for a minimum of 10 seconds. Cool the suspension, and cautiously dilute with water to 100 mL . Pass through a
filter, and add a few drops of hydrogen peroxide TS to 5 mL of the clear filtrate: a yellow-red to orange-red color develops immediately.

Loss on ignition $\langle 733\rangle$-Ignite 4 g , accurately weighed, at $800 \pm 25^{\circ}$ to constant weight: it loses not more than $13 \%$ of its weight.

Water-soluble substances-Suspend 4.0 g in 50 mL of water, mix, and allow to stand overnight. Transfer to a $200-\mathrm{mL}$ volumetric flask, add 2 mL of ammonium chloride TS, and mix. If the Titanium Dioxide* does not settle, add another $2-\mathrm{mL}$ portion of ammonium chloride TS. Allow the suspension to settle, dilute with water to volume, mix, and pass through a double thickness of fine-porosity filter paper, discarding the first 10 mL of the filtrate. Collect 100 mL of the clear filtrate, transfer to a tared platinum dish, evaporate on a hot plate to dryness, and ignite at $650^{\circ}$ in a platinum crucible to constant weight: the residue weighs not more than $5 \mathrm{mg}(0.25 \%)$.

Acid-soluble substances-Suspend 5.0 g in 100 mL of 0.5 N hydrochloric acid, and heat on a steam bath for 30 minutes, with occasional stirring. Pass through an appropriate filter medium until clear. Wash with three $10-\mathrm{mL}$ portions of 0.5 N hydrochloric acid. Evaporate the combined filtrate and washings to dryness, and ignite at $650^{\circ}$ in a platinum crucible to constant weight: the residue weighs not more than 25 mg ( $0.5 \%$ ).

Arsenic, Method $I\langle 211\rangle$ —Prepare the Test Preparation as follows. Add 3.0 g to a $250-\mathrm{mL}$ conical flask fitted with a thermometer and a vapor outlet. Add 50 mL of water, 500 mg of hydrazine sulfate, 500 mg of potassium bromide, 20 g of sodium chloride, and 25 mL of sulfuric acid. Arrange to collect the evolved vapors in 52 mL of water contained in the arsine generator flask, then heat the test specimen to $90^{\circ}$, and maintain the temperature at $90^{\circ}$ to $100^{\circ}$ for 15 minutes. Add 3 mL of hydrochloric acid to the solution in the genera-
tor flask: the resulting solution meets the requirements of the test, the addition of 20 mL of 7 N sulfuric acid specified under Procedure being omitted. The limit is 1 ppm .

## Limit of lead-

Blank solution-Place 10 mL of the dilute hydrochloric acid (1 in 20 ) in a $100-\mathrm{mL}$ beaker. Add 2 mL of dilute acetic acid (1 in 20), dilute with water to 50 mL , and mix.

Standard solution-Pipet 2.0 mL of Standard Lead Solution, (see Special Reagents section under Heavy Metals $\langle 231\rangle$ ) into a $100-\mathrm{mL}$ beaker, add 2 mL of dilute acetic acid (1 in 20), dilute with water to 50 mL , and mix.
Test stock solution-Transfer about 10 g of Titanium Dioxide ${ }^{*}$, accurately weighed, into a $250-\mathrm{mL}$ beaker, and add 50 mL of dilute hydrochloric acid ( 1 in 20). Cover the beaker with a watch glass, boil gently for 15 minutes, and centrifuge to precipitate the insoluble residue. Pass through a filter, and collect the filtrate. Wash the beaker used and the residue three times with $10-\mathrm{mL}$ portions of boiling water, passing each washing through the original filter paper and combining these washings with the above filtrate. Wash the filter paper with a $10-$ to $15-\mathrm{mL}$ portion of boiling water, combine these washings with the previous washings and the filtrate, cool, dilute with water to 100 mL , and mix to obtain the Test stock solution. [NOTE-Save portions of this Test stock solution for use in the tests for Limit of antimony and Limit of mercury.]
Test solution-Transfer 20 mL of the Test stock solution to a $100-\mathrm{mL}$ beaker, add 1 drop of phenolphthalein TS, and add, dropwise, ammonia TS until the solution becomes slightly pink. Add 2 mL of dilute acetic acid (1 in 20), dilute with water to 50 mL , and mix.

Procedure-Concomitantly determine the absorbance of the Standard solution and the Test solution at the lead emission line of 283.3 nm with an atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering
$\langle 851\rangle$ ) equipped with a lead hallow-cathode lamp and an air-acetylene flame, using the Blank solution to set the instrument to zero. The absorbance of the Test solution is not greater than that of the Standard solution (not more than 10 ppm).

## Limit of antimony-

Standard antimony stock solution-Transfer 1.874 g of antimony trichloride, accurately weighed, into a $1000-\mathrm{mL}$ volumetric flask, dissolve in and dilute with 0.3 N hydrochloric acid to volume, and mix.

Standard antimony solution-[NOTE-Prepare this solution immediately before use.] Pipet 1 mL of Standard antimony stock solution into a $100-\mathrm{mL}$ volumetric flask, dilute with 0.3 N hydrochloric acid to volume, and mix.

Standard solution-Transfer 2.0 mL of the Standard antimony solution into a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 1 in 20) to volume, and mix. This solution contains the equivalent of $0.2 \mu \mathrm{~g}$ of antimony per mL .

Blank solution-Use dilute hydrochloric acid (1 in 20).
Test solution-Use the Test stock solution, obtained as directed in the test for Limit of lead.

Procedure-Concomitantly determine the absorbance of equal volumes (about 20 mL ) of the Standard solution and the Test solution at the antimony emission line of 283.3 nm , with a suitable graphite furnace atomic absorption spectrophotometer (see Spectrophotometry and LightScattering $\langle 851\rangle$ ) equipped with an antimony hallow-cathode lamp, using the Blank solution to set the instrument to zero and maintaining the drying temperature of the furnace at $110^{\circ}$, the ashing temperature at $600^{\circ}$, and the atomization temperature at $2100^{\circ}$. The absorbance of the Test solution is not greater than that of the Standard solution (not more than 2 ppm ).

## Limit of mercury-

Mercury stock solution-Transfer 135.4 mg of mercuric chloride, previously dried in a desiccator over silica gel for 6 hours and accurately weighed, to a $1000-\mathrm{mL}$ volumetric flask, add 10 mL of diluted nitric acid, swirl to dissolve, dilute with water to volume, and mix.

Standard mercury solution-[NOTE—Prepare immediately before use.] Transfer 10 mL of Mercury stock solution to a $100-\mathrm{mL}$ volumetric flask, add 1 mL of diluted nitric acid, dilute with water to volume, and mix. Transfer 10 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, add 1 mL of diluted nitric acid, dilute with water to volume, and mix. This Standard mercury solution contains the equivalent of $1.0 \mu \mathrm{~g}$ of mercury per mL .
Stannous chloride-sulfuric acid solution-Dissolve 10 g of stannous chloride in diluted sulfuric acid (3 in 200) to make 100 mL .

Blank solution-Use dilute hydrochloric acid (1 in 40).
Standard solution-Transfer 5.0 mL of the Standard mercury solution into a $50-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid (1in 40) to volume, and mix.

Test solution-Use the Test stock solution, obtained as directed in the test for Limit of lead.

Procedure-Treat the Standard solution and the Test solution similarly as follows. Place 20 mL of the solution in an atomic absorption spectrophotometer sample bottle, add 10 mL of Stannous chloride-sulfuric acid solution, and immediately connect the sample bottle to an atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) equipped with a mercury hallow-cathode lamp. Circulate air through the system to introduce any vaporized mercury into the absorption cell, and determine the absorbance of the solution under test at the mercury emission line of 253.7 nm after the recorder reading has risen rapidly and becomes constant. Use the Blank solution to
set the instrument to zero. The absorbance of the Test solution is not greater than that of the Standard solution (not more than 1 ppm ).

Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

Assay—Accurately weigh about 150 mg of Titanium Dioxide ${ }^{*}$, previously ignited, transfer to a $500-\mathrm{mL}$ conical flask, add 5 mL of water, and shake until a homogeneous, milky suspension is obtained. Add 30 mL of sulfuric acid and 12 g of ammonium sulfate, and mix. Initially heat gently, then heat strongly until a clear solution is obtained. Cool, cautiously add 120 mL of water and 40 mL of hydrochloric acid, and shake. Add 3 g of aluminum metal, and immediately insert a rubber stopper fitted with a U-shaped glass tube while immersing the other end of the U-tube into a saturated solution of sodium bicarbonate contained in a $500-$ mL wide-mouth bottle, and generate hydrogen. Allow to stand for a few minutes after the aluminum metal has dissolved completely to produce a transparent purple solution. Cool to below $50^{\circ}$ in running water, and remove the rubber stopper carrying the U-tube. Add 3 mL of a saturated potassium thiocyanate solution as an indicator, and immediately titrate with 0.2 N ferric ammonium sulfate VS until a faint brown color that persists for 30 seconds is obtained. Perform a blank determination (see Titrimetry $\langle 541\rangle$ ), and make any necessary correction. Each mL of 0.2 N ferric ammonium sulfate is equivalent to 7.988 mg of $\mathrm{TiO}_{2 \cdot} \cdot \mathbf{■ S}^{1 \mathrm{~S}}$ (USP28)

## Briefing

Topiramate, page 533 of PF 29(2) [Jan.-Feb. 2003]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded with changes to In-Process Revision. It is proposed to add a test for Limit of sulfamate and sulfate because
it has been reported that these two ions are possible products of degradation. The analytical method for the test for Limit of sulfamate and sulfate was validated using the IonPac AS11-HC brand of L46 column and the IonPac AG11 brand of L46 guard column. Typical retention times are about 3.3 minutes and about $12.7 \mathrm{~min}-$ utes for the sulfamate and sulfate peaks, respectively. It is also proposed to indicate the use of peak areas in the test for Related compounds and in the Assay. In addition, minor editorial style changes have been made.
(PA3: S. Salado) RTS-40645-1; 40020-5

## Add the following:

## ©Topiramate


$\mathrm{C}_{12} \mathrm{H}_{21} \mathrm{NO}_{8} \mathrm{~S} \quad 339.36$
$\beta$-D-Fructopyranose, 2,3:4,5-bis- $O$-(1-methylethylidene)-, sulfamate.
$2,3: 4,5-\mathrm{Di}-O$-isopropylidene- $\beta$-D-fructopyranose sulfamate [97240-79-4].
» Topiramate contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{12} \mathrm{H}_{21} \mathrm{NO}_{8} \mathrm{~S}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight, light-resistant containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Topiramate $R S$.
USP Topiramate Related Compound A RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $-29^{\circ}$ and $-35^{\circ}$, measured at $20^{\circ}$.

Test solution: 4 mg per mL , in methanol.
Water, Method $I\langle 921\rangle$ : not more than $0.5 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.2 \%$.

## Related compounds-

Mobile phase-Proceed as directed in the Assay.
NOTE-Prepare all solutions fresh before use.
System suitability solution-Transfer about 3 mg of USP Topiramate Related Compound A RS, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Test solution to volume, and mix.
Test solution-Transfer about 1 g of Topiramate, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, and dissolve in Mobile phase with the aid of sonication. Cool to room temperature, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—
The liquid chromatograph is equipped with a refractive index detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The column and the detector temperatures are maintained at $55^{\circ}$. The flow rate is about 0.6 mL per minute. Chromatograph the System suitability solution, and record the peak reseas areas directed for Procedure: the relative retention times are about 0.9 for topiramate related compound A and 1.0 for topiramate; the resolution, $R$, between topiramate related compound A and topiramate is not less than 1.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Inject a volume (about $50 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure all of the peak areas. Record the chromatogram for a period of time equivalent to not less than five times the retention time of the topiramate peak. Calculate the percentage of fructose in the portion of Topiramate taken by the formula:

$$
100(1 / F)\left(r_{U} / r_{s}\right),
$$

in which $F$ is the relative response factor and is equal to 1.2 ; $r_{U}$ is the area of any peak at a relative retention time of about 0.45 ; and $r_{S}$ is the sum of the areas of all the peaks. Calculate the percentage of each impurity in the portion of Topiramate taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak area for each impurity; and $r_{s}$ is the sum of the areas of all the peaks: not more than $0.3 \%$ of fructose is found; not more than $0.3 \%$ of topiramate related compound A is found; not more than $0.1 \%$ of any other individual impurity is found; and not more than $0.5 \%$ of total impurities is found. [NOTE-Discard any peak due to solvents.]

## Limit of sulfamate and sulfate-

Diluent-Prepare a mixture of high-purity water and acetonitrile ( $80: 20$ ).

Solution A-Transfer about 4 g . of sodium hydroxide to a $1000-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with High-Purity Water (see Reagents in Chemical Resis-tance-Glass Containers under Containers $\langle 661\rangle$ ) to volume, filter, and degas.

Solution B-Use filtered and degassed High-Purity Water.

Solution C-Dilute 50 mL of Solution $A$ to $100-\mathrm{mL}$ with High-Purity Water, filter, and degas.

Mobile phase-Use variable mixtures of Solution A, Solution B, and Solution C as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Sulfamic acid stock solution-Transfer about 60 mg , accurately weighed, of sulfamic acid to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Diluent to volume.

Sulfate stock solution-Transfer about 90.7 mg , accurately weighed, of potassium sulfate to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Diluent to volume.

Standard solution-Transfer 3.0 mL each of Sulfamic acid stock solution and Sulfate stock solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.>

Test solution-Transfer about 100 mg , accurately weighed, of Topiramate to a $10-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with High-Purity Water to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a conductivity detector, a $4.0-\mathrm{mm} \times 5-\mathrm{cm}$ guard column that contains packing L46 and a $4.0-\times 25-\mathrm{cm}$ column that contains packing L46. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows. Chromatograph the Standard solution, and record the peak areas as directed for Procedure: the relative retention time is 1.0 for the sulfate peak and about 0.27 for the sulfamate peak; and the relative standard deviation for replicate injections is not more than $2.0 \%$ for both the sulfate and sulfamate peaks.

| Time | Solution $A$ | Solution $B$ | Solution $C$ |  |
| :---: | :---: | :---: | :---: | :--- |
| $($ minutes $)$ | $(\%)$ | $(\%)$ | $(\%)$ | Elution |
| 0 | 0 | 95 | 5 | equilibration |
| $0-7.0$ | 0 | 95 | 5 | isocratic |
| $7.0-15.0$ | $0 \rightarrow 20$ | $95 \rightarrow 0$ | $5 \rightarrow 80$ | linear gradient |
| $15.0-20.0$ | 20 | 0 | 80 | isocratic |
| $20.0-20.1$ | $20 \rightarrow 0$ | $0 \rightarrow 95$ | $80 \rightarrow 5$ | linear gradient |
| $20.1-25.0$ | 0 | 95 | 5 | re-equilibration |

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas for the sulfate and sulfamate peaks. Calculate the percentage of sulfate and sulfamate in the portion of Topiramate taken by the formula:

$$
1000 F(C / W)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of potassium sulfate or sulfamic acid in the Standard solution; $F$ is the correction factor and is equal to 0.551 for sulfate and 0.989 for sulfamate; $W$ is the weight, in mg, of Topiramate taken; and $r_{i}$ and $r_{s}$ are the peak areas of the sulfate or sulfamate ion obtained from the Test solution and the Standard solution, respectively: not more that $0.10 \%$ of sulfate ion is found; and not more than $0.10 \%$ of sulfamate ion is found.

## Limit of residual solvents-

Standard stock solution-Dilute accurately measured volumes of acetone, isopropyl alcohol, acetonitrile, methylene chloride, $n$-hexane, ethyl acetate, and pyridine in dimethylformamide to obtain a solution having known concentrations, in $\mu \mathrm{L}$ per mL , of about $3.0,3.2,0.24,0.20,0.22$, 2.8 , and 0.01 , respectively.

Standard solution-Transfer 10.0 mL of Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with dimethylformamide to volume, and mix. Transfer 5 mL to a $20-\mathrm{mL}$ headspace vial, and crimp immediately.

Blank solution-Use dimethylformamide.
Test solution-Transfer about 0.25 g of Topiramate to a $20-\mathrm{mL}$ headspace vial. Add 5.0 mL of dimethylformamide, and crimp immediately.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The gas chromatograph is equipped with a headspace injector, a flame-ionization detector, and a $0.53-\mathrm{mm} \times 75-\mathrm{m}$ capillary column, the internal wall of which is coated with a $0.3-\mu \mathrm{m}$ film of liquid phase G43. The column temperature is programmed according to Table 1 .

Table 1. Column Temperature Program

|  |  |  | Temperature <br> Incease |
| :---: | :---: | :---: | :---: |
|  | Initial | Final | Increas <br> Temperature <br> (minutes) |
| $\left({ }^{\circ}\right)$ | Temperature <br> $\left({ }^{\circ}\right)$ | minute) |  |
| $0-12$ | 50 | 50 | isothermal |
| $12-22$ | 50 | 150 | 10 |
| $22-27$ | 150 | 150 | isothermal |
| $27-28.3$ | 150 | 230 | 60 |
| $28.3-33.3$ | 230 | 230 | isothermal |

The injection port temperature is maintained at $150^{\circ}$; the headspace sampler temperature is maintained at $80^{\circ}$; and the detector temperature is maintained at $250^{\circ}$. Nitrogen is used as the carrier gas at a flow rate of about 5 mL per minute and a split flow rate of about 15 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the retention time for pyridine is about 21 minutes; the relative retention times are about 0.4 for acetone, about 0.46 for isopropyl alcohol, about 0.49 for acetonitrile, about 0.51 for methylene chloride, about 0.58 for $n$-hexane, about 0.71 for ethyl acetate, and 1.0 for pyridine; the resolution, $R$, between adjacent peaks is not less than 1.0; and the relative standard deviation for consecutive injections of the Standard solution for all analytes is not less than $15.0 \%$. Chromatograph the Blank solution, and record the peak responses as directed for Procedure: there are no interfering peaks due to dimethylformamide.

Procedure-Inject a volume (about 1 mL of the headspace, using a heated gas-tight syringe) of the Standard solution and the Test solution into the chromatograph, record the chromatogram, and measure the areas for the major peaks. Calculate the percentage of each solvent per $g$ of Topiramate taken by the formula:

$$
500\left(C D_{U} / W\right)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mL per mL , of each solvent in the Standard solution; $D_{U}$ is the density, in mg per mL , of each solvent; $W$ is the weight, in mg , of Topiramate taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak areas of the corresponding analyte obtained from the Test solution and the Standard solution, respectively. Not more than $0.50 \%, 0.50 \%, 0.04 \%, 0.05 \%, 0.029 \%, 0.05 \%$, and
$0.02 \%$, (w/w) of acetone, isopropyl alcohol, acetonitrile, methylene chloride, $n$-hexane, ethyl acetate, and pyridine, respectively, is found.

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and water ( $1: 1$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Topiramate RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 2.0 mg per mL .

Assay preparation-Transfer about 50 mg of Topiramate, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with Mobile phase to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a refractive index detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 0.6 mL per minute. The detector and column temperatures are maintained at $50^{\circ}$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 1500 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{12} \mathrm{H}_{21} \mathrm{NO}_{8} \mathrm{~S}$ in the portion of Topiramate taken by the formula:

$$
25 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Topiramate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak resens areas obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## Briefing

Tripelennamine Hydrochloride, USP 27 page 1906. It is proposed to change the upper assay limit in the Definition from 100.5 percent to 102.0 percent so that it reflects the precision of the HPLC procedure and is consistent with other drug substances. It is proposed to revise the formula in the Assay to take into consideration the concentration of the Assay preparation and to specify that the calculation of the quantity is in percentage rather than in mg .
(PA1: K. Russo) RTS-40747-1

## Change to read:

» Tripelennamine Hydrochloride contains not less than 98.0 percent and not more than 100.5 percent
$\square_{102.0}$ percent $_{\text {1S (USP28) }}$
of $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{~N}_{3} \cdot \mathrm{HCl}$, calculated on the dried basis.

## Change to read:

## Assay-

Ion-pair solution-Prepare a 29 mM sodium 1-octanesulfonate solution.

Mobile phase-Transfer 530 mL of methanol to a suitable container, add 1.0 mL of $\mathrm{N}, \mathrm{N}$-dimethyloctylamine, and mix thoroughly. Add 430 mL of the Ion-pair solution, mix, and adjust with phosphoric acid to a pH of 3.0. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Benzaldehyde solution-Transfer 1.0 mL of benzaldehyde to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. Transfer 5.0 mL of the solution so obtained to a $100-$ mL volumetric flask, dilute with Mobile phase to volume, and mix.

System suitability preparation-Transfer about 50 mg of 2-benzylaminopyridine, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, add 10 mL of methanol, sonicate to dissolve, dilute with Mo bile phase to volume, and mix. Transfer 5.0 mL of the solution so obtained to a $100-\mathrm{mL}$ volumetric flask, add 5.0 mL of Benzaldehyde solution, dilute with Mobile phase to volume, and mix.

Standard preparation-Dissolve an accurately weighed quantity of USP Tripelennamine Hydrochloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.5 mg per mL .

Assay preparation-Transfer about 50 mg of Tripelennamine Hydrochloride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $242-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at $35^{\circ}$. [NOTE-New columns are conditioned with Mobile phase overnight before the initial use and may be reconditioned, as necessary, thereafter.] Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.75 for benzaldehyde and 1.0 for 2-benzylaminopyridine; and the resolution, $R$, between benzaldehyde and 2-benzylaminopyridine is not less than 3.5 . Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 10,000 theoretical plates; and the relative standard deviation for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg

■percentage, ${ }^{\text {1s }}$ (USP28)
of $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{~N}_{3} \cdot \mathrm{HCl}$ in the portion of Tripelennamine Hydrochloride taken by the formula:

$$
100 C\left(r_{t}+r_{s}\right)^{2}
$$

$$
\boldsymbol{\square} 100 C_{S}\left(r_{U} / r_{S}\right) / C_{U ■ 1 \mathrm{~S}(U S P 28)}
$$

in which $\epsilon$
${ }^{-} C_{U}$ and $C_{S ■ 1 S}$ (USP28) are the concentrations, in mg per mL , of
the Assay preparation and of ${ }_{1 \mathrm{~m}}$ (USP28)
USP Tripelennamine Hydrochloride RS in the Standard preparation, respectively; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Trolamine Salicylate, USP 27 page 1912. It is proposed to revise the Identification test to specify that the test solution and the Standard solution contain equivalent concentrations of salicylic
acid. It is also proposed to revise the Assay to clarify that the Assay preparation and the Standard preparation contain equivalent concentrations of salicylic acid.
(PA2: D. Bempong) RTS-41297-1

## Change to read:

Identification, Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ -
Solution: 1 mg per mL , in $0.1-\mathrm{cm}$ cells.
-The test solution and the Standard solution contain the equivalent of 1 mg of salicylic acid per mL .■1S (USP28) Medium: methanol.
Absorptivities do not differ by more than $1.0 \%$.

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of water and acetonitrile $(7: 3)$. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Salicylic Acid RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about $48 \mu \mathrm{~g}$ per mL .

Assay preparation-Transfer a portion of Trolamine Salicylate, equivalent to about 300 mg of $\mathrm{G}_{43} \mathrm{H}_{2+} \mathrm{NO}_{6}$

accurately weighed, to a $250-\mathrm{mL}$ volumetric flask, and dilute with methanol to volume. Transfer 2 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with methanol to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )——The liquid chromatograph is equipped with a $308-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 12.5-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at $30^{\circ}$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 8000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $\mathrm{C}_{13} \mathrm{H}_{21} \mathrm{NO}_{6}$ in the portion of Trolamine Salicylate taken by the formula:

$$
100\left(r_{U} / r_{S}\right)
$$

in which $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Briefing

Ursodiol, USP 27 page 1923. It is proposed to clarify the requirements in the test for Related compounds by specifying the limits for chenodiol and for lithocholic acid.
(PA4: E. Gonikberg) RTS-41331-1

## Change to read:

## Related compounds-

Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic silica gel.
Solvent-Prepare a mixture of acetone and water $(9: 1)$.
Standard solution 1-Prepare a solution of chenodiol in Solvent containing $600 \mu \mathrm{~g}$ per mL .
Standard solution 2-Prepare a solution of lithocholic acid in Solvent containing $20 \mu \mathrm{~g}$ per mL .

Test solution-Prepare a solution of Ursodiol in Solvent containing 40 mg per mL .

Diluted test solution-Quantitatively dilute 1 mL of the Test solution with Solvent to obtain a solution having a concentration of $40 \mu \mathrm{~g}$ per mL .
Developing solvent system: a mixture of chloroform, glacial acetic acid, and water ( $85: 15: 0.5$ )

Spray reagent: phosphomolybdic acid TS.
Procedure-Separately apply $10 \mu \mathrm{~L}$ each of Standard solution 1, Standard solution 2, the Test solution, and the Diluted test solution to a thin-layer chromatographic plate (see Thin Layer Chromatography under Chromatography $\langle 621\rangle$ ), and proceed as directed in the chapter, allowing the solvent front to move about threefourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and air-dry the plate. Spray the plate with phosphomolybdic acid TS, dry at $105^{\circ}$ for 5 minutes, and examine the plate: any secondary spot in the chromatogram of the Test solution having the same $R_{F}$ value as the principal spot from Standard solution 1 is not greater in size or intensity than that obtained from Standard solution 1:
$\square_{\text {not }}$ more than $1.5 \%$ of chenodiol is found. $\quad$ 1S (USP28) No secondary spot observed in the chromatogram of the Test solution having the same $R_{F}$ value as the principal spot from Standard solution 2 is greater in size or intensity than that obtained from Standard solution 2:
$\square_{\text {not }}$ more than $0.05 \%$ of lithocholic acid is found.■1S (USP28) No ${ }^{\text {other }} \mathbf{A U S P 2 7}$ secondary spot observed in the chromatogram of the Test Solution is greater in size or intensity than the principal spot obtained from the Diluted test solution: not more than $0.1 \%$
$\square_{\text {of }}$ any other impurity $\mathbf{m}_{1 S}$ (USP28)
is found.

## BRIEFING

Vinorelbine Injection. Because there is no existing USP monograph for this dosage form, a new monograph, based on validation data received, is being proposed. The liquid chromatographic procedure in the Assay and the test for Related compounds is based on analyses performed with a Delta-Pak C18 brand of L1 column. The typical retention times observed are about 10.8 minutes for the photodegradation product, 13.5 minutes for vinorelbine, and 16.2 minutes for vinorelbine related compound A .
(PA6: L. Evans; AMB: D. Porter; PSD: C. Okeke; NL: C. Barnstein) RTS—39915-1; 39915-2

## Add the following:

## ■Vinorelbine Injection

»Vinorelbine Injection is a sterile solution of Vinorelbine Tartrate in Water for Injection. It contains not less than 92.5 percent and not more than 105.0 percent of the labeled amount of $\mathrm{C}_{45} \mathrm{H}_{54} \mathrm{~N}_{4} \mathrm{O}_{8}$.

Caution-Handle Vinorelbine Injection with great care since it is a potent cytotoxic agent.

Packaging and storage-Preserve in single-dose Containers for Injections as described under Injections $\langle 1\rangle$, preferably of Type I glass, protected from light. Store in a refrigerator.

USP Reference standards $\langle 11\rangle$ —USP Endotoxin RS. USP Vinorelbine Related Compound A RS. USP Vinorelbine Tartrate $R S$.

Clarity and color of solution-The solution of Injection ( 10 mg per mL ) is clear. The absorbance of a solution of Injection, determined in a $1-\mathrm{cm}$ cell at 420 nm , with a suitable spectrophotometer, using water as the blank, is not greater than 0.060 .

Identification-The retention time and the UV spectrum of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Bacterial endotoxins $\langle 85\rangle$-It contains not more than 3.0 USP Endotoxin units per mg of vinorelbine.

Sterility $\langle 71\rangle$ —It meets the requirements when tested as directed for Membrane Filtration under Test for Sterility of the Product to be Examined.
$\mathbf{p H}\langle 791\rangle$ : between 3.3 and 3.8.
Particulate matter $\langle 788\rangle$ : meets the requirements for small-volume injections.

## Related compounds-

Mobile phase, System suitability solution, Standard solution, Diluted standard solution-Proceed as directed in the test for Related compounds under Vinorelbine Tartrate.

Chromatographic system-Proceed as directed in the Assay.

Test solution-Dilute a portion of Injection with Mobile phase to obtain a solution containing 1.0 mg of vinorelbine per mL.

Procedure_Proceed as directed for Procedure in the test for Related compounds under Vinorelbine Tartrate. Not more than $1.0 \%$ of the photodegradation product is found; not more than $0.3 \%$ of vinorelbine related compound A is
found; not more than $0.2 \%$ of any other individual impurity is found; and the sum of all impurities, excluding any peaks that are below the limit of quantitation $(0.02 \%)$, is not more than $2.0 \%$.

Other requirements-It meets the requirements under Injections $\langle 1\rangle$.

## Assay-

Phosphate buffer, Mobile phase, and System suitability solution-Proceed as directed in the test for Related compounds under Vinorelbine Tartrate.

Standard preparation-Dissolve an accurately weighed quantity of USP Vinorelbine Tartrate RS in water to obtain a solution having a known concentration of about 0.10 mg of vinorelbine (base) per mL.

Assay preparation-Transfer an accurately measured volume of Injection, equivalent to about 10 mg of vinorelbine, to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a diode-array detector and a $3.9-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The column temperature is maintained at $40^{\circ}$. The flow rate is about 1.0 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.8 for the photodegradation product, 1.0 for vinorelbine, and about 1.2 for vinorelbine related compound A ; and the relative retention between vinorelbine tartrate and vinorelbine is not less than 1.1.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the vinorelbine peaks, using a
diode-array detector. Calculate the quantity, in mg , of vinorelbine $\left(\mathrm{C}_{45} \mathrm{H}_{54} \mathrm{~N}_{4} \mathrm{O}_{8}\right)$ in each mL of the Injection taken by the formula:

$$
C(L / D)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Vinorelbine RS in the Standard preparation; $L$ is the labeled quantity, in mg , of vinorelbine in each mL of Injection taken; $D$ is the concentration, in mg per mL , of vinorelbine in the Assay preparation; and $r_{U}$ and $r_{S}$ are the peak responses at 267 nm obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## Briefing

Bacteriostatic Water for Injection, USP 27 page 1949 and page 3087 of the First Supplement; Sterile Water for Inhalation, USP 27 page 1950 and page 3087 of the First Supplement; Sterile Water for Injection, USP 27 page 1950 and page 3088 of the First Supplement; Water for Hemodialysis, page 3089 of the First Supplement. A revision is proposed in the test for Bacterial endotoxins to harmonize the text with that found in the European Pharmacopoeia and to be consistent with the language in the general chapter Bacterial Endotoxins Test $\langle 85\rangle$.
(PW: F. Barletta; AMB: D. Porter) RTS-41256-3

## Change to read:

Bacterial endotoxins $\langle 85\rangle$ - It contains more
$\boldsymbol{-}^{\text {less }_{15}}{ }_{\text {(USP28) }}$
than 0.5 USP Endotoxin Unit per mL.

## Briefing

Sterile Water for Inhalation, USP 27 page 1950 and page 3087 of the First Supplement-See briefing under Bacteriostatic Water for Injection.
(PW: F. Barletta; AMB: D. Porter) RTS-41256-2

## Change to read:

Bacterial endotoxins $\langle 85\rangle$ - It contains mere
$\square^{\text {less }_{115}}$ (USP28)
than 0.5 USP Endotoxin Unit per mL.

## Briefing

Sterile Water for Injection, USP 27 page 1950 and page 3088 of the First Supplement-See briefing under Bacteriostatic Water for Injection.
(PW: F. Barletta; AMB: D. Porter) RTS-41256-1

## Change to read:

Bacterial endotoxins $\langle 85\rangle$-It contains more
$\square^{-} \operatorname{less}_{115}$ (USP28)
than 0.25 USP Endotoxin Unit per mL .
intent of the Definition in this monograph is to prevent the use of waste or sewer water; to prevent the use of recycling waste or nonpotable water; and to prevent the use of drinking water that does not meet some basic minimum acceptable norm. This proposal extends the minimum acceptable norms to those specified by the WHO.
(PW: F. Barletta) RTS-41213-1

## Change to read:

» Purified Water is water obtained by a suitable process. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or comparable regulations of the European Union, Japan,

## $\square_{\text {or the World Health Organization's Guidelines }}$

## for Drinking Water Quality.n.1S (USP28)

It contains no added substance.
NOTE-Purified Water is intended for use as an ingredient of official preparations and in tests and assays unless otherwise specified (see Water in Ingredients and Processes and in Tests and Assays under General Notices and Requirements). Where used for sterile dosage forms, other than for parenteral administration, process the article to meet the requirements under Sterility Tests $\langle 71\rangle$, or first render the Purified Water sterile and thereafter protect it from microbial contamination. Do not use Purified Water in preparations intended for parenteral administration. For such purposes use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection. The tests for Total organic carbon and Conductivity apply to Purified Water produced on site for use as an ingredient of official preparations and in tests and assays. Purified Water packaged in bulk for commercial use elsewhere meets the requirements of all of the tests under Sterile Purified Water, except Labeling and Sterility $\langle 71\rangle$.

Purified Water, USP 27 page 1950 and page 3089 of the First Supplement; Water for Injection, USP 27 page 1949 and page 3087 of the First Supplement. As a result of discussions during and subsequent to the March 3, 2004 meeting of the Pharmaceutical Waters Expert Committee, it is proposed to revise the Definition to include drinking water that meets the WHO guidelines. The

## BRIEFING

Sterile Purified Water, USP 27 page 1950, page 3089 of the First Supplement, and page 947 of PF 30(3) [May-June 2004]. It is proposed to clarify the preparation of the control in the test for Chloride.
(PW: F. Barletta) RTS-41288-1

## Change to read:

Ammonia-For containers having a fill volume of less than 50 mL , dilute 50 mL of it with 50 mL of High-Purity Water (see Reagents under Containers $\langle 661\rangle$ ), and use this dilution as the test solution; where the fill volume is 50 mL or more, use 100 mL of it as the test solution. To 100 mL of the test solution add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing $30 \mu \mathrm{~g}$ of added ammonia : ffrmished by adding 1.76 mL of 1.0 N amme nitm hydroxide) (1s (uspoz)
-(furnished by adding 1 mL of the final solution prepared by diluting 3.0 mL of ammonia TS with High-Purity Water to $100 \mathrm{~mL} ; 1.0 \mathrm{~mL}$ of this solution is further diluted to 100 $\mathrm{mL})_{15}$ (USP28)
in 100 mL of High -Purity Water. This corresponds to a limit of 0.6 mg per L for containers having a fill volume of less than 50 mL and 0.3 mg per L where the fill volume is 50 mL or more.

## Change to read:

Chloride-To 20 mL in a color-comparison tube add 5 drops of nitric acid and 1 mL of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 mL of
$\boldsymbol{m}_{\text {a solution of sodium chloride } \mathrm{in}_{1 \mathrm{IS}} \text { (USP28) }}$
High-Purity Water (see Reagents under Containers $\langle 661\rangle$ ), containing $10 \mu \mathrm{~g}$ of Cl ( 0.5 mg per L),
$-825 \mu \mathrm{~g}$ of sodium chloride per $\mathrm{L}(10 \mu \mathrm{~g}$ of Cl in 20
mL ), ${ }^{1 \mathrm{~S}}$ (USP28)
viewed downward over a dark surface with light entering the tubes from the sides.

## Briefing

Water for Hemodialysis, page 3089 of the First SupplementSee briefing under Bacteriostatic Water for Injection.
(PW: F. Barletta; AMB: D. Porter) RTS-41256-4

## Change to read:

Bacterial endotoxins $\langle 85\rangle$ - It contains mere
$\square^{-} \operatorname{less}_{\text {■1S (USP28) }}$
than 2 USP Endotoxin Units per mL.

## Briefing

Excipients, USP and NF Excipients, Listed by Category, $N F$ 22 page 2809 and page 961 of $P F 30(3)$ [May-June 2004]. The proposed revision complements the proposed new monograph, Polydecene, which appears elsewhere in this number of $P F$.

$$
(\mathrm{EMC}) \quad \text { RTS-39281-1 }
$$

## Change to read:

Acidifying Agent
Acetic Acid
Acetic Acid, Glacial
Gitric Acid
${ }^{\Delta}$ Citric Acid, Anhydrous $\mathbf{\Delta N F 2 3}$
${ }^{\Delta}$ Citric Acid Monohydrate $\mathbf{\Delta N F 2 3}$
Fumaric Acid
Hydrochloric Acid
Hydrochloric Acid, Diluted
Malic Acid
Nitric Acid
Phosphoric Acid
Phosphoric Acid, Diluted
Propionic Acid
Sulfuric Acid
Tartaric Acid

## Change to read:

Antifoaming Agent
Dimethicone
${ }^{\text {■ Palmitic }}$ Acid $_{\text {■ }}{ }^{1 S}$ (NF23)
Simethicone

## Change to read:

Antimicrobial Preservative
Benzalkonium Chloride
Benzalkonium Chloride Solution
Benzethonium Chloride
Benzoic Acid
Benzyl Alcohol
Butylparaben
${ }^{\Delta}$ Cetrimonium Bromide $\boldsymbol{\Delta N F 2 2}$
Cetylpyridinium Chloride
Chlorobutanol
Chlorocresol
Cresol
Ethylparaben
Methylparaben
Methylparaben Sodium
Phenol
${ }^{\Delta}$ 2-Phenoxyethanol $\mathbf{A N F 2 3}$
Phenylethyl Alcohol
Phenylmercuric Acetate
Phenylmercuric Nitrate
Potassium Benzoate
Potassium Sorbate
Propylparaben
Propylparaben Sodium
Sodium Benzoate
Sodium Dehydroacetate
Sodium Propionate
Sorbic Acid
Thimerosal
Thymol

## Change to read:

Antioxidant
Ascorbic Acid
Ascorbyl Palmitate
Butylated Hydroxyanisole
Butylated Hydroxytoluene
Hypophosphorous Acid
Monothioglycerol
Potassium Metabisulfite
Propyl Gallate
Sodium Formaldehyde Sulfoxylate
Sodium Metabisulfite
${ }^{\mathbf{\Delta}}$ Sodium Sulfite ${ }_{\mathbf{A} N F 23}$
Sodium Thiosulfate
Sulfur Dioxide
Tocopherol
Tocopherols Excipient

## Change to read:

Buffering Agent
Acetic Acid
${ }^{\boldsymbol{\Delta}}$ Adipic Acid ${ }_{\mathbf{\Delta N F 2 3}}$ Ammonium Carbonate Ammonium Phosphate
Boric Acid
Gitric Acid
${ }^{\Delta}$ Citric Acid, Anhydrous ${ }_{\Delta N F 23}$
${ }^{\mathbf{4}}$ Citric Acid Monohydrate $\mathbf{\Delta N F 2 3}$
Lactic Acid
Phosphoric Acid
Potassium Citrate
Potassium Metaphosphate
Potassium Phosphate, Monobasic
Sodium Acetate
Sodium Citrate
Sodium Lactate Solution
Sodium Phosphate, Dibasic
Sodium Phosphate, Monobasic
${ }^{\mathbf{\Delta}}$ Succinic Acid $_{\mathbf{\Delta N F 2 3}}$

## Change to read:

## Coating Agent

-Ammonio Methacrylate Copolymer ${ }_{\text {■S (NF23) }}$
-Ammonio Methacrylate Copolymer Dispersion ■S $^{\text {2S (NF22) }}$
Carboxymethylcellulose, Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
Gellulese Acetate Butyrate
${ }^{\mathbf{4}}$ Cellaburate $_{\mathbf{\Delta N F 2 3}}$
Cellulose Acetate Phthalate (see Cellacefate)
${ }^{\boldsymbol{4}}$ Copovidone $_{\mathbf{\Delta N F 2 3}}$
${ }^{\boldsymbol{\Delta}}$ Corn Syrup Solids ${ }_{\mathbf{\Delta N F 2 3}}$
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose ${ }^{\mathbf{\Delta}}$ (see Hypromellose) $\mathbf{\Delta N F 2 2}$
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
${ }^{\mathbf{4}}$ Hypromellose (formerly Hydroxypropyl Methylcellu-
lose) $\boldsymbol{\Delta A F 2 2}$
${ }^{\mathbf{4}}$ Hypromellose Acetate Succinate ${ }_{\mathbf{\Delta N F 2 3}}$
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate Shellac
${ }^{\boldsymbol{\Delta}}$ Starch, Pregelatinized Modified ${ }_{\Delta N F 23}$
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

## Change to read:

## Emollient

Alkyl (C12-15) Benzoate
-Hydrogenated Soybean Oil!1S (NF22)
■Polydecene $_{\mathbf{■ 1 S}^{1(N F 23)}}$

## Change to read:

Emulsifying and/or Solubilizing Agent Acacia
Cholesterol
Diethanolamine (Adjunct)
$\square_{\text {Diethylene Glycol Stearates }}^{1 S}$ (NF22) $^{\text {( }}$
$\square_{\text {Ethylene Glycol Stearates }}^{\square} 1 \mathrm{~S}$ (NF22)
${ }^{\Delta}$ Glyceryl Distearate ${ }_{\mathbf{A} N F 22}$
${ }^{\Delta}$ Glyceryl Monolinoleate ANF22
$\Delta_{\text {Glyceryl Monooleate }}^{\mathbf{A N F 2 2}}$
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 40 Stearate
-Polyoxyl Lauryl Ether ${ }_{\text {1S (NF22) }}$
-Polyoxyl Stearyl Ether ${ }_{\text {■ }}$ (NF22)
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
■Sodium Cetostearyl Sulfate $_{\mathbf{■}_{1 S} \text { (NF22) }}$
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Stearic Acid
Trolamine
Wax, Emulsifying

## Change to read:

## Flavors and Perfumes

Anethole
Benzaldehyde
Ethyl Vanillin

- Maltol $_{\text {■ }}^{1 S}$ (NF23)

Menthol
Methyl Salicylate
Monosodium Glutamate

Peppermint
Peppermint Oil
Peppermint Spirit
Rose Oil
Rose Water, Stronger
Thymol
Vanillin

## Change to read:

## Humectant

${ }^{\Delta}$ Corn Syrup Solids ${ }_{\mathbf{A N F 2 3}}$
Glycerin
Hexylene Glycol
Propylene Glycol
Sorbitol
${ }^{\boldsymbol{\Delta}}$ Sorbitol, Anhydrized Liquid $\mathbf{\Delta N F 2 3}$

## Change to read:

Ointment Base
Gapryloeaproyl Macrogolglycerides
${ }^{\text {4 }}$ Caprylocaproyl Polyoxylglycerides $\mathbf{\Delta N F 2 3}$
Diethylene Glycol Monoethyl Ether
${ }^{\text {L }}$ Lauroyl Macrogolglycerides $\mathbf{\Delta N F 2 3}$
Lineoyl Maerogelglyeerides
${ }^{\mathbf{\Delta}}$ Lineoyl Polyoxylglycerides ${ }_{\Delta N F 23}$
Lanolin
Ointment, Hydrophilic
Ointment, White
Oleoyl Macregolglyeerides
${ }^{\boldsymbol{\Delta}}$ Oleoyl Polyoxylglycerides ${ }_{\mathbf{\Delta N F 2 3}}$
Ointment, Yellow
Polyethylene Glycol Ointment
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White
■Polydecene $_{\mathbf{m}_{1 S}(N F 23)}$
Rose Water Ointment
Squalane
Stearoyl Macrogolglycerides
${ }^{\text {a }}$ Stearoyl Polyoxylglycerides ${ }_{\Delta N F 23}$
Vegetable Oil, Hydrogenated, Type II

## Change to read:

Plasticizer
Acetyltributyl Citrate
Acetyltriethyl Citrate
Castor Oil
Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin

Polyethylene Glycol
Propylene Glycol
${ }^{\mathbf{\Delta}}$ Sorbitol, Anhydrized Liquid ${ }_{\mathbf{A N F 2 3}}$
Triacetin
Tributyl Citrate
Triethyl Citrate

## Change to read:

## Polymer Membrane

■Ammonio Methacrylate Copolymer $_{\mathbf{I S ~}_{\text {(NF23) }}}$
$■_{\text {Ammonio Methacrylate Copolymer Dispersion }}^{\text {■ }^{2 S} \text { (NF22) }}$ Cellulose Acetate

Cellulose Acetate Butyrate
${ }^{\boldsymbol{\Delta}}$ Cellaburate $_{\mathbf{A N F 2 3}}$
Change to read:
Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)
${ }^{\boldsymbol{\Delta}}$ Sodium Tartrate $\mathbf{A N F 2 3}$

Change to read:

## Solvent

Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol
Capryleaproyl Macregelglyeerides
${ }^{\boldsymbol{4}}$ Caprylocaproyl Polyoxylglycerides ${ }_{\mathbf{\Delta N F 2 3}}$
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
${ }^{\mathbf{4}}$ Lauroyl Macrogolglycerides ${ }_{\mathbf{A N F 2 3}}$
Lineoyl Macrogolglycerides
${ }^{\mathbf{\Delta}}$ Lineoyl Polyoxylglycerides $\mathbf{\Delta N F 2 3}$
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Oleoyl Maeregolglycerides
${ }^{\boldsymbol{\Delta}}$ Oleoyl Polyoxylglycerides ${ }_{\mathbf{A} N F 23}$ Peanut Oil
-Polydecene $_{\text {1S (NF23) }}$
Polyethylene Glycol

Propylene Glycol
Sesame Oil
Stearoyl Macregelglyeerides
${ }^{\mathbf{4}}$ Stearoyl Polyoxylglycerides $\mathbf{\Delta N F 2 3}$
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

## Change to read:

Suspending and/or Viscosity-increasing Agent
Acacia
Agar
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
${ }^{\Delta}$ Carbomer Homopolymer $\mathbf{A}_{\mathbf{A N F 2 3}^{\prime}}$
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium
${ }^{\boldsymbol{\Delta}}$ Corn Syrup Solids ${ }_{\triangle N F 23}$
Dextrin
Gelatin
Gellan Gum $_{1 \text { (NF22) }}$
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose ${ }^{\mathbf{\Delta}}$ (see Hypromellose) $\mathbf{\Delta N F 2 2}^{2}$
${ }^{\wedge}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) $\mathbf{A}_{N F 22}$
Magnesium Aluminum Silicate
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
${ }^{\mathbf{4}}$ Starch, Corn $_{\mathbf{\Delta N F 2 3}}$
${ }_{\Delta}$ Starch, Potato $_{\mathbf{\Delta} N F 23}$
${ }^{\boldsymbol{\Delta}}$ Starch, Tapioca $\mathbf{A N F 2 2}$
${ }^{\Delta}$ Starch, Wheat ${ }_{\Delta N F 23}$
Tragacanth
Xanthan Gum

## Change to read:

## Sweetening Agent

${ }^{\boldsymbol{\Delta}}$ Acesulfame Potassium $\mathbf{A N F 2 3}$
Aspartame
${ }^{\Delta}$ Aspartame Acesulfame $\mathbf{A N F 2 2}$
${ }^{\mathbf{4}}$ Corn Syrup Solids $\mathbf{\Delta N F 2 3}$
Dextrates
Dextrose
Dextrose Excipient
Fructose
${ }^{\mathbf{4}}$ Galactose $\mathbf{\Delta N F 2 3}$

- Maltose $_{\text {■ } 2 \text { S (NF22) }}$

Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

## Change to read:

## Tablet Binder

Acacia
Alginic Acid
-Ammonio Methacrylate Copolymer ${ }_{\text {1S (NF23) }}$
■Ammonio Methacrylate Copolymer Dispersion $_{\mathbf{■ S S}^{\text {(NF22) }}}$
${ }^{\boldsymbol{\Delta}}$ Carbomer Homopolymer $\mathbf{A}_{\mathbf{A} N 23}$
Carboxymethylcellulose, Sodium
Cellulose, Microcrystalline
${ }^{\Delta}$ Copovidone $\mathbf{\Delta N F 2 3 ~}$
${ }^{\mathbf{4}}$ Corn Syrup Solids ${ }_{\mathbf{\Delta N F} 23}$
Dextrin
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
Hydroxypropyl Methylcellulose $^{\boldsymbol{\Delta}}$ (see Hypromellose) ${ }_{\text {aNF22 }}$
${ }^{\boldsymbol{\Delta}}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) ${ }_{\Delta N F 22}$
${ }^{\mathbf{\Delta}}$ Hypromellose Acetate Succinate $\mathbf{\Delta N F 2 3}$

- Maltose $_{\text {■2S (NF22) }}$

Methylcellulose
Polyethylene Oxide
Povidone
${ }^{\boldsymbol{\Delta}}$ Starch, Corn $_{\mathbf{\Delta N F 2 3}}$
${ }^{\mathbf{4}}$ Starch, Potato $_{\mathbf{\Delta N F 2 3}}$
Starch, Pregelatinized
${ }^{\boldsymbol{\Delta}}$ Starch, Pregelatinized Modified ${ }_{\Delta N F 23}$
${ }^{\boldsymbol{\Delta}}$ Starch, Tapioca $\mathbf{\Delta N F 2 2}$
${ }^{\boldsymbol{\Delta}}$ Starch, Wheat $\mathbf{\Delta N F 2 3}^{\text {a }}$
Syrup
Change to read:
Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered
${ }^{\boldsymbol{\Delta}}$ Corn Syrup Solids ${ }_{\mathbf{\Delta N F 2 3}}$
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose
■ Maltose $_{\text {■2S }}{ }^{\text {(NF22) }}$
Mannitol
Sorbitol
Stareh
${ }^{\Delta}$ Starch, Corn $_{\mathbf{\Delta N F 2 3}}$
${ }^{\Delta}$ Starch, Potato ${ }_{\mathbf{A N F 2 3}}$
Starch, Pregelatinized
${ }_{\Delta}^{\Delta}$ Starch, Pregelatinized Modified $\boldsymbol{\Delta N F 2 3}$
${ }^{\boldsymbol{\Delta}}$ Starch, Tapioca ${ }_{\mathbf{\Delta N F 2 2}}$
${ }^{\Delta}$ Starch, Wheat ${ }_{\Delta N F 23}$
Sucrose
Sugar, Compressible
Sugar, Confectioner's

## Change to read:

## Tablet Disintegrant

Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone

- Maltose $_{\text {n2S (NF22) }}$

Polacrilin Potassium
Sodium Starch Glycolate
Stareh
${ }^{\boldsymbol{4}}$ Starch, Corn ${ }_{\mathbf{\Delta N F 2 3}}$
${ }^{\mathbf{4}}$ Starch, Potato $\mathbf{A N F 2 3}^{\boldsymbol{N}}$
Starch, Pregelatinized
${ }_{\Delta}$ Starch, Pregelatinized Modified $_{\Delta N F 23}$
${ }^{\boldsymbol{4}}$ Starch, Tapioca ${ }_{\mathbf{A} N 22}$
${ }^{\boldsymbol{\Delta}}$ Starch, Wheat $\mathbf{\Delta N F 2 3}^{\text {N }}$
Change to read:

## Tonicity Agent

${ }^{\boldsymbol{\Delta}}$ Corn Syrup Solids $\mathbf{\Delta N F 2 3}$
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

## Change to read:

## Vehicle

FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound
${ }^{\text {4 }}$ Corn Syrup Solids ${ }_{\mathbf{\Delta N F 2 3}}$
Peppermint Water
Sorbitol Solution
Syrup
oleaginous
Alkyl (C12-15) Benzoate
Almond Oil
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
$\square_{\text {Polydecene }}^{1 \mathrm{IS}(\mathrm{NF} 23)}$
Safflower Oil
Sesame Oil
Soybean Oil
Squalane
SOLID CARRIER
Sugar Spheres
STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

MONOGRAPHS (NF)

BRIEFING


#### Abstract

Adipic Acid, page 593 of $P F$ 30(2) [Mar.-Apr. 2004]. It is proposed to add a USP Reference standards $\langle 11\rangle$ section to this monograph. (EMC: K. Russo) RTS-41311-1


## Add the following:

## -Adipic Acid


$\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{4} \quad 146.1$
Hexanedioic acid.

1,4-Butanedicarboxylic acid [124-04-9].
» Adipic Acid contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{4}$, calculated on the dried basis.

Packaging and storage-Store in tight containers.

## Add the following:

-USP Reference standards $\langle 11\rangle —$ USP Adipic Acid
$R S$.n| (NF23)
Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
Melting range $\langle 741\rangle$ : between $151^{\circ}$ and $154^{\circ}$.

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ to constant weight: it loses not more than $0.2 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.

## Limit of nitrates-

Standard stock solution-Dissolve about 815 mg of potassium nitrate in 500 mL of water, and mix.

Standard solution-Dilute 1 mL of the Standard stock solution with water to 10 mL , and mix. Dilute 1 mL of this solution with water to 50 mL to obtain a solution containing 2 ppm of nitrate. Use 1.5 mL of this solution, and proceed as directed for Procedure, beginning with "add 2 mL of concentrated ammonia".

Test solution-Transfer 5 g of Adipic Acid to a $50-\mathrm{mL}$ volumetric flask. Dissolve in water, with heating, and dilute with water to volume. Allow to cool and crystallize, then pass through a sintered-glass filter. Wash the filter with water, and collect the filtrate and washings until a volume of 50 mL is obtained. [NOTE-This solution is to be used in the tests for Chloride, Sulfate, Iron, and Heavy metals.]

Procedure-To 1.0 mL of the Test solution add 2 mL of concentrated ammonia, 0.5 mL of manganese sulfate solution (1 in 100), 1 mL of sulfanilamide solution (1 in 100), and dilute with water to 20 mL . Add 100 mg of zinc powder, and cool in an ice bath for 30 minutes, shaking periodically. Filter 10 mL of the solution, and cool in an ice bath, then add 2.5 mL of hydrochloric acid and 1 mL of a naphthylethylenediamine dihydrochloride solution (1 in 100). Allow to stand at room temperature for 15 minutes: the color of the Test solution is not darker than a concomitantly prepared Standard solution; and the limit is $0.003 \%$. The test is invalid if a concomitantly prepared blank solution (prepared using 1 mL of water instead of 1 mL of the Test solution) is darker than a solution containing 2 mg of potassium permanganate per L .

Chloride $\langle 221\rangle$ —A 5-mL portion of the Test solution from the test for Limit of nitrates shows no more chloride than a corresponding $0.14-\mathrm{mL}$ portion of 0.020 N hydrochloric acid: the limit is $0.02 \%$.

Sulfate $\langle 221\rangle$-A $5-\mathrm{mL}$ portion of the Test solution from the test for Limit of nitrates shows no more sulfate than a corresponding $0.26-\mathrm{mL}$ portion of 0.020 N sulfuric acid: the limit is $0.05 \%$.

Iron $\langle 241\rangle$-Use a $10-\mathrm{mL}$ portion of the Test solution from the test for Limit of nitrates: the limit is $0.001 \%$.

Heavy metals, Method $I\langle 231\rangle: \quad 0.001 \%$.
Assay-Dissolve 60 mg of Adipic Acid in 50 mL of water.
Add 0.2 mL of phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS to a permanent pale pink endpoint. Each mL of 0.1 N sodium hydroxide is equivalent to 7.31 mg of $\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{4 \cdot \boldsymbol{\Delta} N F 23}$

## BriEFING

Betadex, NF 22 page 2831 and page 595 of PF 30(2) [Mar.Apr. 2004]; Sodium Starch Glycolate, $N F 22$ page 2933. It is proposed to revise the Identification section to change the name of the iodine and potassium iodide TS to iodine and potassium iodide TS 1, which appears in the section Reagents, Indicators, and Solutions in this issue of PF. See also the Harmonization section of this $P F$ for the proposed revision of the monograph for Sodium Starch Glycolate.
(BPC: M. Marques) $\quad$ RTS-41175-2

## Change to read:

» Betadex is a nonreducing cyclic compound composed of seven alpha-(1-4) linked D-glucopyranosyl units. It contains not less than 98.0 percent and not more than 101.0

- $102.0_{\Delta N F 23}$
percent of $\left(\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{5}\right)_{7}$, calculated on the anhydrous basis.


## Change to read:

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$ : on undried specimen.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

C: Prepare a test solution in water containing 15 mg per mL . Separately apply $2 \mu \mathrm{~L}$ each of the test solution and a Standard solution of USP Beta Cyclodextrin RS in water containing 5 mg per mL to a suitable thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ) coated with a $0.25-\mathrm{mm}$ layer of chromatographic silica gel. Allow the applications to dry, and develop the chromatogram in a solvent system consisting of a mixture of $n$-propyl alcohol, water, ethyl acetate, and ammonium hydroxide ( $6: 3: 1: 1$ ) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with iodine and potassium iodide TS
-1:-1S (NF23)
the $R_{F}$ value of the principal spot obtained from the test solution corresponds to that obtained from the Standard solution.

D: Mix 0.2 g with 2 mL of iodine TS, warm in a water bath to dissolve the test specimen, and allow to stand at room temperature: a yellow-brown precipitate is formed.

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and water ( $65: 35$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard solution-Dissolve 2.0 g of glycerol in water contained in a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Pass through a $0.45-\mu \mathrm{m}$ membrane filter. Use fresh, or store in a freezer, thaw in hot water, and mix.

Standard preparation-Dissolve an accurately weighed quantity of USP Beta Cyclodextrin RS in water, and quantitatively dilute with water to obtain a solution having a known concentration of about 10 mg per mL . Use fresh, or store in a freezer, thaw in hot water, and mix. Mix 1.0 mL of this solution with 1.0 mL of Internal standard solution.

System suitability preparation-Prepare a solution in water containing about 5 mg per mL each of USP Alpha Cyclodextrin RS and USP Beta Cyclodextrin RS. Pass through a $0.45-\mu \mathrm{m}$ membrane filter.

Assay preparation-Transfer about 1 g of Betadex, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Pass this solution through a $0.45-\mu \mathrm{m}$ membrane filter. Mix 1.0 mL with 1.0 mL of Internal standard solution.

Chromatographic system (see Chromatography. $\langle 621\rangle$ )-The liquid chromatograph is equipped with a refractive index detector that is maintaned at constant temperature of $25^{\circ}$, a $4.6 \mathrm{~mm}-*$ 25 cm column that contains $10 \mu \mathrm{~mm}$ packing L 8 , and a guard col thm that contains packing $\mathrm{L8}$. The columms are maintained at a mL per minute.
${ }^{\Delta}$ The chromatograph is equipped with a refractive index detector, a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $10-\mu \mathrm{m}$ packing L8, and a guard column that contains packing L8. The columns and, if necessary, the detector are maintained at a constant temperature of about $25 \pm 2^{\circ}$, and the flow rate is about 2.0 mL per minute. If the detector or the columns are operated at a temperature other than $25 \pm 2^{\circ}$, the system also must be shown to meet all system suitability require-
ments. $\Delta N F 23$
Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the alpha cyclodextrin and beta cyclodextrin peaks exhibit baseline separation, the relative retention times being about 0.8 and 1.0 , respectively; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Assay preparation and the Standard preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\left(\mathrm{C}_{6} \mathrm{H}_{10} \mathrm{O}_{5}\right)_{7}$ in the portion of Betadex taken by the formula:

$$
100 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of anhydrous beta cyclodextrin in the Standard preparation, as determined from the concentration of USP Beta Cyclodextrin RS, corrected for moisture content by a titrimetric water determination; and $R_{U}$ and $R_{S}$ are the peak response ratios of the beta cyclodextrin peak to the internal standard peak obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Caprylocaproyl Polyoxylglycerides, page 688 of $P F$ 29(3) [May-June 2003]. It is proposed to adopt Caprylocaproyl Polyoxylglycerides as the title of this proposed new monograph. A monograph on this excipient first appeared in Pharmacopeial Previews in PF 24(5) [Sept.-Oct. 1998] and under In-Process Revision in PF 28(4) [July-Aug. 2002] with the name Caprylocaproyl Macrogolglycerides and, subsequently, under In-Process Revision in PF 29(3) [May-June 2003] with the name Caprylocaproyl Polyoxylglycerides. The use of the prefix "Polyoxyl-" instead of "Macro-gol-" is consistent with terminology used in the United States, particularly in the titles of other monographs on excipients. The name "Polyethylene Glycol" and the "Polyoxyl-" designation for esters and ethers formed with polyethylene glycol and organic acids and alcohols or polyols replace the "Macrogol" name that is used for polyethylene glycol in some locations outside the United States.

Caprylocaproyl Polyoxylglycerides is proposed by the Expert Committee on Nomenclature and Labeling to be the title of the monograph for this excipient, which is proposed for inclusion in the First Supplement to USP 28-NF 23, but with an official date
of April 1, 2010, which is sixty months later than the April 1, 2005, official date of the First Supplement to USP 28-NF 23. The 60month extension will provide the time deemed necessary for labeling changes to be made for the article and the numerous preparations in which it is an ingredient, and for practitioners, consumers, and regulatory agencies to become familiar with the terminology.

Also, on the basis of comments received, changes are proposed to improve the procedure and visualization of results obtained in the Thin-Layer Chromatographic Identification Test procedure (Identification test $B$ ). Comparison is specified with Rhodamine 6G, which replaces reagent Rhodamine B; and visualization to compare developed spots obtained from the Test solution and a Standard solution replaces the designation of approximate numerical $R_{F}$ values for components of the polyoxylglycerides.
(EMC: C. Sheehan; NL: C. Barnstein) RTS-41339-1

## Add the following:

## ■Caprylocaproyl Macrogolglycerides Polyoxylglycerides

(Monograph under this new title-to become official April 1, 2010)
(Currently, there is no official NF monograph for this article)

## » Caprylocaproyl Macrogolglyeerides Polyoxyl-

 glycerides are mixtures of monoesters, diesters, and triesters of glycerol and monoesters and diesters of maerogols polyethylene glycols with a mean relative molecular weight between 200 and 400 . They are produced by partial alcoholysis of medium-chain triglycerides with macregel, polyethylene glycol, by esterification of glycerol and maergel polyethylene glycol with caprylic acid and capric acid, or as a mixture of glycerol esters and ethylene oxide condensate with caprylic acid and capric acid. The average molecular weight is not less than 90.0 percent and not more than 110.0 percent of the labeled nominal value.Packaging and storage-Preserve in tight containers, protected from light and moisture. Store at controlled room temperature.

Labeling-Label it to indicate the average nominal molecular weight of esters as part of the official title. The label also indicates the nominal hydroxyl value and saponification value.

USP Reference standards $\langle 11\rangle$ —USP Caprylocaproyl Macrogolgherides Polyoxylglycerides RS.

## Identification-

A: - 197 K$\rangle$ Infrared Absorption $\langle 197 \mathrm{~F}\rangle$.
B: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -
Test solution: $\quad 0.05 \mathrm{~g}$ per mL , prepared by dissolving 1.0 g of Caprylocaproyl Macergerides Polyoxylglycerides in methylene chloride, and diluting with methylene chloride to 20 mL .

Developing solvent system: a mixture of ether and solvent hexane ( $7: 3$ ).

Procedure-Proceed as directed in the chapter (except for Caprylocaproyl Polyglycerides apply $50 \mu \mathrm{~L}$ of the Test solution and $50 \mu \mathrm{~L}$ of the Standard solution). Then spray the plate with reagent solution, prepared by dissolving 0.01 g of rhodamine B in 100 mL of aleohel, and examine the plate tuder UV light at 365 nm : the chromatogram of the Test solution exhibits a spot comesponding to triglyeerides at an $R_{\mu}$ value of about 0.9 and spets at $R_{\mu}$ value of about $0.7,0.6,0.1$, and 0 correspending to 1,3 -diglyeerides, 1,2 diglyeerides, menoglyeerides, and esters of macrogols, polyethylene glyeols, respectively. rhodamine 6 G in 100 mL of isopropyl alcohol, and examine the plate under UV light at 365 nm : the $R_{F}$ values of the principle spots obtained from the Test solution correspond to those obtained from the Standard solution.

Acid value $\langle 401\rangle$ : not more than 2.0 , determined on a $2.0-\mathrm{g}$ specimen.

Hydroxyl value $\langle 401\rangle$-The hydroxyl value, between 170 and 205, does not differ by more than 20 units from the nominal value, when determined on a $1.0-\mathrm{g}$ specimen, accurately weighed.
Iodine value $\langle 401\rangle$ : not more than 2.0.
Peroxide value $\langle 401\rangle$ : not more than 6.0, determined on a $2.0-\mathrm{g}$ specimen.

Saponification value $\langle 401\rangle$-The saponification value, between 85 and 105 , does not differ by more than 10 units from the nominal value, determined on a $2.0-\mathrm{g}$ specimen.

Fatty acid composition $\langle 401\rangle$ : between $50 \%$ and $80 \%$ of caprylic acid is found; not more than $2.0 \%$ of caproic acid is found; between $20 \%$ and $50 \%$ of capric acid is found; not more than $3.0 \%$ of lauric acid is found; and not more than $1.0 \%$ of myristic acid is found.

Water, Method $I\langle 921\rangle$ : not more than $1.0 \%$, determined on a $1.0-\mathrm{g}$ specimen.

Total ash $\langle 561\rangle$ : not more than $0.1 \%$, determined on a $1.0-\mathrm{g}$ specimen.

Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.001 \%$.
Limit of free ethylene oxide and dioxane-
Caution-Ethylene oxide is toxic and flammable. Prepare all solutions in a well-ventilated hood. The operator must protect hands and face by wearing polyethylene protective gloves and an appropriate face mask. Store all solutions in hermetic containers, and refrigerate at a temperature between $4^{\circ}$ and $8^{\circ}$.

NOTE-Perform all determinations three times.
Ethylene oxide stock solution-Into a dry, clean test tube, cooled in a mixture of 1 part of sodium chloride and 3 parts of crushed ice, introduce a slow current of ethylene oxide gas, allowing condensation onto the inner wall of the test
tube. Using a glass syringe, previously cooled to $-10^{\circ}$, transfer about $300 \mu \mathrm{~L}$ of liquid ethylene oxide, equivalent to about 0.25 g , to 50 mL of polyethylene glycol 200 . Determine the absorbed quantity of ethylene oxide by weighing before and after absorption. Dilute with polyethylene glycol 200 to 100.0 mL , and mix. This is the Ethylene oxide stock solution.

Transfer 10.0 mL of magnesium chloride solution, prepared by adding 5 g of magnesium chloride to 10 mL of alcohol, to a volumetric flask. Add 20.0 mL of 0.1 M alcoholic hydrochloric acid VS. Insert the stopper, shake to obtain a saturated solution, and allow to equilibrate overnight. Transfer 5.00 mL of Ethylene oxide stock solution, accurately measured, to the flask, and allow to stand for 30 minutes. Titrate with 0.1 M alcoholic potassium hydroxide VS, determining the endpoint potentiometrically. Perform a blank titration, using the same quantity of polyethylene glycol 200 instead of Ethylene oxide stock solution, and note the difference in volumes required. Each mL of the difference in volumes of 0.1 M alcoholic potassium hydroxide VS consumed is equivalent to 4.404 mg of ethylene oxide. Calculate the concentration of ethylene oxide, in mg per g , in the Ethylene oxide stock solution.
Ethylene oxide solution-Quantitatively dilute a volume of Ethylene oxide stock solution, accurately measured, with polyethylene glycol 200 to obtain a solution containing about $50 \mu \mathrm{~g}$ of ethylene oxide per g . Dilute 1.0 mL of this solution with water to 5.0 mL to obtain a solution having a known concentration of about $10 \mu \mathrm{~g}$ of ethylene oxide per mL . [NOTE-Prepare immediately before use.]

Dioxane stock solution-Dissolve about 1.00 g of dioxane, accurately weighed, in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 1.0 mg per mL .

Dioxane solution-Quantitatively dilute a volume of the Dioxane stock solution, accurately measured, with water to obtain a solution having a known concentration of about 0.5 mg of dioxane per mL .

Standard solution 1-Transfer about 1.0 g of the substance under test, accurately weighed, to a $10-\mathrm{mL}$ vial, and add 1.0 mL of $\mathrm{N}, \mathrm{N}$-dimethylacetamide, 0.1 mL of Ethylene oxide solution, and 0.1 mL of Dioxane solution. Close the vial, and mix to obtain a homogenous solution. Allow to stand at $90^{\circ}$ for 45 minutes.

Standard solution 2-Transfer 0.1 mL of Ethylene oxide solution to a $10-\mathrm{mL}$ vial, add 0.1 mL of a freshly prepared solution of acetaldehyde, containing about 10 mg of acetaldehyde per L, and add 0.1 mL of Dioxane solution. Close the vial, and mix to obtain a homogenous solution.

Test solution-Transfer about 1.0 g of the substance under test, accurately weighed, to a $10-\mathrm{mL}$ vial, and add 1.0 mL of $\mathrm{N}, \mathrm{N}$-dimethylacetamide and 0.2 mL of water. Close the vial, and mix to obtain a homogenous solution. Allow to stand at $90^{\circ}$ for 45 minutes.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-[NOTE-Headspace apparatus that automatically transfers a measured amount of headspace may be used.] The gas chromatograph is equipped with a flame-ionization detector and contains a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ glass or quartz capillary column bonded with a $1.0-\mu \mathrm{m}$ layer of phase G1. The carrier gas is helium, flowing at a rate of about 1 mL per minute. The detector and injection port temperatures are maintained at $250^{\circ}$ and $150^{\circ}$, respectively. The column temperature is programmed as follows. Initially it is maintained at $50^{\circ}$ for 5 minutes after injection, then increased to $180^{\circ}$ at a rate of $5^{\circ}$ per minute, further increased to $230^{\circ}$ at a rate of $30^{\circ}$ per minute, and maintained at this temperature for 5 minutes. Chromatograph the gaseous phase of Standard solution 2, and record the peak responses as directed for

Procedure, adjusting the sensitivity of the system so that the peak heights of the two principal peaks in the chromatogram are not less than $15 \%$ of the full scale of the recorder: the relative retention times are about 0.94 for acetaldehyde and 1.0 for ethylene oxide; the resolution, $R$, between acetaldehyde and ethylene oxide is not less than 2.0 ; and the relative standard deviation for replicate injections is not more than $15.0 \%$.

Procedure-Using a heated, gas-tight gas chromatographic syringe, separately inject equal volumes (about 1 mL ) of the gaseous headspace of Standard solution 1 and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses: the mean areas of the ethylene oxide and dioxane peaks in the chromatogram obtained from the Test solution are not greater than half the mean areas of the corresponding peaks in the chromatogram obtained from Standard solution 1, equivalent to about $1 \mu \mathrm{~g}$ of ethylene oxide per g and $50 \mu \mathrm{~g}$ of dioxane per g. Calculate the concentration of ethylene oxide, in $\mu \mathrm{g}$ per g , in the test specimen taken by the formula:

$$
C r_{U} /\left(r_{S} M_{U}-r_{U} M_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of ethylene oxide in Standard solution 1; $r_{U}$ and $r_{S}$ are the peak responses of ethylene oxide obtained from the Test solution and Standard solution 1, respectively; and $\mathrm{M}_{U}$ and $\mathrm{M}_{s}$ are the quantities, in g , of the substance under test taken to prepare the Test solution and Standard solution 1, respectively: not more than $1 \mu \mathrm{~g}$ per g is found. Calculate the concentration of dioxane, in $\mu \mathrm{g}$ per g , in the test specimen taken by the formula:
in which $C_{D}$ is the concentration, in $\mu \mathrm{g}$, of dioxane in Standard solution 1; $d_{U}$ and $d_{S}$ are the peak responses of dioxane obtained from the Test solution and Standard solution 1, respectively; and $\mathrm{M}_{U}$ and $\mathrm{M}_{s}$ are as defined above: not more than $10 \mu \mathrm{~g}$ per g is found.

Limit of free glycerol-Dissolve 1.20 g of the substance under test in 25 mL of methylene chloride, heating if necessary. Cool, and add 100 mL of water and 25.0 mL of periodic acid solution, prepared by dissolving 150 mg of periodic acid in 25 mL of water. Shake, and allow to stand for 30 minutes. Add 40 mL of potassium iodide solution, prepared by dissolving 3 g of potassium iodide in 40 mL of water, and allow to stand for 1 minute. Add 1 mL of starch TS, and titrate the liberated iodine with 0.1 M sodium thiosulfate. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Each mL of 0.1 M sodium thiosulfate is equivalent to 2.3 mg of glycerol: not more than $5.0 \%$ is found. 1 S (NF23)

## BRIEFING

Carbomer 940, $N F 22$ page 2838. It is proposed to revise the immersion depth in the test for Viscosity.
(EMC: C. Sheehan) RTS-41306-1

## Change to read:

Viscosity—Proceed as directed in the test for Viscosity under Carbomer $934 P$, except to use a spindle having a shaft 0.32 cm in diameter, the distance from the top of the shaft to the lower tip of the shaft being 5.04 cm , and the immersion depth being 0.95 cm
$\square^{5.6} \mathrm{~cm}_{1 \mathrm{~S}(\mathrm{NF} 23)}$
(No. 7 spindle). The viscosity is between 40,000 and 60,000 centipoises.

## BRIEFING

Gellan Gum, page 3172 of the First Supplement. On the basis of the stability information received, it is proposed to revise the Packaging and storage section for this excipient.
(EMC: E. Gonikberg; PSD: C. Okeke) RTS-41272-1

## Change to read:

Packaging and storage-Preserve in well-closed containers, protect from moisture. Store in a cool, dry place.

■and store at room temperature.■1S (NF23)

## BRIEFING

Linoleoyl Polyoxylglycerides, page 700 of $P F$ 29(3) [MayJune 2003]. It is proposed to adopt Linoleoyl Polyoxylglycerides as the title of this proposed new monograph. A monograph on this excipient first appeared in Pharmacopeial Previews in PF 24(5) [Sept.-Oct. 1998] and in In-Process Revision in PF 26(2) [Mar.Apr. 2000] and PF 28(4) [July-Aug. 2002] under the name Linoleoyl Macrogolglycerides and, subsequently, in In-Process Revision in PF 29(3) [May-June 2003] with the name Linoleoyl Polyoxylglycerides. See also briefing under Caprylocaproyl Polyoxylglycerides.
(EMC: C. Sheehan; NL: C. Barnstein) RTS-41339-2

## Add the following:

## ■Linoleoyl Maerogolglyeerides Polyoxylglycerides

(Monograph under this new title-to become official April 1, 2010)
(Currently, there is no official NF monograph for this article)
» Linoleoyl Maerogely ides are mixtures of monoesters, diesters, and triesters of glycerol and monoesters and diesters of macrogels polyethylene glycols with a mean relative molecular weight between 300 and 400 . They are produced by partial alcoholysis of unsaturated oils, mainly containing triglycerides of linoleic acid, with macrogel, polyethylene glycol, by esterification of glycerol and maerol polyethylene glycol with fatty acids, or as a mixture of glycerol esters and ethylene oxide condensate with the fatty acids of the unsaturated oils. The average molecular weight is not less than 90.0 percent and not more than 110.0 percent of the labeled nominal value.

Packaging and storage-Preserve in tight containers, protected from light and moisture. Store at controlled room temperature.

Labeling-Label it to indicate the average nominal molecular weight of esters as part of the official title.

USP Reference standards $\langle 11\rangle$ —USP Linoleoyl golslides Polyoxylglycerides RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~F}\rangle$.
B: It meets the requirements for Identification test $B$ under Caprylocaproyl Macrogolglyeerides Polyoxylglycerides.

Acid value $\langle 401\rangle$ : not more than 2.0, determined on a $2.0-$ g specimen.

Hydroxyl value $\langle 401\rangle$ : between 45 and 65, determined on a $1.0-\mathrm{g}$ specimen, accurately weighed.

Iodine value $\langle 401\rangle$ : between 90 and 110.
Peroxide value $\langle 401\rangle$ : not more than 12.0, determined on a $2.0-\mathrm{g}$ specimen.

Saponification value $\langle 401\rangle$ : between 150 and 170 , determined on a $2.0-\mathrm{g}$ specimen.

Fatty acid composition $\langle 401\rangle$ : between $4 \%$ and $20 \%$ of palmitic acid is found; not more than $6 \%$ of stearic acid is found; not more than $1.0 \%$ each of arachidic acid and eicosenoic acid is found; between $20 \%$ and $35 \%$ of oleic acid is found; between $50 \%$ and $65 \%$ of linoleic acid is found; and not more than $2 \%$ of linolenic acid is found.

Refractive index $\langle 831\rangle$ : between 1.465 and 1.475 at $20^{\circ}$. Water, Method $I\langle 921\rangle$ : not more than $1.0 \%$, determined on a $1.0-\mathrm{g}$ specimen.

Total ash $\langle 561\rangle$ : not more than $0.1 \%$, determined on a $1.0-\mathrm{g}$ specimen.

Heavy metals, Method II $\langle 231\rangle$ : $0.001 \%$.
Limit of free ethylene oxide and dioxane-Proceed as directed in the test for Limit of free ethylene oxide and dioxane under Caprylocaproyl Magolglyerdes Polyoxylglycerides: not more than $1 \mu \mathrm{~g}$ of ethylene oxide per g is found; and not more than $10 \mu \mathrm{~g}$ of dioxane per g is found.

Limit of free glycerol-Proceed as directed in the test for Limit of free glycerol under Caprylocaproyl MacrogolglyPolyoxylglycerides: not more than $5.0 \%$ is found. 1 (NF23)

Briefing

Mono- and Di-glycerides, NF 22 page 2897 and page 1600 of PF 29(5) [Sept.-Oct. 2003]. It is proposed to revise the Chromatographic system in the Assay for monoglycerides by adding a note which provides an alternative to the $60-\mathrm{cm}$ column.
(EMC: K. Russo) RTS-41260-1

## Change to read:

Iodine value $\langle 401\rangle$ : not less than $90.0 \%$ and not more than $110.0 \%$ of the value indicated in the labeling.
$\square$ If the value stated in the labeling is less than 10 , the Iodine value is not more than 10.■2S (NF22)

## Change to read:

## Assay for monoglycerides-

Mobile phase-Use filtered and degassed tetrahydrofuran. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Assay preparation-Transfer about 200 mg of Mono- and Diglycerides, accurately weighed, to a $5-\mathrm{mL}$ volumetric flask, dissolve in and dilute with tetrahydrofuran to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a refractive index detector and a $7-\mathrm{mm} \times 60-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L21 ( $100 \AA$ ). The flow rate is about 1 mL per minute. The column and detector temperatures are maintained at $40^{\circ}$.
■ [NOTE—Two or three $7.5-\mathrm{mm} \times 30-\mathrm{cm}$ L21 columns may be used in place of one $60-\mathrm{cm}$ column provided that system suitability requirements are met. $]_{\text {IS }}$ (NF23)
Chromatograph the Assay preparation, and
Chromatograph the Assay preparation, and record the peak responses as directed for Procedure. the relative retention times are about 1.0 for glycerin, 0.86 for moneglycerides, 0.81 for diglycer ides, and 0.77 for triglyeerides; and
-The order of elution is triglycerides, diglycerides, monoglycerides, and glycerin. 2 2S (NF22)
The relative standard deviation for replicate injections determined from the monoglycerides peak is not more than $1.0 \%$.
Procedure-Inject a volume (about $40 \mu \mathrm{~L}$ ) of the Assay preparation into the chromatograph, record the chromatogram, and measure the responses for the major peaks. Calculate the percentage of monoglycerides in the portion of Mono- and Di-glycerides taken by the formula:

$$
100\left(r_{U} / r_{S}\right)
$$

in which $r_{U}$ is the peak response for monoglycerides; and $r_{S}$ is the sum of the responses of all the peaks, except the solvent peak.

Briefing

Oleoyl Polyoxylglycerides, page 701 of $P F$ 29(3) [May-June 2003]. It is proposed to adopt Oleoyl Polyoxylglycerides as the title of this proposed new monograph. A monograph on this excipient first appeared in Pharmacopeial Previews in PF 24(5) [Sept.Oct. 1998] and under In-Process Revision in PF 26(2) [Mar.-Apr. 2000] and $P F$ 28(4) [July-Aug. 2002] with the name Oleoyl Macrogolglycerides and, subsequently, under In-Process Revision in PF 29(3) [May-June 2003] with the name Oleoyl Polyoxylglycerides. See also the portion of the briefing pertaining to nomenclature under Caprylocaproyl Polyoxylglycerides.
(EMC: C. Sheehan; NL: C. Barnstein) RTS-41339-3

## Add the following:

## ■Oleoyl Macrogolglycerides Polyoxylglycerides

## (Monograph under this new title-to become official April 1,

 2010)(Currently, there is no official NF monograph for this article)

## » Oleoyl Macrolglyeerides Polyoxylglycerides

 are mixtures of monoesters, diesters, and triesters of glycerol and monoesters and diesters of macregols polyethylene glycols with a mean relative molecular weight between 300 and 400. They are produced by partial alcoholysis of unsaturated oils, mainly containing triglycerides of oleic acid, with macrogol, polyethylene glycol, by esterification of glycerol and macrogel polyethylene glycol with fatty acids, or as a mixture of glycerol estersand ethylene oxide condensate with fatty acids of the unsaturated oils. The average molecular weight is not less than 90.0 percent and not more than 110.0 percent of the labeled nominal value.

Packaging and storage-Preserve in tight containers, protected from light and moisture. Store at controlled room temperature.

Labeling-Label it to indicate the average nominal molecular weight of esters as part of the official title.

USP Reference standards $\langle 11\rangle$ —USP Oleoyl Mat gheres Polyoxylglycerides RS.

## Identification-

A: Infrat Abshedion Infrared Absorption $\langle 197 \mathrm{~F}\rangle$.

B: It meets the requirements for Identification test $B$ under Caprylocaproyl Macrogolglycerides Polyoxylglycerides.

Acid value $\langle 401\rangle$ : not more than 2.0, determined on a $2.0-\mathrm{g}$ specimen.

Hydroxyl value $\langle 401\rangle$ : between 45 and 65, determined on a $1.0-\mathrm{g}$ specimen, accurately weighed.

Iodine value $\langle 401\rangle$ : between 75 and 95.
Peroxide value $\langle 401\rangle$ : not more than 12.0 , determined on a $2.0-\mathrm{g}$ specimen.

Saponification value $\langle 401\rangle$ : between 150 and 170, determined on a $2.0-\mathrm{g}$ specimen.

Fatty acid composition $\langle 401\rangle$ : between $4.0 \%$ and $9.0 \%$ of palmitic acid is found; not more than $6.0 \%$ of stearic acid
is found; not more than $2.0 \%$ each of linolenic acid, arachidic acid, and eicosenoic acid is found; between $58.0 \%$ and $80.0 \%$ of oleic acid is found; and between $15.0 \%$ and $35.0 \%$ of linoleic acid is found.

Water, Method $I\langle 921\rangle$ : not more than $1.0 \%$, determined on a $1.0-\mathrm{g}$ specimen.

Total ash $\langle 561\rangle$ : not more than $0.1 \%$, determined on a $1.0-\mathrm{g}$ specimen.

Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.001 \%$.
Limit of free ethylene oxide and dioxane-Proceed as directed in the test for Limit of free ethylene oxide and dioxane under Caprylocaproyl Polyoxylglycerides: not more than $1 \mu \mathrm{~g}$ of ethylene oxide per g is found; and not more than $10 \mu \mathrm{~g}$ of dioxane per g is found.

Limit of free glycerol-Proceed as directed in the test for Limit of free glycerol under Caprylocaproyl Polyoxylglycerides: not more than $5.0 \%$ is found.■1S (NF23)

## Briefing

Polydecene, page 1284 of $P F$ 28(4) [July-Aug. 2002]. This new monograph, which previously appeared in Pharmacopeial Previews, is now forwarded to In-Process Revision. It is also proposed to revise the limits for the content of decene oligomers that appear in the table in the Definition to include polydecene supplied by other manufacturers.
(EMC: D. Bempong) RTS—39281-1

## Add the following:

## ■Polydecene

$\mathrm{C}_{30 \leq n \leq 70} \mathrm{H}_{2 n+2}$
1-Decene, homopolymer, hydrogenated [68037-01-4].
» Polydecene is a mixture of saturated, synthetic hydrocarbons in the range $\mathrm{C}_{30} \mathrm{H}_{62}$ through $\mathrm{C}_{70} \mathrm{H}_{142}$ made from direct oligomerization of 1-de-
cene ( $\mathrm{C}_{10}$ alpha olefin). The oligomer mixture may be distilled to fractions of the desired viscosity and hydrogenated to reach saturation or may be hydrogenated to reach saturation and then distilled to the desired viscosity. The requirements for specific gravity, viscosity, and content of decene oligomer differ for the various types of polydecene, as set forth in the accompanying table. Polydecene may contain a suitable stabilizer.

|  | Specific Gravity | Viscosity (eentipeises centistokes) | Content of Decene Oligomer (\%) |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Type | Range | Range | $\mathrm{C}_{30} \mathrm{H}_{62}$ | $\mathrm{C}_{40} \mathrm{H}_{82}$ | $\mathrm{C}_{50} \mathrm{H}_{102}$ | $\mathrm{C}_{60} \mathrm{H}_{122}$ | $\mathrm{C}_{70} \mathrm{H}_{142}$ |
| Light polydecene | 0.814-0.819 | 16.0-20.0 | $\begin{aligned} & 70-86 \\ & 70-93 \end{aligned}$ | $\begin{array}{r} 12-25 \\ 5-25 \end{array}$ | 0-5 | $0-1$ | $0-1$ |
| Medium <br> polyde- <br> cene | 0.823-0.827 | 28.0-34.0 | $\begin{aligned} & 13-37 \\ & 13-40 \end{aligned}$ | 35-70 | 9-25 | 0-7 | 0-2 |
| Heavy polydecene | 0.828-0.832 | 40.0-52.0 | 3-15 | $\begin{aligned} & 25-40 \\ & 25-55 \end{aligned}$ | 25-40 | 13-28 | 0-10 |

Packaging and storage-Preserve in tight containers.
Labeling-Label it to indicate, as part of the official title, the Polydecene type, and label it to indicate the name and concentration of any added stabilizer.

Identification-The chromatogram of the Test solution obtained from the test for Content of decene oligomer exhibits major peaks for trimers, tetramers, pentamers, hexamers,
and possibly heptamers. The decene oligomer content is within the range given in the table above for the labeled type of polydecene.

Specific gravity $\langle 841\rangle$ : meets the requirements of the specific gravity range specified in the accompanying table, for the labeled type, determined at $20^{\circ}$.

Viscosity $\langle 911\rangle$ : meets the requirements of the viscosity range specified in the accompanying table for the labeled type, determined using a capillary viscosimeter giving a flow time of not less than 200 seconds, in a liquid bath maintained at $40.0^{\circ}$.

Readily carbonizable substances $\langle 271\rangle$ —Transfer 5 mL of Polydecene to a glass-stoppered test tube previously treated to remove organic matter (see Cleaning Glass Apparatus $\langle 1051\rangle$ ), add 5 mL of sulfuric acid TS , and heat in a boiling water bath for 30 seconds. Quickly remove the test tube, and, while holding the stopper in place, shake three times in a vertically reciprocating cycle with an amplitude of about 13 cm . Repeat this procedure every 30 seconds for 10 minutes. Do not keep the test tube out of the water bath any longer than 3 seconds for each shaking cycle. Remove the test tube from the water bath, and let it cool for about 20 minutes to room temperature: the oil phase may turn hazy, but remains colorless; the interface between the two layers is free from solids; and the acid layer does not become darker than the standard color produced by overlaying 5 mL of Matching Fluid E (see Color and Achromicity $\langle 631\rangle$ ) with 5 mL of Polydecene in a similar test tube.

Limit of nickel-[To come.]

## Limit of short-chain hydrocarbons-

Test solution, System suitability solution, Chromatographic system, and Procedure-Proceed as directed in the test for Content of decene oligomer. Calculate the percentage of each of the short-chain hydrocarbons present by the formula:

$$
100\left(r_{U} / r_{s}\right)
$$

in which $r_{U}$ is the response of any peak obtained from a hydrocarbon smaller than a trimer but different from the solvent peak; and $r_{s}$ is the sum of the responses of all the peaks in the chromatogram, excluding the solvent peak: not more than $2.5 \%$ of total short-chain hydrocarbons is found.

## Content of decene oligomer-

Test solution-Dissolve about 0.1 mL of Polydecene in about 10 mL of pentane.

System suitability solution-Dissolve accurately weighed quantities of hexadecane, squalane, and tetradecane in pentane to obtain a solution having known concentrations of about 10 mg per $\mathrm{mL}, 10 \mathrm{mg}$ per mL , and 1 mg per mL , respectively.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The gas chromatograph is equipped with a flame-ionization detector and a $0.52-\mathrm{mm} \times 16-\mathrm{m}$ fused-silica capillary column coated with $0.1-\mathrm{mm}$ stationary phase G2. The carrier gas is helium, flowing at a rate of about 10 mL per minute. The chromatograph is programmed as follows. Initially, the column is maintained at a temperature of $35^{\circ}$, then immediately after injection, the temperature is increased at a rate of $5^{\circ}$ per minute to a temperature of $50^{\circ}$, then increased to $170^{\circ}$ at a rate of $12^{\circ}$ per minute, then increased from $170^{\circ}$ to $310^{\circ}$ at a rate of $10^{\circ}$ per minute, and maintained at $310^{\circ}$ for 18 minutes. The injection port temperature is maintained isothermally at about $35^{\circ}$, and the detector temperature is maintained isothermally at about $320^{\circ}$. Chromatograph the System suitability solution, and record the responses as directed for Procedure: the retention time for squalane is about 18 minutes; the relative retention times are about 0.5 for tetradecane, 0.6 for hexadecane and, 1.0 for squalane; the resolution, $R$, between tetradecane and hexadecane is not less than 10 ; and the relative standard deviation for replicate injections for each peak is not more than $2.0 \%$.
Procedure-Inject a volume (about $2 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the areas for the major peaks. The pentamer oligomer has a retention time of about 23 minutes. The trimer, tetramer, pentamer, hexamer, and heptamer oligomers, if present, have relative retention times of about $0.7,0.9$,
$1.0,1.1$, and 1.3 , respectively. Calculate the percentage of each oligomer present by the formula:

$$
100\left(r_{o} / r_{s}\right)
$$

in which $r_{o}$ is the response of each oligomer; and $r_{s}$ is the sum of the responses of all the peaks in the chromatogram, excluding the solvent peak: the decene oligomer content is within the limits specified in the accompanying table. ${ }^{1 S}$ (NF23)

Briefing

Modified Starch, page 995 of PF 30(3) [May-June 2004]. On the basis of comments received, this new monograph is being presented again with additional changes. It is proposed to include the Botanic characteristics under the Identification test section to be consistent with the harmonization effort for the Corn Starch, Wheat Starch, and Potato Starch monographs. Botanic characteristics will be referred to as Identification test $A$. It is also proposed to change the Loss on drying limit for Tapioca starch from not more than $15 \%$ to not more than $18 \%$ to be consistent with EU Food Law dir. 2000/63/EC. In addition, it is proposed to increase the Residue on ignition limit from $0.5 \%$ to $1.5 \%$ on the basis of comments received that some treatments require the addition of salts that are very difficult to remove.
(EMC: C. Sheehan) RTS-41322-1

## Add the following:

## ■Modified Starch

» Modified Starch is Starch modified by chemical means. Food Starch may be acid-modified, bleached, oxidized, esterified, or etherified, or treated enzymatically to change the functional properties (21 CFR 172.892).

## Packaging and storage-Preserve Store in well-elosed

 entainers at emperatures ranging from $0^{\circ}$ to $55^{\circ}$. Preserve in well-closed containers. No storage requirements specified.
## Botanic characteristies

Eorn stareh Polygonal, rounded or spheroidal granules up to about $35 \mu \mathrm{~m}$ in diameter and ustally having a cireular or several rayed central cleft.

Fapioa stareh Spherieal granules with one truneated side, typieally 5 - $0-35 \mathrm{~mm}$ in diameter and ustally having a cireular or several rayed central cleft.

Potatostareh Irregularly shaped, ovoid, or pear shaped granules, usually 30 to $100 \mathrm{\mu m}$ in size but oceasionally ex eeeding $100 \mathrm{\mu m}$; or rounded, 10 to $35 \mathrm{\mu m}$ in size. There are eceasional cempernd grantles having two four compenents. The ovoid and pear shaped granules have an ec eentric hilum, and the rounded granules have aceentric or slightly eceentric hiltum. All grantles show clearly visible eoncentric striations.

Wheat starch-Large and small gramules, usually 10 to-60 fmim diameter. The central hiltum and striations are-visible er barely visible.

## Identification-

A: Corn starch: polygonal, rounded, or spheroidal granules up to about $35 \mu \mathrm{~m}$ in diameter and usually having a circular or several-rayed central cleft.
Tapioca starch: spherical granules with one truncated side, typically 5 to $35 \mu \mathrm{~m}$ in diameter and usually having a circular or several-rayed central cleft.
Potato starch: irregularly shaped, ovoid, or pearshaped granules, usually 30 to $100 \mu \mathrm{~m}$ in size but occasionally exceeding $100 \mu \mathrm{~m}$; or rounded, 10 to $35 \mu \mathrm{~m}$ in size. There are occasional compound granules having two to four components. The ovoid and pear-shaped granules have an
eccentric hilum, and the rounded granules have accentric or slightly eccentric hilum. All granules show clearly visible concentric striations.

Wheat starch: large and small granules, usually 10 to $60 \mu \mathrm{~m}$ in diameter. The central hilum and striations are visible or barely visible.

A B: Prepare a smooth mixture of 1 g of Modified Starch with 2 mL of cold water, stir into 15 mL of boiling Whater, boil gently for 2 minntes, and cool to room tempera tre: the product is elear. Prepare a $2 \%(\mathrm{w} / \mathrm{w})$ sodium hydroxide solution. Weigh 0.6 g of Modified Starch, and transfer to a $25-\mathrm{mL}$ glass vial with a plastic cap. Add 9.4 g of water, cap, and shake vigorously to evenly disperse the starch. Add 10 g of $2 \%$ sodium hydroxide solution, cap, and shake vigorously for 1 minute to create a smooth mixture. Evaluate within 1 minute. The final solution is translucent to opaque with a fluid consistency. A yellow tint of the final solution is acceptable.

B: C: A water slurry of the Modified Starch is colored reddish violet orange-red to deep blue by iodine TS.

Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total aerobic microbial count does not exceed 1000 cfu per g ; the total combined molds and yeasts count does not exceed 100 cfu per $g$.
$\mathbf{p H}\langle 791\rangle$ —Weigh $20.0 \pm 0.1 \mathrm{~g}$ of Modified Starch, transfer to a suitable nonmetallic container, and add 100 mL of water to obtain a slurry. Stir using a magnetic stirrer at a moderate rate for about 5 minutes, and determine the pH to the nearest 0.1 unit: between 4.5 and 8.0. 3.0 and 9.0.

Loss on drying $\langle 731\rangle$ —Dry it at $120^{\circ}$ for 4 hours. it loses mere the it inght. Corn starch and Wheat starch: Tat not more than 15.0\%; Tapioca starch: not more than 18.0\%; and Potato starch: not more than $21.0 \%$.

Residue on ignition $\langle 281\rangle$ : not more than $0.5 \% 1.5 \%$, a test specimen of $2.0 \pm 0.1 \mathrm{~g}$ being used.

Iron $\langle 241\rangle$ : $0.002 \%$, the Test Preparation being prepared as follows. Dissolve the residue obtained in the test for Residue on ignition in 8 mL of hydrochloric acid with the aid of gentle heating. Dilute with water to 100 mL in a volumetric flask, and mix. Dilute 25 mL of this solution with water to $47 \pm 1 \mathrm{~mL}$.

Oxidizing substances-To 5-Modified Stareh add 20 mL of a mixttre of methanol and water ( $1: 1$ ), then add 4 mL of 6 N acetic acid, and stir until a homogeneous suspension is btained. Add 0.5 mL of a freshly prepared saturated solution of potassium iodide, mix, and allow to stand for 5 minttes: no distinet blue, brown, or purple color is ob served. Transfer 4.0 g to a glass-stoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 12.6 mL of 0.002 N sodium thiosulfate is required ( $180 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ): not more than $0.018 \%$ of oxidizing substances is found.

Limit of sulfur dioxide-Mix $20.0 \pm 0.1 \mathrm{~g}$ of Modified Starch with 200 mL of $5 \%$ alcohol until a smooth suspension is obtained, and vacuum filter through paper (Whatman No. 1 or equivalent). To 100 mL of the filtrate add 3 mL of starch TS, and titrate with 0.10 N iodine to the first perma-
nent blue color. Not more than 2.7 mL is consumed: not more than $0.008 \% 0.005 \%$ of sulfur dioxide is found.■1S (NF23)

BRIEFING

Tapioca Starch, NF 22 page 2940, page 3181 of the First Supplement, and page 998 of $P F$ 30(3) [May-June 2004]. It is proposed to modify this monograph to align it with the proposed monographs for Corn Starch, Potato Starch, and Wheat Starch. It is proposed to move the test for Botanic characteristics under the new Identification test $A$ and to add a new test solution, Iodine and potassium iodide TS 2, under the revised Identification test $C$.
(EMC: J. Lane) RTS-41144-4

## Change to read:

Packaging and storage-Preserve in well-closed containers.
■ No storage requirements specified.■1S (NF23) $^{\text {( }}$

## Delete the following:

Botanie characteristies-Examine Tapioca-Stareh under a mi eroseope, using not less tham $20 \times$ magnifieation and using glyeer in as the mounting agent: it appears as spherical granules with one traneated side, typieally having a $5-10-35 \mathrm{\mu m}$ diameter and having eireular-or several rayed central clefts.an 1 S (NF23)

## Change to read:

## Identification-

A: Suspend 1 gof Tapioca Stareh in 50 mL of water, beil for 4
minute, and eool: a thin, cloudy mueilage is formed.
B: To 10 mL of the murilage obtained in Identifieation test $A$ add 0.04 mL each of iodine and potassium iodide $T S$ : a reddish violet to dark blue color is produced, which disappears on heating and reappears on cooling.

■ A: Examine Tapioca Starch under a microscope, using not less than $20 \times$ magnification and using glycerin as the mounting agent: it appears as spherical granules with one truncated side, typically having a 5 - to $35-\mu \mathrm{m}$ diameter and having circular or several-rayed central clefts.

B: Suspend 1 g of Tapioca Starch in 50 mL of water, boil for 1 minute, and cool: a thin, cloudy mucilage is formed.

C: To 1 mL of the mucilage obtained in Identification test $B$ add 0.05 mL of iodine and potassium iodide TS 2 : an orange-red to dark blue color is produced, which disappears on heating. $\quad$ IS (NF23)

## BRIEFING

Stearoyl Polyoxylglycerides, page 1135 of $P F$ 29(4) [JulyAug. 2003]. It is proposed to adopt Stearoyl Polyoxylglycerides as the title of this proposed new monograph. A monograph on this excipient first appeared in Pharmacopeial Previews in PF 24(5) [Sept.-Oct. 1998] and under In-Process Revision in PF 26(2) [Mar.-Apr. 2000] and PF 28(4) [July-Aug. 2002] with the name Stearoyl Macrogolglycerides and, subsequently, under In-Process Revision in PF 29(4) [July-Aug. 2003] under the name Stearoyl Polyoxylglycerides. See also the briefing under Caprylocaproyl Polyoxylglycerides.
(EMC: C. Sheehan; NL: C. Barnstein) RTS-41339-4

## Add the following:

## ■Stearoyl Macrogolglyeerides Polyoxylglycerides

(Monograph under this new title-to become official April 1, 2010)
(Currently, there is no official NF monograph for this article)

## » Stearoyl Macregelglycerides Polyoxylglycerides are mixtures of monoesters, diesters, and triesters of glycerol and monoesters and diesters of macregels polyethylene glycols with a nominal mean relative molecular weight between 300

and 4000 . They are produced by partial alcoholysis of saturated oils, mainly containing triglycerides of stearic acid, with macrol, polyethylene glycol, by esterification of glycerol and merer polyethylene glycol with fatty acids, or as a mixture of glycerol esters and ethylene oxide condensate with the fatty acids of the hydrogenated oils. The Hydroxyl Value does not differ by more than 15 units from the nominal value, and the Saponification Value does not differ by more than 10 units from the nominal value. The average molecular weight is not less than 90.0 percent and not more than 110.0 percent of the labeled nominal value.

Packaging and storage-Preserve in tight containers, protected from light and moisture. Store at controlled room temperature.

Labeling-Label it to indicate the average nominal molecular weight of esters as part of the official title. The label also indicates the Hydroxyl Value and the Saponification Value.

USP Reference standards $\langle 11\rangle$ —USP Stearoyl Margor shler Polyoxylglycerides RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: It meets the requirements for Identification test $B$ under Caprylocaproyl Magolglyerides Polyoxylglycerides.

Acid value $\langle 401\rangle$ : not more than 2.0, determined on a $2.0-\mathrm{g}$ specimen.

Hydroxyl value $\langle 401\rangle$-The Hydroxyl Value, between 25 and 56 , does not differ by more than 15 units from the nominal value, determined on a $1.0-\mathrm{g}$ specimen, accurately weighed.

Iodine value $\langle 401\rangle$ : not more than 2.0.
Peroxide value $\langle 401\rangle$ : not more than 6.0, determined on a $2.0-\mathrm{g}$ specimen.

Saponification value $\langle 401\rangle$-The Saponification Value, between 67 and 112, does not differ by more than 10 units from the nominal value, determined on a $2.0-\mathrm{g}$ specimen.

Fatty acid composition $\langle 401\rangle$ : not more than $5.0 \%$ each of lauric acid and myristic acid is found; between $40.0 \%$ and $50.0 \%$ of palmitic acid is found; and between $48.0 \%$ and $58.0 \%$ of stearic acid is found.

Water, Method $I\langle 921\rangle$ : not more than $1.0 \%$, determined on a $1.0-\mathrm{g}$ specimen.

Total ash $\langle 561\rangle$ : not more than $0.2 \%$, determined on a $1.0-\mathrm{g}$ specimen.

Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.001 \%$.
Limit of free ethylene oxide and dioxane-Proceed as directed in the test for Limit of free ethylene oxide and dioxane under Caprylocaproyl Molyoxylglycerides: not more than $1 \mu \mathrm{~g}$ of ethylene oxide per g is found; and not more than $10 \mu \mathrm{~g}$ of dioxane per g is found.

Limit of free glycerol-Proceed as directed in the test for Limit of free glycerol under Caprylocaproyl Macrogoly Polyoxylglycerides: not more than $5.0 \%$ is found. 1 S (NF23)

## GENERAL CHAPTERS

## General Tests and Assays

## General Requirements for Tests and Assays

## BRIEFING

<11〉 USP Reference Standards, USP 27 page 2111, page 3099 of the First Supplement, the First Interim Revision Announcement on page 31 of PF 30(1) [Jan.-Feb. 2004], the Second Interim Revision Announcement on page 416 of PF 30(2) [Mar.-Apr. 2004], the Third Interim Revision Announcement on page 783 of PF 30(3) [May-June 2004], page 5180 of $P F$ 23(6) [Nov.-Dec. 1997], page 6925 of PF 24(5) [Aug.-Sept. 1998], page 8222 of $P F$ 25(3) [May-June 1999], page 8561 of $P F 25(4)$ [July-Aug. 1999], page 8893 of $P F 25(5)$ [Sept.-Oct. 1999], page 218 of $P F$ 26(1) [Jan.Feb. 2000], page 793 of $P F$ 26(3) [May-June 2000], page 1101 of $P F$ 26(4) [July-Aug. 2000], page 1369 of $P F$ 26(5) [Sept.-Oct. 2000], page 1832 of $P F 27$ (1) [Jan.-Feb. 2001], page 2268 of PF 27(2) [Mar.-Apr. 2001], page 3071 of PF 27(5) [Sept.-Oct. 2001], page 3348 of $P F$ 27(6) [Nov.-Dec. 2001], page 433 of PF 28(2) [Mar.-Apr. 2002], page 839 of PF 28(3) [May-June 2002], page 1224 of $P F$ 28(4) [July-Aug. 2002], page 1468 of $P F$ 28(5) [Sept.-Oct. 2002], page 1913 of $P F$ 28(6) [Nov.-Dec. 2002], page 163 of $P F$ 29(1) [Jan.-Feb. 2003], page 483 of $P F$ 29(2) [Mar.-Apr. 2003], page 710 of $P F$ 29(3) [May-June 2003], page 1137 of $P F 29(4)$ [July-Aug. 2003], page 1601 of PF 29(5) [Sept.-Oct. 2003], page 2022 of $P F$ 29(6) [Nov.-Dec. 2003], page 211 of $P F$ 30(1) [Jan.-Feb. 2004], page 613 of $P F$ 30(2) [Mar.-Apr. 2004], and page 998 of PF 30(3) [May-June 2004].
(HDQ) RTS—35120-1; 39513-6; 40316-7; 40414-3; 405071; 40645-2; 40682-1; 40852-1; 40866-1; 40938-1; 40948-1; 40948-2; 40955-1; 40996-1; 41012-1; 41012-2; 41050-1; 412401 ; 41240-2; 41110-1; 41134-2; 41134-3; 41282-2; 41282-3; 41311-2

## Add the following:

■USP Adipic Acid RS.■1S (USP28)

## Add the following:

-USP Calcitonin Salmon RS-Preserve in a freezer at $-20^{\circ}$ to $-10^{\circ}$; and after opening the vial, store in a tight container. Do not dry before use for tests and assays.■1S (USP28)

## Add the following:

-USP Calcitonin Salmon Related Compound A RS [ $N$ -acetyl-cys ${ }^{1}$-calcitonin] $\left(\mathrm{C}_{146} \mathrm{H}_{243} \mathrm{~N}_{44} \mathrm{O}_{49} \mathrm{~S}_{2} \diamond 3463\right)$ —Preserve in a freezer at $-20^{\circ}$ to $-10^{\circ}$; and after opening the vial, store in a tight container. Do not dry before use for tests and assays.■1S (USP28)

## Add the following:

■USP Clarithromycin Identity RS.■1S (USP28)

## Add the following:

-USP Fenbendazole Related Compound A RS [methyl ( 1 H -benzimidazole-2-yl) carbamate] $\left(\mathrm{C}_{9} \mathrm{H}_{9} \mathrm{~N}_{3} \mathrm{O}_{2} \diamond\right.$ 191.19)—Do not dry. Keep container tightly closed. Protect from light. 1 (USP28)

## Add the following:

-USP Fenbendazole Related Compound B RS [methyl [5(6)-chlorobenzimidazole-2-yl]carbamate] $\left(\mathrm{C}_{9} \mathrm{H}_{8} \mathrm{ClN}_{3} \mathrm{O}_{2}\right.$ $\Delta 225.63$ )—Do not dry. Keep container tightly closed. Protect from light. $\quad$ IS (USP28)

## Add the following:

-USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs VRS-[To come.] $]_{\text {1S (USP28) }}$

## Add the following:

- USP Human Fibroblast-Derived Temporary Skin Substitute Reference Photomicrographs VRS-[To come.] $]_{\text {1S (USP28) }}$


## Change to read:

USP Fluoxetine Related Compound B
■Solution $_{\text {n } 1 S}$ (USP28)
RS [ $N$-methyl-3-phenylpropylamine] $\left(\mathrm{C}_{10} \mathrm{H}_{15} \mathrm{~N} \curvearrowright 149.24\right)$ - ${ }^{\bullet}$ This is a solution containing approximately 2 mg of fluoxetine related compound B in diluted hydrochloric acid (approximately 0.01 N ). Store in a refrigerator. After opening the ampul, store it in a tightly closed container. ${ }^{3}$

## Add the following:

-USP Fluticasone Propionate RS [ $S$-(fluoromethyl) $6 \alpha, 9 \alpha$ -difluoro-11 $\beta$,17-dihydroxy-16 $\alpha$-methyl-3-oxoandrosta-1,4-diene-17 $\beta$-carbothioate, 17-propionate] $\left(\mathrm{C}_{25} \mathrm{H}_{31} \mathrm{~F}_{3} \mathrm{O}_{5} \mathrm{~S} \triangleleft\right.$ 500.6. 1 (USP28)

## Add the following:

-USP Fluticasone Propionate Resolution Mixture RSIt is a mixture of fluticasone propionate and fluticasone propionate related compound D. $\quad$ IS (USP28)

## Add the following:

-USP Fluticasone Propionate System Suitability Mixture RS—It is a mixture of USP Fluticasone Propionate RS and fluticasone propionate related compounds $\mathrm{A}, \mathrm{B}$, C, D, and E.

Fluticasone propionate related compound $A[6 \alpha, 9 \alpha$-di-fluoro-11 $\beta$-hydroxy-16 $\alpha$-methyl-3-oxo-17 $\alpha$-propionyloxy-androsta-1,4-diene-17 $\beta$-carbonylsulfenic acid].

Fluticasone propionate related compound $B[6 \alpha$, $9 \alpha$-difluoro-11 $\beta$-hydroxy-16 $\alpha$-methyl-2', $3,4^{\prime}$-trioxo-17 $\alpha$ -spiro(androsta-1,4-diene-17,5'-(1,3)oxathiolane)].

Fluticasone propionate related compound C [ $[$-fluoromethyl $17 \alpha$-acetyloxy- $6 \alpha, 9 \alpha$-difluoro-11 $\beta$-hydroxy-16 $\alpha$ -methyl-3-oxo-androsta-1,4-diene-17 $\beta$-carbothioate].

Fluticasone propionate related compound $D[S$-methyl $6 \alpha, 9 \alpha$-difluoro- $11 \beta$-hydroxy- $16 \alpha$-methyl-3-oxo- $17 \alpha$-pro-pionyloxy-androsta-1,4-diene-17 $\beta$-carbothioate].

Fluticasone propionate related compound $E[6 \alpha, 9 \alpha$-di-fluoro-11 $\beta, 17 \alpha$-dihydroxy-16 $\alpha$-methyl-3-oxo-androsta-1,4-diene-17 $\beta$-carboxylic acid $6 \alpha, 9 \alpha$-difluoro-17 $\beta$-(fluoromethylthio) carbonyl-11 $\beta$-hydroxy-16 $\alpha$-methyl-3-oxo-an-drosta-1,4-dien-17 $\alpha$-yl ester]. 1 (USP28)

## Add the following:

-USP Fluvastatin Sodium RS.■1S (USP28)

## Add the following:

-USP Fluvastatin Related Compound A RS [fluvastatin hydroxydiene].■1S (USP28)

## Add the following:

-USP Fluvastatin Related Compound B RS [fluvastatin $t$-butyl ester].■1S (USP28)

## Add the following:

-USP Fluvastatin for System Suitability RS [fluvastatin sodium and fluvastatin sodium anti-isomer].[1S (USP28)

## Add the following:

-USP Fluvoxamine Maleate RS.■1S (USP28)

## Add the following:

-USP Gonadorelin Acetate RS $\left[\mathrm{C}_{55} \mathrm{H}_{75} \mathrm{~N}_{17} \mathrm{O}_{13} \cdot x \mathrm{CH}_{3}\right.$ $\mathrm{COOH} \triangleleft 1182.3$ (acetate free)]-[To come.] $]_{\text {IS (USP28) }}$

## Add the following:

-USP Gonadorelin Acetate Related Compound A RS [gonadorelin free acid] $\left(\mathrm{C}_{55} \mathrm{H}_{74} \mathrm{~N}_{16} \mathrm{O}_{14} \diamond 1183.3\right)$-[To come.] $]_{1 S}$ (USP28)

## Add the following:

-USP Graftskin Reference Photomicrographs
VRS.■1S (USP28)
Add the following:
-USP Mefloquine Related Compound A RS.■1S (USP28)

## Add the following:

-USP Naratriptan Resolution Mixture RS—A mixture of naratriptan hydrochloride with approximately $1 \%$ of naratriptan related compound A [3-(1-methylpiperidin-4-yl)$1 H$-indole hydrochloride] and naratriptan related compound B [2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-in-dole-5-yl]ethanesulfonic acid methylamide oxalate].■1S (USP28)

## Add the following:

■USP Ofloxacin Related Compound A RS [9-fluoro-3-methyl-7-oxo-10-(piperazin-1-yl)-2,3-dihydro-7H-pyri-do[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid].■1S (USP28)

## Add the following:

■USP Paclitaxel Related Compound C RS [benzyl analog: baccatin III 13-ester with $(2 R, 3 S)$-2-hydroxy-3-phe-nyl-3-(2-phenylacetylamino)propanoic acid].■1S (USP28)

## Add the following:

■USP Phenylethyl Alcohol RS.■1S (USP28)

## Add the following:

${ }^{\Delta}$ USP Phenyltoloxamine Dihydrogen Citrate RS——Dry it in a vacuum at $80^{\circ}$ for 3 hours. Keep the container tightly closed. Protect from light. $\Delta$ USP28

## Add the following:

${ }^{4}$ USP Phenyltoloxamine Pihydrogen-Citrate Related
Compound A RS [3-(2-dimethylaminoethoxy)diphenylmethane] $\left(\mathrm{C}_{17} \mathrm{H}_{21} \mathrm{NO} \diamond 255.35\right)$-Do not dry. Keep the container tightly closed. Protect from light. $\triangle$ USP28

## Add the following:

-USP Cultured Rat Pheochromocytoma Reference
Photomicrographs VRS...1S (USP28)

## Add the following:

■Sodium Starch Glycolate Type A RS—Do not dry. Keep container tightly closed.■1S (USP28)

## Add the following:

■Sodium Starch Glycolate Type B RS——Do not dry. Keep container tightly closed.■1S (USP28)

## Add the following:

-USP Topiramate RS-Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. 1 IS (USP28)

## Add the following:

-USP Topiramate Related Compound A RS [2,3:4,5-bis- $O$-(1-methylethylidene)- $\beta$-D-fructopyranose] $\left(\mathrm{C}_{12} \mathrm{H}_{20} \mathrm{O}_{6}\right.$ $\diamond 260.28$ ). Preserve in tight, light resistant containers between $2^{\circ}$ and $8^{\circ} \cdot 1$ 1S (USP28)

## OTHER TESTS AND ASSAYS

BRIEFING
$\langle 571\rangle$ Vitamin A Assay, USP 27 page 2247. It is proposed to revise this general chapter by adding the Chromatographic Method as an alternative assay method. The liquid chromatographic procedure is based on analyses performed with the Zorbax brand of L8 column.
(DSN: L. Evans) RTS-41059-1

## Change to read:

## ■ CHEMICAL METHOD $_{\text {■ } 1 \mathrm{~S}(U S P 28)}$

The following procedure is provided for the determination of vitamin A as an ingredient of Pharmacopeial preparations. It conforms to that which was adopted in 1956 for international use by the International Union of Pure and Applied Chemistry.

Complete the assay promptly, and exercise care throughout the procedure to keep to a minimum the exposure to actinic light and to atmospheric oxygen and other oxidizing agents, preferably, by the use of low-actinic glassware and an atmosphere of an inert gas.

## Special Reagents-

ETHER-Use ethyl ether, and use it within 24 hours after opening the container.

ISOPROPYL ALCOHOL-Use spectrophotometric-grade isopropyl alcohol (see Isopropyl Alcohol under Reagent Specifications in the section Reagents, Indicators, and Solutions).

Procedure-Accurately weigh, count, or measure a portion of the test specimen expected to contain the equivalent of not less than 0.15 mg of retinol but containing not more than 1 g of fat. If in the form of capsules, tablets, or other solid, so that it cannot be saponified efficiently by the ensuing instructions, reflux the portion taken in 10 mL of water on a steam bath for about 10 minutes, crush the remaining solid with a blunt glass rod, and warm for about $5 \mathrm{~min}-$ utes longer.

Transfer to a suitable borosilicate glass flask, and add 30 mL of alcohol, followed by 3 mL of potassium hydroxide solution ( 9 in 10). Reflux in an all-borosilicate glass apparatus for 30 minutes. Cool the solution, add 30 mL of water, and transfer to a conical separator. Add 4 g of finely powdered sodium sulfate decahydrate. Extract by shaking with one $150-\mathrm{mL}$ portion of ether for 2 minutes, and then, if an emulsion forms, with three $25-\mathrm{mL}$ portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 mL of water. Repeat the washing more vigorously with three additional $50-\mathrm{mL}$ portions of water. Transfer the washed ether extract to a $250-\mathrm{mL}$ volumetric flask, add ether to volume, and mix.

Evaporate a $25.0-\mathrm{mL}$ portion of the ether extract to about 5 mL . Without applying heat and with the aid of a stream of inert gas or vacuum, continue the evaporation to about 3 mL . Dissolve the residue in sufficient isopropyl alcohol to give an expected concentration of the equivalent to $3 \mu \mathrm{~g}$ to $5 \mu \mathrm{~g}$ of vitamin A per mL or such that it will give an absorbance in the range 0.5 to 0.8 at 325 nm . Determine the absorbances of the resulting solution at the wavelengths $310 \mathrm{~nm}, 325 \mathrm{~nm}$, and 334 nm , with a suitable spectrophotometer fitted with matched quartz cells, using isopropyl alcohol as the blank.

WHEN TOCOPHEROL IS PRESENT-Transfer to a suitable borosilicate glass flask a test specimen, accurately measured, or not less than 5 previously crushed capsules or tablets. Reflux in an all-borosilicate glass apparatus with 30 mL of alcohol and 3 mL of potassium hydroxide solution ( 9 in 10) for 30 minutes. Add through the condenser 2.0 g of citric acid monohydrate, washing the walls of the condenser with 10 mL of water. Cool, and transfer the solution to a conical separator with the aid of 20 mL of water. Add 4 g of finely powdered sodium sulfate decahydrate. Extract with one 150mL portion of ether and then, if an emulsion forms, with three 25mL portions of ether. Combine the ether extracts, if necessary, and wash by swirling gently with 50 mL of water. Repeat the washing more vigorously with three additional $50-\mathrm{mL}$ portions of water. Transfer the washed ether extract to a $250-\mathrm{mL}$ volumetric flask, and add ether to volume. Transfer a $100.0-\mathrm{mL}$ aliquot of the resulting ether solution to a conical separator, and wash once with 50 mL of potassium hydroxide solution ( 1 in 33), using alcohol, if necessary, to break any emulsion that forms. Wash by swirling gently
with 50 mL of water. Repeat the washing more vigorously with three additional $50-\mathrm{mL}$ portions of water. Transfer the washed ether extract to a $100-\mathrm{mL}$ volumetric flask, add ether to volume, and mix.

Evaporate a $50.0-\mathrm{mL}$ aliquot of the ether solution of the unsaponifiable extract to about 5 mL . Without applying heat and with the aid of a stream of inert gas or vacuum, remove the residual ether. Dissolve the residue in 50.0 mL of isopropyl alcohol.

Hydrogenated portion-Pipet 15.0 mL of the isopropyl alcohol solution into a $50-\mathrm{mL}$ centrifuge tube, add approximately 200 mg of palladium catalyst, stir with a glass rod, and hydrogenate for 10 minutes in a Hydrogenator such as is described in the Alpha Tocopherol Assay $\langle 551\rangle$, using isopropyl alcohol in the blank tube. Add about 300 mg of chromatographic siliceous earth, stir with a glass rod, and immediately centrifuge until the solution is clear.

Test a $1-\mathrm{mL}$ aliquot of the solution by removing the solvent by evaporation, dissolving the residue in 1 mL of chloroform, and adding 10 mL of phosphomolybdic acid TS: no detectable bluegreen color appears. [NOTE-If a blue-green color appears, repeat the hydrogenation for a longer time period, or with a new lot of catalyst.]

Into two separate flasks pipet equal volumes of the Hydrogenated portion and the untreated isopropyl alcohol solution, respectively, and add sufficient isopropyl alcohol to give an expected concentration of vitamin A equivalent to $3 \mu \mathrm{~g}$ to $5 \mu \mathrm{~g}$ per mL . Determine the absorbances of the untreated solution against the solution from the Hydrogenated portion as a blank, at the wavelengths $310 \mathrm{~nm}, 325 \mathrm{~nm}$, and 334 nm , with a suitable spectrophotometer fitted with matched quartz cells.

Calculation-Calculate the vitamin A content as follows:

$$
\text { Content }(\text { in } \mathrm{mg})=0.549 A_{325} / L C
$$

in which $A_{325}$ is the observed absorbance at $325 \mathrm{~nm} ; L$ is the length, in cm , of the absorption cell; and $C$ is the amount of test specimen expressed as g , capsule, or tablet in each 100 mL of the final isopropyl alcohol solution, provided that $A_{325}$ has a value not less than $\left[A_{325}\right] / 1.030$ and not more than $\left[A_{325}\right] / 0.970$, where $\left[A_{325}\right]$ is the corrected absorbance at 325 nm and is given by the equation:

$$
\left[A_{325}\right]=6.815 A_{325}-2.555 A_{310}-4.260 A_{334}
$$

in which $A$ designates the absorbance at the wavelength indicated by the subscript.

Where $\left[A_{325}\right]$ has a value less than $A_{325} / 1.030$, apply the following equation:

$$
\text { Content }(\text { in } \mathrm{mg})=0.549\left[A_{325}\right] / L C
$$

in which the values are as defined herein. Each mg of vitamin A (alcohol) represents 3333 USP Units of vitamin A.

Confidence Interval-The range of the limits of error, indicating the extent of discrepancy to be expected in the results of different laboratories at $P=0.05$, is approximately $\pm 8 \%$.

## Add the following:

## ■CHROMATOGRAPHIC METHOD

The following pressurized liquid chromatographic procedure is provided for the determination of Vitamin A. Where the use of vitamin A ester (retinyl acetate or retinyl palmi-
tate) is specified in the following procedure, use the chemical form present in the raw material. Use low-actinic glassware throughout this procedure

USP Reference Standards $\langle 11\rangle$ - [NOTE-Use USP Vita$\min A R S$, all-trans retinyl acetate, for assaying pharmaceutical dosage forms that are labeled to contain retinol or vitamin A ester (retinyl acetate or retinyl palmitate).]

Mobile Phase-Use $n$-hexane.
System Suitability Preparation-Dissolve an accurately weighed quantity of retinyl palmitate and USP Vitamin A RS in $n$-hexane to obtain a solution containing about $7.5 \mu \mathrm{~g}$ per mL of each.

Standard Preparation-Dissolve an accurately weighed quantity of USP Vitamin A RS in $n$-hexane, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about $15 \mu$ g of retinyl acetate per mL.

Assay Preparation-Transfer about 15 mg of vitamin A ester (retinyl acetate or retinyl palmitate), accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with $n$-hexane to volume, and mix. Pipet 5.0 mL of this solution into a $50-\mathrm{mL}$ volumetric flask, dilute with $n$-hexane to volume, and mix.

Chromatographic System (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $325-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L8. The flow rate is about 1 mL per minute. Chromatograph the System Suitability Preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between retinyl acetate and retinyl palmitate is not less than 10 ; and the relative standard deviation for replicate injections is not more than $3.0 \%$.

Procedure-Separately inject equal volumes (about 40 $\mu \mathrm{L}$ ) of the Standard Preparation and the Assay Preparation into the chromatograph, record the chromatograms, and
measure the responses for retinyl acetate obtained from the Standard Preparation and the peak area for retinyl acetate or retinyl palmitate in the chromatogram of the Assay Preparation. Calculate the quantity, in mg , of vitamin A as the retinol equivalent $\left(\mathrm{C}_{20} \mathrm{H}_{30} \mathrm{O}\right)$ in the portion of vitamin A taken by the formula:

$$
0.872 C D\left(r_{U} / r_{S}\right)
$$

in which 0.872 is the factor used to convert retinyl acetate, obtained from USP Vitamin A RS to its retinol equivalent; $C$ is the concentration, in mg per mL, of USP Vitamin A RS in the Standard Preparation; $D$ is the dilution factor, in mL , for the Assay Preparation; and $r_{U}$ and $r_{S}$ are the peak responses of the retinyl ester obtained from the Assay Preparation and the Standard Preparation, respectively. [NOTEThe molar responses of retinyl acetate and retinyl palmitate are equivalent.] ${ }_{\text {IS (USP28) }}$

## Physical Tests and Determination

## BRIEFING

[^170]posed to add critical engineering dimensions to the USP description of the Andersen Mk II cascade impactor (Apparatus 1 and 3) and remove ambiguities from the specifications for other equipment items, thereby easing their manufacture.
(AER: K. Zaidi) RTS-41343-1

## Change to read:

〈601〉 AEROSOLS,

##  <br> METERED-DOSE INHALERS, AND DRY POWDER INHALERS

## Change to read:

This general chapter contains test methods for propellants, pressurized topical aerosols,
${ }^{\Delta}$ nasal sprays, $\mathbf{n}$ USP28
metered-dose inhalers, and propellant-free dry powder inhalers used to aerosolize, or to aerosolize and meter, doses of powders for inhalation. Apply these methods, where indicated, in the testing of the appropriate dosage forms.

## Change to read:

## TOPICAL AEROSOLS

${ }^{\Delta}$ The following tests are applicable to topical aerosols containing drug, in suspension or solution, packaged under pressure, and released upon activation of an appropriate valve system. $\Delta U S P 28$

## Delivery Rate and Delivered Amount

Only perform these tests on containers fitted with continuous valves.

Delivery Rate-Select not less than four aerosol containers, shake, if the label includes this directive, remove the caps and covers, and actuate each valve for 2 to 3 seconds. Weigh each container accurately, and immerse in a constant-temperature bath until the internal pressure is equilibrated at a temperature of $25^{\circ}$ as determined by constancy of internal pressure as directed under the Pressure Test below. Remove the containers from the bath, remove excess moisture by blotting with a paper towel, shake, if the label includes this directive, actuate each valve for 5.0 seconds (accurately timed by use of a stopwatch), and weigh each container again. Return the containers to the constant-temperature bath,
and repeat the foregoing procedure three times for each container. Calculate the average Delivery Rate, in $g$ per second, for each container.

Delivered Amount-Return the containers to the constant-temperature bath, continuing to deliver 5 second actuations to waste, until each container is exhausted. [NOTE-Ensure that sufficient time is allowed between each actuation to avoid significant canister cooling.] Calculate the total weight loss from each container. This is the Delivered Amount.

## Pressure Test

Only perform this test on topical aerosols fitted with continuous valves.

Select not less than four aerosol containers, remove the caps and covers, and immerse in a constant-temperature bath until the internal pressure is constant at a temperature of $25^{\circ}$. Remove the containers from the bath, shake, and remove the actuator and water, if any, from the valve stem. Place each container in an upright position, and determine the pressure in each container by placing a calibrated pressure gauge on the valve stem, holding firmly, and actuating the valve so that it is fully open. The gauge is of a calibration approximating the expected pressure and is fitted with an adapter appropriate for the particular valve stem dimensions. Read the pressure directly from the gauge.

## Minimum Fill

Topical aerosols meet the requirements for aerosols under Minimum Fill $\langle 755\rangle$.

## Leakage Test

Only perform this test on topical aerosols fitted with continuous valves.

Select 12 aerosol containers, and record the date and time to the nearest half hour. Weigh each container to the nearest mg , and record the weight, in mg, of each as $W_{1}$. Allow the containers to stand in an upright position at a temperature of $25.0 \pm 2.0^{\circ}$ for not less than 3 days, and again weigh each container, recording the weight, in mg , of each as $W_{2}$ and recording the date and time to the nearest half hour. Determine the time, $T$, in hours, during which the containers were under test. Calculate the leakage rate, in mg per year, of each container taken by the formula:

$$
(365)(24 / T)\left(W_{1}-W_{2}\right)
$$

Where plastic-coated glass aerosol containers are tested, dry the containers in a desiccator for 12 to 18 hours, and allow them to stand in a constant-humidity environment for 24 hours prior to determining the initial weight as indicated above. Conduct the test under the same constant-humidity conditions. Empty the contents of each container tested by employing any safe technique (e.g., chill to reduce the internal pressure, remove the valve, and pour). Remove any residual contents by rinsing with suitable solvents, then rinse with a few portions of methanol. Retain as a unit the container, the valve, and all associated parts, and heat them at $100^{\circ}$ for 5 minutes. Cool, weigh, record the weight as $W_{3}$, and determine the net fill weight $\left(W_{1}-W_{3}\right)$ for each container tested. [NOTE-If the average net fill weight has been determined previously, that value may be used in place of the value $\left(W_{1}-W_{3}\right)$ above.] The requirements are met if the average leakage rate per year for the 12 containers is not more than $3.5 \%$ of the net fill weight, and none of the containers leaks more than $5.0 \%$ of the net fill weight per year. If 1 container leaks more than $5.0 \%$ per year, and if none of the containers leaks more than $7.0 \%$ per year, determine the leakage rate of an additional 24 containers as direct-
ed herein. Not more than 2 of the 36 containers leak more than $5.0 \%$ of the net fill weight per year, and none of the 36 containers leaks more than $7.0 \%$ of the net fill weight per year. Where the net fill weight is less than 15 g and the label bears an expiration date, the requirements are met if the average leakage rate of the 12 containers is not more than 525 mg per year and none of the containers leaks more than 750 mg per year. If 1 container leaks more than 750 mg per year, but not more than 1.1 g per year, determine the leakage rate of an additional 24 containers as directed herein. Not more than 2 of the 36 containers leak more than 750 mg per year, and none of the 36 containers leaks more than 1.1 g per year. This test is in addition to the customary in-line leak testing of each container.

## Fotal" ${ }_{\text {1S }}^{1 S}$ (USP28) ${ }^{\text {Number of Discharges per Container }}$

Only perform this test on topical aerosols fitted with dose-metering valves, at the same time as, and on the same containers used for, the test for Uniformity of Desage Units- $\langle 905\rangle$. Determine the tal
-Delivered-Dose Uniformity. Determine the $\mathbf{1}_{1 \mathrm{~S}}$ (USP28) number of discharges or deliveries by counting the number of priming discharges plus those used in determining the spray contents, and continue to fire er diseharge until the entainer or inhaler is emply
$\square_{\text {until the label claim number of discharges. } \quad \text { 1S (USP28) }}$
The requirements are met if all the containers or inhalers tested contain not less than the number of discharges stated on the label.

## Delivered Dose Uniformity

The test for Delivered Dose Uniformity is required for topical aerosols fitted with dose-metering valves. For collection of the minimum dose, proceed as directed in the test for Delivered Dose Uniformity under Metered-Dose Inhalers and Dry Powder Inhalers, as described below, except to modify the dose sampling apparatus so that it is capable of quantitatively capturing the delivered dose from the preparation being tested. Unless otherwise stated in the individual monograph, apply the acceptance criteria for Me -tered-Dose Inhalers and Dry Powder Inhalers as described below.

## Add the following:

## ${ }^{\wedge}$ NASAL SPRAYS

The following test is applicable to nasal sprays, formulated as aqueous suspensions or solutions of drug, presented in multi-dose containers and fitted with dose-metering valves. In all cases, and for all tests, prepare and test the nasal spray as directed on the label and the instructions for use.

## Delivered-Dose Uniformity

Unless otherwise directed in the individual monograph, the drug content of the minimum delivered doses (minimum number of sprays per nostril as described on the label, or instructions for use) collected at the beginning of unit life (after priming as described on the label, or instructions for use) and at the label claim number of metered sprays, from each of 10 separate containers, must meet the following acceptance criteria: not more than 2 of the 20 doses are outside the range of $80 \%$ to $120 \%$ of label claim, and none are outside the range of $75 \%$ to $125 \%$ of label claim, while the mean for each of the beginning and end doses falls within the range of $85 \%$ to $115 \%$ of label claim. If 3 to 6 doses of the 20 doses collected are outside of $80 \%$ to $120 \%$ of the label claim, but none are outside of $75 \%$ to $125 \%$ of label claim, and the means for each of the beginning and end doses fall within $85 \%$ to $115 \%$ of label claim, select 20 additional containers for second-tier testing. For second-tier testing, the requirements are met if not more than 6 of the 60 doses collected are outside the range of $80 \%$ to $120 \%$ of label claim, none are outside the range of $75 \%$ to $125 \%$ of label claim, and the means for each of the beginning and end doses fall within the range of $85 \%$ to $115 \%$ of label claim.

SAMPLING FOR DELIVERED-DOSE UNIFORMITY OF METEREDDOSE NASAL SPRAYS

General Sampling Procedure-To ensure reproducible in-vitro dose collection, it is recommended that a mechanical means of actuating the pump assembly be employed to deliver doses for collection. The mechanical actuation procedure should have adequate controls for the critical mechanical actuation parameters (e.g., actuation force, actuation speed, stroke length, rest periods, etc.). The test must be performed on units that have been primed according to the patient-use instructions. The test unit should be actuated
in a vertical or near vertical, valve-up, position. The two doses collected at the beginning and end of the container life should be the dose immediately following priming and the dose corresponding to the last label claim number of doses from the container.

For suspension products, the delivered dose should be delivered into a suitable container (e.g., scintillation vial) in which quantitative transfer from the container under test can be accomplished. A validated analytical method is employed to determine the amount of drug in each delivered dose, and data are reported as a percent of label claim. For solution products, the delivered dose can be determined gravimetrically from the weight of the delivered dose, and the concentration and density of the fill solution of the product under test. $\triangle$ USP28

## Change to read:

## METERED-DOSE INHALERS AND DRY POWDER INHALERS

The following tests are applicable to metered-dose inhalers that are formulated as suspensions or solutions of active drug in propellants and dry powder inhalers presented as single or multidose units. The following test methods are specific to the aforementioned inhalers and may require modification when testing alternative inhalation technologies (for example, breath-actuated metereddose inhalers, or dose-metering nebulizers). However, Pharmacopeial requirements for all dose-metering inhalation dosage forms require determination of the delivered dose and Aerodynamic Size Distribution. In all cases, and for all tests, prepare and test the inhaler as directed by the label and the instructions for use. When these directions are not provided by the product manufacturer, follow the precise dose discharge directions included in the tests below.

## Delivered-Dose Uniformity

The test for Delivered Dese Uniformity is required for inhalers (e.g., metered dose inhalers or dry powder inhalers) containing drug formalation (e.g., solution, suspension, or pewder) either in reserveirs or im premetered desage units and for drug formatations packaged in reserveirs or in premetered dosage units where these eentainers are labeled for use with a named inhalation deviee. (For inhalations packaged in premetered dosage units, see also Unifor mityof Desage Units $\langle 905\rangle \rightarrow$.

Unless otherwise directed in the individualmonegraph, the drug eentent of the minimum delivered dese from-each of 10 separate eontainers is determined in aceordance with the procedure deseribed below.

Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if not less than 9 of the 10 dese are between $75 \%$ and $125 \%$ of the labelclaim and nene is eutside the range $65 \%$ to $135 \%$ f the label claim. If the eontents of not more than thre doses are outside the range of $75 \%$ to $125 \%$ of the labelelaim, but within the range of $65 \%$ to $135 \%$ of the label elaim, select 20 additional containers, and follow the preseribed procedure for analyzing one minimum dose from each. The requirements are met if not mere than three results, out of the 30 val Hes, lie outside the range of $75 \%$ 10 $125 \%$ flabelclaim and none is outside the range of $65 \%$ to $135 \%$ of the label claim.

- The test for Delivered-Dose Uniformity is required for inhalers (e.g., metered-dose inhalers or dry powder inhalers) containing drug formulation (e.g., solution, suspension, or powder) either in reservoirs or in premetered dosage units, and for drug formulations packaged in reservoirs or in premetered dosage units where these containers are labeled for use with a named inhalation device. (For inhalations packaged in premetered dosage units, see also Uniformity of Dosage Units $\langle 905\rangle$.) Note that the target-delivered dose is the expected mean drug content for a large number of delivered doses collected from many inhalers of the chosen product. In many cases, its value may depend upon the manner in which the test for delivered dose is performed. For metered-dose inhalers, the target-delivered dose is specified by the label claim, unless otherwise specified in the individual monograph. For dry powder inhalers, where the label claim is usually the packaged or metered-dose of drug, the target-delivered dose is specified in the individual monograph and is usually less than the label claim. Its value reflects the expected mean drug content for a large number of delivered doses collected from the product, using the method specified in the monograph.

Unless otherwise directed in the individual monograph, the drug content of the minimum delivered dose from each of 10 separate containers is determined in accordance with the procedure described below.
Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if not less than 9 of the 10 doses are between $75 \%$ and $125 \%$ of the specified target-delivered dose and none is outside the range
of $65 \%$ to $135 \%$ of the specified target-delivered dose. If the contents of not more than 3 doses are outside the range of $75 \%$ to $125 \%$ of the specified target-delivered dose, but within the range of $65 \%$ to $135 \%$ of the specified target-delivered dose, select 20 additional containers, and follow the prescribed procedure for analyzing 1 minimum dose from each. The requirements are met if not more than 3 results, out of the 30 values, lie outside the range of $75 \%$ to $125 \%$ of the specified target-delivered dose, and none is outside the range of $65 \%$ to $135 \%$ of the specified target-delivered dose. $\quad$ USP28

## SAMPLING THE DELIVERED DOSE FROM METERED-DOSE INHALERS

To determine the content of active ingredient in the discharged spray from a metered-dose inhaler, use the sampling apparatus described below, using a flow rate of 28.3 L of air per minute $( \pm 5 \%)$, unless otherwise stated in the individual monograph.

Apparatus A-The apparatus (see Fig. 1) consists of a filter support base with an open-mesh filter support, such as a stainless steel screen, a collection tube that is clamped or screwed to the fil-
ter support base, and a mouthpiece adapter to ensure an airtight seal between the collection tube and the mouthpiece. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the sample collection tube
-opening of the inhaler mouthpiece is flush with the front face or $2.5-\mathrm{mm}$ indented shoulder in the sample collection
tube, as appropriate. IS (USP28)
The vacuum connector is connected to a system comprising a vacuum source, flow regulator, and flowmeter. The source should be capable of pulling air through the complete assembly, including the filter and the inhaler to be tested, at the desired flow rate. When testing metered-dose inhalers, air should be drawn continuously through the system to avoid loss of drug into the atmosphere. The filter support base is designed to accommodate $25-\mathrm{mm}$ diameter filter disks. At the airflow being used, the sample collection tube and the filter disk must be capable of quantitatively collecting the Delivered Dose. The filter disk and other materials used in the construction of the apparatus must be compatible with the drug and the solvents that are used to extract the drug from the filter. One end of the collection tube is designed to hold the filter disk tightly against the filter support base. When assembled, the joints between the components of the apparatus are airtight so that when a vacuum is applied to the base of the filter, all of the air drawn through the collection device passes through the inhaler.


Fig. 1. Sampling apparatus for pressurized metered-dose inhalers.

Procedure-Prepare the inhaler for use according to the label instructions. Unless otherwise specified in the individual monograph, with the vacuum pump running, ensuring an airflow rate through the inhaler of 28.3 L of air per minute ( $\pm 5 \%$ ), discharge the minimum recommended dose into the apparatus through the mouthpiece adapter by depressing the valve for a duration sufficient to ensure that the dose has been completely discharged. Detach the inhaler from Apparatus $A$, and disconnect the vacuum. Assay the contents of the apparatus for drug after rinsing the filter and the interior of the apparatus with a suitable solvent.

## SAMPLING THE DELIVERED DOSE FROM DRY POWDER INHALERS

To determine the content of active ingredient emitted from the mouthpiece of a dry powder inhaler, use Apparatus B (see Fig. 2). This apparatus is capable of sampling the emitted doses at a variety of airflow rates.


Fig. 2. Apparatus B: Smppling apparatus for dry pouder inhaters. (See Table 1 for compenent specifieations.)


Fig. 2. Apparatus B: Sampling apparatus for dry powder inhalers. (See Table 1 for component specifications.)

Table 1. Component Specifications for Apparatus B (see Fig. 2)

| Code | Item | Description | Dimensions |
| :---: | :---: | :---: | :---: |
| A | Sample collection tube ${ }^{\text {a }}$ | See Fig. 2 | $34.85-\mathrm{mm}$ ID $\times 12-\mathrm{cm}$ length |
| B | Filter ${ }^{\text {b }}$ | See Fig. 2 | $47-\mathrm{mm}$ glass fiber filter |
| C | Connector | (e.g., short metal coupling with low diameter branch to P3) | $\geq 8$-mm ID |
| D | Vacuum tubing | (e.g., silicon tubing with an outside diameter of 14 mm and an internal diameter of 8 mm ) | -a length of suitable tubing $\geq 8 \mathrm{~mm}$ ID |
|  |  |  | with an internal volume of $25 \pm 5$ mL . 1 S (USP28) |
| E | Two-way solenoid valve ${ }^{\text {c }}$ | See Fig. 2 | Minimum cirflew- orifice having an intemal <br> diameter of $\geq 8$ mm and a maximmm <br> respense time of 100 milliseconds |
|  |  |  | -2-way, 2-port solenoid valve having an |
|  |  |  | ID $\geq 8 \mathrm{~mm}$ and an opening response |
|  |  |  | time of $\leq 100$ milliseconds. 1 (USP28) Pump must be capable of drawing the |
| F | Vacuum pump ${ }^{\text {d }}$ | See Fig. 2 | required flow rate through the assembled apparatus with the dry powder inhaler in the mouthpiece adapter. Connect the pump to the solenoid valve using short and wide ( $\geq 10-\mathrm{mm}$ ID) vacuum tubing and connectors to minimize pump capacity requirements. |

Table 1. Component Specifications for Apparatus B (see Fig. 2) (Continued)

| Code | Item | Description | Dimensions |
| :---: | :---: | :---: | :---: |
| G | Timer ${ }^{\text {e }}$ | See Fig. 2 | The timer switches current directly to the solenoid valve for the required duration. |
| P1 | pressure tap | See Fig. 2 | $2.2-\mathrm{mm}$ ID, $3.1-\mathrm{mm}$ OD flush with the internal surface of the sample collection tube, centered and burr free, its inlet |
|  |  |  | $\square 59 \mathrm{~mm}$ from its inlet. The pressure |
|  |  |  | taps P1, P2, and P3 must not be open |
|  |  |  | to the atmosphere during dose collec- |
|  |  |  | tion.■1S (USP28) |
| $\begin{gathered} \mathrm{P} 1, \mathrm{P} 2, \mathrm{P} 3 \\ \mathrm{H} \end{gathered}$ | pressure measurements ${ }^{f}$ <br> Flow-control valve ${ }^{g}$ | See Fig. 2 | Adjustable regulating valve with |
|  |  |  | maximum $\mathrm{C}_{\mathrm{v}} \geq 1^{\mathrm{h}}$ |

${ }^{\text {a }}$ An example being a Millipore product number XX40 04700 (Millipore Corporation, 80, Ashby Road, Bedford, MA 01732), modified so that the exit tube has an ID $\geq 8-\mathrm{mm}$, fitted with Gelman product number 61631.
${ }^{\mathrm{b}}$ A/E (Gelman Sciences Inc., 600 South Wagner Road, Ann Arbor, MI 48106) or equivalent.
${ }^{\text {c }}$ ASCO product number 8030G13, Automatic Switch Company, 60 Hanover Road, Florham Park, NJ 07932.
${ }^{d}$ Gast product type 1023, 1423, or 2565 (Gast Manufacturing Inc., PO Box 97, Benton Harbor, MI 49022) or equivalent.
${ }^{\mathrm{e}}$ Eaton Product number 45610-400 (Eaton Corporation, Automotive Products Division, 901, South 12th Street, Watertown, WI 53094) or equivalent.
${ }^{\mathrm{f}}$ An example being a PDM 210 pressure meter (Air-Neotronics Ltd., Neotronics Technology plc, Parsonage Road, Takeley, Bishop's Stortford, CM22 6PU, UK), or equivalent.
${ }^{\mathrm{g}}$ Parker Hannifin type 8FV12LNSS (Parker Hannifin plc., Riverside Road, Barnstable, Devon EX31 1NP, UK) or equivalent.
${ }^{\text {h }}$ Flow Coefficient, as defined by ISA S75.02 "Control valve capacity test procedure" in Standards and Recommended Practices for Instrumentation and Control, 10th ed., Vol. 2, 1989. Published by Instrument Society of America, 67 Alexander Drive, P.O. Box 1227, Research Triangle Park, NC 27709, U.S.A.

Apparatus B-The apparatus is similar to that described in Fig. 1 for testing metered-dose inhalers. In this case, however, the filter and collection tube have a larger internal diameter to accommodate $47-\mathrm{mm}$ diameter filter disks. This feature enables dosage collection at higher airflow rates-up to 100 L of air per minute-when necessary. A mouthpiece adapter ensures an airtight seal between the collection tube and the mouthpiece of the dry powder inhaler being tested. The mouthpiece adapter must ensure that the tip of the inhaler mouthpiece is flush with the open end of the sample collection tube. Tubing connectors, if they are used, should have an internal diameter greater than or equal to 8 mm to preclude their own internal diameters from creating significant airflow resistance. A vacuum pump with excess capacity must be selected in order to draw air, at the designated volumetric flow rate, through both the sampling apparatus and the inhaler simultaneously. A timer-controlled, low resistance, solenoid-operated, two-way valve is interposed between the vacuum pump and the flow-control valve to control the duration of flow. This type of valve enables 4.0 liters of air $( \pm 5 \%)$ to be withdrawn from the mouthpiece of the inhaler at the designated flow rate. Flow control is achieved by ensuring that critical (sonic) flow occurs in the flow-control valve (absolute pressure ratio $\mathrm{P} 3 / \mathrm{P} 2 \leq 0.5$ under conditions of steady-state flow).

Procedure-Operate the apparatus at an airflow rate, $Q^{2}$
^AUSP28
which produces a pressure drop of $4 \mathrm{kPa}\left(40.8 \mathrm{~cm} \mathrm{H}_{2} \mathrm{O}\right)$ over the inhaler to be tested, and a duration, $\mathcal{F}$,
© $\Delta$ USP28
consistent with the withdrawal of 4 L of air from the mouthpiece of the inhaler. [NOTE If $Q$ and $T$ are defined otherwise in the monegraph, use values of $Q$ and $T$ that are within $5 \%$ of those values. Betermine the value of $Q$ ]
${ }^{\boldsymbol{\Delta}}$ [NOTE-If the flow rate and duration are defined otherwise in the monograph, adjust the system to within $5 \%$ of those values.] Determine the test flow rate $\mathbf{\Delta U S P 2 8}$
using Apparatus $B$ as follows. Insert an inhaler into the mouthpiece adapter to ensure an airtight seal. In cases where the drug packaging modifies the inhaler's resistance to airflow, use a loaded, drugfree inhaler (with previously emptied packaging). In other cases, use an unloaded (drug free) inhaler. Connect one port of a differential pressure transducer to the pressure tap, P1, and leave the other open to the atmosphere. Switch on the pump, and open the two-way solenoid valve. Adjust the flow-control valve until the pressure drop across the inhaler is $4.0 \mathrm{kPa}\left(40.8 \mathrm{~cm} \mathrm{H}_{2} \mathrm{O}\right)$. Ensure that critical (sonic) flow occurs in the flow-control valve by determining the individual values for absolute pressure, P 2 and P 3 , so that their ratio $\mathrm{P} 3 / \mathrm{P} 2$ is less than or equal to 0.5 . If this criterion cannot be achieved, it is likely that the vacuum pump is worn or of insufficient capacity. Critical (sonic) flow conditions in the flowcontrol valve are required in order to ensure that the volumetric airflow is unaffected by pump fluetuations and miner changes in airflow resistanee at the inhaler intet.
${ }^{\boldsymbol{\Delta}}$ drawn from the mouthpiece is unaffected by pump fluctuations and changes in airflow resistance of the inhaler. $\mathbf{U S P 2}$. ${ }^{2}$ Remove the inhaler from the mouthpiece adapter and, without disturbing the flow-control valve, measure the airflow rate, $Q$, neeting a flowneter
$\Delta_{\text {drawn }}$ from the mouthpiece, $Q_{\text {out }}$, by connecting a flowmeter to the mouthpiece adaptor in an airtight fashion. Use a flowmeter $\mathbf{A}_{\mathbf{U S P 2 8}}$
calibrated for the volumetric flow leaving the meter the mouthpiece adapter in an airtight fashion
${ }^{\boldsymbol{\Delta}}$ in an airtight fashion IS (USP28) to directly determine $Q_{\text {out }}$ or, if such a meter is unobtainable, calculate the volumetric flow leaving the meter ( $Q_{\text {out }}$ ) using the ideal gas law. For example, for a meter calibrated for the entering volumetric flow ( $Q_{i n}$ ), use the formula:

$$
Q_{\text {out }}=Q_{\text {in }} P_{0} /\left(P_{0}-\Delta P\right),
$$

where $P_{0}$ is the atmospheric pressure and $\Delta \mathrm{P}$ is the pressure drop over the meter. $\triangle$ USP28
If the flow rate is greater than 100 L of air per minute, adjust the flow-control valve until $Q$
${ }^{\wedge} Q_{\text {out }} \mathbf{\Delta U S P 2 8}$
equals 100 L per minute; otherwise, record the value of $\Theta$
${ }^{\Delta} Q_{\text {our }, \mathbf{\Delta} U S P 28}$
and leave the flow-control valve undisturbed. Define the test flow duration, $T=240$
${ }^{\boldsymbol{\Delta}} T=240 / Q_{\text {out }}, \boldsymbol{\Delta}$ USP28
in seconds, so that a volume of 4.0 L of air $( \pm 5 \%)$ is withdrawn from the inhaler during the withdrawal of the test dese
$\Delta^{\text {at }}$ the test flow rate $Q_{\text {our }} \mathbf{\Delta U S P 2 8}$
and adjust the timer controlling the operation of the two-way solenoid valve accordingly. Prime or load the inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the solenoid valve closed, insert the inhaler mouthpiece horizontally into the mouthpiece adapter. Discharge the powder into the sampling apparatus by activating the timer controlling the solenoid valve and withdrawing 4.0 L of air from the inhaler at the previously defined airflow rate. If the labeled instructions so direct, repeat the operation so as to simulate the use of the inhaler by the patient (e.g., inhale two or three times, if necessary, to empty the capsule). Repeat the whole operation $n-1$ times be-, ginning with the text, "Prime or load the inhaler with powder,", where $n$ is the number of times defined in the labeling as the minimum recommended dose. Detach the dry powder inhaler from the sampling apparatus, and disconnect the vacuum tubing, D. Assay the contents of the apparatus for drug after rinsing the filter and the interior of the apparatus with a suitable solvent. Where specified in individual monographs, perform this test under conditions of controlled temperature and humidity.

## Delivered-Dose Uniformity over the Entire Contents

The test for Delivered-Dose Uniformity over the Entire Contents is required for inhalers (e.g., metered-dose inhalers or dry powder inhalers) containing multiple doses of drug formulation (e.g., solution, suspension, or dry powder) either in reservoirs or in premetered dosage units (e.g., blisters), and for drug formulations packaged in reservoirs or in multiple-dose assemblies of premetered dosage units that have a predetermined dose sequence, where these multiple-dose assemblies are labeled for use with a named inhalation device. The test for delivered dose uniformity over the entire contents also ensures that multidose products supply
the total number of discharges stated on the label. Unless otherwise directed in the individual monograph, the drug content of at least 9 of the 10 doses collected from one inhaler, in accordance with the procedure below, are between $75 \%$ and $125 \%$ of tabelaim
${ }^{\Delta}$ the target-delivered dose,, USP28
and none is outside the range of $65 \%$ to $135 \%$ of taim
$\Delta_{\text {the }}$ target-delivered dose. $\mathbf{\Delta U S P 2 8}$
If the contents of not more than three doses are outside the range of $75 \%$ to $125 \%$, but within the range of $65 \%$ to $135 \%$ of tabelelaim
© the target-delivered dose, $\mathbf{\Delta U S P 2 8}$
select two additional inhalers and follow the prescribed procedure for analyzing 10 doses from each. The requirements are met if not more than three results, out of the 30 values, lie outside the range of $75 \%$ to $125 \%$ of tabel claim
${ }^{\boldsymbol{\Delta}}$ the target-delivered dose,, USP28 and none is outside the range of $65 \%$ to $135 \%$ of tabelaim
©the target-delivered dose. $\triangle$ USP28

## METERED-DOSE INHALERS

Apparatus-Use Apparatus $A$ as directed in Sampling the Delivered Dose from Metered-Dose Inhalers under Delivered-Dose Uniformity at a flow rate of 28.3 liters of air per minute $( \pm 5 \%)$.

Procedure-A single dose is defined as the number of sprays specified in the product labeling as the minimum recommended dose. Select a single metered-dose inhaler, and follow the labeled instructions for priming, shaking, cleaning, and firing the inhaler throughout. Unless otherwise prescribed in the patient instructions, shake the inhaler for 5 seconds, and fire one minimum recommended dose to waste. Wait for 5 seconds, and collect the next dose. Detach the inhaler from Apparatus $A$, and disconnect the vacuum. Assay the contents of the apparatus for drug after rinsing the filter and the interior of the apparatus with a suitable solvent. Collect two more doses, allowing at least 5 seconds between doses. Discharge the device to waste, waiting for not less than 5 seconds between actuations (unless otherwise specified in the individual monograph), until ( $n / 2$ ) +1 minimum recommended doses remain, in which $n$ is the number of minimum recommended doses on the label. Collect four more doses, allowing at least 5 seconds between doses, unless otherwise specified in the individual monograph. Discharge the device to waste, as before, until three doses remain. Collect the final three doses, allowing at least 5 seconds between doses. Note that the rate of discharges to waste should not be such to cause excessive canister cooling.

## DRY POWDER INHALERS

Apparatus-Use Apparatus $B$ as directed in Sampling the Delivered Dose from Dry Powder Inhalers under Delivered-Dose Uniformity at the appropriate airflow rate for testing.

Procedure-Proceed as directed for Procedure in Sampling the Delivered Dose from Dry Powder Inhalers under Delivered-Dose Uniformity. A single dose is defined as the number of actuations stated in the product labeling as the minimum recommended dose. Select a single inhaler and follow the labeled instructions for loading with powder, discharging and cleaning throughout. Collect a total of 10 doses-three doses at the beginning, four in the middle $[(n / 2)-1$ to $(n / 2)+2$, where $n$ is the number of minimum recommended doses on the label], and three at the end-of the labeled contents following the labeled instructions. Prior to collecting each of the doses to be analyzed, clean the inhaler as directed in the labeling.

## Particle Size

The particle or droplet size distribution in the spray discharged from metered-dose inhalers, and the particle size distribution in the cloud discharged from dry powder inhalers, are important characteristics used in judging inhaler performance. While particle size measurement by microscopy can be used to evaluate the number of large particles, agglomerates, and foreign particulates in the emissions of metered-dose inhalers (e.g., Epinephrine Bitartrate Inhalation Aerosol), whenever possible this test should be replaced with a method to determine the aerodynamic size distribution of the drug aerosol leaving the inhaler. The aerodynamic size distribution defines the manner in which an aerosol deposits during inhalation. When there is a log-normal distribution, the aerodynamic size distribution may be characterized by the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). The aerodynamic size distribution of the drug leaving me-tered-dose and dry powder inhalers is determined using Apparatus 1, 2, 3, өf 4

## $\Delta_{4}, 5$, or $6_{\mathbf{\Delta S P 2 8}}$

as specified in this chapter. A fine particle dose or fine particle fraction can also be determined as that portion of the inhaler output having an aerodynamic diameter less than the size defined in the individual monograph. This may be expected to correlate with the drug dose or that fraction of the drug dose that penetrates the lung during inhalation. Individual monographs may also define the emitted fractions of the delivered dose in more than one aerodynamic size range.

## AERODYNAMIC SIZE DISTRIBUTION

Cascade impaction devices classify aerosol particles and droplets on the basis of those particles' aerodynamic diameters. The principle of their operation, whereby they separate aerosol particles and droplets from a moving airstream on the basis of particle or droplet inertia, is shown in Figure 3. Because the dimensions of the induction port used to connect inhalers to the cascade impactors and impingers (shown in Appatatus 1, 2, 3, 4 and
(shown in Apparatus 1, 2, 3, 4, 5, and 6) $\boldsymbol{\Delta U S P 2 8}^{\text {, }}$
also define the mass of drug that enters the aerodynamic sizing device, these are carefully defined and, where possible, are held constant between each apparatus (see Figures 4, 6, 7, \&, and
© 8 , and 9). $\mathbf{\Delta U S P 2 8}$
Because the size distributions produced by different impactors are often a function of impactor design and the airflow rate through them, there is a need to standardize the instruments that are used to test inhalers (i.e., Apparatus 1 for metered dose inhalers)
$\Delta_{\text {(i.e., Apparatus }} 1$ or 6 for metered-dose inhalers $)_{\Delta U S P 28}$ or to provide guidelines on system suitability where different apparatuses may be used (i.e., Appratu-2, 3, or 4 for dry powder inhalers).
©(i.e., Apparatus 2, 3, 4, or 5 for dry powder inhalers). $\mathbf{\Delta U S P 2 8}$


Fig. 3. Schematic representation of the principle of operation of cascade impactors. (A single jet per impactor stage is shown. Impactors with multiple jets in each stage function in the same manner.)


Fig. 4. Apparatus 1: Assembly of induction port and entrance cone mounted on cascade impactor.


Fis. 4a. Apparatus 1: Expanded view of induction pori for use with metered dose and dry powder inhalers.


Fig. 4a. Apparatus 1: Expanded view of induction port for use with metered-dose and dry powder inhalers. $\quad 1$ IS (USP28)


Fig. $4 b$. Apparatus 1: Expanded view of the entrance cone for mounting induction port on the Andersen caseade impactor without preseparator:?


Dimensions are in mm unless otherwise stated.
Fig. 4b. Apparatus 1: Expanded view of the entrance cone for mounting induction port on the Andersen cascade impactor without preseparator. Material may be aluminum, stainless steel, or other suitable material. Surface roughness (Ra) should be approximately $0.4 \mu \mathrm{~m}$. $\quad$ IS (USP28)




Fig. 6. Apparatus 2: Assembly of induction port, stage collector, and filter holder. (Marple-Miller impactor, Model 160 with USP induction port.)



Fig. 7. Apparatus 3: Expanded views of top for the Andersen preseparator adapted to the USP induction port. Material may be aluminum, stainless steel, or other suitable material; interior bore should be polished to surface roughness (Ra) approximately

$$
0.4 \mu \mathrm{~m} \cdot{ }^{1 \mathrm{~S}}(\mathrm{USP28)}
$$



Fig. 8. Apparatus 4: Schematic of multistage liquid impinger. (See Table 3- Table 4■1S (USP28) for component specifications.)

Because of the varied nature of the formulations and devices being tested, the cascade impaction system and technique selected for testing an inhaler should fulfill a number of criteria.

Stage Mensuration-Manufacturers of cascade impaction devices provide a definitive calibration for the separation characteristics of each impaction stage in terms of the relationship between the stage collection efficiency and the aerodynamic diameter of particles and droplets passing through it as an aerosol. Calibration is a property of the jet dimensions, the spatial arrangement of the jet and its collection surface, and the airflow rate passing through it. Because jets can corrode and wear over time, the critical dimensions of each stage, which define that impaction stage's calibration, must be measured on a regular basis. This process, known as stage mensuration, replaces the need for repetitive calibration (using standard aerosols) and ensures that only devices that conform to specifications are used for testing inhaler output. The process involves the measurement and adjustment of the critical dimensions of the instrument.

Inter-Stage Drug Loss (wall losses)—Where method variations are possible and there is no apparatus specified in the monograph, the selected technique should ensure that not more than $5 \%$ of the inhaler's total delivered drug mass (into the impactor) is subject to loss between the impaction device's sample collection surfaces. In the event that inter-stage drug losses are known to be greater than $5 \%$, either the procedure should be performed in such a way that wall losses are included along with the associated collection plate, or an alternative apparatus should be used. As an example, the following procedures described for Apparatus 1 and 3 have been written to include wall losses along with the associated collection plate.

Provided, however, that such losses are known to be less than or equal to $5 \%$ of the total delivered drug mass into the impactor and that there are no instructions to the contrary in an individual monograph, the technique may be simplified by only assaying drug on the collection plates.

Re-Entrainment-Where method variations are possible, the selected technique should seek to minimize particle re-entrainment (from an upper to a lower impaction stage) on stages that contribute to size fractions defined in the individual monograph, especially where this may affect the amounts of drug collected. Minimizing the number of sampled doses, the use of coated particle collection surfaces, and proving that multiple-dose techniques produce statistically similar results to those from smaller numbers of doses, are all methods that can be used for this purpose. In the event that reentrainment cannot be avoided, the number of doses collected, the time interval between doses, and the total duration of airflow through the cascade impaction device should be standardized. Under these circumstances, the presentation of impaction data should not presume the validity of the impactor's calibration (i.e., aerodynamic diameter ranges should not be assigned to drug masses collected on specific stages).

By using appropriate assay methods and a suitable mensurated impaction device, aerodynamic particle size distributions can be determined for drugs leaving the mouthpieces of metered-dose or dry powder inhalers. If temperature or humidity limits for use of the inhaler are stated on the label, it may be necessary to control the temperature and humidity of the air surrounding and passing
through the device to conform to those limits. Ambient conditions are presumed, unless otherwise specified in individual monographs.

Mass Balance-In addition to the size distribution, good analytical practice dictates that a mass-balance be performed in order to confirm that the amount of the drug discharged from the inhaler, which is captured and measured in the induction port-cascade impactor apparatus is within an acceptable range around the tabet elaim
© expected value. $\Delta U S P 28$
The total mass of drug collected in all of the components (material balance) divided by the total number of minimum recommended doses discharged is not less than $75 \%$ and not more than $125 \%$ of the average minimum recommended dose determined during testing for Delivered-Dose Uniformity. This is not a test of the inhaler but serves to ensure that the test results are valid.

Use one of the multistage impaction devices shown below, or an equivalent, to determine aerodynamic particle size distributions of drugs leaving the mouthpieces of metered-dose or dry powder inhalers. Appactus 1 (Figure - $)$ is
©Apparatus 1 and 6 [Figures 4 and 9 (without preseparator), respectively] $\operatorname{are}_{\Delta U S P 28}$
intended for use with metered-dose inhalers at a single airflow rate. Apparatus 2, 3, and 4 (Figures 6, 7, and \&, respectively)
${ }^{\wedge}$ Apparatus 2, 3, 4, and 5 (Figures 6, 7, 8, and 9, respectively) $\mathbf{\Delta U S P 2 8}$
are intended for use with dry powder inhalers at the appropriate airflow rate, Q-determined earlier, provided that the value $Q$
${ }^{\Delta} Q_{\text {out }}$, determined earlier, provided that the value of $Q_{\text {out }}$ USP28 falls in the range 30 to 100 L per minute.

NOTE-If Qis greater than 100 L per minute, testing should be performed at 100 L per minute; if $Q<30$ L per mintute, testing is performed at 30 L per minte.
$\mathbf{\Delta}_{\text {NOTE-If }} Q_{\text {out }}$ is greater than 100 L per minute, testing should be performed with $Q_{\text {out }}$ set at 100 L per minute; if $Q_{\text {out }}$ is less than 30 L per minute, testing is performed with $Q_{o u t}$ at

## 30 L per minute. $\Delta$ USP28

Apparatus 1 for Metered-Dose Inhalers-Use this apparatus, or an equivalent, at a flow rate of 28.3 L per minute $( \pm 5 \%)$, as specified by the manufacturer of the cascade impactor.

Design-The design and assembly of this apparatus and the induction port to connect the device to an inhaler are shown in Figs. 4, $4 a$, and $4 b .^{2}$

[^171]-Critical engineering dimensions applied by manufacturers to the stages of Apparatus 1 are provided in Table 2. During use, some occlusion and blockage of jet nozzles may occur and therefore, "in use" mensuration tolerances need to be justified.

Table 2. Critical Dimensions for the Jet Nozzles of Apparatus 1.

| Stage \# | Number of Jets | Nozzle Diameter <br> $(\mathrm{mm})$ |
| :---: | :---: | :---: |
| 0 | 96 | $2.55 \pm 0.025$ |
| 1 | 96 | $1.89 \pm 0.025$ |
| 2 | 400 | $0.914 \pm 0.0127$ |
| 3 | 400 | $0.711 \pm 0.0127$ |
| 4 | 400 | $0.533 \pm 0.0127$ |
| 5 | 400 | $0.343 \pm 0.0127$ |
| 6 | 400 | $0.254 \pm 0.0127$ |
| 7 | 201 | $0.254 \pm 0.0127$ |

-1S (USP28)
Procedure-Set up the multistage cascade impactor as described in the manufacturer's literature with an after filter below the final stage to capture any fine particles that otherwise would escape from the device.
${ }^{\mathbf{\Delta}}$ To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent,
unless it has been demonstrated to be unnecessary. $\mathbf{\Delta S P 2 8}$ Attach the induction port and mouthpiece adapter to produce an airtight seal between the inhaler mouthpiece and the induction port as shown in Fig. 4. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the cascade impactor are connected with airtight seals to prevent leaks. Turn on the vacuum pump to draw air through the cascade impactor, and calibrate the airflow through the system with an appropriate flowmeter attached to the open end of the induction port. Adjust the flow-control valve on the vacuum pump to achieve steady flow through the system at the required rate, and ensure that the airflow through the system is within $\pm 5 \%$ of the flow rate specified by the manufacturer. Unless otherwise prescribed in the patient instructions, shake the inhaler for 5 seconds and discharge one delivery to waste. With the vacuum pump running, insert the mouthpiece into the mouthpiece adapter and immediately fire the minimum recommended dose into the cascade impactor. Keep the valve depressed for a duration sufficient to ensure that the dose has been completely discharged. If additional sprays are required for the sample, wait for 5 seconds before removing the inhaler from the mouthpiece adapter, shake the inhaler, reinsert it into the mouthpiece adapter, and immediately fire the next minimum recommended dose. Repeat until the required number of doses have been discharged. The number of
minimum recommended doses discharged must be sufficient to ensure an accurate and precise determination of Aerodynamic Size Distribution. [NOTE-The number of minimum recommended doses is typically not greater than 10.] After the last dose has been discharged, remove the inhaler from the mouthpiece adapter. Rinse the mouthpiece adapter and induction port with a suitable solvent, and dilute quantitatively to an appropriate volume. Disassemble the cascade impactor, place each stage and its associated collection plate or filter in a separate container, and rinse the drug from each of them. [NOTE-If it has been determined that wall losses in the impactor are less than or equal to $5 \%$, then the collection plates only may be used.]

Dilute each quantitatively to an appropriate volume. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the components. To analyze the data, proceed as directed under Data Analysis.

## Apparatus 2 for Dry Powder Inhalers-

Design-The design and assembly of Apparatus 2, and the induction port to connect the device to an inhaler, are shown in Fig. $6 .^{3}$ [NOTE-The induction port is shown in detail in Fig. 4a.] The impactor has five impaction stages and an after filter. At a volumetric airflow rate of 60 L per minute (the nominal flow rate, $Q_{n}$ ), the cutoff aerodynamic diameters $D_{50}, Q_{n}$ of Stages 1 to 5 are $10,5,2.5,1.25$, and $0.625 \mu \mathrm{~m}$, respectively. The after filter effectively retains aerosolized drug in the particle size range up to $0.625 \mu \mathrm{~m}$. Set up the multistage cascade impactor with the control system as specified in Fig. 5. If necessary, coat the particle collection surface of each of the stages tomsure that partieles that impact en a given stage are not re entrained in the flowing airstream. As semble the impactor as deseribed in the manufacturer's literature with an after filter below the final stage to eaptrre any fine particles that othervise would eseape from the deviee. Attach the induction pert and mouthpiece adapter to produce an airtight seal between the inhaler mouthpiese and the induction port. Use a mouthpiece adapter that enstres that the tip of the inhaler mouthpiece is flush with the open end of the induction pert. Ensure that the various stage of the cascade impactor are connected with airtight seals to prevent leaks.
${ }^{\Delta}$ To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent,
unless it has been demonstrated to be unnecessary. $\mathbf{\Delta}$ USP28
Assemble the impactor as described in the manufacturer's literature with an after filter below the final stage to capture any fine particles that otherwise would escape from the device. Attach the induction port and mouthpiece adapter to produce an airtight seal between the inhaler mouthpiece and the induction port. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the cascade impactor are connected with airtight seals to prevent leaks.

Turn on the vacuum pump, open the solenoid valve, and calibrate the airflow through the system as follows. Connect a flowmeter, calibrated for the volumetric flow rate leaving the meter, to the induetion pert.
$\Delta$ to the induction port. Use a flowmeter calibrated for the volumetric flow leaving the meter to directly determine $Q_{\text {ou }}$, or, if such a meter is unobtainable, calculate the volumetric

[^172]flow leaving the meter ( $Q_{\text {out }}$ ) using the ideal gas law. For example, for a meter calibrated for the entering volumetric flow ( $Q_{i n}$ ), use the formula:
$$
Q_{\text {out }}=Q_{\text {int }} P_{0} /\left(P_{0}-\Delta P\right),
$$
where $P_{0}$ is the atmospheric pressure and $\Delta P$ is the pressure drop over the meter. $A$ USP28
Adjust the flow-control valve to achieve a steady flow through the system at the required rate, $Q$
${ }^{\wedge} Q_{\text {ou }}$, so that $Q_{\text {ou }}$ USP28
is within $\pm 5 \%$ of the value determined during testing for Deliv-ered-Dose Uniformity. Ensure that critical flow occurs in the flow-control valve, at the oflue $Q$ to be used during testing,
$\Delta_{\text {airflow }}$ rate to be used during testing, by $\boldsymbol{A}_{\mathbf{U S P 2 8}}$
using the following procedure. With the inhaler in place, and the intended flow running, measure the absolute pressure on both sides of the flow-control valve (P2 and P3 in Fig. 5). A ratio of P3/P2 $\leq 0.5$ indicates critical flow. Switch to a more powerful pump and remeasure the test flow rate if $\mathrm{P} 3 / \mathrm{P} 2>0.5$. Adjust the timer controlling the operation of the two-way solenoid valve so that it opens this valve for a duration of $T$ seconds
$\boldsymbol{\Delta}^{\boldsymbol{a s}}$ determined during testing for Delivered-Dose Uniformi-
ty. $\mathbf{\Delta U S P 2 8}$
Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Discharge the powder into the apparatus by opening the two-way solenoid valve for a duration of $T$ seconds. After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to the labeled instructions, reinsert the mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, switch off the vacuum pump.
Rinse the mouthpiece adapter and induction port with a suitable solvent, and dilute quantitatively to an appropriate volume. Disassemble the cascade impactor, and place the after filter in a separate container. Rinse the drug from each of the stages and the filter, and dilute each quantitatively to an appropriate volume. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the components. Determine the cutoff diameters of each of the individual stages of the impactor, at the value of $\theta$
${ }^{\wedge} Q=Q_{\text {ou }} \backslash U S P 28$
employed in the test by the formula:
\[

$$
\begin{equation*}
D_{50, \underline{Q}}=D_{50, Q_{n}}\left(Q_{n} / Q\right)^{1 / 2}, \tag{Eq.1}
\end{equation*}
$$

\]

where $D_{50, Q}$ is the cutoff diameter at the flow rate, $Q$, employed in the test, and the subscript, $n$, refers to the nominal values determined when $Q_{n}$ equals 60 L per minute. Thus, when $Q$ equals 40

L per minute, the cutoff diameter of Stage 2 is given by the formula:

$$
D_{50,40 \mathrm{LPM}}=5 \mu \mathrm{~m} \times[60 / 40]^{1 / 2}=6.1 \mu \mathrm{~m} .
$$

General Procedure-Perform the test using Apparatus 2 at the airflow rate, $Q$,
${ }^{\boldsymbol{4}} \mathrm{Q}_{\text {out } \mathbf{\Delta U S P 2 8}}$
determined earlier, during testing for Delivered-Dose Uniformity, provided $Q$
${ }^{\Delta} \mathrm{Q}_{\text {out } \boldsymbol{\Delta} \text { USP28 }}$
is less than or equal to 100 L per minute. [NOTE-If $Q$
${ }^{\mathbf{\Delta}} Q_{\text {out } \mathbf{\Delta} \text { USP28 }}$
is greater than 100 L per minute, use an airflow rate of 100 L per minute.] Connect the apparatus to a flow control system that is based upon critical (sonic) flow as specified in Fig. 5 (see also For ble 2.)
-Table 3).■1S (USP28)

Table 2.
-Table 3.■1S (USP28)
Component Specifications for Figure 5

| Code | Item | Description | Dimensions |
| :---: | :---: | :---: | :---: |
| A | Connector | (e.g., short metal coupling with $\geq 8$-mm ID low diameter branch to P3) |  |
| B | Vacuum tubing | (e.g., silicon tubing with an outside diameter of 14 mm and an internal diameter of 8 mm ) | $8 \pm 0.5 \mathrm{~mm}$ ID $\times 50 \pm 10 \mathrm{em}$ length <br> - A length of suitable tubing $\geq 8 \mathrm{~mm}$ ID with an in- |
| C | Two-way solenoid valve ${ }^{\text {a }}$ | See Fig. 5 | ternal volume of $25 \pm 5 \mathrm{~mL}$. 1 IS (USPP8) <br> Internal diameter orifice of 9.5 mm and a $\mathrm{C}_{*}=1.8$, mini $\rightarrow$ mal resistanee 0 irflow and a respense time $<100$ -milliseconds. |
|  |  |  | 2-way, 2-port solenoid valve having an ID $\geq 8 \mathrm{~mm}$ and an opening response time of $\leq 100$ milli |
| D | Vacuum pump ${ }^{\text {b }}$ | See Fig. 5 | seconds. 1 (USP28) <br> Pump must be capable of drawing the required flow rate |
| D | Vacuum pump |  | through the assembled apparatus with the dry powder inhaler in the mouthpiece adapter. Connect the pump to the solenoid valve using short and wide ( $\geq 10-\mathrm{mm}$ ID) vacuum tubing and connectors to minimize pump capacity requirements. |
| E | Timer ${ }^{\text {c }}$ | See Fig. 5 | The timer switches current directly to the solenoid valve for the required duration. |
| P2, P3 | Pressure measurements |  | Determine under steady-state flow conditions with an absolute pressure transducer. |
| F | Flow control valve ${ }^{\text {d }}$ | See Fig. 5 | Adjustable regulating valve with maximum $\mathrm{C}_{\mathrm{v}} \geq 1$. |

[^173]
## Table 3.

-Table 4. ${ }^{1 S}$ (USP28)
Component Units of Multi-stage Liquid Impinger (see Fig. 8)

| Code ${ }^{1}$ | Item | Description | Dimensions ${ }^{2}$ |
| :---: | :---: | :---: | :---: |
| A,H | Jet tube | Metal tube screwed onto partition wall sealed by gasket (C), polished inner surface | see Fig. $8 a$ |
| B,G | Partition wall | Circular metal plate, diameter | $120$ |
|  |  | Thickness | see Fig. 8 a |
| C | Gasket | e.g., PTFE | to fit jet tube |
| D | Impaction plate | Porosity O sintered-glass disk, diameter | see Fig. $8 a$ |
| E | Glass cylinder | Plane polished cut glass tube |  |
|  |  | Height, including gaskets | 46 |
|  |  | Outer diameter | 100 |
|  |  | Wall thickness | 3.5 |
|  |  | Sampling port (F) diameter | 18 |
|  |  | Stopper in sampling port | ISO 24/25 |
| J | Metal frame | L-profiled circular frame with slit |  |
|  |  | Inner diameter | to fit impaction plate |
|  |  | Height |  |
|  |  | Thickness of vertical section | 2 |
| K | Wire | Steel wire interconnecting metal frame and sleeve (two for each frame) |  |
|  |  | Diameter | 1 |
| L | Sleeve | Metal sleeve secured on jet tube by screw |  |
|  |  | Inner diameter | to fit jet tube |
|  |  | Height | 6 |
|  |  | Thickness | 5 |
| M | Gasket | e.g., Silicone | to fit glass cylinder |
| N | Bolt | Metal bolt with nut (six pairs), length | 205 |
|  |  | Diameter | 4 |
| P | O-ring | Rubber O-ring, diameter $\times$ thickness | $66.34 \times 2.62$ |
| Q | O-ring | Rubber O-ring, diameter $\times$ thickness | $29.1 \times 1.6$ |
| R | Filter holder | Metal housing with stand and outlet |  |
|  |  |  | see Fig. $8 b$ |
| S | Filter support | Perforated sheet metal, diameter | 65 |
|  |  | Hole Diameter | 3 |
|  |  | Distance between holes (center-points) | 4 |
| T | Snap-locks |  |  |
| U | Multi-jet tube | Jet tube (H) ending in multi-jet arrangement | see inserts Fig. $8 a$ |
| V | Outlet | Outlet and nozzle for connection to vacuum | Internal diameter $\geq 10$ (Fig. 8b) |

[^174]


Fig. 8b. Apparatus 4: Expanded view of Stage 5. (See 3-
Table 4■1S (USP28)
for component specifications.)

Fig. 8a. Apparatus 4: Details of jet tube and impaction plate. Inserts show end of multi-jet tube U leading to Stage 4. (See Table 4■

$$
\begin{gathered}
\text { Table } 5_{\text {■1S (USP28) }} \\
\text { for dimension specifications.) }
\end{gathered}
$$

Table-4.
-Table 5. ${ }^{\text {1S }}$ (USP28)
Apparatus 4: Dimensions ${ }^{1}$ of Jet Tube with Impaction Plate (see Fig. 8a).
$\left.\begin{array}{lcccccc}\hline & & & & & \\ \text { Type } & \text { Code }^{2} & \text { Stage 1 } & & \\ \text { Filter } \\ \text { (Stage 5) }\end{array}\right]$

[^175]Under steady flow conditions, at the appropriate volumetric airflow rate through the entire apparatus, ensure that critical (sonic) flow occurs in the flow control valve by determining the individual values for absolute pressure, P 2 and P 3 , so that their ratio $\mathrm{P} 3 / \mathrm{P} 2$ is less than or equal to 0.5 . If neessay,
${ }^{\wedge}$ UUSP28
Coat the particle collection surface of each of the stages of the cascade impactor to ensure that particles that have impacted on a given stage are not re-entrained in the flowing airstream This may be achieved by coating collection surfaces with silicene fluid, slyeerel, or other adhesive substanees.
${ }^{\Delta}$ unless this has been shown to be unnecessary. $\mathbf{\Delta U S P 2 8}$ Analyze the data as directed under Data Analysis.

## Apparatus 3 for Dry Powder Inhalers-

Design-Apparatus 3 is identical to Apparatus 1 (Fig. 4), except that the manufacturer's preseparator is added atop Stage 0 to collect large masses of noninhalable powder prior to their entry into the impactor, and the outlet nipple, used to connect to vacuum tubing B (Fig. 5), is replaced with one having an internal diameter $\geq 8$ mm . To connect the preseparator of the impactor to the induction port (Fig. 4a), a specially designed top for the preseparator must be used. This is shown in Fig. 7. ${ }^{4}$ The impactor, therefore, has eight stages, a preseparator (to collect large particulates), and an after filter. At a volumetric airflow rate of 28.3 L per minute (the nominal flow rate, $Q_{n}$ ), the cutoff aerodynamic diameters $D_{50}, Q_{n}$ of Stages 0 to 7 are $9.0,5.8,4.7,3.3,2.1,1.1,0.7$, and $0.4 \mu \mathrm{~m}$, respectively. The after filter effectively retains aerosolized drug in the particle size range up to $0.4 \mu \mathrm{~m}$. Connect the cascade impactor into the control system specified in Fig. 5. Omit Stage 6 and Stage 7 from the impactor if the test flow rate, $Q$,
${ }^{\Delta} Q_{\text {ou }}$
Qout, USP28
used during testing for Delivered-Dose Uniformity was greater than or equal to 60 L per minute. If neeessary, ceat the particlecel-lection-strface of each of the stages to ensure that particles that impact on a given stage are not re-entrained in the flowing air stream.
${ }^{\mathbf{\Delta}}$ To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary. AUSP28 Assemble the impactor as described in the manufacturer's literature with an after filter below the final stage to capture any fine particles that otherwise would escape from the device. Place an appropriate volume (up to 10 mL ) of an appropriate solvent into the preseparator, or coat the particle collection surfaces of the preseparator to prevent re-entrainment of impacted particles. [Caution-Some solvents form flammable vapor-air mixtures that may be ignited during passage through a vacuum pump. Take appropriate precautions (alternative solvents, use of vapor traps, minimal pump operating times, etc.) to ensure operator safety during testing.] Attach a molded mouthpiece adapter to the end of the induction port to produce an airtight seal between the inhaler mouthpiece and the induction port. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the cascade impactor are connected with airtight seals to prevent leaks.
${ }^{4}$ The cascade impactor is available as the Andersen 1ACFM Non-Viable Cascade Impactor (Mark II) from Graseby Ine., 500 -Techmolegy Court, Smyma, GA, 30082 Thermo-Electron, 27 Forge Parkway, Franklin, MA 02038. 1 (USP28) The impactor is used with the preseparator.

Turn on the vacuum pump, open the two-way solenoid valve, and calibrate the airflow through the system as follows. Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Once the inhaler is positioned, discharge the powder into the apparatus by activating the timer and opening the two-way solenoid valve for the required duration, $T \pm 5 \%$
$\boldsymbol{\Delta}^{\boldsymbol{a s}}$ determined during testing for Delivered-Dose Uniformi-

## ty. $\mathbf{A S S P} 28$

After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to the labeled instructions, reinsert the mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, remove the inhaler from the mouthpiece adapter, and switch off the vacuum pump.

Carefully disassemble the apparatus. Using a suitable solvent, rinse the drug from the mouthpiece adapter, induction port, and preseparator, and dilute quantitatively to an appropriate volume. Rinse the drug from each stage, and the impaction plate immediately below, into appropriately sized flasks. Quantitatively dilute each flask to an appropriate volume. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the samples. The aerodynamic cutoff diameters of the individual stages of this device, in the airflow range between 30 and 100 L per minute, are currently
$\Delta_{\text {not well }}$ established. $\Delta$ USP28
Do not use the formula in Equation 1 to calculate cutoff diameters.
Procedure-Proceed as directed in the General Procedure under Apparatus 2, except to use Apparatus 3.

Apparatus 4 for Dry Powder Inhalers-
${ }^{\mathbf{4}}$ NOTE-Apparatus 4 , the multistage liquid impinger, has a small number of stages and is used extensively outside the
USA. It is provided here for the benefit of users in countries
other than the USA. $\Delta$ USP28
Design-The design and assembly of Apparatus 4 are shown in Figs. 8, 8a, and $8 b .^{5}$ The induction port, used to connect the device to an inhaler, is shown in Fig. 4a. The device is a multi-stage liquid impinger consisting of impaction Stages 1, 2, 3, and 4 and an integral after filter (Stage 5). The collection stages of the liquid impinger (see Fig. 8 and Table 3
-Table 4) 1 (USP28)
are kept moist, unlike those of traditional impactors, such as ant ratus 1, 2, and 3;
-Apparatus 1, 2, 3, 5, and 6; $\quad$ IS (USP28)
wetting may produce an effect similar to coating the stages of $4 p$ paratus 2 and 3
$\mathbf{- A p p a r a t u s ~ 2 , ~ 3 , ~}^{\text {3, }}$, and $6_{\text {(USP28) }}$
at certain flow rates, although this should be confirmed by demonstrating control over re-entrainment as described earlier. An impaction stage comprises an upper horizontal metal partition wall (B) through which a metal inlet jet tube (A) with its impaction plate

[^176](D) is protruding; a glass cylinder (E) with sampling port (F), forming the vertical wall of the stage; and a lower horizontal metal partition wall (G) through which a jet tube (H) connects to the lower stage. The tube into Stage 4 (U) ends in a multi-jet arrangement. The impaction plate (D) is secured in a metal frame (J), which is fastened by two wires (K) to a sleeve (L) secured on the jet tube (C). For more detail of the jet tube and impaction plate, see Fig. $8 a$. The horizontal plane of the collection plate is perpendicular to the axis of the jet tube and centrally aligned. The upper surface of the impaction plate is slightly raised above the edge of the metal frame. A recess around the perimeter of the horizontal partition wall guides the position of the glass cylinder. The glass cylinders are sealed against the horizontal partition walls with gaskets (M) and clamped together by six bolts ( N ). The sampling ports are sealed by stoppers. The bottom side of the lower partition wall of Stage 4 has a concentric protrusion fitted with a rubber O-ring ( P ) that seals against the edge of a filter placed in the filter holder. The filter holder (R) is a basin with a concentric recess in which a perforated filter support ( S ) is flush-fitted. The filter holder is designed for 76mm diameter filters. The whole impaction stage assembly is clamped onto the filter holder by two snap locks (T). The impinger is equipped with an induction port (Fig. 4a) that fits onto the Stage 1 inlet jet tube. A rubber O-ring on the jet tube provides an airtight connection to the induction port. An elastomeric mouthpiece adapter to fit the inhaler being tested provides an airtight seal between the inhaler and the induction port.

At a volumetric airflow rate of 60 L per minute (the nominal flow rate, $Q_{n}$ ), the cutoff aerodynamic diameters $D_{50, Q_{n}}$ of Stages 1 to 4 are $13.0,6.8,3.1$, and $1.7 \mu \mathrm{~m}$, respectively. The after filter effectively retains aerosolized drug in the particle size range up to $1.7 \mu \mathrm{~m}$. Ensure that Apparatus 4 is clean and free of drug solution from any previous tests. Place a $76-\mathrm{mm}$ diameter filter in the filter stage, and assemble the apparatus. Use a low pressure filter capable of quantitatively collecting the passing drug aerosol, which also allows a quantitative recovery of the collected drug. Set up Apparatus 4 using the control system as specified in Fig. 5. Attach the induction port (Fig. 4a) and mouthpiece adapter to produce an airtight seal between the inhaler mouthpiece and the induction port. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the apparatus are connected with airtight seals to prevent leaks. Turn on the vacuum pump, open the twoway solenoid valve, and calibrate the airflow through the system as follows. Connect a flowmeter, calibrated for the volumetric flow rate leaving the meter, to the induction port. Adjust the flow-control valve to achieve a steady flow through the system at the required rate, $Q$, se that $Q$
${ }^{\mathbf{\Delta}} Q_{\text {out }}$, so that $Q_{\text {out } \mathbf{\Delta S P 2 8}}$
is within $\pm 5 \%$ of the value determined during testing for Deliv-ered-Dose Uniformity. Ensure that critical flow occurs in the flow-control valve, at the value of $Q$
${ }^{\mathbf{\Delta}} Q_{\text {ou }} \mathbf{\Delta U S P 2 8}$
to be used during testing, using the following procedure. With the inhaler in place, and the intended flow running, measure the absolute pressure on both sides of the flow-control valve (P2 and P3 in Fig. 5). A ratio of $\mathrm{P} 3 / \mathrm{P} 2 \leq 0.5$ indicates critical flow. Switch to a more powerful pump and remeasure the test flow rate if P3/ $\mathrm{P} 2>0.5$. Adjust the timer controlling the operation of the twoway solenoid valve so that it opens that valve for the same duration, $T$, as used during testing for Delivered-Dose Uniformity. Dispense 20 mL of a solvent, capable of dissolving the drug, into each of the four upper stages of Apparatus 4, and replace the stoppers. [Caution-Some solvents form flammable vapor-air mixtures that may be ignited during passage through a vacuum pump. Take appropriate precautions (alternative solvents, use of vapor traps, minimal pump operating times, etc.) to ensure operator safety during testing.] Tilt the apparatus to wet the stoppers, thereby neutralizing their electrostatic charge. Adjust the timer controlling the operation of the two-way solenoid valve so that it opens the valve
for the same duration, $T$, as used during testing for Delivered-Dose Uniformity. Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Discharge the powder into the apparatus by activating the timer and opening the two-way solenoid valve for the required duration, $T \pm 5 \%$. After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to the labeled instructions, reinsert the mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, switch off the vacuum pump.

Dismantle the filter stage of Apparatus 4. Carefully remove the filter, and extract the drug with solvent. Rinse the mouthpiece adapter and induction port with a suitable solvent, and dilute quantitatively to an appropriate volume. Rinse the inside of the inlet jet tube to Stage 1 (Fig. 8), allowing the solvent to flow into the stage. Rinse the drug from the inner walls and the collection plate of each of the four upper stages of the apparatus, into the solution in the respective stage, by tilting and rotating the apparatus, while ensuring that no liquid transfer occurs between the stages. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the six volumes of solvent. Ensure that the method corrects for possible evaporation of the solvent during the test. This may involve the use of an internal standard (of known original concentration in the solvent and assayed at the same time as the drug) or the quantitative transfer of the liquid contents from each of the stages, followed by dilution to a known volume. Determine the cutoff diameters of each of the individual stages of the impactor, at the value of $Q$
${ }^{\Delta} Q=Q_{\text {out } \mathbf{\Lambda} U S P 28}$
employed in the test by the formula:

$$
D_{50, Q}=D_{50, Q_{n}}(Q n / Q)^{1 / 2}
$$

where $D_{50, Q}$ is the cutoff diameter at the flow rate, $Q$, employed in the test, and the subscript, ${ }_{n}$, refers to the nominal values determined when $Q_{n}$ equals 60 L of air per minute. Thus, when $Q$ equals 40 L of air per minute, the cutoff diameter of Stage 2 is given by the formula:

$$
D_{50,40 \mathrm{LPM}}=6.8 \mu \mathrm{~m} \times(60 / 40)^{1 / 2}=8.3 \mu \mathrm{~m}
$$

Procedure-Proceed as directed in the General Procedure under Apparatus 2, except to use Apparatus 4.

## ${ }^{\wedge}$ Apparatus 5 for Dry Powder Inhalers

Design—The design and assembly of Apparatus $5^{6}$ are shown in Figures 9, 9a, 9b, 9c, and 9d. The induction port, used to connect the device to an inhaler, is shown in Figure $4 a$. The device is a cascade impactor with seven stages and a micro-orifice collector (MOC). Over the design flow-rate range of 30 to 100 L per minute, the $50 \%$ efficiency cut-

[^177]off diameters of the stages ( $\mathrm{D}_{50}$ values) range between 0.24 $\mu \mathrm{m}$ to $11.7 \mu \mathrm{~m}$, evenly spaced on a logarithmic scale. In the design flow-rate range, there are always at least five stages with $\mathrm{D}_{50}$ values between $0.5 \mu \mathrm{~m}$ and $6.5 \mu \mathrm{~m}$. The collection efficiency curves for each stage are sharp and minimize overlap between stages. -Material may be aluminum, stainless steel, or other suitable material.■1S (USP28)

The impactor layout has removable impaction cups with all the cups in one plane (Figures 9-9c). There are three main sections to the impactor: the bottom frame that holds
the impaction cups, the seal body that holds the jets, and the lid that contains the interstage passageways (shown in Figures 9-9b). Multiple nozzles are used at all but the first stage (Figure 9c). The flow passes through the impactor in a sawtooth pattern.
Stage mensuration is performed periodically together with confirmation of other dimensions critical to the effective operation of the impactor. Critical dimensions are provided below in Fable 5- Table 6.■1S (USP28)

## Table 5. Gritieal-Dimensions-for the Next Generation-Phafmaceutieal Impaetor

-Table 6. Critical Dimensions for Apparatus 5 and 6.■1S (USP28)

| Description | $\begin{aligned} & \text { Dimension } \\ & (\mathrm{mm}) \end{aligned}$ |
| :---: | :---: |
| Preseparator (dimension a-see Figure 9d) | $12.80 \pm 0.05$ |
| Stage $1^{1}$ Nozzle diameter | $14.30 \pm 0.05$ |
| Stage $2^{1}$ Nozzle diameter | $4.882 \pm 0.04$ |
| Stage $3^{1}$ Nozzle diameter | $2.185 \pm 0.02$ |
| Stage $4^{1}$ Nozzle diameter | $1.207 \pm 0.01$ |
| Stage $5^{1}$ Nozzle diameter | $0.608 \pm 0.01$ |
| Stage $6^{1}$ Nozzle diameter | $0.323 \pm 0.01$ |
| Stage $7^{1}$ Nozzle diameter | $0.206 \pm 0.01$ |
| MOC ${ }^{1}$ | 0.070 (meminally - $0.065-0.072$ ) |
|  | -approximately $0.070^{\text {■1S (USP28) }}$ |
| Cup Depth (Dimension b-see Figure 9b) | $14.625 \pm 0.10$ |
| Collection cup surface roughness | 0.5 to $2 \mu \mathrm{~m}$ |
| Stage 1 Nozzle to seal body distance ${ }^{2}$-dimension c | $0 \pm 0.14$ |
|  | $\mathbf{n}_{1.15(\text { USP28) }}$ |
| Stage 2 Nozzle to seal body distance ${ }^{2}$-dimension c | $5.186 \pm 5.286$ |
|  | $\bullet_{5.236} \pm 0.736_{\text {■1S (USP28) }}$ |
| Stage 3 Nozzle to seal body distance ${ }^{2}$-dimension c | $8.415-8.475$ |
|  | $\bullet 8.445 \pm 0.410^{\mathbf{1 S} \text { (USP28) }}$ |


| Description | Dimension (mm) |
| :---: | :---: |
| Stage 4 Nozzle to seal body distance ${ }^{2}$-dimension c | 41.349-11.409 |
|  |  |
| Stage 5 Nozzle to seal body distance ${ }^{2}$-dimension c | +3.146tol3.206 |
|  | $\bullet^{13.176} \pm 0.341_{115}{ }^{\text {(USP28) }}$ |
| Stage 6 Nozzle to seal body distance ${ }^{2}$ - dimension c | 13.969-14.029 |
|  | -13.999 $\pm 0.071_{\text {■ }}^{1 S}$ (USP28) |
| Stage 7 Nozzle to seal body distance ${ }^{2}$-dimension c | 13.970-14.030 |
|  | -14.000 $\pm 0.071_{1 / 15}$ (USP28) |
| MOC Nozzle to seal body distance ${ }^{2}$ - dimension c | +4.470-14.530 |
|  | -14.429-14.571 $\mathbf{\\|}^{1 S}$ (USP28) |

[^178]In routine operation, the seal body and lid are held together as a single assembly. The impaction cups are accessible when this assembly is opened at the end of an inhaler test. The cups are held in a support tray, so that all cups can be removed from the impactor simultaneously by lifting out the tray. The impactor is ready for another test as as another tray of eups is inserted and the lid is elosed.
$A$ man $\mathrm{An}_{11 S}$ (USP28) induction port with internal dimensions identical to those defined in Figure $4 a$ is connected to the impactor inlet. When necessary, with dry powder inhalers, a preseparator can be added to avoid overloading the first stage. This preseparator connects between the induction port and the impactor. A suitable mouthpiece adapter is used to provide an airtight seal between the inhaler and the induction port.

At a volumetric airflow rate of 60 L per minute (the assigned reference flow rate for cutoff-diameter calculations, $Q_{n}$ ), the cutoff-aerodynamic diameters $\mathrm{D}_{50, \varrho_{n}}$ of Stages 1 to 7 are $8.06,4.46,2.82,1.66,0.94,0.55$ and $0.34 \mu \mathrm{~m}$, respectively. The apparatus contains a terminal micro-orifice collector (MOC) that for most formulations may eliminate the need for a final filter as determined by method validation. The MOC is an impactor nozzle plate and collection cup. The nozzle plate contains, nominally, 4032 jets, each a neminal approximately $_{\text {1S (USP28) }} 70 \mu \mathrm{~m}$ in diameter. Most particles not captured on Stage 7 of the impactor will be captured on the cup surface below the MOC. (For impactors operated at 60 L per minute, the MOC is capable of collecting $80 \%$ of $0.14-\mu \mathrm{m}$ particles). For formulations with a significant fraction of particles not captured by the MOC, there
is an optional filter holder that can replace the MOC or be placed downstream of the MOC containing a suitable afterfilter (glass fiber is often suitable).

Procedure-Assemble the apparatus with the preseparator (Figure 9d), unless experiments have shown that its omission does not result in increased interstage drug losses ( $>5 \%$ ) or particle re-entrainment, in which case the preseparator may be omitted.

Place fresh"1s (USP28) cups into the apertures in the cup tray. To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary. Insert the cup tray into the bottom frame, and lower into place. Close the impactor lid with the seal body attached, and operate the handle to lock the impactor together so that the system is airtight.

The preseparator may be assembled as follows: assemble the preseparator insert into the preseparator base; fit the preseparator base to the impactor inlet; add 15 mL of the solvent used for sample recovery to the central cup of the preseparator insert; place the preseparator body on top of this assembly; and close the two catches. [Caution-Some solvents form flammable vapor-air mixtures that may be ignited during passage through a vacuum pump. Take appropriate precautions (e.g., alternative solvents, use of vapor traps, minimal pump operating times, etc.) to ensure operator safety during testing.]

Connect dimensions as defined in Figure $4 a$ either to the impactor inlet or to the preseparator inlet atop the cascade impactor (Figure 9d). Place a suitable mouthpiece adapter in position at the end of the induction port so that the mouthpiece end of the inhaler, when inserted, lines up along the horizontal axis of the induction port. The front face of the inhaler mouth-
piece is flush with the front face of the induction port, - producing an airtight seal.■1S (USP28) When attached to the mouthpiece adapter, the inhaler should be positioned in the same orientation as intended for use. Connect the apparatus to a flow system according to the scheme specified in Figure 5.

Unless otherwise prescribed, conduct the test at the flow rate used in the test for Delivered-Dose Uniformity drawing 4 L of air from the mouthpiece of the inhaler and through the apparatus. Connect a flowmeter to the induction port. Use a flowmeter calibrated for the volumetric flow leaving the meter, or calculate the volumetric flow leaving the meter $\left(Q_{o u}\right)$ using the ideal gas law. For a meter calibrated for the entering volumetric flow ( $Q_{i n}$ ), use the formula:

$$
Q_{\text {out }}=Q_{\text {int }} P_{0} /\left(P_{0}-\Delta P\right),
$$

where $P_{0}$ is the atmospheric pressure and $\Delta P$ is the pressure drop over the meter. Adjust the flow control valve to achieve steady flow through the system at the required rate, $Q_{\text {out }}$ ( $\pm 5 \%$ ). Ensure that critical flow occurs in the flow-control valve by the procedure described for Apparatus 2. Adjust the timer controlling the operation of the two-way solenoid valve so that it opens the valve for the same duration, $T$, as used during testing for Delivered-Dose Uniformity.

Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Discharge the powder into the apparatus by activating the timer and opening the twoway solenoid valve for the required duration, $T+5 \%$. - $T( \pm 5 \%)$. ${ }^{1 \text { S }}$ (USP28) After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to the labeled instructions, reinsert the
mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, switch off the vacuum pump.

Dismantle the apparatus, and recover drug for analysis as follows: remove the induction port and mouthpiece adapter from the preseparator and extract the drug into an aliquot of solvent; remove the preseparator from the impactor, without spilling the eup liquid into the impactor; seal the outlet of the preseparator with a suitable-stopper, add an aliquot of drug recovery solvent, if necessary; seal the preseparator in tet with another stitable stopper; and shake and rotate the preseparator gently and stowly, to extract the active ingredient from all inner surfaces. -if used, remove the preseparator from the impactor, without spilling the solvent into the impactor; and recover the active ingredient from all inner surfaces.11S (USP28)
Open the impactor by releasing the handle and lifting the lid. Remove the cup tray, with the collection cups, and recover the active ingredient from each cup into an aliquot of solvent. Using the method of analysis specified in the individual monograph, determine the mass of drug contained in each of the aliquots of solvent.

Determine the cutoff diameters of each of the individual stages of the impactor, at the value of $Q=Q_{\text {out }}$ employed in the test by the formula:

$$
D_{50, Q}=D_{50, Q_{n}}\left(Q_{\mathrm{n}} / Q\right)^{X}, \quad \text { (Eq. 2) }
$$

where $D_{50, Q}$ is the cutoff diameter at the flow rate, $Q$, employed in the test, and the subscript, $n$, refers to the nominal or reference value for $Q_{n}=60 \mathrm{~L}$ of air per minute (see Table母.-Table 7).■1S (USP28) The values for the exponent, $x$, are listed in Table 7 .als (USP28) Thus, when $Q=40 \mathrm{~L}$ of air per minute, the cutoff diameter of Stage 2 is given by the formula:

$$
D_{50,40 \mathrm{LPM}}=4.46 \mu \mathrm{~m} \times(60 / 40)^{0.52}=5.51 \mu \mathrm{~m} .
$$

Analyze the data as directed under Data Analysis.

## Table 6.

-Table 7.■1S (USP28) Cutoff Aerodynamic Diameter for Stages of Apparatus 5 and 6

Use Eq. 2 to calculate $D_{50, Q}$ for flow rates, $Q$, in the range 30 to 100 L per minute with $Q_{n}=60 \mathrm{~L}$ per minute.

| Stage | $D_{50, Q n}$ | $x$ |
| :---: | :---: | :---: |
| 1 | 8.06 | 0.54 |
| 2 | 4.46 | 0.52 |
| 3 | 2.82 | 0.50 |
| 4 | 1.66 | 0.47 |
| 5 | 0.94 | 0.53 |
| 6 | 0.55 | 0.60 |
| 7 | 0.34 | 0.67 |



Fig. 9. Compenent of Apparatus -5.


Fig. 9. Apparatus 5 (shown with the preseparator in place).. 1 (USP28)


Fig. 9a. Compenent of Apparatus. 5.
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Fig. 9a. Components of Apparatus 5. 1 (USP28)


Fig. 9b. Layout of interstage passageways of Apparatus 5.


Fig. 9e. Nozzle dimensions and layou of Apparatus. 5
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Fig. 9c. Nozzle configuration of Apparatus 5 .n ${ }^{1 \mathrm{~S}}$ (USP28)


Fig. 9d. Pre-separator layout for Apparatus 5.

## Apparatus 6 for Metered-Dose Inhalers

Design-Apparatus 6 is identical to Apparatus 5 (Figures 9-9d), except that the preseparator is not to be used. Use this apparatus at a flow rate of 30 L per minute ( $\pm 5 \%$ ), unless otherwise prescribed in the individual monograph.

Procedure-Assemble the apparatus without the preseparator. Place fresh! ${ }_{1 S}$ (USP28) cups into the apertures in the cup tray. To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary. Insert the cup tray into the bottom frame, and lower into place. Close the impactor lid with seal body attached,
and operate the handle to lock the impactor together so that the system is airtight. Connect $\mathbf{a n}_{1 S}$ (USP28) induction port with internal dimensions as defined in Figure $4 a$ to the impactor inlet. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Turn on the vacuum pump to draw air through the cascade impactor, and calibrate the airflow through the system with an appropriate flowmeter attached to the open end of the induction port. Adjust the flow-control valve on the vacuum pump to achieve steady flow through the system at the required rate, and ensure that the airflow through the system is within $\pm 5 \%$ of this flow rate. Unless otherwise prescribed in the patient instructions, shake the inhaler for 5 seconds, and discharge one delivery to waste. With the vacuum pump running, insert the mouth-
piece into the mouthpiece adapter, and immediately fire the minimum recommended dose into the cascade impactor. Keep the valve depressed for a duration sufficient to ensure that the dose has been completely discharged. If additional sprays are required for the sample, wait for 5 semefore removing the inhaler from the mouthpiece adapter, $\|_{\text {IS (USP28) }}$ shake the inhaler, reinsert it into the mouthpiece adapter, and immediately fire the next minimum recommended dose.

Repeat until the required number of doses have been discharged. The number of minimum recommended doses discharged must be sufficient to ensure an accurate and precise determination of Aerodynamic Size Distribution. [NOTEThe number of minimum recommended doses is typically not greater than 10.] After the last dose has been discharged, remove the inhaler from the mouthpiece adapter. Rinse the mouthpiece adapter and induction port with a suitable solvent, and dilute quantitatively to an appropriate volume.
Dismantle the apparatus, and recover the drug for analysis as follows: remove the induction port and mouthpiece adapter from the apparatus, and recover the deposited drug into an aliquot of solvent; open the impactor by releasing the handle and lifting the lid; remove the cup tray, with the collection cups; and extract the active ingredient in each cup
into an aliquot of solvent. Using the method of analysis specified in the individual monograph, determine the quantity of active ingredient contained in each of the aliquots of solvent.

Determine the cutoff diameters of each of the individual stages of the impactor, at the value of $Q$ employed in the test by using Eq. 2 with values obtained from Table 6-Table 7. 1 (USP28) Thus, when $Q=30 \mathrm{~L}$ of air per minute, the cutoff diameter of Stage 2 is given by the formula:

$$
D_{50,30 \mathrm{LPM}}=4.46 \mu \mathrm{~m} \times(60 / 30)^{0.52}=6.40 \mu \mathrm{~m} .
$$

To analyze the data, proceed as directed under Data Analysis. $\mathbf{U S S P 2 8}$

## Data Analysis

This section describes the data analysis required to define the Aerodynamic Size Distribution of the drug output from the test inhaler, after the use of Apparatus 1, 2, 3, e-4
${ }^{4} 4,5$, or $6 . \Delta U S P 28$
Enter the data collected from Apparatus 1, 2, 3, or-4
$\Delta_{4,5}$, or $6_{\mathbf{\Delta U S P 2 8}}$ in the table of mass summaries as shown in 5.
${ }^{\mathbf{4}}$ Table 7.-Table 8. 1 IS (USP28) $\mathbf{\Delta U S P 2 8}$
Perform only those calculations specified in the individual monograph. $\mathbf{U S P 2 8}$

Table 5. Table of Mass-Summaries for Analyses of Metered-dose Inhalers and-Dry Powder Inhalers.

| Mass | Apparates 1 |  | Apparatus 2 |  | Apparates ${ }^{\text {3 }}$ |  | Apparatus $4^{\text {b }}$ |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Mouthpieee adapter |  |  |  |  |  |  |  |  |
| -tinduction pert | $\mathrm{A}_{\text {i }}$ | - | ${ }_{\text {A }}$ | - | $\mathrm{A}_{\text {i }}$ | - | $\mathrm{A}_{\text {i }}$ | - |
| Preseparator |  | - | - | - | $\mathrm{A}_{p}$ | - | - | - |
| Stage 0-0f impactor | $\mathrm{A}_{\theta}$ | $\mathrm{B}_{4}$ | - | - | $\mathrm{A}_{4}$ | $\mathrm{B}_{6}$ | A | - |
| Stage 1-of impactor/impinger | $\mathrm{A}_{+}$ | $\mathrm{B}_{+}$ | $\mathrm{A}_{+}$ | - | $\mathrm{A}_{+}$ | $\mathrm{B}_{4}$ | $\mathrm{A}_{+}$ | - |
| Stage 2 of impactor/impinger | $\mathrm{A}_{3}$ | $\mathrm{B}_{2}$ | $\mathrm{A}_{2}$ | $\mathrm{B}_{2}$ | $\mathrm{A}_{3}$ | $\mathrm{B}_{3}$ | $\mathrm{A}_{3}$ | $\mathrm{B}_{2}$ |
| Stage 3-of impactor/impinger | $\mathrm{A}_{3}$ | $\mathrm{B}_{3}$ | $\mathrm{A}_{3}$ | $\mathrm{B}_{3}$ | $\mathrm{A}_{3}$ | $\mathrm{B}_{3}$ | $\mathrm{A}_{3}$ | $\mathrm{B}_{3}$ |
| Stage 4 - f impactor/impinger | $\mathrm{A}_{4}$ | $\mathrm{B}_{4}$ | $\mathrm{A}_{4}$ | $\mathrm{B}_{4}$ | $\mathrm{A}_{4}$ | $\mathrm{B}_{4}$ | $\mathrm{A}_{4}$ | $\mathrm{B}_{4}$ |
| Stage 5-of impactor/impinger | $\mathrm{A}_{5}$ | $\mathrm{B}_{5}$ | $\mathrm{A}_{s}$ | $\mathrm{B}_{5}$ | $\mathrm{A}_{5}$ | $\mathrm{B}_{5}$ | - | - |
| Stage 6-of impactor/impinger | $\mathrm{A}_{6}$ | $\mathrm{B}_{6}$ | - | - | $\mathrm{A}_{6}$ | $\mathrm{B}_{6}$ | - | - |
| Stage 7 of impactor/impinger | $\mathrm{A}_{7}$ | $\mathrm{B}_{7}$ | , | , | $\mathrm{A}_{7}$ | $\mathrm{B}_{7}$ | , | - |
| Filter |  | ${ }_{\text {B }}^{\text {b }}$ |  | $\begin{gathered} \mathrm{B}_{\mathrm{F}} \\ \underset{\mathrm{R}}{ } \end{gathered}$ | $\stackrel{A_{p}^{+}}{A_{i}}$ | ${ }_{\text {B }}^{\text {B }}$ | $\underset{A_{P}}{A_{i}}$ | $\underset{\mathrm{B}_{\mathrm{F}}}{\stackrel{1}{2}}$ |
| Sums Of Masses | EAe | $\pm B^{\prime}$ | EAe | $E B^{\circ}$ | EA | $\Sigma B^{\circ}$ | EA | $\Sigma B^{e}$ |

${ }^{2}$ Stuge 6 and 7 are mitted from-Apparts -3 at aifllow rates $\geq 60$ L per minete.
${ }^{6}$ Stage 5 of 4 pparatus 4 is the filter stage (see Fig. 8).
 beneath the uppermost stage (APpatratus 2, 3, and-4).

## $\Delta_{\text {Table }}$.

-Table 8. ${ }_{\text {1s }}^{\text {(USP28) }}$

Table of Mass Summaries for Analyses of Metered-Dose Inhalers and Dry Powder Inhalers

| Mass | Apparatus 1 |  | Apparatus 2 |  | Apparatus $3^{\text {a }}$ |  | Apparatus $4^{\text {b }}$ |  | Apparatus $5^{\text {d }}$ |  | Apparatus $6^{\text {d }}$ |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Mouthpiece adapter | $\mathrm{A}_{\text {i }}$ | - | $\mathrm{A}_{\mathrm{i}} \mathrm{A}_{\mathrm{i}}$ | - | $\mathrm{A}_{\text {i }}$ | - | $\mathrm{A}_{\text {i }}$ | - | $\mathrm{A}_{\mathrm{i}}$ | - | $\mathrm{A}_{\mathrm{i}}$ | - |
| Preseparator | - | - | - | - | $\mathrm{A}_{\mathrm{P}}$ | - | - | - | $\mathrm{A}_{\mathrm{P}}$ | - | - | - |
| Stage 0 of impactor | $\mathrm{A}_{0}$ | $\mathrm{B}_{0}$ | - | - | $\mathrm{A}_{0}$ | $\mathrm{B}_{0}$ | - | - | - | - | - | - |
| Stage 1 of impactor/ impinger | $\mathrm{A}_{1}$ | $\mathrm{B}_{1}$ | $\mathrm{A}_{1}$ | - | $\mathrm{A}_{1}$ | $\mathrm{B}_{1}$ | $\mathrm{A}_{1}$ | - | $\mathrm{A}_{1}$ | $\mathrm{B}_{1}$ | $\mathrm{A}_{1}$ | $\mathrm{B}_{1}$ |
| Stage 2 of impactor/ impinger | $\mathrm{A}_{2}$ | $\mathrm{B}_{2}$ | $\mathrm{A}_{2}$ | $\mathrm{B}_{2}$ | $\mathrm{A}_{2}$ | $\mathrm{B}_{2}$ | $\mathrm{A}_{2}$ | $\mathrm{B}_{2}$ | $\mathrm{A}_{2}$ | $\mathrm{B}_{2}$ | $\mathrm{A}_{2}$ | $\mathrm{B}_{2}$ |
| Stage 3 of impactor/ impinger | $\mathrm{A}_{3}$ | $\mathrm{B}_{3}$ | $\mathrm{A}_{3}$ | $\mathrm{B}_{3}$ | $\mathrm{A}_{3}$ | $\mathrm{B}_{3}$ | $\mathrm{A}_{3}$ | $\mathrm{B}_{3}$ | $\mathrm{A}_{3}$ | $\mathrm{B}_{3}$ | $\mathrm{A}_{3}$ | $\mathrm{B}_{3}$ |

${ }^{4}$ Table 7.
-Table 8.■1S (USP28)
Table of Mass Summaries for Analyses of Metered-Dose Inhalers and Dry Powder Inhalers (Continued)
Mass $\quad$ Apparatus $1 \quad$ Apparatus $2 \quad$ Apparatus $3^{\mathrm{a}} \quad$ Apparatus $4^{\mathrm{b}} \quad$ Apparatus $5^{\mathrm{d}} \quad$ Apparatus $6^{\mathrm{d}}$

| Stage 4 of | $\mathrm{A}_{4}$ | $\mathrm{~B}_{4}$ | $\mathrm{~A}_{4}$ | $\mathrm{~B}_{4}$ | $\mathrm{~A}_{4}$ | B 4 | $\mathrm{~A}_{4}$ | $\mathrm{~B}_{4}$ | A 4 | $\mathrm{~B}_{4}$ | $\mathrm{~A}_{4}$ | $\mathrm{~B}_{4}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| impactor/ |  |  |  |  |  |  |  |  |  |  |  |  |

impinger

Stage 5 of $\quad \mathrm{A}_{5} \quad \mathrm{~B}_{5} \quad \mathrm{~A}_{5} \quad \mathrm{~B}_{5} \quad \mathrm{~A}_{5} \quad \mathrm{~B}_{5} \quad-\quad-\quad$|  | $\mathrm{A}_{5}$ | $\mathrm{~B}_{5}$ | $\mathrm{~A}_{5}$ | $\mathrm{~B}_{5}$ |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| impactor/ |  |  |  |  |

impinger

| Stage 6 of | $\mathrm{A}_{6}$ | $\mathrm{B}_{6}$ | - | - | $\mathrm{A}_{6}$ | $\mathrm{B}_{6}$ | - | - | $\mathrm{A}_{6}$ | B6 | $\mathrm{A}_{6}$ | $\mathrm{B}_{6}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| impactor/ |  |  |  |  |  |  |  |  |  |  |  |  |
| impinger |  |  |  |  |  |  |  |  |  |  |  |  |
| Stage 7 of | $\mathrm{A}_{7}$ | $\mathrm{B}_{7}$ | - | - | $\mathrm{A}_{7}$ | $\mathrm{B}_{7}$ | - | - | $\mathrm{A}_{7}$ | $\mathrm{B}_{7}$ | $\mathrm{A}_{7}$ | $\mathrm{B}_{7}$ | impactor/

impinger

| Filter | $\mathrm{A}_{\mathrm{F}}$ | $\mathrm{B}_{\mathrm{F}}$ | $\mathrm{A}_{\mathrm{F}}$ | $\mathrm{B}_{\mathrm{F}}$ | $\mathrm{A}_{\mathrm{F}}$ | $\mathrm{B}_{\mathrm{F}}$ | $\mathrm{A}_{\text {F }}$ | $\mathrm{B}_{\mathrm{F}}$ | $\mathrm{A}_{\mathrm{F}}$ | $\mathrm{B}_{\mathrm{F}}$ | $\mathrm{A}_{\mathrm{F}}$ | $\mathrm{B}_{\mathrm{F}}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Sums Of | $\Sigma \mathrm{A}^{\text {c }}$ | $\Sigma B^{\text {c }}$ | $\Sigma \mathrm{A}^{\text {c }}$ | $\Sigma B^{\text {c }}$ | $\Sigma \mathrm{A}^{\text {c }}$ | $\Sigma B^{\text {c }}$ | $\Sigma \mathrm{A}^{\mathrm{c}}$ | $\Sigma B^{\text {c }}$ | $\Sigma \mathrm{A}^{\text {c }}$ | $\Sigma B^{\text {c }}$ | $\Sigma \mathrm{A}^{\mathrm{c}}$ | $\Sigma \mathrm{B}^{\text {c }}$ |

${ }^{\mathrm{a}}$ S Stages 6 and 7 are omitted from Apparatus 3 at airflow rates $>60 \mathrm{~L}$ per minute.
${ }^{\mathrm{b}}$ Stage 5 of Apparatus 4 is the filter stage (see Figure 8).
c $\Sigma \mathrm{A}$ is the total drug mass recovered from the apparatus; $\Sigma \mathrm{B}$ is the mass of drug recovered from the impactor (Apparatus 1,3 ,
5 and 6) or from the impactor stages beneath the uppermost stage (Apparatus 2, and 4).
${ }^{\text {d }}$ For Apparatus 5 and 6 , values for the drug masses AF and BF refer to collections from the MOC, and/or the after-filter if used.

## CALCULATIONS

Fine Particle Dose and Fine Particle Fraction-Calculate the total mass, $\Sigma \mathrm{A}$, of drug delivered from the mouthpiece of the inhaler into the apparatus. Then calculate the total mass, $R$, of drug found on the stages of the apparatus and the filter that captured the drug in the fine particle size range appropriate for the particular drug being tested. The Fine Particle Dose is calculated by the formula:

$$
R / n
$$

where $R$ is as stated above, and $n$ is the number of doses discharged during the test. The Fine Particle Fraction that would be delivered from the inhaler is then calculated by the formula:
$R / \Sigma \mathrm{A}$.

Cumulative Percentage (Cum\%) of Drug Mass Less Than Stated Aerodynamic Diameter-Construct Fable
${ }^{\Delta}$ Table-8 Table 911S (USP28) $\mathbf{\Delta U S P 2 8}$ by dividing the mass of drug on the filter stage by $\Sigma \mathrm{B}$ (see fable -5).

- (see Fable 7■ Table 8).■1S (USP28) $\mathbf{\Delta U S P 2 8}$

Multiply the quotient by 100 , and enter this number as a percentage opposite the effective cutoff diameter of the stage immediately above it in the impactor or impinger stack. For Apparatus 2 or 4, use Equation 1 to calculate the stage cutoff diameters, $D_{50, Q}$, at the airflow rate, $Q$, employed during the test.
${ }^{\Delta}$ For Apparatus 5 and 6, use Eq. 2 with Table 6 Table
7. 1 S (USP28) $\mathbf{\Delta S P} 28$

For Apparatus 1, use the cutoff diameters quoted by the manufacturer. For Apparatus 3, present the data as cumulative percentages of mass on and below the stated stage, and avoid assigning values to stage cutoff diameters. $\triangle$ USP28

Repeat the calculation for each of the stages in the impactor or impinger stack, in reverse numerical order (largest to smallest stage number). For each stage, calculate the cumulative percentage of mass less than the stated aerodynamic diameter by adding the percentage of the mass on that stage to the total percentage from the stages below and entering the value opposite the effective cutoff diameter of the stage above it in the stack. Thus, the percentage of drug on the filter can be seen to have aerodynamic diameters less than the cutoff diameter of the stage above the filter, and the percentage on the filter plus the percentage on the stage above have diameters less than the cutoff diameter of the stage above that, and so on. (erable -
${ }^{\wedge}$ (see Table 8-Table 9).■1S (USP28) $\mathbf{\Delta U S P 2 8}$

Table 6. Cumulative Pereentage (Cum\%) of Mass Less than-Stated-Aerodynamie Diameter

| Mass | Apparates 1 |  | Apparatus 2 |  | Apparatus $3^{\text {a }}$ |  | Apparatus-4 ${ }^{\text {b }}$ |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Cum\%o | $\theta_{50}{ }^{\text {d }}$ | Cum\% | $\theta_{5059}{ }^{\text {a }}$ | Exm\%o | $\theta_{50} 0^{\circ}$ | Cum\% | $\mathrm{B}_{50}{ }^{\text {a }}{ }^{4}$ |
| Filter |  | 0.4 |  | 0.625 |  | 0.4 |  | 1.7 |
| Stage 7 | $b$ | 0.7 | - | - | $b$ | 0.7 | - | - |
| Stage 6 | e | 1.4 | - | - | e | 1.4 | - | - |
| Stage 5 | d | 2.4 | $b$ | 1.25 | d | 2.4 | - | - |
| Stage-4 | e | 3.3 | e | 2.5 | e | 3.3 | $b$ | 3.1 |
| Stage 3 | £ | 4.7 | 4 | 5.0 | f | 4.7 | e | 6.8 |
| Stage 2 | \% | 5.8 | 100 | 10.0 | g | 5.8 | 100 | 13.0 |
| Stage 1 | h | 9.0 | - | - | h | 9.0 | - | - |
| Ster 0 | 100 | - | - | - | 100 | - | - | - |

${ }^{2}$ Stuges 6 and 7 are
${ }^{6}$ The filter stage in Apprantur-4is Stage-5 (see Fig. - 8).

- $[($ mass $1 \Sigma \mathrm{~B}) \times 100] \%$ (total\% of $\Sigma \mathrm{B}$ from-stage below).

 respectively.
- The $\mathrm{D}_{\text {se }}$ values are only valid at a flow rate of 28.3 L per minte.

| $\Delta_{\text {Table }} 8$. |  |  |  |  |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| -Table 9.■ ${ }_{1 S}$ (USP28) Cumulative Percentage (Cum\%) of Mass Less than the Stated Aerodynamic Diameter |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Apparatus 1 |  | Apparatus 2 |  | Apparatus $3^{\text {a }}$ |  | $\text { Apparatus } 4^{b}$ |  | Apparatus 5 |  | Apparatus 6 |  |
| Mass | $\begin{aligned} & \mathrm{Cu} \\ & \mathrm{~m} \% \mathrm{c} \end{aligned}$ | $D_{50}{ }^{\mathrm{d}}$ | $\begin{aligned} & \mathrm{Cu} \\ & \mathrm{~m} \% \mathrm{c} \end{aligned}$ | $D_{50, \mathrm{Q}}{ }^{\mathrm{d}}$ | $\begin{aligned} & \mathrm{Cu} \\ & \mathrm{~m} \%^{\mathrm{c}} \end{aligned}$ | $D_{50, \mathrm{Q}} \mathrm{e}$ | $\begin{aligned} & \mathrm{Cu} \\ & \mathrm{~m} \% \mathrm{c} \end{aligned}$ | $D_{50, \mathrm{Q}}{ }^{\mathrm{d}}$ | $\begin{aligned} & \mathrm{Cu} \\ & \mathrm{~m} \% \mathrm{c} \end{aligned}$ | $D_{50, \mathrm{Q}}{ }^{\mathrm{d}}$ | $\begin{aligned} & \mathrm{Cu}- \\ & \mathrm{m} \%^{\mathrm{c}} \end{aligned}$ | $D_{50, \mathrm{Q}}{ }^{\mathrm{d}}$ |
| Filter |  | 0.4 |  | 0.625 |  | 0.4 |  | 1.7 |  | 0.34 |  | 0.34 |
| Stage 7 | b | 0.7 | - | - | b | 0.7 | - | - | b | 0.55 | b | 0.55 |
| Stage 6 | c | 1.1 | - | - | c | 1.1 | - | - | c | 0.94 | c | 0.94 |
| Stage 5 | d | 2.1 | b | 1.25 | d | 2.1 | - | - | d | 1.66 | d | 1.66 |
| Stage 4 | e | 3.3 | c | 2.5 | e | 3.3 | b | 3.1 | e | 2.82 | e | 2.82 |
| Stage 3 | f | 4.7 | d | 5.0 | f | 4.7 | c | 6.8 | f | 4.46 | f | 4.46 |
| Stage 2 | g | 5.8 | 100 | 10.0 | g | 5.8 | 100 | 13.0 | g | 8.06 | g | 8.06 |
| Stage 1 | h | 9.0 | - | - | h | 9.0 | - | - | - | - | - | - |
| Stage 0 | 100 | - | - | - | 100 | - | - | - | 100 | - | 100 | - |

[^179]If necessary, and where appropriate, plot the percentage of mass less than the stated aerodynamic diameters, versus aerodynamic diameter, $D_{50, \varrho}$, on $\log$ probability paper. Calculate the GSD by the equation:

Use these data and/or plot to determine values for MMAD and GSD etc., as appropriate and when necessary (see Fig.10).

$$
G S D=\sqrt{\frac{\text { Size } X}{\text { Size } Y}}
$$


 diameter ${ }^{(l o g}$ scale). ${ }^{1 S}$ (USP28)
$\langle 611\rangle$ Alcohol Determination, USP 27 page 2270 and page 617 of PF 30(2) [Mar.-Apr. 2004]. On the basis of comments received, it is proposed to revise the System Suitability Test under Method II to increase the tailing factor of the alcohol peak from not greater than 1.5 to not greater than 2.0 .

METHOD II—GAS-LIQUID CHROMATOGRAPHIC METHOD
Method II is to be used where specified in the individual monograph. For a discussion of the principles upon which it is based, see Gas Chromatography under Chromatography $\langle 621\rangle$.
(PA2: H. Pappa) RTS-41214-1


#### Abstract

${ }^{\wedge}$ USP Reference Standards-USP Alcohol Determina- tion-Acetonitrile RS. USP Alcohol Determination-Alcohol RS.』USP28

Apparatus-Under typical conditions, use a gas chromatograph equipped with a flame-ionization detector and a $4-\mathrm{mm} \times$ $1.8-\mathrm{m}$ glass column packed with 100 - to 120 -mesh chromatographic column packing No. S3, using nitrogen or helium as the carrier gas. Prior to use, condition the column overnight at $235^{\circ}$ with a slow flow of carrier gas. The column is maintained at $120^{\circ}$, and the injection port and detector are maintained at $210^{\circ}$. Adjust the carrier flow and temperature so that acetonitrile, the internal standard, elutes in 5 to 10 minutes.


## Solutions-

Standed Solution Dilute- 5.0 mL of dehy drated aleehel with water to 250 mL .

Internal Standed Solution-Dilute 5.0 mL of ace nitrile with water to 250 mL .

4 $4 U S P 28$
Test Stock Preparation-Dilute the specimen under examination stepwise with water to obtain a solution containing approximately $2 \%(\mathrm{v} / \mathrm{v})$ of alcohol.

Test Preparation-Pipet 10 mL each of the Test the Internal Standetud Solution into a- 100 mb
${ }^{\Delta} 5 \mathrm{~mL}$ each of the Test Stock Preparation and the USP Alcohol Determination-Acetonitrile RS [NOTE-Alternatively, a $2 \%$ aqueous solution of acetonitrile of suitable quality may be used as the internal standard solution.] into

```
a 50-mL_
volumetric flask, and dilute with water to volume.
    Standard Preparation - Pipet 10 mL each of the Statard Solu
tion and the Internal Standetd Solution inte a 100-mL
```

$\triangle 5 \mathrm{~mL}$ each of the USP Alcohol Determination-Alcohol RS and the USP Alcohol Determination-Acetonitrile RS [NOTE-Alternatively, a 2\% aqueous solution of acetonitrile of suitable quality may be used as the internal standard solution.] into a $50-\mathrm{mL}_{\mathbf{A} U S P 28}$ volumetric flask, dilute with water to volume, and mix.

Procedure—Inject about $5 \mu \mathrm{~L}$ each of Test Preparation and Standard Preparation, in duplicate, into the gas chromatograph, record the chromatograms, and determine the peak response ratios. Calculate the percentage of alcohol $(\mathrm{v} / \mathrm{v})$ in the specimen under test according to the formula:

$$
2 R_{t} P / R_{s}
$$

$$
{ }^{\mathbf{\Delta}} C D\left(R_{U} / R_{S}\right), \mathbf{\Delta U S P 2 8}
$$

in which
${ }^{\Delta} C$ is the labeled concentration of USP Alcohol Determina-tion-Alcohol RS; ${ }_{\mathbf{\Delta S P 2 8}}$
$D$ is the dilution factor (the ratio of the volume of the Test Stock Preparation to the volume of the specimen taken); and $R_{U}$ and $R_{S}$ are the peak response ratios obtained for the Test Preparation and the Standard Preparation, respectively.

System Suitability Test-In a suitable chromatogram, the resolution factor, $R$, is not less than 2 ; the tailing factor of the alcohol peak is not greater than 4.5
-2.0; ${ }^{1 S}$ (USP28)
and six replicate injections of the Standard Preparation show a relative standard deviation of not more than $2.0 \%$ in the ratio of the peak of alcohol to the peak of the internal standard.

## Briefing

$\langle 645\rangle$ Water Conductivity, USP 27 page 2286 and page 233 of PF 30(1) [Jan.-Feb. 2004]. On the basis of comments received, it is proposed to include an accuracy requirement for the temperature measurement under Instrument Specifications and Operating Parameters.
(PW: F. Barletta) RTS-41218-1

## Change to read:

## INSTRUMENT SPECIFICATIONS AND OPERATING PARAMETERS

Water conductivity must be measured accurately using calibrated instrumentation. The conductivity cell constant, a factor used as a multiplier for the scale reading from the meter, must be known within $\pm 2 \%$. The cell constant can be verified directly by using a solution of known conductivity, or indirectly by comparing the instrument reading taken with the cell in question to readings from a cell of known or certified cell constant.

Meter calibration is accomplished by replacing the conductivity cell with NIST-traceable precision resistors (accurate to $\pm 0.1 \%$ of the stated value) or an equivalently accurate adjustable resistance device, such as a Wheatstone Bridge, to give a predicted instrument response. Each scale on the meter may require separate calibration prior to use. The frequency of recalibration is a function of instrument design, degree of use, etc. However, because some multiple scale instruments have a single calibration adjustment, recalibration may be required between each use of a different scale. The instrument must have a minimum resolution of $0.1 \mu \mathrm{~S} / \mathrm{cm}^{*}$ on the lowest range. Excluding the cell accuracy, the instrument accuracy must be $\pm 0.1 \mu \mathrm{~S} / \mathrm{cm}$.

Because temperature has a substantial impact on conductivity readings of specimens at high and low temperatures, many instruments automatically correct the actual reading to display the value that theoretically would be observed at the nominal temperature of $25^{\circ}$. This is done using a temperature sensor in the conductivity cell probe and an algorithm in the instrument's circuitry. This tem-

[^180]perature compensation algorithm may not be accurate. Conductivity values used in this method are nontemperature-compensated measurements.

- Accuracy of the temperature measurement must be $\pm 2^{\circ} \cdot \mathbf{1 S}$ (USP28)
The procedure described below is designed for measuring the conductivity of Purified Water and Water for Injection. Stage 1 of the procedure below may alternatively be performed (with the appropriate modifications to Step 1) using on-line instrumentation that has been appropriately calibrated, whose cell constants have been accurately determined, and whose temperature compensation function has been disabled. The suitability of such on-line instrumentation for quality control testing is also dependent on its location(s) in the water system. The selected instrument location(s) must reflect the quality of the water used.


## Change to read:

## PROCEDURE

## Stage 1

1. Determine the temperature of the water and the conductivity of the water using a nontemperature-compensated conductivity reading. The measurement may be performed in a suitable container or as an on-line measurement.
2. Using the Stage 1-Temperature and Conductivity Requirements table, find the temperature value that is not greater than the measured temperature,
${ }^{\Delta}$ i.e., the next lower temperature. $\quad$ USP28
The corresponding conductivity value is the limit at that tare.
${ }^{\Delta}$ on this table is the limit. [NOTE-Do not interpolate.] ${ }_{\boldsymbol{\Delta} U S P 28}$
3. If the measured conductivity is not greater than the table value, the water meets the requirements of the test for conductivity. If the conductivity is higher than the table value, proceed with Stage 2.

Stage 1-Temperature and Conductivity Requirements (for nontemperature-compensated conductivity measurements only) (Continued)

| Temperature | Conductivity Requirement $(\mu \mathrm{S} / \mathrm{cm})$ |
| :---: | :---: |
| 95 | 2.9 |
| 100 | 3.1 |

## Stage 2

4. Transfer a sufficient amount of water ( 100 mL or more) to a suitable container, and stir the test specimen. Adjust the temperature, if necessary, and, while maintaining it at $25 \pm 1^{\circ}$, begin vigorously agitating the test specimen while periodically observing the conductivity. When the change in conductivity (due to uptake of atmospheric carbon dioxide) is less than a net of $0.1 \mu \mathrm{~S} / \mathrm{cm}$ per 5 minutes, note the conductivity.
5. If the conductivity is not greater than $2.1 \mu \mathrm{~S} / \mathrm{cm}$, the water meets the requirements of the test for conductivity. If the conductivity is greater than $2.1 \mu \mathrm{~S} / \mathrm{cm}$, proceed with Stage 3.

## Stage 3

6. Perform this test within approximately 5 minutes of the conductivity determination in Step 5, while maintaining the sample temperature at $25 \pm 1^{\circ}$. Add a saturated potassium chloride solution to the same water sample $(0.3 \mathrm{~mL}$ per 100 mL of the test specimen), and determine the pH to the nearest 0.1 pH unit, as directed under $\mathrm{pH}\langle 791\rangle$.
7. Referring to the Stage 3-pH and Conductivity Requirements table, determine the conductivity limit at the measured pH value. If the measured conductivity in Step 4 is not greater than the conductivity requirements for the pH determined in Step 6, the water meets the requirements of the test for conductivity. If either the measured conductivity is greater than this value or the pH is outside the range of 5.0 to 7.0 , the water does not meet the requirements of the test for conductivity.

Stage 3-pH and Conductivity Requirements
(for atmosphere and temperature equilibrated samples only)

|  | Conductivity Requirement $(\mu \mathrm{S} / \mathrm{cm})$ |
| :---: | :---: |
| 5.0 | 4.7 |
| 5.1 | 4.1 |
| 5.2 | 3.6 |
| 5.3 | 3.3 |
| 5.4 | 3.0 |
| 5.5 | 2.8 |
| 5.6 | 2.6 |
| 5.7 | 2.5 |
| 5.8 | 2.4 |
| 5.9 | 2.4 |
| 6.0 | 2.4 |
| 6.1 | 2.4 |
| 6.2 | 2.5 |
| 6.3 | 2.4 |
| 6.4 | 2.3 |
| 6.5 | 2.2 |
| 6.6 | 2.1 |
| 6.7 | 2.6 |
| 6.8 | 3.1 |
| 6.9 | 3.8 |
| 7.0 | 4.6 |

## GENERAL CHAPTERS

## General Information

## BRIEFING

$\langle\mathbf{1 2 2 5}\rangle$ Validation of Compendial Methods, USP 27 page 2622 and page 1634 of $P F 29(5)$ [Sept.-Oct. 2003]. On the basis of comments received, it is proposed to revise the Validation section to add the analytical characteristic "Robustness" to Table 1, to change the Definition under Robustness to indicate that this characteristic should be determined during the development of the analytical procedure, and to delete the previously proposed revision regarding dilution parallelism in the Determination under Specificity.
(PA4: H. Pappa) RTS-41073-1

## Change to read:

Test procedures for assessment of the quality levels of pharmaceutical products are subject to various requirements. According to Section 501 of the Federal Food, Drug, and Cosmetic Act, assays and specifications in monographs of the United States Pharmacopeia and the National Formulary constitute legal standards. The Current Good Manufacturing Practice regulations [21 CFR 211.194(a)] require that test methods, which are used for assessing compliance of pharmaceutical products with established specifications, must meet proper standards of accuracy and reliability. Also, according to these regulations [21 CFR 211.194(a)(2)], users of analytical methods described in the $U S P$ and the $N F$ are not required to validate accuracy and reliability of these methods, but merely verify their suitability under actual conditions of use. Recognizing the legal status of $U S P$ and $N F$ standards, it is essential, therefore, that proposals for adoption of new or revised compendial analytical methods
mpocedures $_{\mathbf{n}_{1 S} \text { (USP28) }}$
be supported by sufficient laboratory data to document their validity.

The text of this information chapter harmonizes, to the extent possible, with the Tripartite International Conference on Harmonization (ICH) documents Validation of Analytical Procedures and the Methodology extension text, which are concerned with analytical procedures included as part of registration applications submitted within the EC, Japan, and the USA. Some aspects (dissolution, drug release), which form part of this chapter, are only dealt with in passing in the ICH documents and are to be discussed in the future. Complete harmonization has not been possible, in part because of different uses of terminology. For example, the ICH use of "procedure" presents difficulty, as this term has a specific and different use throughout the $U S P-N F$.

## Change to read:

## SUBMISSIONS TO THE COMPENDIA

Submissions to the compendia for new or revised analytical methods

- procedures $_{\text {■1S (USP28) }}$
should contain sufficient information to enable members of the
USP Committe of Revision
-USP Council of Experts and its Expert Commit-


## tees $\quad 1 \mathrm{~S}$ (USP28)

to evaluate the relative merit of proposed procedures. In most cases, evaluations involve assessment of the clarity and completeness of the description of the analytical
$\square_{\text {procedures, }}^{\text {■ }}$ 1S (USP28)
determination of the need for the methods,

- procedures, ${ }^{1 S}$ (USP28)
and documentation that they have been appropriately validated. Information may vary depending upon the type of method involved. However, in most cases a submission will consist of the following sections.
Rationale-This section should identify the need for the methed

■ procedure $_{\text {n1S (USP28) }}$
and describe the capability of the specific
■ procedure $_{\text {(1S (USP28) }}$.
proposed and why it is preferred over other types of determinations. For revised procedures, a comparison should be provided of limitations of the current compendial
$\boldsymbol{m}_{\text {procedure }}{ }_{\text {1S (USP28) }}$
and advantages offered by the proposed methed.
$\square_{\text {procedure. }}$.1S (USP28)
Proposed Analytical Procedure-This section should contain a complete description of the analytical methed
$\square_{\text {procedure }}{ }_{\text {1S (USP28) }}$
sufficiently detailed to enable persons "skilled in the art" to replicate it. The write-up should include all important operational parameters and specific instructions such as preparation of reagents, performance of systems suitability tests, description of blanks used, precautions, and explicit formulas for calculation of test results.

Data Elements-This section should provide thorough and complete documentation of the validation of the analytical
■procedure.п1S (USP28)
It should include summaries of experimental data and calculations substantiating each of the applicable analytical performance characteristics. These characteristics are described in the following section.

## Change to read:

## VALIDATION

Validation of an analytical methed
$\square_{\text {procedure }} \mathbf{m}_{1 S}$ (USP28)
is the process by which it is established, by laboratory studies, that the performance characteristics of the

## $\square_{\text {procedure }}^{\mathbf{■}_{1 S}(\text { USP28) }}$

meet the requirements for the intended analytical applications. Typical analytical performance characteristics that should be considered in the validation of the types of methods
$\square_{\text {procedures }}{ }_{\text {■S (USP28) }}$
described in this document are listed in Table 1. Since opinions may differ with respect to terminology and use, each of the performance characteristics is defined in the next section of this chapter along with a delineation of a typical method or methods by which it may be measured.

Table 1. Typical Analytical Characteristics Used in Method Validation.
Accuracy
Precision
Specificity
Detection Limit
Quantitation Limit
Linearity
Range
■Robustness
Ruggedness $_{\text {■1S (USP28) }}$

In the case of compendial metheds,
$\square_{\text {procedures, }}$ ■1S (USP28)
revalidation may be necessary in the following cases: a submission to the USP of a revised analytical medt;

■procedure; ${ }^{1 \mathrm{IS} \text { (USP28) }}$
or the use of an established general
$\boldsymbol{m}_{\text {procedure }}{ }_{\text {■1S (USP28) }}$
with a new product or raw material (see below under Data Elements Required for Assay Validation).

The ICH documents give guidance on the necessity for revalidation in the following circumstances: changes in the synthesis of the drug substance; changes in the composition of the drug product; and changes in the analytical procedure.

## Analytical Performance Characteristics

## ACCURACY

Definition-The accuracy of an analytical
$\square_{\text {procedure }}{ }_{\text {■1S (USP28) }}$
is the closeness of test results obtained by that methed
■ procedure $_{\text {IS (USP28) }}$
to the true value. The accuracy of an analytical
$\square_{\text {procedure }}^{\mathbf{m}_{1 S} \text { (USP28) }}$
should be established across its range.
Determination-In the case of the assay of a drug substance, accuracy may be determined by application of the analytical methed
procedure $_{\text {■ } 1 \mathrm{~S}}$ (USP28)
to an analyte of known purity (e.g., a Reference Standard) or by comparison of the results of the methed
$\square_{\text {procedure }}^{1 S}{ }_{\text {IS }}{ }^{\text {(USP28) }}$
with those of a second, well-characterized
■ procedure, $\boldsymbol{m}_{1 S}$ (USP28)
the accuracy of which has been stated or defined.
In the case of the assay of a drug in a formulated product, accuracy may be determined by application of the analytical methed
$■_{\text {procedure }}^{\mathbf{n}_{1 S}(\text { USP28) }}$
to synthetic mixtures of the drug product components to which known amounts of analyte have been added within the range of the method.
$\square_{\text {procedure. }}$.1S (USP28)
If it is not possible to obtain samples of all drug product components, it may be acceptable either to add known quantities of the analyte to the drug product (i.e., "to spike") or to compare results with those of a second, well-characterized methe,

- procedure, $\boldsymbol{\square}$ 1S (USP28)
the accuracy of which has been stated or defined.
In the case of quantitative analysis of impurities, accuracy should be assessed on samples (of drug substance or drug product) spiked with known amounts of impurities. Where it is not possible to obtain samples of certain impurities or degradation products, results should be compared with those obtained by an independent methed.
${ }^{\square}$ procedure. $\quad 1 \mathrm{~S}$ (USP28)
In the absence of other information, it may be necessary to calculate the amount of an impurity based on comparison of its response to that of the drug substance; the ratio of the responses of equal amounts of the impurity and the drug substance (response factor) should be used if known.

Accuracy is calculated as the percentage of recovery by the assay of the known added amount of analyte in the sample, or as the difference between the mean and the accepted true value, together with confidence intervals.

The ICH documents recommend that accuracy should be assessed using a minimum of nine determinations over a minimum of three concentration levels, covering the specified range (i.e., three concentrations and three replicates of each concentration).

- Assessment of accuracy can be accomplished in a variety of ways, including evaluating the recovery of the analyte (percent recovery) across the range of the assay, or evaluating the linearity of the relationship between estimated and actual concentrations. The statistically preferred criterion is that the confidence interval for the slope be contained in an interval around 1.0 , or alternatively, that the slope be close to 1.0 . In either case, the interval or the definition of closeness should be specified in the validation protocol. The
acceptance criterion will depend on the assay and its variability and on the product. Setting an acceptance criterion based on the lack of statistical significance of the test of the null hypothesis that the slope is 1.0 is not an acceptable approach.■1S (USP28)


## PRECISION

Definition-The precision of an analytical med
mprocedure $_{\text {■1S (USP28) }}$
is the degree of agreement among individual test results when the method
$\square_{\text {procedure }}^{\mathbf{■}_{1 S}(\text { USP28) }}{ }^{\text {a }}$
is applied repeatedly to multiple samplings of a homogeneous sample. The precision of an analytical

■rocedure $_{\text {■1S (USP28) }}$
is usually expressed as the standard deviation or relative standard deviation (coefficient of variation) of a series of measurements. Precision may be a measure of either the degree of reproducibility or of repeatability of the analytical

- $_{\text {procedure }}^{\mathbf{■}_{1 S}(U S P 28)}$
under normal operating conditions. In this context, reproducibility refers to the use of the analytical procedure in different laboratories, as in a collaborative study. Intermediate precision expresses within-laboratory variation, as on different days, or with different analysts or equipment within the same laboratory. Repeatability refers to the use of the analytical procedure within a laboratory over a short period of time using the same analyst with the same equipment. For most purposes, repeatability is the criterion of concern in USP analytical procedures, although reproducibility between laboratories or intermediate precision may well be considered during the standardization of a procedure before it is submitted to the Pharmacopeia.

Determination-The precision of an analytical methed
$\square_{\text {procedure }}{ }_{\text {1S (USP28) }}$
is determined by assaying a sufficient number of aliquots of a homogeneous sample to be able to calculate statistically valid estimates of standard deviation or relative standard deviation (coefficient of variation). Assays in this context are independent analyses of samples that have been carried through the complete analytical procedure from sample preparation to final test result.

The ICH documents recommend that repeatability should be assessed using a minimum of nine determinations covering the specified range for the procedure (i.e., three concentrations and three replicates of each concentration or using a minimum of six determinations at $100 \%$ of the test concentration).

## SPECIFICITY

Definition-The ICH documents define specificity as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities, degradation products, and matrix components. Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedures. [NOTE-Other reputable international authorities (IUPAC, AOAC)

have preferred the term "selectivity," reserving "specificity" for those procedures that are completely selective.] For the or as say metheds
$\square_{\text {tests discussed }}^{\text {1S (USP28) }}$
below, the above definition has the following implications:
Identification Tests: ensure the identity of the analyte.
Purity Tests: ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte (e.g., related substances test, heavy metals limit, organic volatile impurity limit).

## $\boldsymbol{■}_{\text {impurities). }}$.1S (USP28)

Assays: provide an exact result, which allows an accurate statement on the content or potency of the analyte in a sample.
Determination-In the case of qualitative analyses (identification tests), the ability to select between compounds of closely related structure that are likely to be present should be demonstrated. This should be confirmed by obtaining positive results (perhaps by comparison to a known reference material) from samples containing the analyte, coupled with negative results from samples that do not contain the analyte and by confirming that a positive response is not obtained from materials structurally similar to or closely related to the analyte.

In the case of analytical preedure
■procedures $_{\text {■1S (USP28) }}$
for impurities, specificity may be established by spiking the drug substance or product with appropriate levels of impurities and demonstrating that these impurities are determined with appropriate accuracy and precision.

In the case of the assay, demonstration of specificity requires that it can be shown that the procedure is unaffected by the presence of impurities or excipients. In practice, this can be done by spiking the drug substance or product with appropriate levels of impurities or excipients and demonstrating that the assay result is unaffected by the presence of these extraneous materials.

Fer assay or impurity procedures, this can be dene alter-
natively by demenstrating dilution parallelism between the standard and the sample-over the same range used for linearity. The respenses frem the standard and the analyte are plotted against the respective dilutions (or after appropriate mathematical transformation, if necessary) and the wo dilu tion curves are shown to be parallel within the limits of varration determined by the preset confidence interval for the

## procedure.

If impurity or degradation product standards are unavailable, specificity may be demonstrated by comparing the test results of samples containing impurities or degradation products to a second well-characterized procedure (e.g., a Pharmacopeial or other validated procedure). These comparisons should include samples stored under relevant stress conditions (e.g., light, heat, humidity, acid/base hydrolysis, oxidation). In the case of the assay, the results should be compared; in the case of chromatographic impurity tests, the impurity profiles should be compared.

The ICH documents state that when chromatographic procedures are used, representative chromatograms should be presented to demonstrate the degree of selectivity, and peaks should be appropriately labeled. Peak purity tests (e.g., using diode array or mass spectrometry) may be useful to show that the analyte chromatographic peak is not attributable to more than one component.

## DETECTION LIMIT

Definition-The detection limit is a characteristic of limit tests. It is the lowest amount of analyte in a sample that can be detected, but not necessarily quantitated, under the stated experimental conditions. Thus, limit tests merely substantiate that the amount of analyte is above or below a certain level. The detection limit is usually expressed as the concentration of analyte (e.g., percentage, parts per billion) in the sample.

Determination-For noninstrumental methods,
$\square_{\text {procedures, }}^{\boldsymbol{m}}$ 1S (USP28)
the detection limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.

For instrumental procedures, the same method
■approach $_{\text {■1S (USP28) }}$
may be used as for noninstrumental
■procedures.■1S (USP28)
In the case of methods
■ procedures $_{\text {■ } 1 \text { (USP28) }}$
submitted for consideration as official compendial
${ }^{\square}$ procedures, $\quad$ 1S (USP28)
it is almost never necessary to determine the actual detection limit. Rather, the detection limit is shown to be sufficiently low by the analysis of samples with known concentrations of analyte above and below the required detection level. For example, if it is required to detect an impurity at the level of $0.1 \%$, it should be demonstrated that the procedure will reliably detect the impurity at that level.

In the case of instrumental analytical procedures that exhibit background noise, the ICH documents describe a common approach, which is to compare measured signals from samples with known low concentrations of analyte with those of blank samples. The minimum concentration at which the analyte can reliably be detected is established. Typically acceptable signal-to-noise ratios are $2: 1$ or $3: 1$. Other approaches depend on the determination of the slope of the calibration curve and the standard deviation of responses. Whatever method is used, the detection limit should be subsequently validated by the analysis of a suitable number of samples known to be near, or prepared at, the detection limit.

## QUANTITATION LIMIT

Definition-The quantitation limit is a characteristic of quantitative assays for low levels of compounds in sample matrices, such as impurities in bulk drug substances and degradation products in finished pharmaceuticals. It is the lowest amount of analyte in a sample that can be determined with acceptable precision and accuracy under the stated experimental conditions. The quantitation limit is expressed as the concentration of analyte (e.g., percentage, parts per billion) in the sample.

Determination-For noninstrumental methods,
■procedures, ■1S (USP28)
the quantitation limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be determined with acceptable accuracy and precision.

For instrumental procedures, the same methe
$\boldsymbol{m}_{\text {approach }}{ }_{\text {■1S (USP28) }}$
may be used as for noninstrumental
${ }^{\text {■ procedures.■1S (USP28) }}$

In the case of methods
■procedures $_{\text {■ }}{ }_{\text {(USP28) }}$
submitted for consideration as official compendial metheds,
$\square_{\text {procedures, }}$ ■1S (USP28)
it is almost never necessary to determine the actual quantitation limit. Rather, the quantitation limit is shown to be sufficiently low by the analysis of samples with known concentrations of analyte above and below the quantitation level. For example, if it is required to assay an analyte at the level of 0.1 mg per tablet, it should be demonstrated that the methed
$\square_{\text {procedure }}^{\text {■1S (USP28) }}$
will reliably quantitate the analyte at that level.
In the case of instrumental analytical
$\square_{\text {procedures }}^{\text {■ }}$ (USP28)
that exhibit background noise, the ICH documents describe a common approach, which is to compare measured signals from samples with known low concentrations of analyte with those of blank samples. The minimum concentration at which the analyte can reliably be quantified is established. A typically acceptable sig-nal-to-noise ratio is $10: 1$. Other approaches depend on the determination of the slope of the calibration curve and the standard deviation of responses. Whatever methed

■approach $_{\square 1 S}$ (USP28)
is used, the quantitation limit should be subsequently validated by the analysis of a suitable number of samples known to be near, or prepared at, the quantitation limit.

## LINEARITY AND RANGE

Definition of Linearity-The linearity of an analytical method
$\square_{\text {procedure }}{ }_{\text {■1S (USP28) }}$
is its ability to elicit test results that are directly, or by a well-defined mathematical transformation, proportional to the concentration of analyte in samples within a given range.
$\square_{\text {Thus, }}$ in this section, linearity refers to the linearity of the relationship of concentration and assay measurement. In some cases, to attain linearity, the concentration and/or the measurement may be transformed. (Note that the weighting factors used in the regression analysis may change when a transformation is applied.) Possible transformations may include log, square root, or reciprocal, although other transformations are acceptable. If linearity is not attainable, a nonlinear model may be used. The goal is to have a model, whether linear or nonlinear, that describes closely the con-centration-response relationship.■1S (USP28)

Definition of Range-The range of an analytical

is the interval between the upper and lower levels of analyte (including these levels) that have been demonstrated to be determined with a suitable level of precision, accuracy, and linearity using the methed
$\square_{\text {procedure }}{ }_{\text {1S (USP28) }}$
as written. The range is normally expressed in the same units as test results (e.g., percent, parts per million) obtained by the analytical method.

■procedure.■1S (USP28)
Determination of Linearity and Range-Linearity should be established across the range of the analytical procedure. It should be established initially by visual examination of a plot of signals as a function of analyte concentration of content. If there appears to be a linear relationship, test results should be established by appropriate statistical methods (e.g., by calculation of a regression line by the method of least squares). In some tween the respense of an malyte and its concentration, the test data may have to be subjected to a mathematieal transformation.

■1S (USP28)
Data from the regression line itself may be helpful to provide mathematical estimates of the degree of linearity. The correlation coefficient, y-intercept, slope of the regression line, and residual sum of squares should be submitted.

The range of the

is validated by verifying that the analytical
$\square_{\text {procedure }}{ }_{\text {■1S (USP28) }}$
provides acceptable precision, accuracy, and linearity when applied to samples containing analyte at the extremes of the range as well as within the range.

ICH recommends that, for the establishment of linearity, a minimum of five concentrations normally be used. It is also recommended that the following minimum specified ranges should be considered:

Assay of a Drug Substance (or a finished product): from $80 \%$ to $120 \%$ of the test concentration.

Determination of an Impurity: from $50 \%$ to $120 \%$ of the sir fieation.
$\boldsymbol{\square}_{\text {acceptance criterion. }}$ 1S (USP28)
For Content Uniformity: a minimum of $70 \%$ to $130 \%$ of the test concentration, unless a wider or more appropriate range, based on the nature of the dosage form (e.g., metered-dose inhalers) is justified.

For Dissolution Testing: $\pm 20 \%$ over the specified range (e.g., if the speifieations
$\boldsymbol{m a c c e p t a n c e}$ criteria $_{1 \text { 1S (USP28) }}$
for a controlled-release product cover a region from $20 \%$, after 1 hour, and up to $90 \%$, after 24 hours, the validated range would be $0 \%$ to $110 \%$ of the label claim).

## RUGGEDNESS

Definition-The ruggedness of an analytical ise the gree of repreduribility of test results abtained by the analysis of the same samples under a varie of conditions, steh as different laboratories, different analysts, different instrments, different lots of reagents, different elapsed assay times, different assay temperafures, different days, ete. Ruggedness is normally expressed as the lack of influence on test results of operational and environmen tal variables of the analytieal method. Pugsedness is a measure of repredueibility of test results under the variation in conditions nor mally expected from laberatery to laboratory and frem analyst to analyst.

- procedure is the lack of influence on test results obtained by the analysis of the same samples under a variety of conditions, such as different analysts, different instruments, different lots of reagents, different elapsed assay times, different days, and other operational and environmental variables external to the analytical procedure documenta-
tion.■1S (USP28)
Determination-The ruggedness of an analytical
-procedure $_{\text {1S (USP28) }}$
is determined by analysis of aliquots from homogeneous lots in different laberateries,

■1S (USP28)
by different analysts, using operational and environmental conditions that may differ but are still within the specified parameters of the assay. The degree of reproducibility of test results is then determined as a function of the assay variables. This reproducibility may be compared to the precision of the assay under normal conditions to obtain a measure of the ruggedness of the analytical methed.

- procedure.■1S (USP28)


## ROBUSTNESS

Definition-The robustness of an analytical
$\square_{\text {procedure }}$ ■1S (USP28)
is a measure of its capacity to remain unaffected by small but deliberate variations in mether parameters and provides an indieation of its reliability
$\square_{\text {procedural parameters listed in the procedure documenta- }}$
tion and provides an indication of its suitability ${ }_{\square 1 S}$ (USP28) during normal usage.
■Robustness should be determined during development of the analytical procedure.■1S (USP28)

## SYSTEM SUITABILITY

If measurements are susceptible to variations in analytical conditions, these should be suitably controlled, or a precautionary statement should be included in the

■procedure.■1S (USP28)
One consequence of the evaluation of robustness and ruggedness should be that a series of system suitability parameters is established to ensure that the validity of the analytical methed
■ procedure $_{\text {1S (USP28) }}$
is maintained whenever used. Typical variations are the stability of analytical solutions, different equipment, and different analysts. In the case of liquid chromatography, typical variations are the pH of the mobile phase, the mobile phase composition, different lots or
suppliers of columns, the temperature, and the flow rate. In the case of gas chromatography, typical variations are different lots or suppliers of columns, the temperature, and the flow rate.

System suitability tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular methed

■ procedure $_{\mathbf{n}_{1 S}(\text { USP28) }}$
depend on the type of methed
$\square_{\text {procedure }}{ }_{\text {■1S (USP28) }}$
being evaluated. They are especially important in the case of chromatographic methods, and submissions
$\square_{\text {procedures. Submissions }}^{\mathbf{m}_{1 S} \text { (USP28) }}$
to the USP should make note of the requirements under the System Suitability section in the general test chapter Chromatography $\langle 621\rangle$.

## Data Elements Required for Assay

## ■1S(USP28) Validation <br> Compendial assay procedtres

$\boldsymbol{m}_{\text {test }}$ requirements ${ }_{\text {■ }}^{1 S}$ (USP28)
vary from highly exacting analytical determinations to subjective evaluation of attributes. Considering this of assays,
-broad variety, ${ }^{\text {■1S (USP28) }}$
it is only logical that different test methods
$\boldsymbol{\square}_{\text {procedures }} \boldsymbol{■ 1 S}$ (USP28)
require different validation schemes. This chapter covers only the most common categories of assays

■ tests $_{\text {■1S (USP28) }}$
for which validation data should be required. These categories are as follows:

Category I-Analytical
$\square_{\text {procedures }}{ }^{1 \mathrm{~S}}$ (USP28)
for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products.

Category II-Analytical metheds
■ procedures $_{\text {■1S }_{\text {(USP28) }}}$
for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These metheds
$\square_{\text {procedures }}^{\boldsymbol{\square 1 S} \text { (USP28) }}$
include quantitative assays and limit tests.
Category III-Analytical
■procedures $_{\text {п1S (USP28) }}$
for determination of performance characteristics (e.g., dissolution, drug release).
Category IV-Identification tests.
For each assay
$\square_{\text {■1S (USP28) }}$
category, different analytical information is needed. Listed in Table 2 are data elements that are normally required for each of theat egories of assays.
$\square_{\text {these categories.■1S (USP28) }}$

Table 2. Data Elements Required for Assay

| Analytical | Assy | Assay |  | Assy | Assy |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Characteristics | $\square_{\text {1S (USP28) }}$ <br> Category I | als (USP28) <br> Category II |  | $\square_{\text {■1S (USP28) }}$ <br> Category III | ■!1S (USP28) <br> Category IV |
|  |  | Quantitative | Limit Tests |  |  |
| Accuracy | Yes | Yes | * | * | No |
| Precision | Yes | Yes | No | Yes | No |
| Specificity | Yes | Yes | Yes | * | Yes |
| Detection Limit | No | No | Yes | * | No |
| Quantitation Limit | No | Yes | No | * | No |
| Linearity | Yes | Yes | No | * | No |
| Range | Yes | Yes | * | * | No |
| ■Ruggedness | Yes | Yes | Yes | Yes | $\mathrm{Yes}_{\mathbf{\square 1 S} \text { (USP28) }}$ |

* May be required, depending on the nature of the specific test.

Already established general assays and tests (e.g., titrimetric method of water determination, bacterial endotoxims test)
$\square_{\text {procedures (e.g., titrimetric determination of water, bacte- }}$
rial endotoxins) $\quad$ 1S (USP28)
should be revalidated to verify their accuracy (and absence of possible interference) when used for a new product or raw material. The validity of an analytical
$\boldsymbol{m}_{\text {procedure }}{ }_{\text {■ } 1 \text { (USP28) }}$
can be verified only by laboratory studies. Therefore, documentation of the successful completion of such studies is a basic requirement for determining whether a methed
$\square_{\text {procedure }}^{\mathbf{■ 1 S}_{\text {(USP28) }}}$
is suitable for its intended application(s). Appropriate documentation should accompany any proposal for new or revised compendial analytical procedures.

## BRIEFING

$\langle\mathbf{1 2 3 0}\rangle$ Water for Health Applications, page 3146 of the First Supplement. On the basis of comments received, the Pharmaceutical Waters Expert Committee is proposing revisions to this general information chapter primarily in the Microbial Considerations section.
(PW: F. Barletta) RTS-41262-1

## Change to read:

## WATER FOR HEMODIALYSIS

Chemical and microbial components that can be found in drinking water meeting U.S. Environmental Protection Agency National Primary Drinking Water Regulations (or equivalent)

## $\square_{\text {may }}^{1 S}$ (USP28)

have the potential to produce significant negative effects in patients undergoing hemodialysis. It is, therefore, necessary to subject the water to further treatment to reduce these components to acceptable levels. The Water for Hemodialysis monograph provides bacterial and chemical tests that are required to ensure patient safety. Additional testing is recommended as follows:
(1) Excess levels of aluminum, fluorides, and chlorides may be found seasonally in drinking water as a result of chemicals used in water treatment. These components should be monitored in Water for Hemodialysis being produced in accordance with established standard operating procedures. The maximum acceptable levels of these elements and compounds are listed in Table 1.
(2) A comprehensive validation testing of the system producing Water for Hemodialysis should be performed, at least annually, to ensure that the water treatment equipment is functioning properly. The maximum acceptable levels of elements and compounds are listed in Table 1. Routine testing is performed in accordance with the monograph.

Table 1. Maximum Allowable Chemical Levels in Water for Hemodialysis (water used to prepare dialysate and concentrates from powder at a dialysis facility and to reprocess dialyzers for multiple use)*

|  | Element or <br> Compound |
| :--- | :---: |
| Calcium | Maximum Concentration <br> $(\mathrm{mg} / \mathrm{L})$ |
| Magnesium | $2(0.1 \mathrm{mEq} / \mathrm{L})$ |
| Potassium | $4(0.3 \mathrm{mEq} / \mathrm{L})$ |
| Sodium | $8(0.2 \mathrm{mEq} / \mathrm{L})$ |
| Antimony | $70(3.0 \mathrm{mEq} / \mathrm{L})$ |
| Arsenic | 0.006 |
| Barium | 0.005 |
| Beryllium | 0.10 |
| Cadmium | 0.0004 |
| Chromium | 0.001 |
| Lead | 0.014 |
| Mercury | 0.005 |
| Selenium | 0.0002 |
| Silver | 0.09 |
| Aluminum | 0.005 |
| Chloramines | 0.01 |
| Free chlorine | 0.10 |
| Copper | 0.50 |
| Fluoride | 0.10 |
| Nitrate (as N) | 0.20 |
| Sulfate | 2.00 |
| Thallium | 100.00 |
| Zinc | 0.002 |

* Reprinted with permission from ANSI/AAMI RD62: 2001, Water treatment equipment for hemodialysis applications, copyright Association for the Advancement of Medical Instrumentation, Arlington, VA.

The chemical limits included in Table 1 have been recognized by federal government agencies as standards for Water for Hemodialysis. Written standard operating procedures for water testing should be established by the physician in charge or the designated facility manager. The test frequency decision should be based upon historical data analysis, the quality of the source water as reported by the municipal water treatment facility or public health agency in the area, etc. Records should be maintained to document levels and any necessary action taken.

Chemical analysis of water components listed should be performed using methods referenced in the American Public Health Association's Standard Methods for the Examination of Water and Wastewater, $19^{\text {th }}$ Edition, ${ }^{1}$ those referenced in the U.S. Environmental Protection Agency's Methods for the Determination of Metals in Environmental Samples, ${ }^{2}$ or equivalent methods as described in ANSI/AAMI RD 62:2001.

## Change to read:

## MICROBIAL CONSIDERATIONS

The Water for Hemodialysis monograph includes microbial limits of 100 cfu per mL and endotoxin limits of 2 USP Endotoxin Units per mL . Culture media should be tryptic soy agar or equivalent, and colonies should be counted after incubation at a temperature range between $30^{\circ}$ and $35^{\circ}$, for no less than 48 hours. Sampling the water should be done at the end of the water purification cascade at the point where the water enters the equipment.

[^181]- dialysis equipment. Samples should be assayed within 30 minutes of collection or immediately refrigerated and then assayed within 24 hours of collection. $\quad$ IS (USP28)
Quantification of bacterial endotoxins is performed using the Limulus Amebocyte Lysate (LAL) clotting method
$\square_{\text {or any other LAL test }}{ }_{1 S}{ }_{\text {(USP28) }}$
found in the USP general test chapter Bacterial Endotoxins Test $\langle 85\rangle$.

Because of the incubation time required to obtain definitive microbiological results, water systems should be microbiologically monitored to confirm that they continue to produce water of acceptable quality. "Alert" and "Action Levels" are therefore necessary for the monitoring and control of the system. An Alert Level constitutes a warning and does not require a corrective action. An Action Level indicates a drift from normal operating conditions and requires that corrective action be taken
-to bring the process back into the normal operating range.
Exceeding an Alert or Action Level does not imply that water quality has been compromised. 1 . (USP28)
The recommended Action Level for a total viable microbial count in the product water is 50 cfu per mL , and the recommended Alert Level for bacterial endotoxins is 0.5 USP Endotoxin Unit per mL (also see Microbial Considerations under Water for Pharmaceutical Purposes $\langle 1231\rangle$ ).

## REAGENTS, INDICATORS, AND SOLUTIONS Reagent Specifications

## BRIEFING


#### Abstract

Ammonium Hydroxide, 6 N, page 3158 of the First Supplement. It is proposed to correct the instructions to prepare this reagent.


(HDQ: M. Marques) RTS-41334-2

## Change to read:

Ammonium Hydroxide, 6 N -Use-Ammenia TS.
-Prepare by diluting 400 mL of Ammonia Water, Stronger (see Reagents section) with water to make 1000 mL . 1 (USP28)

## Briefing

Bromofluoromethane. This new reagent is used in the preparation of the Standard stock solution in the test for Bromofluoromethane content in the proposed new monograph for Fluticasone Propionate, appearing elsewhere in this number of $P F$.
(HDQ: M. Marques) RTS-40414-4

## Add the following:

-Bromofluoromethane-Use a suitable grade.■1S (USP28)

## Briefing

Calf Thymus DNA. This new reagent is used to prepare the Calf thymus DNA solution in the test for DNA content under Cryopreserved Human Fibroblast-Derived Dermal Substitute, a proposed new monograph appearing elsewhere in this issue of $P F$.

$$
\text { (HDQ: M. Marques) } \quad \text { RTS-41308-7 }
$$

## Add the following:

-Calf Thymus DNA-Use a suitable grade.
[NOTE—A suitable grade is commercially available from Worthington Biochemical Corp., www.worthingtonbiochem.com.] $]_{\text {1S (USP28) }}$

Chromotrope 2R. This new reagent is used to prepare Gomori's trichrome solution in the test for Histological characterization, Collagen staining under Cryopreserved Human Fibroblast-Derived Dermal Substitute, a proposed new monograph appearing elsewhere in this issue of $P F$.
(HDQ: M. Marques) RTS-41308-1

## Add the following:

-Collagenase-Use a suitable grade.
[NOTE-A suitable grade is commercially available as Collagenase Type 2, CLS-2, from Worthington Biochemical Corp., www.worthington-biochem.com.] $]_{1 S}$ (USP28)

## BRIEFING

Direct Red 80. This new reagent is used to prepare the Sirius red solution in the test for Total collagen content under Cryopreserved Human Fibroblast-Derived Dermal Substitute, a proposed new monograph appearing elsewhere in this issue of $P F$.
(HDQ: M. Marques) RTS-41308-4

## Add the following:

-Direct Red 80, $\mathrm{C}_{45} \mathrm{H}_{26} \mathrm{~N}_{10} \mathrm{Na}_{6} \mathrm{O}_{21} \mathrm{~S}_{6}-\mathbf{1 3 7 3 . 0 7}$ [2610-10-8]-Red powder. Soluble in water; poorly soluble in alcohol. Use a suitable grade.■1S (USP28)

## BRIEFING

Ether, Peroxide-Free, USP 27 page 2685. It is proposed to include the option of using peroxide test strips in the Peroxide test for this reagent.
(HDQ: M. Marques) RTS—37165-1

## Change to read:

Ether, Peroxide-Free (Diethyl Ether; Ether), $\left(\mathrm{C}_{2} \mathrm{H}_{5}\right)_{2} \mathrm{O}-$ 74.12-Use ACS reagent grade.

Peroxide-Transfer 8 mL of potassium iodide and starch TS to a $12-\mathrm{mL}$ ground glass-stoppered cylinder about 15 mm in diameter. Fill completely with the substance under test, mix, and allow to stand protected from light for 5 minutes. No color develops.

- Alternatively, peroxide test strips may be used.
[NOTE-Suitable peroxide test strips can be obtained from
EMD Chemicals, www.emdchemicals.com or from J. T. Ba-
ker, www.jtbaker.com.■1S (USP28)

Fast Green FCF, USP 27 page 2686. It is proposed to add descriptive information for this reagent that is used in the test for Histological characterization, Collagen staining, in the proposed new monograph for Cryopreserved Human Fibroblast-Derived Dermal Substitute, appearing elsewhere in this issue of $P F$.
(HDQ: M. Marques) RTS-41308-2

## Change to read:

Fast Green FCF, $\mathrm{C}_{37} \mathrm{H}_{34} \mathrm{~N}_{2} \mathrm{Na}_{2} \mathrm{O}_{10} \mathrm{~S}_{3}-\mathbf{8 0 8 . 8 6}$ [2353-45-9]-
■Red to brown-violet powder or crystals. Soluble in water; sparingly soluble in ethanol.■1S (USP28)
Use a suitable grade.

Briefing

2'-(4-Hydroxyphenyl)-5-(4-methyl-1-piperazinyl)-2,5'-bi1 H -benzimidazole Trihydrochloride Pentahydrate. This new reagent is used to prepare the DNA staining solution in the test for DNA content under Cryopreserved Human Fibroblast-Derived Dermal Substitute, a proposed new monograph appearing elsewhere in this issue of $P F$.
(HDQ: M. Marques) RTS-41308-8

## Add the following:

-2'-(4-Hydroxyphenyl)-5-(4-methyl-1-piperazinyl)-

## 2,5'-bi-1 $H$-benzimidazole Trihydrochloride Pentahy-

 drate-623.97 [23491-44-3]——Dark yellow to tan powder with a green cast. Use a suitable grade.■1s (USP28)Iodine, USP 27 page 2690 . It is proposed to revise the entry for this reagent to replace the atomic weight with the molecular weight value.
(HDQ: M. Marques) RTS-41173-1

## Change to read: <br> Iodine, $\Psi$ At. Wt. 126.9045

■ $\mathrm{I}_{2}-\mathbf{2 5 3 . 8 1}_{\text {■ }_{1 \mathrm{~S}} \text { (USP28) }}$
-Use ACS reagent grade.

## Briefing

Methylene Blue, USP 27 page 2696. It is proposed to revise the entry for this reagent to reflect products currently available on the market.
(HDQ: M. Marques) RTS-41173-2

## Change to read:

Methylene Blue, $\mathrm{C}_{16} \mathrm{H}_{18} \mathrm{ClN}_{3} \mathrm{~S} \cdot 3 \mathrm{H}_{2} \mathrm{O}-\mathbf{3 7 3 . 9 0}$-Dark green crystals or a crystalline powder, having a bronze-like luster. One g dissolves in about 25 mL of water and in about 65 mL of alcohol. Soluble in chloroform.

Absorptive ratio The ratio of its absorptivity (See Spectrophemetry and Light Seattering $(854)$ ) at 635 mm to that at 665 mm, measured in a dilute solution of the dye in diluted aleohol, is between 0.56 and 0.62 .

Residue on ignition (Reagent test) Ignite 1 g with 0.5 mL of sulfurie acid: the residue weighs not more than 10 mg ( $1 \%$ ).
Lessendrying $\left\langle 731\right.$ )- Dry it at $105^{\circ}$ for 18 herrs: it leses net mere than $15.0 \%$ of its weight.
-Use a suitable grade with a dye content of not less than $85 \%$. 1 (USP28)

Octoxynol 9. It is proposed to add this new reagent. [NOTENonionic wetting agent is a new reagent proposed on page 1047 of PF 30(3) [May-June 2004].]
(HDQ: M. Marques) RTS-41334-1

## Add the following:

■Octoxynol 9——See Nonionic wetting agent.■1S (USP28)

## Briefing

Rhodamine 6G. This new reagent is used in the new monograph Caprylocaproyl Polyoxylglycerides, which also appears in this $P F$.
(HDQ: M. Marques) RTS-41339-5

## Add the following:

■Rhodamine 6G, $\mathrm{C}_{28} \mathrm{H}_{31} \mathrm{ClN}_{2} \mathrm{O}_{3}-\mathbf{4 7 9 . 0 2}$ [989-38-8]—
Use a suitable grade.■1S (USP28)

## Briefing

Sodium Phosphate, Monobasic, USP 27 page 2712. It is proposed to include the synonyms for this reagent.
(HDQ: M. Marques) RTS-44341-1

## Change to read:

Sodium Phosphate, Monobasic

- (Sodium Biphosphate; Sodium Dihydrogen Phosphate; Acid Sodium Phosphate; Monosodium Orthophos-
phate), ${ }^{1 \mathrm{IS}}$ (USP28)
$\mathrm{NaH}_{2} \mathrm{PO}_{4} \cdot \mathrm{H}_{2} \mathrm{O}-\mathbf{1 3 7 . 9 9}$-Use ACS reagent grade.

1,3,7-Trichlorodibenzo-p-dioxin, $U S P 27$ page 2718. It is proposed to update the information on a possible supplier for this reagent.
(HDQ: M. Marques) RTS-41338-1

## Change to read:

1,3,7-Trichlorodibenzo-p-dioxin, $\mathrm{C}_{12} \mathrm{H}_{3} \mathrm{Cl}_{3} \mathrm{O}_{2}-\mathbf{2 8 7 . 5 3}$ [67028-17-5]-Use a suitable grade.

■ [NOTE—A suitable grade is available from Cambridge Isotope Laboratories, www.isotope.com, catalog number ED-4090, at $50 \mu \mathrm{~g}$ per mL in nonane.] $]_{\square 1 \mathrm{~S}}$ (USP28)

## Test Solutions

## BRIEFING

Test Solutions (TS), USP 27 page 2725, page 3162 of the First Supplement, and page 316 of PF 30(1) [Jan.-Feb. 2004]. For Iodine and Potassium Iodide TS, it is proposed to change the name to Iodine and Potassium Iodide TS 1, to differentiate from the new test solution, Iodine and Potassium Iodide TS 2. This new TS is used as a reagent in Identification test $C$ in the monographs for Corn Starch, Potato Starch, Tapioca Starch, and Wheat Starch, which appear elsewhere in this issue of $P F$. Other proposals include a correction in the preparation of Ammonia TS and a modification in the Potassium Pyroantimonate TS to exclude the use of sodium hydroxide because the test solution is used in the general chapter Sodium $\langle 191\rangle$.
(HDQ: M. Marques) RTS-41144-5; 41173-3; 41301-1; 41334-3

## Change to read:

Ammonia TS-It contains between $9.5 \%$ and $10.5 \%$ of $\mathrm{NH}_{3}$. Prepare by diluting 400 mb
$\square^{-350} \mathrm{~mL}_{\text {1S (USP28) }}$
of Ammonia Water, Stronger (see in the section, Reagents) with water to make 1000 mL .

## Change to read:

Hydroxylamine Hydrochloride TS-Dissolve 3.5 g of hydroxylamine hydrochloride in 95 mL of 60 percent alcohol, and add 0.5 mL of bromophenol blue solution ( 1 in 1000)
$\Delta_{(1}$ in 1000 of alcohol $)_{\Delta U S P 28}$
and 0.5 N alcoholic potassium hydroxide until a greenish tint develops in the solution. Then add 60 percent alcohol to make 100 mL .

## Change to read:

## Iodine and Potassium Iodide TS

## $\square_{115(U S P 28)}$

—Dissolve 500 mg of iodine and 1.5 g of potassium iodide in 25 mL of water.

## Add the following:

■Iodine and Potassium Iodide TS 2—Dissolve 12.7 g of iodine and 20 g of potassium iodide in water, and dilute with water to 1000.0 mL . To 10.0 mL of this solution, add 0.6 g of potassium iodide, and dilute with water to 100.0
mL . Prepare immediately before use. ${ }^{1 S}$ (USP28)

## Change to read:

Methyl Yellow TS-Dilute with aleoholacommereially available steck solution of methyl yellow in aleohel to obtain a solution hav ing a concentration of 0.10 mg per mL.

■Prepare a solution containing 0.10 mg per mL in alcohol.■2S (USP27)

ENOTE A suitable-steck solution is available commereially as "Topfer Reagent" ( $0.5 \%$ methyl yellow in aleohel), from Ander sen Laboratories, Ine., 5901 Fitzhugh Ave., P.O. Box 8429, Fort Worth, TX $76112 . \mathrm{J}$

## Change to read:

Potassium Pyroantimonate TS-Dissolve 2 g of potassium pyroantimonate in 95 mL
$\square 85 \mathrm{~mL}_{\text {■ }}$ 1S (USP28)
of hot water. Cool quickly, and add selution 2.5 of petassium hydroxide in 50 mL of water and 1 mL of sodium hy droxide-solution (8.5 in 100).
$\mathbf{\square} 10 \mathrm{~mL}$ of a solution of potassium hydroxide (3 in
20).■1S (USP28)

Allow to stand for 24 hours, filter, and dilute with water to 150 mL .
${ }^{-} 100 \mathrm{~mL}$.■1S (USP28)

## Volumetric Solutions

## BRIEFING

Volumetric Solutions, USP 27 page 2732, page 3162 of First Supplement, and page 1048 of PF 30(3) [May-June 2004]. It is proposed to include the calculations for the standardization of the volumetric solutions.
(HDQ: M. Marques) RTS-41236-1; 41236-2; 41236-3; 41236-4; 41236-5; 41236-6; 41236-7; 41236-8; 41236-9; 4123610 ; 41236-11; 41236-12; 41236-13; 41236-14; 41236-15; 41236$16 ; 41236-17 ; 41236-18 ; 41236-35 ; 41236-36$.

## Change to read:

```
Ammonium Thiocyanate, Tenth-Normal (0.1 N)
    NH4
    7.612g in 1000 mL
```

Dissolve about 8 g of ammonium thiocyanate in 1000 mL of water, and standardize the solution as follows.

Measure accurately about 30 mL of 0.1 N silver nitrate VS into a glass-stoppered flask. Dilute with 50 mL of water, then add 2 mL of nitric acid and 2 mL of ferric ammonium sulfate TS, and titrate with the ammonium thiocyanate solution to the first appearance of a red-brown color. Ealeulate the nermality.

$$
{ }^{\boldsymbol{N}}=\frac{\mathrm{mL} \mathrm{AgNO}_{3} \times \mathrm{NAgNO}_{3}}{\mathrm{~mL} \mathrm{NH}_{4} \mathrm{SCN} \text { Solution }} \square_{1 \mathrm{~S}(\text { USP28) }}
$$

If desirable, 0.1 N ammonium thiocyanate may be replaced by 0.1 N potassium thiocyanate where the former is directed in various tests and assays.

## Change to read:

> Bromine, Tenth-Normal $(\mathbf{0 . 1} \mathbf{~ N})$
> $\mathrm{Br}, 79.90$
> 7.990 g in 1000 mL

Dissolve 3 g of potassium bromate and 15 g of potassium bromide in water to make 1000 mL , and standardize the solution as follows.

Measure accurately about 25 mL of the solution into a $500-\mathrm{mL}$ iodine flask, and dilute with 120 mL of water. Add 5 mL of hydrochloric acid, insert the stopper in the flask, and shake it gently. Then add 5 mL of potassium iodide TS, again insert the stopper, shake the mixture, allow it to stand for 5 minutes, and titrate the
liberated iodine with 0.1 N sodium thiosulfate VS , adding 3 mL of starch TS as the endpoint is approached. Galeulate the normality.

■1S (USP28)
Preserve in dark amber-colored, glass-stoppered bottles.

$$
{ }^{\mathbf{N}}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{\mathrm{~mL} \mathrm{Br}} \mathrm{r}_{2} \text { Solution } \mathbf{m}_{1 \mathrm{~S}(U S P 28)}
$$

## Change to read:

Ceric Ammonium Nitrate, Twentieth-Normal ( 0.05 N ) $\mathrm{Ce}\left(\mathrm{NO}_{3}\right)_{4} \cdot 2 \mathrm{NH}_{4} \mathrm{NO}_{3}, \mathbf{5 4 8 . 2 2}$
2.741 g in 100 mL

Dissolve 2.75 g of ceric ammonium nitrate in 1 N nitric acid to obtain 100 mL of solution, and filter. Standardize the solution as follows.

Measure accurately 10 mL of freshly standardized 0.1 N ferrous ammonium sulfate VS into a flask, and dilute with water to about 100 mL . Add 1 drop of nitrophenanthroline TS, and titrate with the ceric ammonium nitrate solution to a colorless endpoint. From the volume of 0.1 N ferrous ammenium sulfate VS taken and the wh ume-of ceric ammonitm nitrate solution consumed, caleulate the formality.

$$
\boldsymbol{\mathrm { N }}=\frac{\mathrm{mL} \mathrm{Fe}\left(\mathrm{NH}_{4}\right)_{2}\left(\mathrm{SO}_{4}\right)_{2} \times \mathrm{N} \mathrm{Fe}\left(\mathrm{NH}_{4}\right)_{2}\left(\mathrm{SO}_{4}\right)_{2}}{\mathrm{mLCe}\left(\mathrm{NO}_{3}\right)_{4} \cdot 2 \mathrm{NH}_{4} \mathrm{NO}_{3}} \quad 1 \mathrm{~S}(\text { USP28) }
$$

## Change to read:

Ceric Sulfate, Tenth-Normal ( 0.1 N )
$\mathrm{Ce}\left(\mathrm{SO}_{4}\right)_{2}, 332.24$
33.22 g in 1000 mL

Transfer 59 g of ceric ammenium nitrate to a beaker, add 31 mL of sulfuric acid, mix, and eautiously add water, in 20 mL pertions, until solution is complete. Cover the beaker, allow to stand-over fight, filter through a fine peresity, sintered glass crucible, dilute with water to 1000 mL , and mix.
-Use commercially available volumetric standard solution. 1 B (USP28)
Standardize the solution as follows. fNOTE-Prepare the osmitum tetroxide solution used in this procedure in a well ventilated hood, as peiseneus rapers are given off by this compound.] Weigh at eurately 200 mg of arsenic trioxide, previously dried at $105^{\circ}$ for 4 hour, and transfer to a 500 mL conieal flack. Wash down the inner walls of the flask with 25 mL of sodium hydroxide solution ( 2 in 25), swirl to dissolve the substance, and when solution is complete, add 100 mL of water, and mix. Add 10 mL of dilute culfuric acid ( 1 in 3), then add 2 dreps each of orthophenanthroline TS and a 1 in 400 solution of osmitm tetroxide in 0.1 N sulfurie acid, and slowly titrate with the cerie sulfate solution until the pink color is changed to a very pale blue. Caleulate the normality. Each 4.946 mg of ar senic trioxide is equivalent to 1 mL of 0.1 N ceric sulfate.

- Accurately weigh about 0.2 g of sodium oxalate, primary standard, previously dried for 2 hours at $105^{\circ}$, and dissolve in 75 mL of water. Add, with stirring, 2 mL of sulfuric acid that has previously been mixed with 5 mL of water, mix well, add 10 mL of hydrochloric acid, and heat to between $70^{\circ}$ and $75^{\circ}$. Titrate with 0.1 N ceric sulfate to a permanent slight yellow color. Each 6.700 mg of sodium oxalate is equivalent to 1 mL of 0.1 N ceric sulfate.

$$
\mathrm{N}=\frac{\mathrm{mg} \mathrm{As}_{2} \mathrm{O}_{3}}{67.00 \times \mathrm{mLCe}^{\left(\mathrm{SO}_{4}\right)_{2} \text { solution }} \quad \mathbf{m S}_{\text {IS }(U S P 28)}}
$$

## Change to read:

> Cupric Nitrate, Tenth Normal $(\mathbf{0 . 1} \mathbf{~ N})$
> $\mathrm{Cu}\left(\mathrm{NO}_{3}\right)_{2} \cdot 2.5 \mathrm{H}_{2} \mathrm{O}, \mathbf{2 3 2 . 5 9}$
> 23.26 g in 1000 mL 24.16 g in 1000 mL

Dissolve 23.3 g of cupric nitrate 2.5 hydrate, or 24.2 g of the trihydrate, in water to make 1000 mL . Standardize the solution as follows.

Transfer 20.0 mL of the solution to a $250-\mathrm{mL}$ beaker. Add 2 mL of 5 M sodium nitrate, 20 mL of ammonium acetate TS, and sufficient water to make 100 mL . Titrate with 0.05 M edetate disodium VS. Determine the endpoint potentiometrically using a cupric iondouble junction reference electrode system. Perform a blank determination, and make any necessary correction. Galeulate the nor mality by the formula:

## $+M / 20.0$,

in whieh $V$ is the volume, in mL, ofedetatedisedium consumed, M is the melarity of the edetate disoditum, and 20.0 is the number of mL of eupric nitrate solution taken.
${ }^{\square} \mathrm{N}=\frac{\mathrm{mL} \text { edetate disodium (corrected for the blank) } \times \mathrm{M} \text { edetate disodium }}{20.0} \square_{\text {1S (USP28) }}$

## Change to read:

## Standard Dichlorophenol-Indophenol Solution

To 50 mg of 2,6-dichlorophenol-indophenol sodium that has been stored in a desiccator over soda lime add 50 mL of water containing 42 mg of sodium bicarbonate, shake vigorously, and when the dye is dissolved, add water to make 200 mL . Filter into an amber, glass-stoppered bottle.

[^182]Standardize the solution as follows.
Weigh accurately 50 mg of USP Ascorbic Acid RS, and transfer to a glass-stoppered, $50-\mathrm{mL}$ volumetric flask with the aid of a sufficient volume of metaphosphoric-acetic acids TS to make 50 mL . Immediately transfer 2 mL of the ascorbic acid solution to a $50-\mathrm{mL}$ conical flask containing 5 mL of the metaphosphoric-acetic acids TS, and titrate rapidly with the dichlorophenol-indophenol solution until a distinct rose-pink color persists for at least 5 seconds. Perform a blank titration by titrating 7 mL of the metaphosphoric-acetic acids TS plus a volume of water equal to the volume of the dichlorophenol solution used in titrating the ascorbic acid solution. Express the concentration of the standard solution in terms of its equivalent in mg of ascorbic acid.

## Change to read:

Edetate Disodium, Twentieth-Molar ( 0.05 M ) $\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{~N}_{2} \mathrm{Na}_{2} \mathrm{O}_{8} \cdot 2 \mathrm{H}_{2} \mathrm{O}, \mathbf{3 7 2 . 2 4}$<br>18.61 g in 1000 mL

Dissolve 18.6 g of edetate disodium in water to make 1000 mL , and standardize the solution as follows.

Accurately weigh about 200 mg of chelometric standard calcium carbonate, previously dried at $110^{\circ}$ for 2 hours and cooled in a desiccator, transfer to a $400-\mathrm{mL}$ beaker, add 10 mL of water, and swirl to form a slurry. Cover the beaker with a watch glass, and introduce 2 mL of diluted hydrochloric acid from a pipet inserted between the lip of the beaker and the edge of the watch glass. Swirl the contents of the beaker to dissolve the calcium carbonate. Wash down the sides of the beaker, the outer surface of the pipet, and the watch glass with water, and dilute with water to about 100 mL . While stirring the solution, preferably with a magnetic stirrer, add about 30 mL of the edetate disodium solution from a $50-\mathrm{mL}$ buret. Add 15 mL of sodium hydroxide TS and 300 mg of hydroxy naphthol blue, and continue the titration with the edetate disodium solution to a blue endpoint. Galeulate the molarity taken by the formma:-

> H/(100.89I),
in whieh $W$ is the weight, in mg, of $\mathrm{CaCO}_{3}$ in the pertion of ealeium earbenate taken, and $V$ is the volume, in mL, of edetate-disodium selution censumed.

$$
\mathbf{m}=\frac{\left(\mathrm{g} \mathrm{CaCO}_{3}\right)(1000)}{100.09 \times \mathrm{mL} \text { EDTA }} \quad \text { 1S (USP28) }
$$

## Change to read:

$$
\begin{gathered}
\text { Ferric Ammonium Sulfate, Tenth-Normal }(\mathbf{0 . 1} \mathbf{~ N}) \\
\mathrm{FeNH}_{4}\left(\mathrm{SO}_{4}\right)_{2} \cdot 12 \mathrm{H}_{2} \mathrm{O}, \mathbf{4 8 2 . 1 9} \\
48.22 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
\end{gathered}
$$

Dissolve 50 g of ferric ammonium sulfate in a mixture of 300 mL of water and 6 mL of sulfuric acid, dilute with water to 1000 mL , and mix. Standardize the solution as follows:

Measure accurately about 40 mL of the solution into a glassstoppered flask, add 5 mL of hydrochloric acid, mix, and add a solution of 3 g of potassium iodide in 10 mL of water. Insert the stopper, allow to stand for 10 minutes, then titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS
as the endpoint is approached. Correct for a blank run on the same quantities of the same reagents. andeulate thermality.

■1S (USP28)
Store in tight containers, protected from light.

$$
{ }^{\mathbf{m}}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{\mathrm{~mL} \mathrm{FeNH}_{4}\left(\mathrm{SO}_{4}\right)_{2}}
$$

## Change to read:

## Ferrous Ammonium Sulfate, Tenth-Normal ( 0.1 N) <br> $\mathrm{Fe}\left(\mathrm{NH}_{4}\right)_{2}\left(\mathrm{SO}_{4}\right)_{2} \cdot 6 \mathrm{H}_{2} \mathrm{O}, 392.14$ <br> 39.21 g in 1000 mL

Dissolve 40 g of ferrous ammonium sulfate in a previously cooled mixture of 40 mL of sulfuric acid and 200 mL of water, dilute with water to 1000 mL , and mix. On the day of use, standardize the solution as follows:

Measure accurately 25 to 30 mL of the solution into a flask, add 2 drops of orthophenanthroline TS, and titrate with 0.1 N ceric sulfate VS until the red color is changed to pale blue. From the volume of 0.1 N -erie sulfate consumed, caleulate the normality.

$$
\mathbf{m}^{\mathrm{N}}=\frac{\mathrm{mL} \mathrm{Ce}^{\mathrm{IV}} \times \mathrm{N} \mathrm{Ce}^{\mathrm{IV}}}{\mathrm{~mL} \mathrm{Fe}^{\mathrm{II}} \text { Solution }} \mathbf{m}_{1 \mathrm{~S}(U S P 28)}
$$

## Change to read:

> Hydrochloric Acid, Normal (1 N)
> $\mathrm{HCl}, \mathbf{3 6 . 4 6}$
> 36.46 g in 1000 mL

Dilute 85 mL of hydrochloric acid with water to 1000 mL . Standardize the solution as follows.

Accurately weigh about 5.0 g of tromethamine, previously dried at $105^{\circ}$ for 3 hours. Dissolve in 50 mL of water, and add 2 drops of bromocresol green TS. Titrate with 1 N hydrochloric acid to a pale yellow endpoint. Galeulate the normality.

■1S (USP28)
Each 121.14 mg of tromethamine is equivalent to 1 mL of 1 N hydrochloric acid.

## Add the following:

■Hydrochloric Acid, Half-Normal (0.5 N)
$\mathrm{HCl}, 36.46$
18.23 g in 1000 mL

To a $1000-\mathrm{mL}$ volumetric flask containing 40 mL of water slowly add 43 mL of hydrochloric acid. Cool, and add water to volume. Standardize the solution as follows.

Weigh accurately about 2.5 g of tromethamine, previously dried at $105^{\circ}$ for 3 hours. Proceed as directed under Hydrochloric Acid, Normal ( 1 N ), beginning with "Dissolve in 50 mL of water."

$$
\mathrm{N}=\frac{\mathrm{mg} \text { tromethamine }}{121.14 \times \mathrm{mL} \mathrm{HCl}} .1 \mathrm{~S}(U S P 28)
$$

## Change to read:

## Hydrochloric Acid, Half-Normal (0.5 N) in Methanol $\mathrm{HCl}, \mathbf{3 6 . 4 6}$ <br> 18.23 g in 1000 mL

To a $1000-\mathrm{mL}$ volumetric flask containing 40 mL of water slowly add 43 mL of hydrochloric acid. Cool, and add methanol to volume. Standardize the solution as follows.

Weigh accurately about 2.5 g of tromethamine, previously dried at $105^{\circ}$ for 3 hours. Proceed as directed under Hydrochloric Acid, Normal $(1 \mathrm{~N})$, beginning with "Dissolve in 50 mL of water."

$$
\mathbf{m}^{\mathrm{N}}=\frac{\mathrm{mg} \text { tromethamine }}{121.14 \times \mathrm{mLHCl}} ■_{1 \mathrm{~S}(\text { USP28) }}
$$

## Add the following:

${ }^{\mathbf{4}}$ Hydrochloric Acid, Alcoholic, Tenth-Molar (0.1 M)

$$
\mathrm{HCl}, 36.46
$$

Dilute 9.0 mL of hydrochloric acid to 1000 mL with aldehyde free alcohol. $\mathbf{\Delta}$ (USP28)

## Change to read:

> Iodine, Tenth-Normal $(\mathbf{0 . 1 ~ N})$ I, $\mathbf{1 2 6 . 9 0}$
> 12.69 g in 1000 mL

[^183]Transfer 25.0 mL of the iodine solution to a $250-\mathrm{mL}$ flask, dilute with water to 100 mL , add 1 mL of 1 N hydrochloric acid, swirl gently to mix, and titrate with 0.1 N sodium thiosulfate VS until the solution has a pale yellow color. Add 2 mL of starch TS and continue titrating until the solution is colorless. Caleula the nor mality.
$\square_{\text {■1S (USP28) }}$
Preserve in amber-colored, glass-stoppered bottles.

$$
\mathbf{m}^{\mathrm{N}}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{25} \square_{1 \mathrm{~S}(\text { USP28) }}
$$

## Change to read:

${ }^{\square}$ Iodine, Hundredth-Normal ( 0.01 N )
I, 126.90
1.269 g in 1000 mL

Dissolve about 1.4 g of iodine in a solution of 3.6 g of potassium iodide in 100 mL of water, add 3 drops of hydrochloric acid, dilute with water to 1000 mL , and standardize the solution as follows.

Transfer 100.0 mL of iodine solution to a $250-\mathrm{mL}$ flask, add 1 mL of 1 N hydrochloric acid, swirl gently to mix, and titrate with 0.1 N sodium thiosulfate VS until the solution has a pale yellow color. Add 2 mL of starch TS, and continue titrating until the solution is colorless. Galeulate the normality.

■1S (USP28)
Preserve in amber-colored, glass-stoppered bottles.■1S (USP27)

$$
\mathrm{N}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{25} \boldsymbol{\square}_{1 \mathrm{~S}(\text { USP28) }}
$$

## Add the following:

-Lead Perchlorate, Tenth-Molar ( 0.1 M )

$$
\begin{gathered}
\mathrm{Pb}\left(\mathrm{ClO}_{4}\right)_{2} \cdot 3 \mathrm{H}_{2} \mathrm{O}, 460.15 \\
46.01 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
\end{gathered}
$$

Dissolve 46 g of lead perchlorate in water, and dilute with water to 1000.0 mL . Accurately weigh about 150 mg of sodium sulfate, previously dried at $105^{\circ}$ for 4 hours, and dissolve in 50 mL of water. Add 50 mL of a mixture of water and formaldehyde ( $1: 1$ ), and stir for about 1 minute. Determine the endpoint potentiometrically using a lead ion selec-
tive electrode. Perform a blank determination, and make any necessary corrections. Each 14.204 mg of sodium sulfate is equivalent to 1 mL of 0.1 M lead perchlorate.

$$
\mathrm{M}=\frac{\mathrm{mg} \text { sodium sulfate }}{142.04 \times \mathrm{mL} \text { lead perchlorate }} \quad \square 1 \mathrm{~S}(\text { USP28) }
$$

## Change to read:

## Lead Perchlorate, Hundredth Molar (0.01 M)

 $\mathrm{Pb}\left(\mathrm{ClO}_{4}\right)_{2} 406.10$Accurately pipet 100 mL of commercially available 0.1 M lead perchlorate solution into a $1000-\mathrm{mL}$ volumetric flask, add a sufficient quantity of water to make 1000 mL , and standardize the solution as follows:

Accurately pipet 50 mL of 0.01 M lead perchlorate solution, as prepared above, into a $250-\mathrm{mL}$ conical flask. Add 3 mL of aqueous hexamethylenetetramine solution ( 2.0 g per 100 mL ) and 4 drops of $0.5 \%$ xylenol orange indicator prepared by adding 500 mg of xylenol orange to 10 mL of alcohol and diluting with water to 100 mL . (Omit the alcohol if the sodium salt of the indicator is used). Titrate with 0.05 M edetate disodium VS to a yellow endpoint. Galeulate the molarity.

$$
\mathbf{M}=\frac{\mathrm{mL} \text { edetate disodium } \times \mathrm{M} \text { edetate disodium }}{50.0} \mathbf{\square 1 S}_{\text {(USP28) }}
$$

## Change to read:

Lithium Methoxide, Fiftieth-Normal (0.02 $\mathbf{~})$ in Methanol
$\mathrm{CH}_{3} \mathrm{LiO}, \mathbf{3 7 . 9 7}$
759.6 mg in 1000 mL
Dissolve 0.12 g of freshly cut lithium metal in 150 mL of methanol, cooling the flask during addition of the metal. When the reaction is complete, add 850 mL of methanol, and mix. Store the solution preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution by titration against benzoic acid as described under Sodium Methoxide, Tenth-Normal( 0.1 N ) (in Toluene), but use only 100 mg of benzoic acid. Each 2.442 mg of benzoic acid is equivalent to 1 mL of 0.02 N lithium methoxide.

NOTE-Restandardize the solution frequently.

## Change to read:

Lithium Methoxide, Tenth-Normal (0.1 N) in Benzene

> Toluene $_{\mathbf{1 s}}$ (USP28)
> $\mathrm{CH}_{3} \mathrm{OLi}, \mathbf{3 7 . 9 7}$
> 3.798 g in 1000 mL

Dissolve 0.6 g

- 500 mg ■1S (USPP28)
of freshly cut lithium metal in 150 mL of methanol, cooling the flask during addition of the metal. When reaction is complete, add 850 mL of benzene


## $\square_{\text {toluene. }}$ IS (USP28)

If cloudiness or precipitation occurs, add sufficient methanol to clarify the solution. Store preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution by titration against benzoic acid as described under Sodium Methoxide, Tenth-Normal ( 0.1 N ) (in Toluene).

NOTE-Restandardize the solution frequently.


## Change to read:

Lithium Methoxide, Tenth-Normal ( 0.1 N ) in Chlorobenzene $\mathrm{CH}_{3} \mathrm{OLi}, 37.97$
3.798 g in 1000 mL

Dissolve 0.7 f

- 500 mg ■1S (USP28)
of freshly cut lithium metal in 150 mL of methanol, cooling the flask during addition of the metal. When reaction is complete, add 850 mL of chlorobenzene. If cloudiness or precipitation occurs, add sufficient methanol to clarify the solution. Store preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution by titration against benzoic acid as described under Sodium Methoxide, Tenth-Normal ( 0.1 N ) (in Toluene).

NOTE-Restandardize the solution frequently.

$$
\mathrm{N}=\frac{\mathrm{mg} \text { benzoic acid }}{122.1 \times \mathrm{mL} \text { lithium methoxide (corrected for the blank) }} \mathbf{\square}_{1 \mathrm{~S} \text { (USP28) }}
$$

## Change to read:

Mercuric Nitrate, Tenth-Molar (0.1 M)<br>$\mathrm{Hg}\left(\mathrm{NO}_{3}\right)_{2}$,<br>32.46 g in 1000 mL

Dissolve about 35 g of mercuric nitrate in a mixture of 5 mL of nitric acid and 500 mL of water, and dilute with water to 1000 mL . Standardize the solution as follows.

Transfer an accurately measured volume of about 20 mL of the solution to a conical flask, and add 2 mL of nitric acid and 2 mL of ferric ammonium sulfate TS. Cool to below $20^{\circ}$, and titrate with 0.1 N ammonium thiocyanate VS to the first appearance of a permanent brownish color. Ealeulate the molarity.

$$
\mathbf{■}^{\mathbf{M}}=\frac{\mathrm{mL} \mathrm{NH}_{4} \mathrm{SCN} \times \mathrm{N} \mathrm{NH}_{4} \mathrm{SCN}}{\mathrm{~mL} \mathrm{Hg}\left(\mathrm{NO}_{3}\right)_{2}} \quad \mathbf{\square}_{1 \mathrm{~S}(\text { USP28) }}
$$

## Delete the following:

## -Morpholine, Half Normal(0.5 N $)$ in Methanol <br> $\mathrm{G}_{4} \mathrm{H}_{9} \mathrm{NO}, 87.12$ <br> 43.56 g in 1000 mL

Transfer 44 mL of recently distilled merpholine to a-1 liter reagent bottle, and add methanol to make abeut 1 liter. Protect frem absorption of earben dioxide during withdrawal of aliquets. It is not neeessary to standardize this solution.■1S (USP28)

## Change to read:

> Oxalic Acid, Tenth-Normal $(\mathbf{0 . 1 ~ N})$ $\mathrm{H}_{2} \mathrm{C}_{2} \mathrm{O}_{4} \cdot 2 \mathrm{H}_{2} \mathrm{O}, \mathbf{1 2 6 . 0 7}$ 6.303 g in 1000 mL

Dissolve 6.45 g of oxalic acid in water to make 1000 mL . Standardize by titration against freshly standardized 0.1 N potassium permanganate VS as directed under Potassium Permanganate, Tenth-Normal ( 0.1 N ).

Preserve in glass-stoppered bottles, protected from light.

## Change to read:

Perchloric Acid, Tenth-Normal (0.1 N) (in Glacial Acetic Acid)

$$
\mathrm{HClO}_{4}, \mathbf{1 0 0 . 4 6}
$$

$$
10.05 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
$$

Note-Where called for in the tests and assays, this volumetric solution is specified as " 0.1 N perchloric acid." Thus, where 0.1 N or other strength of this volumetric solution is specified, the solu-
tion in glacial acetic acid is to be used, unless the words "in dioxane" are stated. [See also Perchloric Acid, Tenth-Normal ( 0.1 N ) in Dioxane.]
Mix 8.5 mL of perchloric acid with 500 mL of glacial acetic acid and 21 mL of acetic anhydride, cool, and add glacial acetic acid to make 1000 mL . Alternatively, the solution may be prepared as follows. Mix 11 mL of 60 percent perchloric acid with 500 mL of glacial acetic acid and 30 mL of acetic anhydride, cool, and add glacial acetic acid to make 1000 mL .
Allow the prepared solution to stand for 1 day for the excess acetic anhydride to be combined, and determine the water content by Method I (see Water Determination $\langle 921\rangle$ ), except to use a test specimen of about 5 g of the 0.1 N perchloric acid that is expected to contain approximately 1 mg of water and the Reagent (see Reagent under Method Ia in Water Determination $\langle 921\rangle$ ) diluted such that 1 mL is equivalent to about 1 to 2 mg of water. If the water content exceeds $0.5 \%$, add more acetic anhydride. If the solution contains no titratable water, add sufficient water to obtain a content of between $0.02 \%$ and $0.5 \%$ of water. Allow the solution to stand for 1 day, and again titrate the water content. The solution so obtained contains between $0.02 \%$ and $0.5 \%$ of water, indicating freedom from acetic anhydride.

Standardize the solution as follows.
Weigh accurately about 700 mg of potassium biphthalate, previously crushed lightly and dried at $120^{\circ}$ for 2 hours, and dissolve it in 50 mL of glacial acetic acid in a $250-\mathrm{mL}$ flask. Add 2 drops of crystal violet TS, and titrate with the perchloric acid solution until the violet color changes to blue-green. Deduct the volume of the perchloric acid consumed by 50 mL of the glacial acetic acid. and ealeulate the normality.

■■1S (USP28)
Each 20.42 mg of potassium biphthalate is equivalent to 1 mL of 0.1 N perchloric acid.

$$
{ }^{■} \mathrm{~N}=\frac{\mathrm{g} \mathrm{KHC}_{8} \mathrm{H}_{4} \mathrm{O}_{4}}{0.20423 \times \mathrm{mL} \mathrm{HClO}_{4} \text { solution (corrected for the blank) }} \quad \begin{array}{|}
\text { 1S (USP28) }
\end{array}
$$

## Change to read:

## Perchloric Acid, Tenth-Normal (0.1 N) in Dioxane

Mix 8.5 mL of perchloric acid with sufficient dioxane to make 1000 mL . Standardize the solution as follows.

Weigh accurately about 700 mg of potassium biphthalate, previously crushed lightly and dried at $120^{\circ}$ for 2 hours, and dissolve in 50 mL of glacial acetic acid in a $250-\mathrm{mL}$ flask. Add 2 drops of crystal violet TS, and titrate with the perchloric acid solution until the violet color changes to bluish green. Beduet the volume of the perehloric acid consumed by 50 mL of the glacial acetic acid, and ealeulate the nermality.
■Carry out a blank determination.■1S (USP28)
Each 20.42 mg of potassium biphthalate is equivalent to 1 mL of 0.1 N perchloric acid.

$$
\mathrm{N}=\frac{\mathrm{g} \mathrm{KHC}_{8} \mathrm{H}_{4} \mathrm{O}_{4}}{0.20423 \times \mathrm{mL} \mathrm{HClO}_{4} \text { solution (corrected for the blank) }} \mathbf{\square}_{1 \mathrm{~S}(U S P 28)}
$$

## Change to read:

## Potassium Bromate, Tenth-Normal ( 0.1 N ) <br> $$
2.784 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
$$

Dissolve 2.784 g of potassium bromate in water to make 1000 mL , and standardize the solution as follows.

Transfer an accurately measured volume of about 40 mL of the solution to a glass-stoppered flask, add 3 g of potassium iodide, and follow with 3 mL of hydrochloric acid. Allow to stand for $5 \mathrm{~min}-$ utes, then titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Correct for a blank run on the same quantities of the same reagents, and calculate the normality.


## Change to read:

## Potassium Bromide-Bromate, Tenth-Normal (0.1 N)

Dissolve 2.78 g of potassium bromate $\left(\mathrm{KBrO}_{3}\right)$ and 12.0 g of potassium bromide ( KBr ) in water, and dilute with water to 1000 mL . Standardize by the procedure set forth for Potassium Bromate, Tenth-Normal (0.1 $N$ ).

$$
\mathrm{N}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{\mathrm{~mL} \mathrm{KBrO}} \mathrm{KBr}_{3} / \mathrm{KBr} \quad ■ 1 \mathrm{~S}(U S P 28)
$$

## Change to read:

> Potassium Dichromate, Tenth-Normal $(\mathbf{0 . 1} \mathbf{~ N})$
> $\mathrm{K}_{2} \mathrm{Cr}_{2} \mathrm{O}_{7}, \mathbf{2 9 4 . 1 8}$
> 4.903 g in 1000 mL

Dissolve about 5 g of potassium dichromate in 1000 mL of water. Standardize the solution as follows.

Transfer 25.0 mL of this solution to a glass-stoppered, $500-\mathrm{mL}$ flask, add 2 g of potassium iodide (free from iodate), dilute with 200 mL of water, add 5 mL of hydrochloric acid, allow to stand for 10 minutes in a dark place, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Correct for a blank rum on the same quantities of the same reagents, and caleutate the nomality.

- Carry out a blank determination.

$$
\mathrm{N}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{25.0} \llbracket 1 \mathrm{~S}(U S P 28)
$$

## Change to read:

## Potassium Ferricyanide, Twentieth-Molar (0.05 M)

$$
\mathrm{K}_{3} \mathrm{Fe}(\mathrm{CN})_{6}, \mathbf{3 2 9 . 2 4}
$$

16.46 g in 1000 mL

Dissolve about 17 g of potassium ferricyanide in water to make 1000 mL . Standardize the solution as follows.

Transfer 50.0 mL of this solution to a glass-stoppered, $500-\mathrm{mL}$ flask, dilute with 50 mL of water, add 10 mL of potassium iodide TS and 10 mL of dilute hydrochloric acid, and allow to stand for 1 minute. Then add 15 mL of zinc sulfate solution ( 1 in 10 ), and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Caleulate the motarity.

■.1S (USP28)
Protect from light, and restandardize before use.

$$
\mathbf{m}^{\mathrm{M}}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{50.0} \square_{1 \mathrm{~S}(U S P 28)}
$$

## Change to read:

Potassium Hydroxide, Normal (1 N)
$\mathrm{KOH}, \mathbf{5 6 . 1 1}$
56.11 g in 1000 mL

Dissolve 68 g of potassium hydroxide in about 950 mL of water. Add a freshly prepared saturated solution of barium hydroxide until no more precipitate forms. Shake the mixture thoroughly, and allow it to stand overnight in a stoppered bottle. Decant the clear liquid, or filter the solution in a tight, polyolefin bottle, and standardize by the procedure set forth for Sodium Hydroxide, Normal ( 1 N ).

$$
\boldsymbol{N}=\frac{\mathrm{g} \mathrm{KHC}_{8} \mathrm{H}_{4} \mathrm{O}_{4}}{0.20423 \times \mathrm{mL} \mathrm{NaOH}} \quad \mathbf{\square}_{1 \mathrm{~S}(U S P 28)}
$$

## Change to read:

Potassium Hydroxide, Alcoholic, Half-Normal ( 0.5 N)

$$
28.06 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
$$

Dissolve about 34 g of potassium hydroxide in 20 mL of water, and add aldehyde-free alcohol to make 1000 mL . Allow the solution to stand in a tightly stoppered bottle for 24 hours. Then quickly decant the clear supernatant liquid into a suitable, tight container, and standardize the solution as follows.

Measure accurately about 25 mL of 0.5 N hydrochloric acid VS. Dilute with 50 mL of water, add 2 drops of phenolphthalein TS, and titrate with the alcoholic potassium hydroxide solution until a permanent, pale pink color is produced. Galeulate the normality.

## ■1S (USP28)

NOTE-Store in tightly stoppered bottles, protected from light.

$$
{ }^{\boldsymbol{m}}=\frac{\mathrm{mL} \mathrm{HCl} \times \mathrm{N} \mathrm{HCl}}{\mathrm{~mL} \mathrm{KOH}} \mathrm{~m}_{\mathrm{SS}(U S P 28)}
$$

## Add the following:

${ }^{\text {T}}$ Potassium Hydroxide, Alcoholic, Tenth-Molar (0.1 M)

$$
\mathrm{KOH}, \mathbf{5 6 . 1 1}
$$

Dilute 20 mL of 0.5 M alcoholic potassium hydroxide to 100.0 mL with aldehyde-free alcohol. $\mathbf{\Delta U S P 2 8}$

## Change to read:

Potassium Hydroxide, Methanolic, Tenth-Normal (0.1 N) 5.612 g in 1000 mL

Dissolve about 6.8 g of potassium hydroxide in 4 mL of water, and add methanol to make 1000 mL . Allow the solution to stand in a tightly stoppered bottle for 24 hours. Then quickly decant the clear supernatant liquid into a suitable, tight container, and standardize the solution as follows.

Measure accurately about 25 mL of 0.1 N hydrochloric acid VS. Dilute with 50 mL of water, add 2 drops of phenolphthalein TS, and titrate with the methanolic potassium hydroxide solution until a permanent, pale pink color is produced. Galeulate the normality.

## ■1S (USP28)

NOTE-Store in tightly stoppered bottles, protected from light.

Weigh accurately about 200 mg of sodium oxalate, previously dried at $110^{\circ}$ to constant weight, and dissolve it in 250 mL of water. Add 7 mL of sulfuric acid, heat to about $70^{\circ}$, and then slowly add the permanganate solution from a buret, with constant stirring, until a pale pink color, which persists for 15 seconds, is produced. The temperature at the conclusion of the titration should be not less than $60^{\circ}$. Calculate the normality. Each 67.00 mg

## $\mathbf{■}_{6.700 \mathrm{mg}}$ ■1S (USP28)

of sodium oxalate is equivalent to 1 mL of 0.1 N potassium permanganate.

Since potassium permanganate is reduced on contact with organic substances such as rubber, the solution must be handled in apparatus entirely of glass or other suitably inert material. It should be frequently restandardized. Store in glass-stoppered, amber-colored bottles.

$$
\mathrm{N}=\frac{\mathrm{g} \mathrm{Na}_{2} \mathrm{C}_{2} \mathrm{O}_{4}}{\mathrm{~mL} \mathrm{KMnO}_{4} \text { solution } \times 0.06700} \boldsymbol{\square} 1 \mathrm{~S}(\text { USP28) }
$$

## Change to read:

$$
\begin{gathered}
\text { Silver Nitrate, Tenth-Normal }(\mathbf{0 . 1} \mathbf{~ N}) \\
\mathrm{AgNO}_{3}, \mathbf{1 6 9 . 8 7} \\
16.99 \mathrm{~g}^{\text {in }} 1000 \mathrm{~mL}
\end{gathered}
$$

Dissolve about 17.5 g of silver nitrate in 1000 mL of water, and standardize the solution as follows.

Transfer about 100 mg , accurately weighed, of reagent-grade sodium chloride, previously dried at $110^{\circ}$ for 2 hours, to a $150-\mathrm{mL}$ beaker, dissolve in 5 mL of water, and add 5 mL of acetic acid, 50 mL of methanol, and about 0.5 mL of eosin Y TS. Stir, preferably with a magnetic stirrer, and titrate with the silver nitrate solution. Galeulate the normality.

$$
\mathrm{N}=\frac{\mathrm{mg} \mathrm{NaCl}}{\mathrm{~mL} \mathrm{AgNO}_{3} \times 58.44} \square_{1 \mathrm{~S}(U S P 28)}
$$

## Change to read:

$$
\begin{gathered}
\text { Sodium Hydroxide, Normal (1 N) } \\
\mathrm{NaOH}, \mathbf{4 0 . 0 0} \\
40.00 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
\end{gathered}
$$

Dissolve 162 g of sodium hydroxide in 150 mL of carbon diox-ide-free water, cool the solution to room temperature, and filter through hardened filter paper. Transfer 54.5 mL of the clear filtrate to a tight, polyolefin container, and dilute with carbon dioxide-free water to 1000 mL .

Weigh accurately about 5 g of potassium biphthalate, previously crushed lightly and dried at $120^{\circ}$ for 2 hours, and dissolve in 75 mL of carbon dioxide-free water. Add 2 drops of phenolphthalein TS,
and titrate with the sodium hydroxide solution to the production of a permanent pink color. Each 204.2 mg of potassium biphthalate is equivalent to 1 mL of 1 N sodium hydroxide.

$$
{ }^{\square}=\frac{g \mathrm{KHC}_{8} \mathrm{H}_{4} \mathrm{O}_{4}}{0.20423 \times \mathrm{mL} \mathrm{NaOH} \text { solution }} \quad \begin{array}{|}
\mathrm{IS}(\text { USP28) }
\end{array}
$$

NOTES-(1) Solutions of alkali hydroxides absorb carbon dioxide when exposed to air. They should be preserved in bottles having well-fitted, suitable stoppers, provided with a tube filled with a mixture of sodium hydroxide and lime (soda-lime tubes) so that air entering the container must pass through this tube, which will absorb the carbon dioxide. (2) Prepare solutions of lower concentration (e.g., $0.1 \mathrm{~N}, 0.01 \mathrm{~N}$ ) by quantitatively diluting accurately measured volumes of the 1 N solution with sufficient carbon diox-ide-free water to yield the desired concentration.

Restandardize the solution frequently.

## Change to read:

## Sodium Hydroxide, Alcoholic, Tenth-Normal (0.1 N) $\mathrm{NaOH}, 40.00$

To 250 mL of alcohol add 2 mL of a $50 \%$ (w/w) solution of sodium hydroxide.

Dissolve about 200 mg of benzoic acid, accurately weighed, in 10 mL of alcohol and 2 mL of water. Add 2 drops of phenolphthalein TS, and titrate with the alcoholic sodium hydroxide solution until a permanent pale pink color is produced. Gateulate the normality as follows:

## H/ 122.12 K ,

in which $W$ is the weight, in mg, of benzoic acid taken, $V$ is the volume, in mL, of aleoholic sodium hydroxide-consumed, and 122.12 is the molecular weight of benzoic acid.

$$
\square \mathrm{N}=\frac{\mathrm{mg} \text { benzoic acid }}{122.1 \times \mathrm{mL} \text { sodium hydroxide }} \square_{1 \mathrm{~S}}(\text { USP28) }
$$

## Change to read:

Sodium Methoxide, Tenth-Normal (0.1 N) (in Toluene) $\mathrm{CH}_{3} \mathrm{ONa}, \mathbf{5 4 . 0 2}$<br>5.402 g in 1000 mL

Cool in ice-water 150 mL of methanol contained in a $1000-\mathrm{mL}$ volumetric flask, and add, in small portions, about 2.5 g of freshly cut sodium metal. When the metal has dissolved, add toluene to make 1000 mL , and mix. Store preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution as follows.

Weigh accurately about 400 mg of primary standard benzoic acid, and dissolve in 80 mL of dimethylformamide in a flask. Add 3 drops of a 1 in 100 solution of thymol blue in dimethylformamide, and titrate with the sodium methoxide to a blue endpoint. Correct for the volume of the sodium methoxide solution consumed by 80 mL of the dimethylformamide. and caleulate the nor mality.
$\square 1$ (USP28)
Each 12.21 mg of benzoic acid is equivalent to 1 mL of 0.1 N sodium methoxide.

$$
\mathrm{N}=\frac{\mathrm{mg} \text { benzoic acid }}{122.1 \times \mathrm{mL} \text { sodium methoxide (corrected for the blank) }} \mathbf{■}_{1 \mathrm{~S}(\text { USP28) }}
$$

NOTES-(1) To eliminate any turbidity that may form following dilution with toluene, add methanol ( 25 to 30 mL usually suffices) until the solution is clear. (2) Restandardize the solution frequently.

## Change to read:

Sodium Methoxide, Half-Normal ( 0.5 N) in Methanol $\mathrm{CH}_{3} \mathrm{ONa}, 54.02$<br>27.01 g in 1000 mL

Weigh 11.5 g of freshly cut sodium metal, and cut into small cubes. Place about 0.5 mL of anhydrous methanol in a round-bottom, $250-\mathrm{mL}$ flask equipped with a ground-glass joint, add 1 cube of the sodium metal, and, when the reaction has ceased, add the remaining sodium metal to the flask. Connect a water-jacketed condenser to the flask, and slowly add 250 mL of anhydrous methanol, in small portions, through the top of the condenser. Regulate the addition of the methanol so that the vapors are condensed and do not escape through the top of the condenser. After addition of the methanol is complete, connect a drying tube to the top of the condenser, and allow the solution to cool. Transfer the solution to a 1liter volumetric flask, dilute with anhydrous methanol to volume, and mix. Standardize the solution as follows.

Measure accurately about 20 mL of freshly standardized 1 N hydrochloric acid VS into a $250-\mathrm{mL}$ conical flask, add 0.25 mL of phenolphthalein TS, and titrate with the sodium methoxide solution to the first appearance of a permanent pink color. Ealeulate the normality.

## Change to read:

Sodium Nitrite, Tenth-Molar ( 0.1 M )<br>$\mathrm{NaNO}_{2}, \mathbf{6 9 . 0 0}$<br>6.900 g in 1000 mL

Dissolve 7.5 g of sodium nitrite in water to make 1000 mL , and standardize the solution as follows.

Weigh accurately about 500 mg of USP Sulfanilamide RS, previously dried at $105^{\circ}$ for 3 hours, and transfer to a suitable beaker. Add 20 mL of hydrochloric acid and 50 mL of water, stir until dissolved, and cool to $15^{\circ}$. Maintaining the temperature at about $15^{\circ}$, titrate slowly with the sodium nitrite solution, placing the buret tip below the surface of the solution to preclude air oxidation of the sodium nitrite, and stir the solution gently with a magnetic stirrer, but avoid pulling a vortex of air beneath the surface. Use the indicator specified in the individual monograph, or, if a potentiometric procedure is specified, determine the endpoint electrometrically, using platinum-calomel or platinum-platinum electrodes. When
the titration is within 1 mL of the endpoint, add the titrant in 0.1mL portions, and allow 1 minute between additions. Galeulate the molarity.

■1S (USP28)
Each 17.22 mg of sulfanilamide is equivalent to 1 mL of 1000 M
$\mathbf{m}_{0.1000} \mathrm{M}_{\mathbf{■}^{1 S}}$ (USP28) sodium nitrite.

$$
\mathbf{m}_{\mathbf{M}}=\frac{\mathrm{mg} \text { of sulfanilamide }}{172.22 \times \mathrm{mL} \mathrm{NaNO}_{2}} \mathbf{■}_{1 \mathrm{~S} \text { (USP28) }}
$$

## Change to read:

Sodium Tetraphenylboron, Fiftieth-Molar (0.02 M)
$\mathrm{NaB}\left(\mathrm{C}_{6} \mathrm{H}_{5}\right)_{4}, \mathbf{3 4 2 . 2 2}$
6.845 g in 1000 mL

Dissolve an amount of sodium tetraphenylboron, equivalent to 6.845 g of $\mathrm{NaB}\left(\mathrm{C}_{6} \mathrm{H}_{5}\right)_{4}$, in water to make 1000 mL , and standardize the solution as follows.

Pipet two $75-\mathrm{mL}$ portions of the solution into separate beakers, and to each add 1 mL of acetic acid and 25 mL of water. To each beaker add, slowly and with constant stirring, 25 mL of potassium biphthalate solution (1 in 20), and allow to stand for 2 hours. Filter one of the mixtures through a filtering crucible, and wash the precipitate with cold water. Transfer the precipitate to a container, add 50 mL of water, shake intermittently for 30 minutes, filter, and use the filtrate as the saturated potassium tetraphenylborate solution in the following standardization procedure. Filter the second mixture through a tared filtering crucible, and wash the precipitate with three $5-\mathrm{mL}$ portions of saturated potassium tetraphenylborate solution. Dry the precipitate at $105^{\circ}$ for 1 hour. Each g of potassium tetraphenylborate is equivalent to 955.1 mg of sodium tetraphenylboron. From the weight of sodimm tetraphenylboron obtained, cal eutate the molarity of the seditm tetraphenylberen solution.

■.1S(USP28)
NOTE-Prepare this solution fresh
■ just before use.■1S (USP28)

## Change to read:

> Sodium Thiosulfate, Tenth-Normal $(\mathbf{0 . 1} \mathbf{N})$
> $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \cdot 5 \mathrm{H}_{2} \mathrm{O}, \mathbf{2 4 8 . 1 9}$
> 24.82 g in 1000 mL

Dissolve about 26 g of sodium thiosulfate and 200 mg of sodium carbonate in 1000 mL of recently boiled and cooled water. Standardize the solution as follows.

Accurately weigh about 210 mg of primary standard potassium dichromate, previously pulverized and dried at $120^{\circ}$ for 4 hours, and dissolve in 100 mL of water in a glass-stoppered, $500-\mathrm{mL}$ flask. Swirl to dissolve the solid, remove the stopper, and quickly add 3 g of potassium iodide, 2 g of sodium bicarbonate, and 5 mL of hydrochloric acid. Insert the stopper gently in the flask, swirl to mix, and allow to stand in the dark for exactly 10 minutes. Rinse the stopper and the inner walls of the flask with water, and titrate the liberated iodine with the sodium thiosulfate solution until the
solution is yellowish green in color. Add 3 mL of starch TS, and continue the titration until the blue color is discharged. Perform a blank determination. Galeulate the nermality.

## -1S (USP28)

Restandardize the solution as frequently as supported by laboratory stability data. In the absence of such data, restandardize the solution weekly.

$$
\mathrm{N}=\frac{\mathrm{mg} \mathrm{~K}_{2} \mathrm{Cr}_{2} \mathrm{O}_{7}}{49.04 \times \mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}} \quad \begin{array}{|c}
\mathrm{S}(\text { USP28) }
\end{array}
$$

## Change to read:

Sulfuric Acid, Half-Normal ( 0.5 N ) in Alcohol<br>$\mathrm{H}_{2} \mathrm{SO}_{4}, 98.08$<br>24.52 g in 1000 mL

Add slowly, with stirring, 13.9 mL of sulfuric acid to a sufficient quantity of dehydrated alcohol to make 1000 mL . Cool, and standardize against tromethamine as described under Hydrochloric Acid, Half-Normal ( 0.5 N ) in Methanol.


## Change to read:

Tetrabutylammonium Hydroxide, Tenth-Normal (0.1 N)
$\left(\mathrm{C}_{4} \mathrm{H}_{9}\right)_{4} \mathrm{NOH}, 259.47$
25.95 g in 1000 mL

Dissolve 40 g of tetra- $n$-butylammonium iodide in 90 mL of anhydrous methanol in a glass-stoppered flask. Place in an ice bath, add 20 g of powdered silver oxide, insert the stopper in the flask, and agitate vigorously for 60 minutes. Centrifuge a few mL, and test the supernatant liquid for iodide (see Iodide $\langle 191\rangle$ ). If the test is positive, add an additional 2 g of silver oxide, and continue to allow to stand for 30 minutes with intermittent agitation. When all of the iodide has reacted, filter through a fine-porosity, sintered-glass funnel. Rinse the flask and the funnel with three $50-\mathrm{mL}$ portions of anhydrous toluene, adding the rinsings to the filtrate. Dilute with a mixture of three volumes of anhydrous toluene and 1 volume of anhydrous methanol to 1000 mL , and flush the solution for $10 \mathrm{~min}-$ utes with dry, carbon dioxide-free nitrogen. [NOTE-If necessary to obtain a clear solution, further small quantities of anhydrous methanol may be added.] Store in a reservoir protected from carbon dioxide and moisture, and discard after 60 days. Alternatively, the solution may be prepared by diluting a suitable volume of commercially available tetrabutylammonium hydroxide solution in methanol with a mixture of 4 volumes of anhydrous toluene and 1 volume of anhydrous methanol. [NOTE-If necessary to obtain a clear solution, further small quantities of methanol may be added.]

Standardize the solution on the day of use as follows. Dissolve about 400 mg of primary standard benzoic acid, accurately weighed, in 80 mL of dimethylformamide, add 3 drops of a 1 in

100 solution of thymol blue in dimethylformamide, and titrate to a blue endpoint with the tetrabutylammonium hydroxide solution, delivering the titrant from a buret equipped with a carbon dioxide absorption trap. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N tetrabutylammonium hydroxide is equivalent to 12.21 mg of benzoic acid.

$$
\mathrm{m}_{\mathrm{N}}=\frac{\text { mg benzoic acid }}{122.1 \times \mathrm{mL}\left(\mathrm{C}_{4} \mathrm{H}_{9}\right)_{4} \mathrm{NOH}} \quad \text { 1S (USP28) } \mathbf{\Delta U S P 2 7}
$$

## Change to read:

## ${ }^{\text {A }}$ Tetrabutylammonium Hydroxide in Methanol/Isopropyl Alcohol, 0.1 N

Prepare as described for Tetrabutylammonium Hydroxide, Tenth-Normal ( 0.1 N ) using isopropyl alcohol instead of toluene, and standardize as described. Alternatively, the solution may be prepared by diluting a suitable volume of commercially available tetrabutylammonium hydroxide solution in methanol with 4 volumes of anhydrous isopropyl alcohol.

$$
\mathbf{m}^{\mathbf{N}}=\frac{\mathrm{mg} \text { benzoic acid }}{122.1 \times \mathrm{mL}\left(\mathrm{C}_{4} \mathrm{H}_{9}\right)_{4} \mathrm{NOH}} \quad \begin{aligned}
& \mathrm{S}(\text { USP28) } \mathbf{\Delta U S P 2 7}
\end{aligned}
$$

## Change to read:

Tetramethylammonium Bromide, Tenth-Molar (0.1 M)

$$
\left(\mathrm{CH}_{3}\right)_{4} \mathrm{NBr}, \mathbf{1 5 4 . 0 5}
$$

15.41 g in 1000 mL

Dissolve 15.41 g of tetramethylammonium bromide in water to make 1000 mL , and standardize the solution as follows.

Transfer an accurately measured volume of about 40 mL of the solution to a beaker, add 10 mL of diluted nitric acid and 50.0 mL of 0.1 N silver nitrate VS, and mix. Add 2 mL of ferric ammonium sulfate TS, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS. Caleulate the molarity.

$$
\mathrm{M}=\frac{\mathrm{mL} \mathrm{AgNO}_{3} \times \mathrm{N} \mathrm{AgNO}_{3}}{\mathrm{~mL}\left(\mathrm{CH}_{3}\right)_{4} \mathrm{NBr}} \quad \square 1 \mathrm{~S}(U S P 28)
$$

## Change to read:

Tetramethylammonium Chloride, Tenth-Molar (0.1 M)

$$
\begin{array}{r}
\left(\mathrm{CH}_{3}\right)_{4} \mathrm{NCl}, \mathbf{1 0 9 . 6 0} \\
10.96 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
\end{array}
$$

Dissolve 10.96 g of tetramethylammonium chloride in water to make 1000 mL , and standardize the solution as follows.

Transfer an accurately measured volume of about 40 mL of the solution to a flask, add 10 mL of diluted nitric acid and 50.0 mL of 0.1 N silver nitrate VS, and mix. Add 5 mL of nitrobenzene and 2 mL of ferric ammonium sulfate TS, shake, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS. Galeulate the melarity.

$$
\mathbf{M}=\frac{\mathrm{mL} \mathrm{AgNO}_{3} \times \mathrm{N} \mathrm{AgNO}_{3}}{\mathrm{~mL}\left(\mathrm{CH}_{3}\right)_{4} \mathrm{NCl}} \square_{1 \mathrm{~S}(\text { USP28) }}
$$

## Change to read:

## Titanium Trichloride, Tenth-Normal (0.1 N) <br> $\mathrm{TiCl}_{3}, \mathbf{1 5 4 . 2 3}$ <br> 15.42 g in 1000 mL

Add 75 mL of titanium trichloride solution (1 in 5) to 75 mL of hydrochloric acid, dilute to 1000 mL , and mix. Standardize the solution as follows, using the special titration apparatus described.

Apparatus-Store the titanium trichloride solution in the reservoir of a closed-system titration apparatus in an atmosphere of hydrogen.

Use a wide-mouth, $500-\mathrm{mL}$ conical flask as the titration vessel, and connect it by means of a tight-fitting rubber stopper to the titration buret, an inlet tube for carbon dioxide, and an exit tube. Arrange for mechanical stirring. All joints must be air-tight. Arrange to have both the hydrogen and the carbon dioxide pass through wash bottles containing titanium trichloride solution (approximately 1 in 50) to remove any oxygen.

If the solution to be titrated is to be heated before or during titration, connect the titration flask with an upright reflux condenser through the rubber stopper.

Standardization-Place an accurately measured volume of about 40 mL of 0.1 N ferric ammonium sulfate VS in the titration flask, and pass in a rapid stream of carbon dioxide until all the air has been removed. Add the titanium trichloride solution from the buret until near the calculated endpoint (about 35 mL ), then add through the outlet tube 5 mL of ammonium thiocyanate TS, and continue the titration until the solution is colorless. Galeulate the farmality.

$$
\mathrm{N}=\frac{\mathrm{mL} \mathrm{FeNH}_{4}\left(\mathrm{SO}_{4}\right)_{2} \times \mathrm{NFeNH}_{4}\left(\mathrm{SO}_{4}\right)_{2}}{\mathrm{~mL} \mathrm{TiCl}}{ }_{3} \quad \llbracket 1 \mathrm{~S}(\mathrm{USP28)}
$$

## Change to read:

> Zinc Sulfate, Twentieth-Molar $(\mathbf{0 . 0 5} \mathbf{~ M})$ $\mathrm{ZnSO}_{4} \cdot 7 \mathrm{H}_{2} \mathrm{O}, \mathbf{2 8 7 . 5 6}$ 14.4 g in 1000 mL

Dissolve 14.4 g of zinc sulfate in water to make 1 liter. Standardize the solution as follows:

Measure accurately about 10 mL of 0.05 M edetate disodium VS into a $125-\mathrm{mL}$ conical flask, and add, in the order given, 10 mL of acetic acid-ammonium acetate buffer TS, 50 mL of alcohol, and 2 mL of dithizone TS. Titrate with the zinc sulfate solution to a clear, rose-pink color. Galeulate the molarity.

NOTE FOr many of the reagents mentioned in the foregoing section, the correspending standards of the 6th edition (1980)-of Reagent Chemicats, published by the Ameriean Chemieal Society, should be consulted. For a limited number of other reagents, the standards are adapted frem these appearimg in Reagent Chemicats and Standatds, 5th edition, by Joseph Resin and copyrighted by the publisher, $D$. Van Nestrand Co., Ine.


## REFERENCE TABLES

## BRIEFING

Container Specifications for Capsules and Tablets, USP 27 page 2741, page 3166 of the First Supplement, and page 1048 of PF 30(3) [May-June 2004].
(HDQ) RTS—38696-1; 40239-1; 40962-1; 41219-1

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the Packaging and storage requirements set forth in the individual monographs. It lists the capsules and tablets that are, or will be, official in the United States Pharmacopeia and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

| Monograph Title | Container <br> Specification |
| :--- | :--- |
| Add the following: |  |
| ■Acetaminophen Extended-Release |  |
| Tablets | $\mathrm{T}_{\mathbf{\square} 1 \mathrm{~S} \text { (USP28) }}$ |
| Add the following: |  |
| AAlendronate Sodium Tablets | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |
| Add the following: | $\mathrm{W}_{\mathbf{\Delta U S P 2 8}}$ |

Container Specifications for Capsules and Tablets (Continued)
Container
Monograph Title Specification

## Add the following:

■Bismuth Subsalicylate Tablets $\mathrm{T}_{\text {■1S (USP28) }}$
Add the following:

| ${ }^{\mathbf{\Delta}}$ Cefaclor Tablets | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |
| :--- | :--- |
| Add the following: |  |
| ${ }^{\boldsymbol{\Delta}}$ Clarithromycin Tablets, Extended- |  |
| Release | $\mathrm{W}_{\Delta U S P 28}$ |

## Add the following:

${ }^{\wedge}$ Black Cohosh Tablets
$T, \operatorname{LR}_{\mathbf{\Delta U S P 2 8}}$
Add the following:
${ }^{\Delta}$ Desogestrel and Ethinyl Estradiol
Tablets
$W_{\Delta U S P 28}$

## Add the following:

-Diethylstilbestrol Diphosphate
Tablets
$W_{\text {■IS (USP28) }}$

## Add the following:

${ }^{\boldsymbol{\Delta}}$ Fluoxetine Capsules, Delayed-Release $\quad \mathrm{T}_{\mathbf{\Delta U S P 2 8}}$

## Add the following:

${ }^{\boldsymbol{4}}$ Gabapentin Capsules $W_{\Delta U S P 28}$

Add the following:
${ }^{\Delta}$ Ginkgo Capsules
T, $\operatorname{LR}_{\mathbf{\Delta U S P 2 8}}$
Add the following:
${ }^{\Delta}$ Ginkgo Tablets
T, $\operatorname{LR}_{\mathbf{\Delta U S P 2 8}}$

## Change to read:

Asian Ginseng Capsules T, $\Perp$ R
${ }_{\Delta}{ }^{\text {USP28 }}$
Add the following:
${ }^{\boldsymbol{4}}$ Indinavir Sulfate Capsules
$\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$

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Container Specifications for Capsules and Tablets (Continued)
Container Specifications for Capsules and Tablets (Continued) Container

## Monograph Title Add the following:

Adrbesartan Tablets
Add the following:
${ }^{\Delta}$ Irbesartan and Hydrochlorothiazide

| Tablets | $\mathrm{W}_{\mathbf{\Delta U S P 2 8}}$ |
| :--- | :--- |
| Add the following: |  |
| ${ }^{\mathbf{\Delta} \text { Isosorbide Mononitrate Tablets }}$ | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |
| Add the following: |  |
| IIsosorbide Mononitrate Tablets, $^{\text {Extended-Release }}$ |  |

## Add the following:

${ }^{\Delta}$ Isradipine Capsules

## Add the following:

© Metformin Hydroch
Add the following:
$\bullet_{\text {Metolazone Tablets }}$

## Add the following:

| $\mathbf{\Delta}^{\text {Misoprostol Tablets }}$ | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |
| :--- | :--- |
| Add the following: |  |
| $\mathbf{\bullet N a p r o x e n}$ Delayed-Release Tablets | $\mathrm{W}_{\mathbf{\square} 1 \mathrm{~S} \text { (USP28) }}$ |

Add the following:

| $\mathbf{\Delta}^{\text {Norgestimate and Ethinyl Estradiol }}$ |  |
| :--- | :--- |
| Tablets | $\mathrm{W}_{\mathbf{\Delta U S P 2 8}}$ |
| Add the following: |  |
| $\mathbf{\Delta}^{\mathbf{4}}$ Oxaprozin Tablets | $\mathrm{T}, \operatorname{LR}_{\mathbf{\Delta U S P 2 8}}$ |

## Add the following:

-Paroxetine Tablets
$\mathrm{T}_{\mathbf{\Delta} U S P 28}$
$\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$
$T, \mathrm{LR}_{\text {(2S }}$ (USP27)
$\mathrm{W}_{\text {■IS (USP28) }}$
$T, \operatorname{LR}_{\mathbf{\Delta U S P 2 8}}$
$\mathrm{W}_{\text {■2S (USP2T) }}$

Container Specifications for Capsules and Tablets (Continued)
Container
Monograph Title
Specification
Add the following:
-Pygeum Capsules $\mathrm{T}_{\mathbf{m i S}^{(U S P 28)}}$
Add the following:
${ }^{\Delta}$ Quinapril Tablets
$W_{\triangle U S P 28}$
Add the following:
$■_{\text {Stavudine Capsules }} \quad \mathrm{T}_{\mathbf{m}_{1 S} \text { (USP28) }}$
Add the following:
■Tolcapone Tablets $^{T_{■ 1 S} \text { (USP28) }}$
Add the following:
${ }^{\Delta}$ Valsartan and Hydrochlorothiazide
Tablets
$\mathrm{W}_{\triangle U S P 28}$

Description and Relative Solubility of USP and NF Articles, USP 27 page 2747, page 3166 of the First Supplement, page 5310 of PF 23(6) [Nov.-Dec. 1997], page 7017 of PF 24(5) [Sept.-Oct. 1998], page 8282 of $P F$ 25(3) [May-June 1999], page 8589 of $P F$ 25(4) [July-Aug. 1999], page 8917 of PF 25(5) [Sept.-Oct. 1999], page 9254 of PF 25(6) [Nov.-Dec. 1999], page 837 of PF 26(3) [May-June 2000], page 1135 of PF 26(4) [July-Aug. 2000], page 1385 of PF 26(5) [Sept.-Oct. 2000], page 1907 of PF 27(1) [Jan.Feb. 2001], page 2281 of $P F$ 27(2) [Mar.-Apr. 2001], page 2839 of PF 27(4) [July-Aug. 2001], page 3374 of PF 27(6) [Nov.-Dec. 2001], page 554 of $P F$ 28(2) [Mar.-Apr. 2002], page 1236 of $P F$ 28(4) [July-Aug. 2002], page 1542 of $P F 28(5)$ [Sept.-Oct. 2002], page 1953 of $P F$ 28(6) [Nov.-Dec. 2002], page 266 of $P F 29(1)$ [Jan.-Feb. 2003], page 509 of PF 29(2) [Mar.-Apr. 2003], page 812 of PF 29(3) [May-June 2003], page 1262 of PF 29(4) [July-Aug. 2003], page 1684 of $P F$ 29(5) [Sept.-Oct. 2003], page 2057 of PF 29(6) [Nov.-Dec. 2003], page 317 of $P F 30(1)$ [Jan.Feb. 2004]; page 650 of PF 30(2) [Mar.-Apr. 2004]; and page 1050 of PF 30(3) [May-June 2004].
(HDQ) RTS-39281-1; 40316-8; 40414-2; 40507-1; 406453; 40682-1; 40866-1; 41050-1; 41110-1; 41222-1; 41223-1; 41282-1; 41289-1; 41289-3

## Change to read:

Ammonio Methacrylate Copolymer: Colorless, clear to white-opaque granules or a white powder, both with a faint amine-like odor. Soluble to freely soluble in methanol, in alcohol, and in isopropyl alcohol, each of which contains small amounts of
water; soluble to freely soluble in acetone, in ethyl acetate, and in methylene chloride. The solutions are clear to slightly cloudy. Insoluble in petroleum ether and in water. NF category: Coating agent;
$\square_{\text {tablet binder; polymer membrane. } \text { ■ }_{1 S} \text { (USP28) }}$

## Add the following:

-Fenbendazole: White to off-white powder. Practically insoluble in water; very slightly soluble in methanol; sparingly soluble in dimethylformamide.■1S (USP28)

## Add the following:

-Fluticasone Propionate (micronized): Fine, white powder.■1S (USP28)

## Add the following:

-Fluvastatin Sodium: White to pale yellow, brownish pale yellow, or reddish pale yellow hygroscopic powder. Soluble in alcohol, in methanol, and in water. $\quad 1$ (USP28)

## Add the following:

-Fluvoxamine Maleate: White to off-white crystalline powder. Freely soluble in alcohol and in chloroform; sparingly soluble in water; and practically insoluble in diethyl ether.■1S (USP28)

## Add the following:

-Gonadorelin Acetate: White to slightly yellowish powder. Soluble in water; sparingly soluble in methanol.■1S (USP28)

## Add the following:

-Mefloquine Hydrochloride: White or slightly yellow, crystalline powder. It exhibits polymorphism. Freely soluble in methanol; soluble in alcohol; very slightly soluble in water. ${ }^{1 S}$ (USP28)

## Change to read:

Methacrylic Acid Copolymer: White powder having a faint, characteristic odor. The polymer is insoluble in water, in diluted acids, in simulated gastric fluid TS, and in buffer solutions of up to pH 5 ; soluble in diluted alkali, in simulated intestinal fluid TS,
and in buffer solutions of pH 7 and above. The solubility between pH 5.5 and pH 7 depends on the content of methacrylic acid units in the copolymer. The polymer is soluble to freely soluble in methanol, in alcohol, in isopropyl alcohol, and in acetone, each of which contains not less than $3 \%$ of water.
${ }^{\text {■ }}$ NF category: Coating agent. $\quad 1 \mathrm{IS}$ (USP28)

## Add the following:

-Polydecene: Clear, colorless, odorless, and tasteless liquid. Very slightly soluble in water. NF category: Emollient; ointment base; solvent; vehicle (oleaginous).■1S (USP28)

## Delete the following:

MTitanium-Dioxide: White, oderless, tasteless pewder. Its 4 in 10 suspension in wher is neutral to litmens. Inseluble in water, in hydrochloric acid, in nitrie acid, and in 2 N sulfaric acid. Dissolves in hydrofluoric acid and in hot sulfaric acid. Is rendered soluble by fusion with petassium bisulfate or with alkali-carbenates or hy drox ides. NF category: Ceating agent.■1S (USP28)

## Add the following:

-Titanium Dioxide [Nomenclature title to come]: White to slightly colored powder. Its 1 in 10 suspension in water is neutral to litmus. Insoluble in water, in hydrochloric acid, in nitric acid, and in 2 N sulfuric acid. Dissolves in hydrofluoric acid and in hot sulfuric acid. Is rendered soluble by fusion with potassium bisulfate or with alkali carbonates or hydroxides.■1S (USP28)

## Add the following:

-Titanium Dioxide: White to slightly colored powder. Its 1 in 10 suspension in water is neutral to litmus. Insoluble in water, in hydrochloric acid, in nitric acid, in 2 N sulfuric acid, in dehydrated alcohol, and in ether. Dissolves in hydrofluoric acid and in hot sulfuric acid. Is rendered soluble by fusion with potassium bisulfate or with alkali carbonates or hydroxides. NF category: Coating agent.■IS (USP28)

## Add the following:

-Topiramate: White to off-white powder. Freely soluble in dichloromethane. 1 (USP28)

Items from Earlier Numbers of PF that Have Not Yet Appeared in a Supplement, and are Therefore Candidates for Subsequent Supplements.

## GENERAL NOTICES AND REQUIREMENTS

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## USP MONOGRAPHS

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Excipients, USP and NF Excipients, Listed by Category-See PF Vol. 29 No. 4, page 1088; PF Vol. 29 No. 6, page 2008; PF Vol. 30 No. 2, page 587; PF Vol 30 No. 3, page 961.

## GENERAL NOTICES AND REQUIREMENTS

"Official" and "Official Articles"-See PF Vol. 28 No. 1, page 88.

## NF MONOGRAPHS

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Adipic Acid-See PF Vol. 30 No. 2, page 593.
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Ammonio Methacrylate Copolymer Dispersion-See PF Vol. 29 No. 6, page 2011.
Ammonium Sulfate-See PF Vol. 30 No. 3, page 966.
L-Asparagine-See PF Vol. 30 No. 1, page 205.
Aspartame Acesulfame-See PF Vol. 29 No. 2, page 453.
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Caprylocaproyl Macrogolglycerides-See PF Vol. 29 No. 3, page 688.

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Proposed Revisions and New Text Previously Presented in PF but Now Canceled
(Canceled proposals may be republished at any time in a future number of Pharmacopeial Forum.) [PF 30(1)-PF 30(6)]


Proposed Revisions and New Text Previously Presented in PF but Now Canceled
(Canceled proposals may be republished at any time in a future number of Pharmacopeial Forum.) [PF 30(1)-PF 30(6)] (continued)

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| :---: | :---: | :---: | :---: |
| Title and Proposal | Vol. | No. | Page(s) |
| Reagents, Indicators, and Solutions |  |  |  |
| Bromobimane (added) | 25 | 2 | 7804 |
| Cesium Chloride (added) | 29 | 6 | 2054 |
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| Starch (Preview) | 21 | 5 | 1243 |

$\dagger$ New cancellations in PF 30(4).

## HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps (Stages).

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In $P F$, this stage appears as OFFICIAL INQUIRY STAGE 4 in the Harmonization section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

## Stage 5: Consensus

## A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

## B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.
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## MONOGRAPHS (USP)

BriEfing

Saccharin Calcium, USP 27 page 1665 and page 1705 of $P F$ 29(5) [Sept.-Oct. 2003]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Saccharin Calcium monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based in part on comments from the Japanese Pharmacopoeia and the European Pharmacopoeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the United States Pharmacopeia.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | - | + |
| Identification B | + | - | + |
| Identification C | - | - | + |
| Water | + | - | + |
| Readily carbonizable <br> substances | + | - | + |
| Limit of benzoate <br> and salicylate | - | - | + |
| Assay | + | - | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Heavy metals, Labeling, Clarity of solution, Color of solution, Limit of toluenesulfonamides, Identification (IR), Packaging and storage.

Specific local attributes: USP: Organic volatile impurities.
Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.

Differences between the ADOPTION STAGE 6 document and the current $N F$ monograph include the following:
(1) In the opening paragraph (the Definition)-The lower limit is changed from not less than 98.0 percent to not less than 99.0 percent.
(2) Packaging and storage-No change.
(3) USP Reference standards-A reference for Saccharin Calcium is added for use in Identification test $A$.
(4) Clarity of solution-This test is added to comply with EP standards.
(5) Color of solution-This test is added to comply with EP standards.
(6) Identification-Identification tests $A, B$, and $D$ are replaced with a more definitive IR absorption test. Identification test $C$ is retained, but separated into two tests ( $B$ and $C$ ).
(7) Water-No change.
(8) Readily carbonizable substances-No change.
(9) Selenium-This test is deleted because it is unnecessary for this compound.
(10) Limit of toluenesulfonamides-The test method and limits are changed to those of the European Pharmacopoeia, which include a more modern test method.
(11) Heavy metals-No change.
(12) Limit of benzoate and salicylate-No change.
(13) Organic volatile impurities-No change.
(14) Assay-No change.
(EMC: J. Lane) RTS-41235-5

## Change to read:

## Saceharin-Caleitm



$$
\begin{aligned}
& \mathrm{E}_{14} \mathrm{H}_{8} \mathrm{CaN}_{2} \Theta_{6} \mathrm{~S}_{2}-31 / 2 \mathrm{H}_{2} \Theta \quad 467.49 \\
& \text { 1,2 Benzisethiazol } 3(2 H) \text { one, } 1,1 \text { dioxide, ealeium salt, hydrate } \\
& \text { (2:7). } \\
& \text { 1,2 Benzisethiazolin-3-one-1,1 dioxide-ealeium salt hydrate } \\
& \text { (2:7) [6381-915]. } \\
& \text { Anhydreas } 404.44 \text { [6485-343]. }
\end{aligned}
$$

H-Saceharin Caleium contains not less than-98.0 pereent and net more than 101.0 pereent of $\mathrm{C}_{4} \mathrm{H}_{8} \mathrm{Ca}$ $\mathrm{N}_{2} \mathrm{O}_{4} \mathrm{~S}_{2}$, caleulated on the anhydrous basis.
Packaging and-storage-Preserve in well closed containers.
Labeling Where the quantity of saceharin caleitm is indieated in the - abeling of any preparation containing Saceharin-Caleium, this shall be expressed in terms of saceharin $\left(\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{NO}_{3} \mathrm{~S}\right)$.
USP Referenee standards $\langle H\rangle$ - USP o Toluenesulfonamide RS. USP $P_{P}$-Toltenesulfontle RS.

## Identifieation-

A: Dissolve about 100 mg in 5 mL of sodimm hydroxide solut tion (1 in 20), evaporate to drymess, and gently fuse the residue over a small flame until it no longer evolves ammenia. Allow the residue to cool, dissolve in 20 mL of water, neutralize with 3 N hydrechloric acid, and filter: the addition of a drep of ferrie ehloride TS to the filtrate produces a violet color.

B: Mix 20 mg with 40 mg of resoreinel, add 10 drops of sut furie acid, and heat the mixture in a suitable liguid bath at $200^{\circ}$ for 3 mintutes. Allow it to cool, and add 10 mL of water and an eveess of 1 N sodium hydroxide: a fluoreseent green liquid results.

C: A solution ( 1 in 10 ) meets the requirements of the tests for Calcium- 191 ):

D: $\quad$ To 10 mL of a solution ( $1 \mathrm{in}-10$ ) add 1 mL of hydrechlorie acid: a crystalline precipitate of saceharin is formed. Wash the preeipitate with cold water, and dry at $105^{\circ}$ for 2 heurs: it melts between $226^{\circ}$ and $230^{\circ}$, the procedure for Class $I$ being used (see Melting Range or Temperatur $\langle 744$ ) •.
Water, Methed $I\langle 924\rangle$ : not more than $15.0 \%$.

Readily carbonizable substances- $\langle 271\rangle$-Dissolve 200 mg in 5 mL of sulfuric acid $T S$, and maintain at a temperature of $48^{\circ}$ to $50^{\circ}$ for 10 minutes: the selution has no more coler than Matehing Flutid 4.
Selenium- $\langle 294\rangle:-0.093 \%$.
Toltenesulfonamides-
Internal standerd solution, Standard stock solution, and Stan dard preparations. Prepare as direeted for Internal standedrd solthtion, Standard stock solution, and Standard preparations in the test for Toluene ulfonamides under Saccharin (see NF monograph).

Test preparation Prepare as directed under Column Partition Chromagraply (see Chromatograpy (624)), employing a chromatographie tube fitted with a perous glass disk in its base, a plastie stopeock on the delivery tube, and a reservir on the top. Adda mixture consisting of 10 g of Solid Support and a solution of 2.0 है, aceuraty weighed, of Saceharin Caleitm in 8.0 mL of sodium earbonate solution ( 1 in 20), and proceed as directed for Test preparation in the test for Toluenesulfonamides under Sachatrin (see NF monegraph), beginning with "Pack the contents."

Chromatographic system and Proedtre Proeeed as direeted for Chrematographic systen and Proeedure in the test for Tolue nesulfonider under Stecharin (see NF menegraph).
Heary metals, Method $I\langle z 34\rangle$ - Dissolve- 4 g in 46 mL of wher, add -4 mL of dilute hydrochloric acid ( 1 in 12 ), mix, and rub the inner wall of the vessel with a glass rod untilerystallization begins. Allow the solution to stand for 1 hour, then pass through a dry fit ter, disearding the frrst 10 mL of the filtrate, and use 25 mL of the subsequen filtrate for the Test Preparation: the limit is $0.001 \%$.
Limit of benzate and salieylate-To 10 mL of a solution (1 in 20), previously acidiffed with 5 drops of 6 N aretic acid, add-3 drops of ferric chloride TS: no precipitate or violet coler appears. Organie volatile impurities, Meth $H\langle 467\rangle$ : meets the requirements.
Assay Aceurately weigh about 500 me of Saceharin Caleinm, and transfer completely to a separator with the aid of 10 mL of water. Add 2 mL of 3 N hydrochloric acid, and extract the precipi ated saceharin frost with 30 mL , then with five 20 mL pertions, of a mixture of chloreform and aleohol ( $9: 1)$. Evaperate the eem bined extracts on a steam bath to dryness, with the aid of acurrent ef air, then dissolve the residte in 40 mL of aleohol, add 40 mL of water, mix, add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Perform a blank determination on a mixture of 40 mL of alcohol and 40 mL of water, and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent 1020.22 mg of $\mathrm{C}_{4} \mathrm{H}_{3} \mathrm{EaN}_{2} \mathrm{O}_{6} \mathrm{~S}_{2}-$

## Saccharin Calcium


$\mathrm{C}_{14} \mathrm{H}_{8} \mathrm{CaN}_{2} \mathrm{O}_{6} \mathrm{~S}_{2} \cdot 31 / 2 \mathrm{H}_{2} \mathrm{O} \quad 467.49$

1,2-Benzisothiazol-3(2H)-one, 1,1-dioxide, calcium salt, hydrate $(2: 7)$.

1,2-Benzisothiazolin-3-one 1,1-dioxide calcium salt hydrate (2:7) [6381-91-5].

Anhydrous 404.44 [6485-34-3].
» Saccharin Calcium contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{14} \mathrm{H}_{8} \mathrm{CaN}_{2} \mathrm{O}_{6} \mathrm{~S}_{2}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in well-closed containers. Store at reom temperature.

Labeling-Where the quantity of saccharin calcium is indicated in the labeling of any preparation containing Saccharin Calcium, this shall be expressed in terms of saccharin $\left(\mathrm{C}_{7} \mathrm{H}_{5} \mathrm{NO}_{3} \mathrm{~S}\right)$.

USP Reference standards $\langle 11\rangle$ —USP Saccharin Calcium
RS. USP o-Toluenesulfonamide RS. USP p-Toluenesulfonamide RS.

Clarity of solution-[NOTE-The Test solution is to be compared to the Reference suspension $A$ and to water in diffused daylight 5 minutes after preparation of Reference suspension A.]

Hydrazine solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Methenamine solution-Transfer 2.5 g of methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.
Primary opalescent suspension-[NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.]

Transfer 25.0 mL of Hydrazine solution to the Methenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE-This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension A. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension B.

Test solution-Dissolve 5.0 g of test material in about 20 mL of a 200 g per L solution of sodium acetate, dilute with the same solution to 25 mL , and mix.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Reference suspension $A$, Reference suspension $B$, water, and a 200 g per L solution of sodium acetate to separate matching test tubes. Compare the Test solution, Reference suspension A, Reference suspension B, water, and a 200 g per L solution of sodium acetate in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). [NOTEThe diffusion of light must be such that Reference suspension $A$ can readily be distinguished from water, and that Reference suspension $B$ can readily be distinguished from Reference suspension A.] The Test solution shows the same clarity as that of water, or the 200 g per L solution of sodium acetate, or its opalescence is not more pronounced than that of Reference suspension $A$.

## Color of solution-

Standard stock solution-Combine 3.0 mL of ferric chloride $\mathrm{CS}, 3.0 \mathrm{~mL}$ of cobaltous chloride $\mathrm{CS}, 2.4 \mathrm{~mL}$ of cupric sulfate CS , and 1.6 mL of dilute hydrochloric acid ( 10 g per L).

Standard solution-[NOTE—Prepare the Standard solution immediately before use.] Transfer 1.0 mL of Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix.

Test solution-Use the Test solution from Clarity of solution.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Standard solution, a 200 g per L solution of sodium acetate, and water to separate matching test tubes. Compare the Test solution, the Standard solution, a 200 g per L solution of sodium acetate, and water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). The Test solution has the appearance of water or the 200 g per L solution of sodium acetate, or is not more intensely colored than the Standard solution.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$ - Dry the specimen at $105^{\circ}$ for 2 hours before use.
B: To a solution ( 1 in 10 ) add 2 drops of methyl red TS, and neutralize with 6 N ammonium hydroxide. Add 3 N hydrochloric acid, dropwise, until the solution is acid to the indicator. Upon the addition of ammonium oxalate TS, a white precipitate is formed. This precipitate is insoluble in 6 N acetic acid but dissolves in hydrochloric acid.
C: Calcium salts moistened with hydrochloric acid impart a transient yellowish red color to a nonluminous flame.

Water, Method I $\langle 921\rangle$ : not more than $15.0 \%$.
Readily carbonizable substances $\langle 271\rangle$ —Dissolve 200 mg in 5 mL of sulfuric acid (between $94.5 \%$ and $95.5 \%$ [w/w] of $\mathrm{H}_{2} \mathrm{SO}_{4}$ ), and keep at a temperature of $48^{\circ}$ to $50^{\circ}$ for 10 minutes: the solution has no more color than Matching Fluid $A$, when viewed against a white background.

Heavy metals, Method I $\langle 231\rangle$ —Dissolve 4 g in 46 mL of water, add 4 mL of dilute hydrochloric acid ( 1 in 12), mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, then pass through a dry filter, discarding the first 10 mL of the filtrate, and use 25 mL of the subsequent filtrate for the Test Preparation: the limit is $0.001 \%$.

## Limit of toluenesulfonamides-

Internal standard solution-Dissolve 25 mg of caffeine in methylene chloride, and dilute with the same solvent to 100 mL .
Reference solution-Dissolve 20.0 mg of USP $o$-Toluenesulfonamide RS and 20.0 mg of USP $p$-Toluenesulfonamide RS in methylene chloride, and dilute with the same solvent to 100.0 mL . Dilute 5.0 mL of the solution with methylene chloride to 50.0 mL . Evaporate 5.0 mL of the final solution to dryness in a stream of nitrogen. Dissolve the residue in 1.0 mL of the Internal standard solution.

Test solution-Suspend 10.0 g of the substance to be examined in 20 mL of water, and dissolve using 5 mL to 6 mL of 10 N sodium hydroxide. If necessary adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to pH 7 to 8 , and dilute with water to 50 mL . Shake the solution with four quantities each of 50 mL of methylene chloride. Combine the lower layers, dry over anhydrous sodium sulfate, and filter. Wash the filter and the sodium sulfate with 10 mL of methylene chloride. Combine the solution and the washings, and evaporate almost to dryness in a water bath at a temperature not exceeding $40^{\circ}$. Using a small quantity
of methylene chloride, quantitatively transfer the residue into a suitable $10-\mathrm{mL}$ tube, evaporate to dryness in a stream of nitrogen, and dissolve the residue in 1.0 mL of the Internal standard solution.

Blank solution-Evaporate 200 mL of methylene chloride to dryness in a water bath at a temperature not exceeding $40^{\circ}$. Dissolve the residue in 1 mL of methylene chloride.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The instrument is equipped with a flame-ionization detector and contains a $0.53-\mathrm{mm} \times 10-\mathrm{m}$ fused silica column, coated with G3 phase (film thickness $2 \mu \mathrm{~m}$ ). The injector port, column, and detector temperatures are maintained at about $250^{\circ}, 180^{\circ}$, and $250^{\circ}$, respectively; and nitrogen is used as the carrier gas at a flow rate of about 10 mL per minute. The injector employs a split ratio of $1: 2$.

Procedure-Inject about $1 \mu \mathrm{~L}$ of the Reference solution. Adjust the sensitivity of the detector so that the height of the peak due to caffeine is not less than $50 \%$ of the full scale of the recorder. The substances are eluted in the following order: $o$-toluenesulfonamide, $p$-toluenesulfonamide, and caffeine. The test is not valid unless the resolution between the peaks due to $o$-toluenesulfonamide and $p$-toluenesulfonamide is at least 1.5. Inject about $1 \mu \mathrm{~L}$ of the Blank solution. In the chromatogram obtained, verify that there are no peaks with the same retention times as the internal standard, $o$-toluenesulfonamide and $p$-toluenesulfonamide. Inject about $1 \mu \mathrm{~L}$ of the Test solution and $1 \mu \mathrm{~L}$ of the Reference solution. If any peaks due to $o$-toluenesulfonamide and $p$ toluenesulfonamide appear in the chromatogram obtained with the Test solution, the ratio of their areas to that of the internal standard is not greater than the corresponding ratio in the chromatogram obtained with the Reference solution ( 10 ppm of $o$-toluenesulfonamide and 10 ppm of $p$-toluenesulfonamide).

Limit of benzoate and salicylate-To 10 mL of a solution ( 1 in 20), previously acidified with 5 drops of 6 N acetic acid, add 3 drops of ferric chloride TS: no precipitate or violet color appears.

Organic volatile impurities, Method $I\langle 467\rangle$ : meets the requirements.

Assay-Dissolve, with the aid of slight heating if necessary, about 150 mg of Saccharin Calcium, accurately weighed, in 50 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrically. Perform a blank titration, if necessary, and make the appropriate correction. Each mL of 0.1 N perchloric acid is equivalent to 20.22 mg of $\mathrm{C}_{14} \mathrm{H}_{8} \mathrm{CaN}_{2} \mathrm{O}_{6} \mathrm{~S}_{2}$. 1 IS (USP28)

Saccharin Sodium, USP 27 page 1665 and page 1708 of $P F$ 29(5) [Sept.-Oct. 2003]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Saccharin Sodium monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based in part on comments from the Japanese Pharmacopoeia and the European Pharmacopoeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the United States Pharmacopeia.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification B | + | + | + |
| Identification C | - | + | + |
| Acidity or alkalinity | + | + | + |
| Water | + | + | + |
| Readily carbonizable <br> substances | + | + | + |
| Limit of benzoate <br> and salicylate | - | + | + |
| Assay | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Packaging and storage, Heavy metals, Labeling, Clarity of solution, Color of solution, Limit of toluenesulfonamides, Identification A (IR).
Specific local attributes: USP: Organic volatile impurities; JP: Description.
Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.
Differences between the ADOPTION STAGE 6 document and the current $N F$ monograph include the following:
(1) In the opening paragraph (the Definition)-The lower limit is changed from not less than 98.0 percent to not less than 99.0 percent.
(2) Packaging and storage-No change.
(3) Labeling-No change.
(4) USP Reference standards-A reference for Saccharin Sodium is added for use in the Identification test $A$.
(5) Clarity of solution-This test is added to comply with EP standards.
(6) Color of solution-This test is added to comply with EP standards.
(7) Identification-Identification tests $A, B$, and $D$ are replaced with a more definitive IR absorption test. Identification test $C$ is retained, but separated into two tests ( $B$ and $C$ ).
(8) Water - No change.
(9) Readily carbonizable substances-No change.
(10) Selenium-This test is deleted because it is unnecessary for this compound.
(11) Limit of toluenesulfonamides-The test method and limits are changed to those of the European Pharmacopoeia, which include a more modern test method.
(12) Heavy metals-No change.
(13) Limit of benzoate and salicylate-No change.
(14) Organic volatile impurities-No change.
(15) Assay - No change.
(EMC: J. Lane) RTS-41235-7

## Change to read:

## Saceharin Sodium


$\mathrm{C}_{7} \mathrm{H}_{4} \mathrm{NNaO}_{3} \mathrm{~S} \cdot 2 \mathrm{H}_{2} \mathrm{O} \quad 241.20$
1,2 Benzisothiazol-3(2H)-one, 1,1 diexide, sodium salt, dihy drate.
1,2 Benzisothiazolin-3-one-1,1 dioxide-sodium salt dihydrate-[6155-57 3].
Anhydreus 205.17 [128-44-9].
\#Saceharin Sodium contains not less than 98.0 percent and not more than 101.0 pereent of $\mathrm{C}_{7} \mathrm{H}_{4} \mathrm{NNa}_{3} \mathrm{~S}$, cal eulated on the anhydrous basis.

Packaging and-storage Preserve in well closed containers.
Eabeling. Where the quantity of saceharin sodimm is indiented in the labeling of any preparation containing Saceharin-Sodium, this shall be expressed in terms of saceharin $\left(\mathrm{C}_{7} \mathrm{H}_{5} \mathrm{NO}_{3} \mathrm{~S}\right)$.
USP Reference standards- $\langle 4\rangle$-USP ${ }_{0}$ Toluenesulfonamide RS. USP p Tolturnesulfonamide RS.

## Identifiention-

A: The residue obtained by igniting it respends to the tests for Soditum $\langle 194$ ):

B: To 10 mL of a solution ( 1 in 10 ) add 1 mL of hydrochlorie reid: a crystalline precipitate of saceharim is formed. Wash the preeipitate with cold water until the last washing is free from chloride, and dry at $105^{\circ}$ for 2 hours: it melts between $226^{\circ}$ and $230^{\circ}$, the procedure for Class I being used (see Melting Range ar Tempera ture (744) خ.
Alkalinity A solution (1-in-10) is neutral or alkaline to litmers, but no red color is produeed with phenolphthalein TS.
Toltenesulfonamides-
Internal standard solution, Standard stock solution, and Stantad preparations- Prepare as directed for Internal standed solt tion, Standad stock solution, and Standerd prepatrations in the test for Toltenesulfonamides under Sachatu (see NF monograph).

Test preparation Prepare as directed under Column Partition Chromatography (see Chromatography (624)), employing a chromatographic tube fitted with a perous glass disk in its base, a plastie stoperck on the delivery tube, and a reservir on the top. Adda mixture ensisting of 10 g of Solid Support and a solution of 2.0 है, aceurately weighed, of Saecharin Soditm in 8.0 mL of sodium ear benate solution ( 1 in 20), and preceed as directed under Test preparation in the test for Tolurnesulfonamides under Sacharin (see NF menegraph), beginning with "Pack the contents."

Chrematographic system and Procedure Preceed as directed for Chromatggraphic syistem and Procedure in the test for Tolue nesulfonde under Sachath (see NF menograph).
Heavy metals, Meth $I\langle 234\rangle$ - Dissolve 4 s in 46 mL of water, add 4 mL of $1 N$ hydrochleric acid, mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, and then flter through a dry fllter, dis earding the first 10 mL of the filtrate: the limit, determined on 25 mL of the subsequent filtrate, is $0.001 \%$.
Organie volatile imptrities, Meth $H$ ( $H 67\rangle$ : meets the requirements.
Other requirements It respends to Identifieation $A$ and $B$, and meets the requirements of the tests-for Water, Benzate and salicylate, Selenium, and Readily earbanizable substanees under Sachatrin Caleinm.
Assay Proceed with Saceharin Sodium as directed in the Assay under Sacchatin Calcium. Each mL of 0.1 N sodium hydroxide is equivalent to $20.52 \mathrm{mg}_{\mathrm{g}}$ of $\mathrm{C}_{7} \mathrm{H}_{4} \mathrm{NNa}_{3} \mathrm{~S}$.

## ■accharin Sodium


$\mathrm{C}_{7} \mathrm{H}_{4} \mathrm{NNaO}_{3} \mathrm{~S} \cdot 2 \mathrm{H}_{2} \mathrm{O} \quad 241.20$
1,2-Benzisothiazol-3(2H)-one, 1,1-dioxide, sodium salt, dihydrate.

1,2-Benzisothiazolin-3-one 1,1-dioxide sodium salt dihydrate [6155-57-3].
Anhydrous 205.17 [128-44-9].
» Saccharin Sodium contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{7} \mathrm{H}_{4} \mathrm{NNaO}_{3} \mathrm{~S} \cdot 2 \mathrm{H}_{2} \mathrm{O}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in well-closed containers. Store at reom temperature.

Labeling-Where the quantity of saccharin sodium is indicated in the labeling of any preparation containing Saccharin Sodium, this shall be expressed in terms of saccharin $\left(\mathrm{C}_{7} \mathrm{H}_{5} \mathrm{NO}_{3} \mathrm{~S}\right)$.

USP Reference standards $\langle 11\rangle — U S P$ Saccharin Sodium RS. USP o-Toluenesulfonamide RS. USP p-Toluenesulfonamide $R S$.

Clarity of solution-[NOTE-The Test solution is to be compared to Reference suspension $A$ and to water in diffused daylight 5 minutes after preparation of Reference suspension $A$.]

Hydrazine solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Methenamine solution-Transfer 2.5 g of methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension-[NOTE-This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of Hydrazine solution to the Methenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE-This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension A. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension B.

Test solution-Dissolve 5.0 g of test material in about 20 mL of a 200 g per L solution of sodium acetate, dilute with * the same solution to 25 mL , and mix.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Reference suspension $A$, Reference suspension B, water, and a 200 g per L solution of sodium acetate to separate matching test tubes. Compare the Test solution, Reference suspension $A$, Reference suspension B, water, and a 200 g per L solution of sodium acetate in diffused daylight, viewing vertically
against a black background (see Visual Comparison under Spectrophotometry and Light-Scattering 〈851〉). [NOTEThe diffusion of light must be such that Reference suspension $A$ can readily be distinguished from water, and that Reference suspension $B$ can readily be distinguished from Reference suspension A.] The Test solution shows the same clarity as that of water, or the 200 g per L solution of sodium acetate, or its opalescence is not more pronounced that that of Reference suspension A.

## Color of solution-

Standard stock solution-Combine 3.0 mL of ferric chloride $\mathrm{CS}, 3.0 \mathrm{~mL}$ of cobaltous chloride $\mathrm{CS}, 2.4 \mathrm{~mL}$ of cupric sulfate CS , and 1.6 mL of dilute hydrochloric acid ( 10 g per L).

Standard solution-[NOTE-Prepare the Standard solution immediately before use.] Transfer 1.0 mL of Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix.
Test solution-Use the Test solution from Clarity of solution.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Standard solution, a 200 g per L solution of sodium acetate, and water to separate matching test tubes. Compare the Test solution, the Standard solution, a 200 g per L solution of sodium acetate, and water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). The Test solution has the appearance of water or the 200 g per L solution of sodium acetate, or is not more intensely colored than the Standard solution.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$ - Dry the specimen at $105^{\circ}$ for 2 hours before use.

B: $\quad$ To a solution ( 1 in 10 ) add 2 mL of $15 \%$ potassium carbonate, and heat to boiling. No precipitate is formed. Add 4 mL of potassium pyroantimonate TS , and heat to boiling. Allow to cool in ice water and, if necessary, rub the inside of the test tube with a glass rod. A dense precipitate is formed.

C: Sodium salts impart an intense yellow color to a nonluminous flame.

Acidity or alkalinity-To a solution of 1.0 g in 10 mL of carbon dioxide-free water add 1 drop of phenolphthalein TS: no pink color is produced. Then add 1 drop of 0.1 N sodium hydroxide: a pink color is produced.

Water, Method I $\langle 921\rangle$ : not more than $15.0 \%$.
Readily carbonizable substances $\langle 271\rangle$ —Dissolve 200 mg in 5 mL of sulfuric acid (between $94.5 \%$ and $95.5 \%$ [w/w] of $\mathrm{H}_{2} \mathrm{SO}_{4}$ ), and keep at a temperature of $48^{\circ}$ to $50^{\circ}$ for 10 minutes: the solution has no more color than Matching Fluid $A$, when viewed against a white background.

Heavy metals, Method $I\langle 231\rangle$ —Dissolve 4 g in 46 mL of water, add 4 mL of dilute hydrochloric acid (1 in 12), mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, then pass through a dry filter, discarding the first 10 mL of the filtrate, and use 25 mL of the subsequent filtrate for the Test Preparation: the limit is $0.001 \%$.

## Limit of toluenesulfonamides-

Internal standard solution-Dissolve 25 mg of caffeine in methylene chloride, and dilute with the same solvent to 100 mL .

Reference solution-Dissolve 20.0 mg of USP $o$-Toluenesulfonamide RS and 20.0 mg of USP $p$-Toluenesulfonamide RS in methylene chloride, and dilute with the same solvent to 100.0 mL . Dilute 5.0 mL of the solution with methylene chloride to 50.0 mL . Evaporate 5.0 mL of the final solution to dryness in a stream of nitrogen. Dissolve the residue in 1.0 mL of the Internal standard solution.

Test solution-Suspend 10.0 g of the substance to be examined in 20 mL of water, and dissolve using 5 mL to 6 mL of 410 N sodium hydroxide. If necessary adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 7 to 8 , and dilute with water to 50 mL . Shake the solution with four quantities each of 50 mL of methylene chloride. Combine the lower layers, dry over anhydrous sodium sulfate, and filter. Wash the filter and the sodium sulfate with 10 mL of methylene chloride. Combine the solution and the washings, and evaporate almost to dryness in a water bath at a temperature not exceeding $40^{\circ}$. Using a small quantity of methylene chloride, quantitatively transfer the residue into a suitable $10-\mathrm{mL}$ tube, evaporate to dryness in a stream of nitrogen, and dissolve the residue in 1.0 mL of the Internal standard solution.

Blank solution-Evaporate 200 mL of methylene chloride to dryness in a water bath at a temperature not exceeding $40^{\circ}$. Dissolve the residue in 1 mL of methylene chloride.

Chromatographic system (see Chromatography $\langle 621\rangle$ ) The instrument is equipped with a flame-ionization detector and contains a $0.53-\mathrm{mm} \times 10-\mathrm{m}$ fused silica column, coated with G3 phase (film thickness $2 \mu \mathrm{~m}$ ). The injector port, column, and detector temperatures are maintained at about $250^{\circ}, 180^{\circ}$, and $250^{\circ}$, respectively; and nitrogen is used as the carrier gas at a flow rate of about 10 mL per minute. The injector employs a split ratio of $1: 2$.

Procedure-Inject about $1 \mu \mathrm{~L}$ of the Reference solution. Adjust the sensitivity of the detector so that the height of the peak due to caffeine is not less than $50 \%$ of the full scale of the recorder. The substances are eluted in the following order: $o$-toluenesulfonamide, $p$-toluenesulfonamide, and caffeine. The test is not valid unless the resolution between the peaks due to $o$-toluenesulfonamide and $p$-toluenesulfonamide is at least 1.5. Inject about $1 \mu \mathrm{~L}$ of the Blank solution. In the chromatogram obtained, verify that there are no peaks with the same retention times as the internal standard, $o$-toluenesulfonamide, and $p$-toluenesulfonamide. Inject about $1 \mu \mathrm{~L}$ of the Test solution and $1 \mu \mathrm{~L}$ of the Reference solution. If any peaks due to $o$-toluenesulfonamide and $p$ toluenesulfonamide appear in the chromatogram obtained with the Test solution, the ratio of their areas to that of the internal standard is not greater than the corresponding ratio in the chromatogram obtained with the Reference solution ( 10 ppm of $o$-toluenesulfonamide and 10 ppm of $p$-toluenesulfonamide).

Limit of benzoate and salicylate-To 10 mL of a solution ( 1 in 20), previously acidified with 5 drops of 6 N acetic acid, add 3 drops of ferric chloride TS: no precipitate or violet color appears.

Organic volatile impurities, Method $I\langle 467\rangle$ : meets the requirements.

Assay-Dissolve, with the aid of slight heating if necessary, about 150 mg of Saccharin Sodium, accurately weighed, in 50 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrically. Perform a blank titration, if necessary, and make the appropriate correction. Each mL of 0.1 N perchloric acid is equivalent to 20.52 mg of $\mathrm{C}_{7} \mathrm{H}_{4} \mathrm{NNaO}_{3} \mathrm{~S}$.■1S (USP28)

## MONOGRAPHS (NF)

BRIEFING

Butylparaben, NF 22 page 2833 and page 1967 of $P F$ 28(6) [Nov.-Dec. 2002]. The European Pharmacopoeia, a member of the Pharmacopoeial Discussion Group, is the coordinating pharmacopoeia in the efforts toward the international harmonization of compendial standards for this monograph. The presented text represents the ADOPTION STAGE 6 draft in the harmonization process.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Appearance of <br> solution | + | + | + |
| Acidity | + | + | + |
| Related substances |  |  |  |
| Sulphated ash | + | + | + |
| Assay | + | + | + |

* JP will not include the system suitability requirement and consequently will not include reference solution (b).

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Identification by infrared spectrophotometry, Storage.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.

Local requirements: JP: Heavy metals (20 ppm); USP: Organic volatile impurities.

Differences between the ADOPTION STAGE 6 document and the current $N F$ monograph include the following:
(1) In the opening paragraph (the Definition)-Calculations using the dried substance are deleted, as the Loss on drying test is deleted. The acceptance range has been widened.
(2) Packaging and storage-No change.
(3) USP Reference standards-The reference standard for Propylparaben has been added for the Related substances test.
(4) Identification-The test for Melting range has been moved under Identification.
(5) Color of solution-This test is added to comply with EP standards.
(6) Melting range-Moved under Identification.
(7) Acidity-The EP test method has replaced the current USP method.
(8) Loss on drying-Deleted.
(9) Residue on ignition-The limits are increased to not more than $0.1 \%$ to comply with EP standards.
(10) Organic volatile impurities-No change.
(11) Related substances-This test is added to comply with EP standards.
(12) Assay-The sample amount and the amount of 1 N sodium hydroxide has changed, and the heating process has changed to a specific temperature and does not include refluxing.
(EMC: J. Lane) RTS-41235-3

## Change to read:

## Butylparaben


$\mathrm{G}_{4} \mathrm{H}_{4} \mathrm{O}_{3} \quad 194.23$
Benzoic acid, 4 hydroxy, butylester:
Butyl p hydroxybenzoate [94-26-8].

HButylparaben contains not less than 99.0 pereent and not more than 100.5 pereent of $\mathrm{C}_{44} \mathrm{H}_{44} \mathrm{O}_{3}$, calculated on the dried basis.

Packaging and storage- Preserve in well closed containers. USP Referenee standards- $\langle 4\rangle$-USP Bullaben RS.
Identifiention, Infrated Abserption $\langle 197 \mathrm{M}\rangle$ ):
Melting range $\langle 744\rangle$ : ben $68^{\circ}$ and $72^{\circ}$.
Aeidity Heat 0.75 g in 15 mL of water at $80^{\circ}$ for 1 minnte, cool, and filter: the filtrate is neutral or acid to litmus. To 10 mb of the filtrate add 0.20 mL of 0.10 N sodium hydroxide and 2 drops of methyl red TS: the solution is yellow.
Loss-on-drying $\langle 734\rangle$-Dry it over silien gel for 5 hours: it leses not more than $0.5 \%$ of its weight.
Residur-0n ignition- $\langle\mathbf{Z 8 4}$ ): net mere than $0.05 \%$.
Organic volatile impurities, Meth $I V\langle 467\rangle$ : meets the requirements.
Assay Transfer about 2 g of Butylparaben, neeurately weighed, to a flack fitted with a ground glass stopper and equipped for refluxing under a water cooled condenser. Add 40.0 mL of 1 N so dium hydroxide VS, and reflux for 1 hour. Cool to room temperattre, and rimse the eondenser with water. Titrate the exeess sodium hydroxide with 1 N sulfuric acid VS, continuing the titration until the second point of inflection and determining the end point potentiometically (see Titrimetry $\langle 544$ )). Perform a blank determination (see Residual Titrations under Titrimetry (544)). Each mL of 1 N sodimm hydroxide is equivalent to 194.2 mg of $\mathrm{E}_{4} H_{44} \Theta_{3}=$

## Butylparaben

$\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{O}_{3} \quad 194.23$

Benzoic acid, 4-hydroxy-, butyl ester.
Butyl $p$-hydroxybenzoate [94-26-8].
» Butylparaben contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{O}_{3}$.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle$ —USP Butylparaben RS. USP Propylparaben RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$.
B: Melting range $\langle 741\rangle$ : between $68^{\circ}$ and $71^{\circ}$.
Color of solution-Dissolve 1 g in alcohol, dilute with alcohol to 10 mL , and mix (Butylparaben solution). This solution is clear and not more intensely colored than alcohol or a solution prepared immediately before use by mixing 2.4 mL of ferric chloride CS, 1.0 mL of cobaltous chloride CS, and 0.4 mL of cupric sulfate CS with 0.3 N hydrochloric acid to make 10 mL , and diluting 5 mL of this solution with 0.3 N hydrochloric acid to make 100 mL . Make the comparison by viewing the solutions downward in matched color-comparison tubes against a white surface (see Color and Achromicity $\langle 631\rangle$ ).

Acidity-To 2 mL of Butylparaben solution prepared in the Color of solution test add 3 mL of alcohol, 5 mL of carbon dioxide-free water, and 0.1 mL of bromocresol green TS, and titrate with 0.10 N sodium hydroxide: not more than 0.1 mL is required to produce a blue color.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on 1.0 g .

## Related substances-

Test solution-Prepare a solution of Butylparaben in acetone containing 10 mg per mL .

Standard solutions-Transfer 0.5 mL of the Test solution to a $100-\mathrm{mL}$ volumetric flask, dilute with acetone to volume, and mix (Standard solution A). Dissolve 10 mg , accurately weighed, of USP Butylparaben RS in 1 mL of the Test solution, and dilute with acetone to 10 mL (Standard solution $B)$.

Procedure-Separately apply $2 \mu \mathrm{~L}$ of the Test solution and $2 \mu \mathrm{~L}$ of each Standard solution to a thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ), coated with a $0.25-\mathrm{mm}$ layer of chromatographic octadecylsilanized silica gel mixture. Develop the chromatogram in a solvent system consisting of a mixture of methanol, water, and glacial acetic acid ( $70: 30: 1$ ) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Examine the plate under short-wavelength UV light, and compare the intensities of any secondary spots observed in the chromatogram of the Test solution with that of the principal spot in the chromatogram of Standard solution $A$ : the intensity of any individual secondary spot in the chromatogram of the Test solution is not greater than that of the principal spot obtained in the chromatogram of Standard solution $A(0.5 \%)$. The test is not valid unless the chromatogram obtained with Standard solution $B$ shows two clearly separated principal spots.

Organic volatile impurities, Method $I V\langle 467\rangle$ : meets the requirements.

Assay-To about 1.000 g of Butylparaben, accurately weighed, add 20.0 mL of 1 N sodium hydroxide VS, and heat at about $70^{\circ}$ for 1 hour. Cool rapidly in an ice bath. Carry out the titration on the solutions at room temperature. Titrate the excess sodium hydroxide with 1 N sulfuric acid VS,
continuing the titration until the second point of inflection and determining the endpoint potentiometrically (see Titrimetry $\langle 541\rangle$ ). Perform a blank determination (see Residual Titrations under Titrimetry $\langle 541\rangle$. Each mL of 1 N sodium hydroxide is equivalent to 194.2 mg of $\mathrm{C}_{11} \mathrm{H}_{14} \mathrm{O}_{3 \cdot \text { - }}$ IS (NF23)

## BRIEFING

Microcrystalline Cellulose, NF 22 page 2845 and page 1305 of PF 29(4) [July-Aug. 2003]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Microcrystalline Cellulose monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based on corresponding monograph for Microcrystalline Cellulose that was prepared by the U.S. Pharmacopeia. This draft was based in part on comments from the European and Japanese Pharmacopoeias in response to the Provisional Harmonized Text Stage 5A and 5B drafts.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Labeling | - | + | + |
| Identification A | + | + | + |
| Identification B | + | + | + |
| Conductivity | + | + | + |
| pH | + | + | + |
| Loss on drying $^{1}$ | + | + | + |
| Residue on ignition | + | + | + |
| Bulk density ${ }^{2}$ | + | + | + |
| Water-soluble <br> substances | + | + |  |
| Ether-soluble <br> substances | + | + |  |

${ }^{1}$ USP will retain, as a specific local attribute, that the value can be within a percentage range, as specified within the labeling.
${ }^{2}$ USP will retain, as a specific local attribute, that the bulk density value is wthin the labeled specification.

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Heavy metals, Microbial limits, Labeling, Packaging and storage.

Specific local attributes: JP: Identification C——Dispersion test; USP: Organic volatile impurities, Particle size distribution estimation by analytical sieving.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.

Differences between the Adoption Stage 6 document and the current $N F$ monograph include the following:
(1) Definition-No change.
(2) Packaging and storage-No change.
(3) Labeling-Additional information is presented to clarify particle size testing.
(4) Identification test $B$-The requirements to be within the labeled specification are deleted.
(5) Microbial limits-No change.
(6) Conductivity-No change.
(7) pH -The upper limit is increased to 7.5 from 7.0 to conform to EP and JP standards and to be consistent with the monograph for Powdered Cellulose.
(8) Loss on drying - No change.
(9) Residue on ignition-The standard for this test was increased to not more than $0.1 \%$, which conforms to EP standards.
(10) Bulk density-No change.
(11) Water-soluble substances-The standard for this test was changed from $0.24 \%$ to $0.25 \%$.
(12) Ether-soluble substances-No change.
(13) Heavy metals-No change.
(14) Organic volatile impurities-No change.
(15) Particle size distribution estimation by analytical sieving-To further strengthen the monograph, a test for the determination of particle size distribution is added. Because the determination of particle size distribution is not a compendial requirement for this article, the test does not contain limit values. The test provides a means for ensuring that suppliers and users of Microcrystalline Cellulose who have an interest in this property may obtain this value by the same method. Users who do not require any definite particle size range material obviously would have no concern about this material property or monograph test.
(EMC: J. Lane) RTS-41235-8

## Change to read:

## Mierocrystalline Cellulose

## Gellulese.

Gellulese [900434-9].
\# Mierocrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

## Packaging and-storage Preserve in tight containers.

Eabeling The labeling indieates the nominallossondrying, bulk density, and degree of polymerization values. Degree of polymer ization compliance is determined using Identificution test $B$. Where the partiele-size distribution-is stated in the labeling, the labeling indientes the $d_{10}, d_{50}$, and $d_{90}$ values and the range for each.

## Identifieation-

A: Prepare iodinated zine chloride solution by dissolving 20 g of zine chlloride and 6.5 g of potassimm iodide in 10.5 mL of water. Add 0.5 g of iodine, and shake for 15 minntes. Place about 10 mg
of Mierecrystalline Cellulose on a watch glass, and disperse in 2 mL of iodinated zine chloride solution: the substance takes on a violet blue color.

B: Transfer 1.3 g of Miereerystalline-Cellulese, aceurately weighed to 0.1 mg, to a 125 mL conieal flack. Add 25.0 mL of water and 25.0 mL of 1.0 M empriethylenediamine hydroxide solution. Immediately purge the solution with nitrogen, insert the stopper, and shake on a wrist action shaker or other suitable mechanieat shaker until completely dissolved. Transfer 7.0 mL of the solution a calibrated number 150 Cannen. Fenske or equivalent ${ }^{+}$- viseosimeter. Allow the solution toquilibrate at $25 \pm 0.1^{\circ}$ for not less than 5 minutes. Time the flow between the 2 marks on the viseo simeter, and record the flow time, $t_{4}$, in seonds. Caleulate the ki nematic viseosity, $(K H)_{4}$, of the Mieroerystalline Cellulose taken by the formma:-

$$
t_{+}\left(\xi_{+}\right),
$$

in which $k_{4}$ is the viscosimeter constant (see-Viseosity $\langle 914$ ) $)$. Ob ain the flow time, $t_{3}$, for a 0.5 M eupriethylenediamine hydroxide solution using a number 100 Cannon Fenske or equivalent ${ }^{+}$-viseosimeter. Caleulate the kinematic viseosity, $(K I)_{3}$, of the solvent by the formmat:-

$$
t_{2}\left(f_{z}\right),
$$

in which $k_{2}$ is the viseosimeter eonstant. Determine the relative viseosity, $\eta_{m,}$, of the Mierocrystalline Cellulose specimen taken by the fermala:-

$$
(K I)_{+}+(K I)_{2}=
$$

Determine the intrinsic viseosity, $[\eta] e$, by interpolation, using the Intrinsic Iiseosity Table in the Reference Tables section. Caleulate the degree of pelymerization, $P$, by the formala:-

$$
\left((95)[n]+\left(4 Y_{s}[(100 \quad 0)\right.\right.
$$

in whieh $W_{s}$-is the weight, in $g$, of the Mierecrystalline Cellulese taken, and $\% L O D$ is the value obtained from the test for Less on drying. The degree of pelymerization is not greater than 350 , and is within the labeled specifieation.
Mierobiallimits $\langle 64\rangle$-The total qerebic mierebial cetnt dees net exeeed 1000 efu per f, the total combined molds and yeasts count dees not exeeed 100 efu per g, and it meets the requirements of the tests for absence-of Staphylococeus attrens and Preudementis aerugingsa and for absence of Escherichia coli and Salmenellat species.
Conductivity Shake about 5_ with 40 mL of water for 20-min utes, andeentrifuge. Retain the-supernatant liquidfor use in the pH test. Using an appropriate enduetivity meter that has been standar dized with a petassitum chloride conductivity ealibration-standard ${ }^{2}$ having a conductivity of 100 uS per cm , measure the conductivity of the-supernatant solution after a-stablereading is obtained, and measure the conductivity of the water used to prepare the test specimen. The conductivity of the supernatant solution does not exceed the conductivity of the water by more than 75 uS per em. $\mathbf{p H}\langle 794\rangle$ : between 5.0 and 7.0 in the-supernatant solution obtained in the Conductivity lest.
Goss-0ndrying $\langle 734\rangle$ - Dry it at $105^{\circ}$ for 3 heurs. it loses net mere than $7.0 \%$ of its weight, or some other lower pereentage, or is within a pereentage range, as specified in the labeling.
Residue-on ignition $\langle\mathbf{Z} 84\rangle$ : net mere than $0.05 \%$

[^184]Bulk density Use a volume meter ${ }^{2}$ that has been fitted with a 10 mesh sereen. The volume meter is freestanding of the brass-or stainless steel cup, which is calibrated to a capacity of $25.0 \pm 0.05 \mathrm{~mL}$ and has an inside diameter of $30.0 \pm 2.0 \mathrm{~mm}$. Weigh the emply eup, pesition it under the chate, and slowly pour the powder from a height of 5.1 cm ( 2 inehes) above the fumet through the volume meter, at a rate suitable to prevent clogeging, until the eup overflows. [NOTE-If exeessive clogging of the sereen oceurs, remove the screen.] Level the excess powder, and weigh the filled eup. Caleulate the bulk density by dividing the weight ef the powder in the eup by the volume of the eup: the bulk density is within the labeled specifiention.
Water-soluble substanees-Shake 5.0 g with about $80-\mathrm{mL}$ of water for 10 minutes, filter with the aid of waymm through filter paper (Whatman No. 42 or equivalent) int a wacemm flack. Trans fer the filtrate to a tared beaker, evaporate to dryness without char ring, dry at $105^{\circ}$ for 1 hour, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight ob tained from a blank determination does not exeed 12.0 mm ( $0.24 \%$ ).
Ether-soluble substanees Place 10.0 gin achrematography eot umn having an internal diameter of about 20 mm , and pass 50 mL ef peroxide free ther through the columm. Evaporate the eluate to dryness in a previously dried and tared evaporating dish with the aid of a current of air in a fume hood. After all the ether has evaporated, dry the residue $105^{\circ}$ for 30 minutes, cool in a desicentor, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not eweed 5.0 mg ( $0.05 \%$ )
Heary metals, Method $I\langle\langle 234\rangle:-0.001 \%$.
Organie volatile impurities, Methad $I V\langle 467)$ : meets the requirements.

## ■Microcrystalline Cellulose

Cellulose.

Cellulose [9004-34-6].
» Microcrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

Packaging and storage-Preserve in tight containers.
Labeling-The labeling indicates the nominal loss on drying, bulk density, and degree of polymerization values. Degree of polymerization compliance is determined using

[^185]Identification test $B$. Where the particle size distribution is stated in the labeling, proceed as directed under Particle Size Distribution Estimation by Analytical Sieving $\langle 786\rangle$; the labeling indicates the $\mathrm{d}_{10}, \mathrm{~d}_{50}$, and $\mathrm{d}_{90}$ values (see Powder Fineness $\langle 811\rangle$ ) and the range for each.

## Identification-

A: Prepare iodinated zinc chloride solution by dissolving 20 g of zinc chloride and 6.5 g of potassium iodide in 10.5 mL of water. Add 0.5 g of iodine, and shake for $15 \mathrm{~min}-$ utes. Place about 10 mg of Microcrystalline Cellulose on a watch glass, and disperse in 2 mL of iodinated zinc chloride solution: the substance takes on a violet-blue color.

B: Transfer 1.3 g of Microcrystalline Cellulose, accurately weighed to 0.1 mg , to a $125-\mathrm{mL}$ conical flask. Add 25.0 mL of water and 25.0 mL of 1.0 M cupriethylenediamine hydroxide solution. Immediately purge the solution with nitrogen, insert the stopper, and shake on a wrist action shaker or other suitable mechanical shaker until completely dissolved. Transfer 7.0 mL of the solution to a calibrated number 150 Cannon-Fenske, or equivalent, viscosimeter. Allow the solution to equilibrate at $25 \pm 0.1^{\circ}$ for not less than 5 minutes. Time the flow between the two marks on the viscosimeter, and record the flow time, $t_{1}$, in seconds. Calculate the kinematic viscosity, $(K V)_{1}$, of the Microcrystalline Cellulose taken by the formula:

$$
t_{1}\left(k_{1}\right)
$$

in which $k_{1}$ is the viscosimeter constant (see Viscosity $\langle 911\rangle$ ). Obtain the flow time, $t_{2}$, for a 0.5 M cupriethylenediamine hydroxide solution using a number 100 CannonFenske, or equivalent, viscosimeter. Calculate the kinematic viscosity, $(K V)_{2}$, of the solvent by the formula:

$$
t_{2}\left(k_{2}\right)
$$

in which $k_{2}$ is the viscosimeter constant. Determine the relative viscosity, $\eta_{r e l}$, of the Microcrystalline Cellulose specimen taken by the formula:

$$
(K V)_{1} /(K V)_{2}
$$

Determine the intrinsic viscosity, $[\eta] c$, by interpolation, using the Intrinsic Viscosity Table in the Reference Tables section. Calculate the degree of polymerization, $P$, by the formula:

$$
(95)[\eta] c / W_{s}[(100-\% L O D) / 100]
$$

in which $W_{S}$ is the weight, in g , of the Microcrystalline Cellulose taken; and $\% L O D$ is the value obtained from the test for Loss on drying. The degree of polymerization is not greater than 350 .

Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed 1000 cfu per g , the total combined molds and yeasts count does not exceed 100 cfu per $g$, and it meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa and for absence of Escherichia coli and Salmonella species.

Conductivity-Shake about 5 g with 40 mL of water for 20 minutes, and centrifuge. Retain the supernatant for use in the $p H$ test. Using an appropriate conductivity meter that has been standardized with a potassium chloride conductivity calibration standard having a conductivity of $100 \mu \mathrm{~S}$ per cm , measure the conductivity of the supernatant after a stable reading is obtained, and measure the conductivity of the water used to prepare the test specimen. The conductivity of the supernatant does not exceed the conductivity of the water by more than $75 \mu \mathrm{~S}$ per cm .
$\mathbf{p H}\langle 791\rangle$ : between 5.0 and 7.5 in the supernatant obtained in the Conductivity test.

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 3 hours: it loses not more than $7.0 \%$ of its weight, or some other lower percentage, or is within a percentage range, as specified in the labeling.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Bulk density-Use a volumeter that has been fitted with a $10-$ mesh screen. The volumeter is freestanding of the brass or stainless steel cup, which is calibrated to a capacity of $25.0 \pm 0.05 \mathrm{~mL}$ and has an inside diameter of $30.0 \pm 2.0$ mm . Weigh the empty cup, position it under the chute, and slowly pour the powder from a height of $5.1 \mathrm{~cm}(2$ inches) above the funnel through the volumeter, at a rate suitable to prevent clogging, until the cup overflows. [NOTE-If excessive clogging of the screen occurs, remove the screen.] Level the excess powder, and weigh the filled cup. Calculate the bulk density by dividing the weight of the powder in the cup by the volume of the cup: the bulk density is within the labeled specification.

## Particle size distribution estimation by analytical sieving

 $\langle 786\rangle$ - [NOTE-In cases where there are no functionality-related concerns regarding the particle size distribution of the article, this test may be omitted.] Where the labeling states the particle size distribution, determine the particle size distribution as directed in the chapter.Water-soluble substances-Shake 5.0 g with about 80 mL of water for 10 minutes, filter with the aid of vacuum through filter paper (Whatman No. 42 or equivalent) into a vacuum flask. Transfer the filtrate to a tared beaker, evaporate to dryness without charring, dry at $105^{\circ}$ for 1 hour, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed $12.5 \mathrm{mg}(0.25 \%)$.

Ether-soluble substances-Place 10.0 g in a chromatographic column having an internal diameter of about 20 mm , and pass 50 mL of peroxide-free ether through the column. Evaporate the eluate to dryness in a previously dried and tared evaporating dish with the aid of a current of air in a fume hood. After all the ether has evaporated, dry the residue at $105^{\circ}$ for 30 minutes, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 5.0 mg ( $0.05 \%$ ).

Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.001 \%$.
Organic volatile impurities, Method $I V\langle 467\rangle$ : meets the requirements.■1S (NF23)

## BRIEFING

Powdered Cellulose, NF 22 page 2847 and page 1307 of $P F$ 29(4) [July-Aug. 2003]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Powdered Cellulose monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based on the corresponding monograph for Powdered Cellulose that was prepared by the U.S. Pharmacopoeia. This draft was based in part on comments from the European and Japanese Pharmacopoeias in response to the Provisional Harmonized Text Stage 5A and 5B drafts.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Labeling | - | + | + |
| Identification A | + | + | + |
| Identification B | + | + | + |
| pH | + | + | + |
| Loss on drying | + | + | + |
| Residue on ignition | + | + | + |
| Water-soluble <br> substances | + | + | + |
| Ether-soluble <br> substances | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Identification C-Dispersion test (JP); Characters, Heavy metals, Microbial limits, Packaging and storage.

Specific local attributes: USP: Organic volatile impurities.
Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.

Differences between the ADOPTION STAGE 6 document and the current $N F$ monograph include the following:
(1) Definition-No change.
(2) Packaging and storage-No change.
(3) Labeling-No change.
(4) Identification test $B$-This test is deleted. The former test $C$ is now labeled as test $B$. The deleted test is considered a func-tionality-related test, which is not appropriate for Harmonization.
(5) Identification test $C$-Now labeled as Identification test $B$. The lower limit for the degree of polymerization is deleted, as are requirements to be within the labeled specification.
(6) Microbial limits-No change.
(7) pH -No change.
(8) Loss on drying - The limit is increased to $6.5 \%$ from $6.0 \%$ to conform to EP and JP standards. The drying time is increased from 2 hours to 3 hours.
(9) Residue on ignition-The addition of sulfuric acid is allowed. The limit has not changed.
(10) Water-soluble substances-No change.
(11) Ether-soluble substances-No change.
(12) Heavy metals-No change.
(13) Organic volatile impurities-No change.
(EMC: J. Lane) RTS-41235-10

## Change to read:

## Powdered Cellulose

\#-Powdered Cellulose is purified, mechanieally disintegrated cellulose prepared by processing alpha celltt lose obtained as a pulp from fibrous plant materials.

Packaging and storage Preserve in tight containers.
Labeling. The labeling indieate the neminal-degree of pelymer ization value. Degree of polymerization compliance is determined using Identification test $C$.

## Identification-

A: Prepare indinated zine chloride solution by dissolving 20 g of zine chloride and 6.5 g of petassimm iodide in 10.5 mL of water. Add 0.5 g of iodine, and shake for 15 minutes. Place about 10 mg of Powdered Cellulese on wateh glass, and disperse in 2 mL of iodinated zine chloride solution: the substance takes on a violet bletecolor.

B: Mix 30 g with 270 mL of water in a single-speed, hight speed (equal to or greater than $18,000-\mathrm{rpm})$ power blender that has a clover shape jar design for 5 minutes. The jar and blades meet the following speciffentions: the jar has an inside diameter of 7.0 em at the bettom and 9.2 cm at the top, and an overall height of 21.9 cm ; and the 4 blades are arranged so that 2 of the blades are peinted up and 2 are peinted down. Transfer 100 mL of the disper
sion to a 100 mL graduated cylinder, and allow to stand for 1 hour: the Powdered Cellulose settles in the cylinder, and a supernatant liquid appears above the layer of the cellulose.
C: Transfer 0.25 of Powdered-Cellulose, aceurately weighed to 0.1 mg , to a 125 mL conienl flask. Proceed as direeted for Identification test $B$ under Mieroerystalline Cellullose, begin ning with " Add 25.0 mL of water." The degree of polymerization is be ween 440 and 2250 and is within the labeled speciffention.
Mierobial limits $\langle 64$-The tatallabic mierobial count not exceed 1000 efu per g, the total combined molds and yeasts count does not exceed 100 efuper g, and it meets the requirement of the tests for absenee of Staphytococus atreus and Psedemand teruginesa and for absence of Eseherichiceoli and Salmenellat species.
$\mathbf{p H}\langle 797\rangle$-Mix 10 g with 90 mL of water, and allow to stand with oceasional-stirring for 1 hour: the pH -f the supernatant liquid is between 5.0 and 7.5.
Less ondrying $\left\langle 731\right.$ ) - Dry it at $105^{\circ}$ for 2 hours: it loses not more than $6.0 \%$ of its weight.
Residue-on-ignition- $\langle 284$ ): not more than 0.3\%, caleulated on the dried basis, the addition of sulfuric acid being omitted frem the procedure.
Water-soluble-substanees Mix 6.0 g with $90-\mathrm{mL}$ of recently beiled and cooled water, and allow to stand with oceasional stirring for 10 minttes. Filter, with the aid of vaettm, diseard the frist 10 mL of the filtrate, and pass the filtrate through the same filter a second time, if necessary, to obtain a clear filtrate. Evaporate a 15.0 mL portion of the filtrate in a tared evaporating dish to dryness without chatring, dry at $105^{\circ}$ for 1 hour, cool in a desiecator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination doe not eweed 15.0 mg ( $1.5 \%$ )

Ether-soluble substanees Place 10.0 gin achrematography col umm having an internal diameter of about 20 mm , and pass 50 mL of peroxide free ether through the column. Evaporate the eluate to dryness in a previously dried and tared evaporating dish with the aid of a current of air in a fume hood. After all the ether has ewaperated, dry the residue at $105^{\circ}$ for 30 minntes, cool in a desiecater, and weigh: the difference be ween the weight of the residue and the weight obtained from a blank determination does not exeeed 15.0 mg ( $0.15 \%$ )
Heary metals, Meth $I\langle\langle 234\rangle:-0.001 \%$.
Organic volatile impurities, Method $W\langle\langle 467\rangle$ : meets the requirements.

Labeling-The labeling indicates the nominal degree of polymerization value. Degree of polymerization compliance is determined using Identification test $B$.

## Identification-

A: Prepare iodinated zinc chloride solution by dissolving 20 g of zinc chloride and 6.5 g of potassium iodide in 10.5 mL of water. Add 0.5 g of iodine, and shake for $15 \mathrm{~min}-$ utes. Place about 10 mg of Powdered Cellulose on a watch glass, and disperse in 2 mL of iodinated zinc chloride solution: the substance takes on a violet-blue color.
B: Transfer 0.25 g of Powdered Cellulose, accurately weighed to 0.1 mg , to a $125-\mathrm{mL}$ conical flask. Add 25.0 mL of water and 25.0 mL of 1.0 M cupriethylenediamine hydroxide solution. Immediately purge the solution with nitrogen, insert the stopper, and shake on a wrist action shaker or other suitable mechanical shaker until completely dissolved. Transfer 7.0 mL of the solution to a calibrated number 150 Cannon-Fenske, or equivalent, viscosimeter. Allow the solution to equilibrate at $25 \pm 0.1^{\circ}$ for not less than 5 minutes. Time the flow between the two marks on the viscosimeter, and record the flow time, $t_{1}$, in seconds. Calculate the kinematic viscosity, $(K V)_{1}$, of the Powdered Cellulose taken by the formula:

$$
t_{1}\left(k_{1}\right)
$$

in which $k_{1}$ is the viscosimeter constant (see Viscosity $\langle 911\rangle$ ). Obtain the flow time, $t_{2}$, for a 0.5 M cupriethylenediamine hydroxide solution using a number 100 CannonFenske, or equivalent, viscosimeter. Calculate the kinematic viscosity, $(K V)_{2}$, of the solvent by the formula:

$$
t_{2}\left(k_{2}\right)
$$

## ■ Powdered Cellulose

» Powdered Cellulose is purified, mechanically disintegrated cellulose prepared by processing alpha cellulose obtained as a pulp from fibrous plant materials.

Packaging and storage-Preserve in tight containers.
in which $k_{2}$ is the viscosimeter constant. Determine the relative viscosity, $\eta_{\text {rel }}$, of the Powdered Cellulose specimen taken by the formula:

$$
(K V)_{1} /(K V)_{2} .
$$

Determine the intrinsic viscosity, $[\eta]$ c, by interpolation, using the Intrinsic Viscosity Table in the Reference Tables section. Calculate the degree of polymerization, $P$, by the formula:

$$
(95)[\eta] c / W_{s}[(100-\% L O D) / 100],
$$

in which $W_{s}$ is the weight, in g , of the Powdered Cellulose taken; and $\% L O D$ is the value obtained from the test for Loss on drying. The degree of polymerization is greater than 440.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed 1000 cfu per g , the total combined molds and yeasts count does not exceed 100 cfu per g , and it meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa and for absence of Escherichia coli and Salmonella species.
$\mathbf{p H}\langle 791\rangle$-Mix 10 g with 90 mL of water, and allow to stand with occasional stirring for 1 hour: the pH of the supernatant is between 5.0 and 7.5 .

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 3 hours: it loses not more than $6.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.3 \%$, calculated on the dried basis.

Water-soluble substances-Mix 6.0 g with 90 mL of recently boiled and cooled water, and allow to stand with occasional stirring for 10 minutes. Filter, with the aid of vacuum, discard the first 10 mL of the filtrate, and pass the filtrate through the same filter a second time, if necessary, to obtain a clear filtrate. Evaporate a $15.0-\mathrm{mL}$ portion
of the filtrate in a tared evaporating dish to dryness without charring, dry at $105^{\circ}$ for 1 hour, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 15.0 mg (1.5\%).

Ether-soluble substances-Place 10.0 g in a chromatography column having an internal diameter of about 20 mm , and pass 50 mL of peroxide-free ether through the column. Evaporate the eluate to dryness in a previously dried and tared evaporating dish with the aid of a current of air in a fume hood. After all the ether has evaporated, dry the residue at $105^{\circ}$ for 30 minutes, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed $15.0 \mathrm{mg}(0.15 \%)$.

Heavy metals, Method II $\langle 231\rangle$ : $0.001 \%$.
Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.■1S (NF23)

## Briefing

Croscarmellose Sodium, NF 22 page 2856 and page 702 of $P F$ 30(2) [Mar.-Apr. 2004]. A modification is made in the test for Degree of substitution to correct the endpoint color to agree with the harmonization text.
(EMC: J. Lane) RTS-41224-1

## Change to read:

## Crosearmellose Sodium

H-Crosearmellose Sodium is a cross linked polymer of earboxymethyleellulose sodium.

Packaging and-storage Preserve in tight containers.

## Identification-

A: Mix $1 \frac{\mathrm{~g}}{\mathrm{~g}}$ of it with 100 mL of methylene blue solution ( 1 im 250,000 ), stir the mixture, and allow it to settle: the Cresearmellese Sodium absorbs the methylene blue and settles as a blue, fibrous mass.

B: Mix 1 g of it with 50 mL of water. Transfer 1 mL of the mixture to a small test tube, and add 1 mL of water and 5 drops of 1 naphthel TS. Ineline the test ube, andearefully add 2 mL of sut furic acid dow the side so that it forms a lower layer: a red purple color develops at the interface.

6: A pertion of the mixture of it with water, prepared as directed in Identifion test $B$, respends to the tests for Sodium〈194〉:
$\mathbf{p H}(794\rangle$ - Mix 1 g of it with-99-mL of water for 1 hour: the pH of the dispersion is between 5.0 and 7.0 .
Loss-0n-drying $\left\langle 734\right.$ ) Dry it at $105^{\circ}$ to constant weight: it loses net more than $10.0 \%$ of its weight.
Sodium-chloride and-sodium-glyeolate-
SODH: CHLORIDE. Weigh aceurately about 5 of it into - 250 mL beaker, add 50 mL of water and 5 mL of $30 \%$ hydrogen per exide, and heat on a steam bath for 20 minutes, stirring oecasion ally to ensure hydration. Cool, add 100 mL of water and 10 mL of nitrie acid, and titrate with 0.05 N silver nitrate VS , determining the endpoint potentiometrieally, using a silver based indientor elee trode and a double jumetion reference electrode containing $10 \%$ potassium nitrate filling solution in the outer jacket and a standard filling solution in the inner jacket, and stirring constantly (see Ti trimetry (544) ). Caleulate the percentage of sodium chloride in the specimen taken by the formmata:

$$
584.4 V N H[(100-b) 47
$$

in which $V$ and $N$ represent the volume, in mL , and the nommality, respectively, of the-silver nitrate, $b$ is the pereentage of Less on drying, determined separately, $W$ is the weight, in of, of the-speei men, and 584.4 is an equivalenee factor for sodium-chloride.

SODUM-GLYCOLATE Transfer about 500 mg of it, aceurately weighed, inte a 100 mL beaker, meisten thereughly with 5 mL of glacial acetic acid, followed by 5 mL of water, and stir with a glass red to ensure proper hydration (usually abeut 15 minutes). Slowly add 50 mL of acetone, with stirring, then add 1 g of sodium ehloride, and stir for several minutes to ensure eomplete precipita tion of the earbexymethyleellulese. Filter threugh aseft, open tex fared paper, previensly wetted with a small amennt of acetene, and evllect the flltrate in a 100 mL volumetric flask. Use an additionat 30 mL of acetone to facilitate the transfer of the selids and to wash the filter cake, then dilute with acetone to volume, and mix.

Prepare a-series of standard solutions as follows. Transfer 100 mg of glyeolic acid, previously dried in a desiceator at roem tem perature overnight and aceurately weighed, to a 100 mL volut metric flask, dissolve-in water, dilute with water to volume, and mix. Use this selution within 30-days. Transfer 1.0, 2.0, 3.0, and 4.0 mL pertions of the selation, respectively, to separate 100 mL volumetric flacks, add water to each flask to make 5 mL , then ade 5 mL of glacial acetic acid, dilute with acetone to volume, and mix.

Transfer 2.0 mL of the test solution and 2.0 mL of each standard selution teseparate 25 mL velumetric flacks, and prepare a blank flask eontaining 2.0 mb of a selution containing $5 \%$ each of glaciat acetic aeid and water in acetene. Place the uncovered flasks in a beiling water bath for 20 minutes, aceurately timed, to remove the acetone, remove from the bath, and cool. Add to each flask 5.0 mL of 2,7 dihydroxynaphthatene TS , mix, add an additionat 15 mL , and again mix. Gover the mouth of each flack with a-small piece of aluminum foil. Place the flasks upright in a boiling water bath for 20 minutes, then remove from the bath, cool, dilute-with sulfuric acid to volume, and mix.

Determine the abserbance of each selution at 540 nm, with a suitable-spectrephotemeter, against the blank, and prepare-a-standardeurve using the absorbanees-obtained from the-standard soltr
tions. From the standard curve and the absorbance of the test specimen, determine the weight (w), in mg, of glycolic acid in the specimen, and calculate the percentage of sodium glycolate in the specimen taken by the formmat:

$$
12.9 w /[(100-b) H]
$$

in which 12.9 is a factor eonverting sfyeolic acid to sodium glyeetate, $b$ is the pereentage of Lass an drying, determined separately, and $W$ is the weight, in s, of the specimen. The sum of the pereentages of sodium chloride and sodium glycolate is not more than $0.5 \%$.
Heary metats, Method $I T\langle Z 31\rangle:-0.001 \%$.
Degree of substitution Transfer about 1 g of it, aceurately weighed, to a glass stoppered, 500 mL conieal flask, add 300 mL of sodium chloride solution ( 1 in 10 ), then add $25.0-\mathrm{mL}$ of 0.1 N sodium hydroxide VS. Insert the stopper, and allow to stand for 5 minates with intermittent shaking. Add 5 drops of m- eresel purple TS, and from abure add about 15 mL of 0.1 N hydrochlorie acidVS. Insert the stopper in the flask, and shake. If the solution is purple, add 0.1 N hydrochloric acid VS in 1 mL portions until the solution beemes yellow, shaking after each addition. Titrate with $\theta .1 \mathrm{~N}$ sodimm hydroxide VS to a priple endpoint. Caleulate the net number of milliequivalents, $M$, of base required for the neutralization of 1 g of Croseamellose Sodium, on the dried basis. Deter mine the pereentage of residue on ignition, $C$, of the Groseamellose Sodium on the dried basis as directed under Resi the on Ignition $\langle 281\rangle$, using sufficient culfaric acid to meisten the entire residue after the initial-charring step, and additional sulfurie acid if an exeessive amount of carbonaceous material remains after the initial complete volatilization of white fumes.
Galeulate the degree of acid earboxymethyl substitution, A, taken by the formma:-

$$
1150 \mathrm{M} /(7102 \quad-412 \mathrm{M} \quad 80 \mathrm{C})
$$

Galculate the degree of sodium carboxymethyl substitution, $S$, ta ken by the formula:

$$
(162+584) C 1(7102 \quad 806)
$$

The degree of substitution is the sum of $A+S$. It is been 0.60 and 0.85 , caleulate on the dried basis.
Content of water-soluble material-Disperse about 10 g, ac eurately weighed, in 800 mL of water, aceurately measured, and stir for 1 minute every 10 minutes during the first 30 minutes. At tou to stand for an additional heur, or centrifuge, if neeessary. De ean about 200 mL of the queous slumy onto a rapid flltering fller paper in a vacuum filtration funnel, apply vacuum, and collect about 150 mL of the filtrate. Pour the filtrate into a tared 250 mL beaker, weigh aceurately, and calculate the weight, in g, of the fil trate, $\mathrm{H}_{3}$, by difference. Coneentrate on a hot plate a amall vol ume, but not to dryness, dry at $105^{\circ}$ for 4 houtrs, again weigh, and ealeulate the weight, in g , of residue- $H_{+}$, by difference. Caleulate the pereentage of water soluble material in the-specimen, on the dried basis, taken by the formula:-

$$
100 H_{+}\left(800+H_{2}\right)\left[H_{2} H_{2}(1-0.01 b)\right],
$$

in which $H_{2}$ is the weight, in $\frac{5}{5}$, of the specimen taken, and $b$ is the pereentage Less on drying of the specimen taken. It is between $4.0 \%$ and $10.0 \%$.
Settling volume $\mathrm{Te}-75 \mathrm{~mL}$ of water in a 100 mL graduated cy linder add 1.5 g of it in 0.5 g pertions, shaking vigoreusly after each addition. Add water to make 100 mL , shake again until all of the powder is homegeneously distributed, and allow to stand for 4 hours. Note the volume of the settled mass. It is between 10.0 and 30.0 mL .

Organie volatile imptrities, Metha $I V\langle 467)$ : meets the requirements.

## ${ }^{\Delta}$ Croscarmellose Sodium

» Croscarmellose Sodium is the sodium salt of a cross-linked, partly $O$-(carboxymethylated) cellulose.

## Change to read:

Packaging and storage-Preserve in well-closed containers. ${ }^{\text {D }}$ No storage requirements specified. ${ }^{1 S}$ (NF23)

## Identification-

A: Mix 1 g of it with 100 mL of methylene blue solution (1 in 250,000 ), stir the mixture, and allow it to settle: the Croscarmellose Sodium absorbs the methylene blue and settles as a blue, fibrous mass.

B: Mix 1 g of it with 50 mL of water. Transfer 1 mL of the mixture to a small test tube, and add 1 mL of water and 5 drops of 1-naphthol TS. Incline the test tube, and carefully add 2 mL of sulfuric acid down the side so that it forms a lower layer: a reddish-violet color develops at the interface.

C: A portion of the mixture of it with water, prepared as directed in Identification test $B$, responds to the flame test for Sodium $\langle 191\rangle$.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed 1000 cfu per g , the total combined molds and yeasts count does not exceed 100 cfu per g , and it meets the requirements of the tests for absence of Escherichia coli. $\mathbf{p H}\langle 791\rangle$-Mix 1 g of it with 100 mL of water for 5 min utes: the pH of the dispersion is between 5.0 and 7.0.
Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 6 hours: it loses not more than $10.0 \%$ of its weight.

## Sodium chloride and sodium glycolate-

SODIUM CHLORIDE-Weigh accurately about 5 g of it into a $250-\mathrm{mL}$ beaker, add 50 mL of water and 5 mL of 30 percent hydrogen peroxide, and heat on a steam bath for 20
minutes, stirring occasionally to ensure hydration. Cool, add 100 mL of water and 10 mL of nitric acid, and titrate with 0.05 N silver nitrate VS, determining the endpoint potentiometrically, using a silver-based indicator electrode and a double-junction reference electrode containing $10 \%$ potassium nitrate filling solution in the outer jacket and a standard filling solution in the inner jacket, and stirring constantly (see Titrimetry $\langle 541\rangle$ ). Calculate the percentage of sodium chloride in the specimen taken by the formula:

$$
584.4 V N /[(100-b) W]
$$

in which 584.4 is the equivalence factor for sodium chloride; $V$ and $N$ represent the volume, in mL , and the normality, respectively, of the silver nitrate; $b$ is the percentage of Loss on drying, determined separately; and $W$ is the weight, in g , of the specimen.

## SODIUM GLYCOLATE-

Test solution-Transfer about 500 mg of Croscarmellose Sodium, accurately weighed, into a $100-\mathrm{mL}$ beaker, moisten thoroughly with 5 mL of glacial acetic acid, followed by 5 mL of water, and stir with a glass rod to ensure proper hydration (usually about 15 minutes). Slowly add 50 mL of acetone, with stirring, then add 1 g of sodium chloride, and stir for several minutes to ensure complete precipitation of the carboxymethylcellulose. Filter through a soft, opentextured paper, previously wetted with a small amount of acetone, and collect the filtrate in a $100-\mathrm{mL}$ volumetric flask. Use an additional 30 mL of acetone to facilitate the transfer of the solids and to wash the filter cake, then dilute with acetone to volume, and mix.

Standard solutions - Transfer 100 mg of glycolic acid, previously dried in a desiccator at room temperature overnight and accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. [NOTE—Use this solution within 30 days.] Transfer 1.0-
$\mathrm{mL}, 2.0-\mathrm{mL}, 3.0-\mathrm{mL}$, and $4.0-\mathrm{mL}$ portions of the solution, respectively, to separate $100-\mathrm{mL}$ volumetric flasks, add water to each flask to make 5 mL , then add 5 mL of glacial acetic acid, dilute with acetone to volume, and mix.

Procedure-Transfer 2.0 mL of the Test solution and 2.0 mL of each of the Standard solutions to separate $25-\mathrm{mL}$ volumetric flasks, and prepare a blank flask containing 2.0 mL of a solution containing $5 \%$ each of glacial acetic acid and water in acetone. Place the uncovered flasks in a boiling water bath for 20 minutes, accurately timed, to remove the acetone, remove from the bath, and cool. Add to each flask 5.0 mL of 2,7-dihydroxynaphthalene TS, mix, add an additional 15 mL , and again mix. Cover the mouth of each flask with a small piece of aluminum foil. Place the flasks upright in a boiling water bath for 20 minutes, then remove from the bath, cool, dilute with sulfuric acid to volume, and mix.

Determine the absorbance of each solution at 540 nm , with a suitable spectrophotometer, against the blank, and prepare a standard curve using the absorbances obtained from the Standard solutions. From the standard curve and the absorbance of the Test solution, determine the weight (w), in mg, of glycolic acid in the Test solution, and calculate the percentage of sodium glycolate in the portion of Croscarmellose Sodium taken by the formula:

$$
12.9 w /[(100-b) W],
$$

in which 12.9 is a factor converting glycolic acid to sodium glycolate; $b$ is the percentage of Loss on drying, determined separately; and $W$ is the weight, in g , of Croscarmellose Sodium taken to prepare the Test solution. The sum of the percentages of sodium chloride and sodium glycolate is not more than $0.5 \%$.

## Change to read:

Residue on ignition $\langle 281\rangle$ : between $14.0 \%$ and $28.0 \%$, calculated on the dried basis, about 1.0 g being used for the test, using sufficient sulfuric acid to moisten the entire residue after the initial charring step, and additional sulfuric acid if an excessive amount of carbonaceous material remains after the initial complete volatilization of white fumes. Ignition merature $60 \pm 50^{\circ}-\square_{1 S}$ (NF23)

Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.001 \%$.

## Change to read:

Degree of substitution-Transfer about 1 g of it, accurately weighed, to a glass-stoppered, $500-\mathrm{mL}$ conical flask, add 300 mL of sodium chloride solution ( 1 in 10), then add 25.0 mL of 0.1 N sodium hydroxide VS. Insert the stopper, and allow to stand for 5 minutes with intermittent shaking. Add 5 drops of $m$-cresol purple TS, and from a buret add about 15 mL of 0.1 N hydrochloric acid VS. Insert the stopper in the flask, and shake. If the solution is ${ }^{\text {vio- }}$ let, $1 \mathrm{SS}\left({ }_{\text {NF23 }}\right)$ add 0.1 N hydrochloric acid VS in $1-\mathrm{mL}$ portions until the solution becomes yellow, shaking after each addition. Titrate with 0.1 N sodium hydroxide VS to a purple ${ }^{\text {violet }}{ }_{1 S}{ }_{\text {(NF23) }}$ endpoint. Calculate the net number of milliequivalents, $M$, of base required for the neutralization of 1 g of Croscarmellose Sodium, on the dried basis.

Calculate the degree of acid carboxymethyl substitution, $A$, by the formula:

$$
1150 M /(7102-412 M-80 C)
$$

in which $C$ is the percentage of residue on ignition of the Croscarmellose Sodium as determined in the test for Residue on Ignition $\langle 281\rangle$.

Calculate the degree of sodium carboxymethyl substitution, $S$, by the formula:

$$
(162+58 A) C /(7102-80 C)
$$

The degree of substitution is the sum of $A+S$. It is between 0.60 and 0.85 , calculated on the dried basis.

Content of water-soluble material-Disperse about 10 g , accurately weighed, in 800 mL of water, accurately measured, and stir for 1 minute every 10 minutes during the first 30 minutes. Allow to stand for an additional hour, or centrifuge, if necessary. Decant about 200 mL of the aqueous slurry onto a rapid-filtering filter paper in a vacuum filtration funnel, apply vacuum, and collect about 150 mL of the filtrate. Pour the filtrate into a tared $250-\mathrm{mL}$ beaker, weigh accurately, and calculate the weight, in g , of the filtrate, $W_{3}$, by difference. Concentrate on a hot plate to a small volume, but not to dryness, dry at $105^{\circ}$ for 4 hours, again weigh, and calculate the weight, in g , of residue $W_{1}$, by difference. Calculate the percentage of water-soluble material in the specimen, on the dried basis, taken by the formula:

$$
100 W_{1}\left(800+W_{2}\right) /\left[W_{2} W_{3}(1-0.01 b)\right]
$$

in which $W_{2}$ is the weight, in g , of the specimen taken; and $b$ is the percentage Loss on drying of the specimen taken: not more than $10.0 \%$ is found.

Settling volume-To 75 mL of water in a $100-\mathrm{mL}$ graduated cylinder add 1.5 g of it in $0.5-\mathrm{g}$ portions, shaking vigorously after each addition. Add water to make 100 mL , shake again until all of the powder is homogeneously distributed, and allow to stand for 4 hours. Note the volume of the settled mass. It is between 10.0 and 30.0 mL .

Organic volatile impurities, Method $I V\langle 467\rangle$ : meets the requirements. $\mathbf{\Delta F F 2 3}$

BRIEFING

Ethylparaben, NF 22 page 2866 and page 1968 of PF 28(6) [Nov.-Dec. 2002]. The European Pharmacopoeia, a member of the Pharmacopoeial Discussion Group, is the coordinating pharmacopoeia in the efforts toward the international harmonization of compendial standards for this monograph. The presented text represents the ADOPTION STAGE 6 draft in the harmonization process.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Appearance of <br> solution | + | + | + |
| Acidity | + | + | + |
| Related substances ${ }^{*}$ | + | + | + |
| Sulphated ash | + | + | + |
| Assay | + | + | + |

* JP will not include the system suitability requirement and consequently will not include reference solution (b).

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Identification by infrared spectrophotometry, Storage.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.

Local requirements: JP: Heavy metals ( 20 ppm ); USP: Organic volatile impurities.

Differences between the ADOPTION STAGE 6 document and the current $N F$ monograph include the following:
(1) In the opening paragraph (the Definition)-Calculations using the dried substance are deleted, as the Loss on drying test is deleted. The acceptance range has been widened.
(2) Packaging and storage - No change.
(3) USP Reference standards-The reference standard for Methylparaben has been added for the Related substances test.
(4) Identification-The test for Melting range has been moved under Identification.
(5) Color of solution - This test is added to comply with EP standards.
(6) Melting range-Moved under Identification.
(7) Acidity-The EP test method has replaced the current USP method.
(8) Loss on drying-Deleted.
(9) Residue on ignition-The limits are increased to not more than $0.1 \%$ to comply with EP standards.
(10) Organic volatile impurities-No change.
(11) Related substances-This test is added to comply with EP standards.
(12) Assay-The sample amount and the amount of 1 N sodium hydroxide has changed and the heating process has changed to a specific temperature and does not include refluxing.
(EMC: J. Lane) RTS-41235-9

## Change to read:

## Ethylparaben



## $\epsilon_{2} H_{42} \theta_{2} \quad 166.17$

Benzoic acid, 4 hydroxy, ethyl ester.
Ethylp hydroxybenzonte $\quad[120-478]$.
\#Ethylparaben contains not less than-99.0 percent and net more than 100.5 percent of $\mathrm{C}_{9} \mathrm{H}_{49} \Theta_{3}$, caleulated on the dried basis.

Packaging and-storage- Preserve in well closed containers.
USP Reference-standards- $\langle 4\rangle$-USP Ethylparaben RS.
Identification, Infrated Absorption- 197 M ) :
Melting range $\langle 744\rangle$ :- between $115^{\circ}$ and $118^{\circ}$.
Organic volatile impurities, Methed $W$ (467): meets therequirements.
Other requirements It meets the requirements for Acidity, Less en drying, and Residue on ignition under Bullparaben.
Assay Proceed with Ethylparaben as directed in the Assay under Buthiparaben. Each mL of 1 N soditm hydroxide is equivalent to $166.2 \mathrm{mg}_{\mathrm{of}} \mathrm{C}_{9} \mathrm{H}_{40} \mathrm{O}_{2}=$

## Ethylparaben

$\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{O}_{3} \quad 166.17$

Benzoic acid, 4-hydroxy-, ethyl ester.

Ethyl p-hydroxybenzoate [120-47-8].
» Ethylparaben contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{O}_{3}$.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle$ —USP Ethylparaben RS. USP Methylparaben RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$.
B: Melting range $\langle 741\rangle$ : between $96^{\circ}$ and $99^{\circ}$.
Color of solution-Dissolve 1 g in alcohol, dilute with alcohol to 10 mL , and mix (Ethylparaben solution). This solution is clear and not more intensely colored than alcohol or a solution prepared immediately before use by mixing 2.4 mL of ferric chloride CS, 1.0 mL of cobaltous chloride CS, and 0.4 mL of cupric sulfate CS with 0.3 N hydrochloric acid to make 10 mL , and diluting 5 mL of this solution with 0.3 N hydrochloric acid to make 100 mL . Make the comparison by viewing the solutions downward in matched color-comparison tubes against a white surface (see Color and Achromicity $\langle 631\rangle$ ).

Acidity-To 2 mL of Ethylparaben solution prepared in the Color of solution test add 3 mL of alcohol, 5 mL of carbon dioxide-free water, and 0.1 mL of bromocresol green TS, and titrate with 0.10 N sodium hydroxide: not more than 0.1 mL is required to produce a blue color.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on 1.0 g .

## Related substances-

Test solution-Prepare a solution of Ethylparaben in acetone containing 10 mg per mL .
Standard solutions-Transfer 0.5 mL of the Test solution to a $100-\mathrm{mL}$ volumetric flask, dilute with acetone to volume, and mix (Standard solution A). Dissolve 10 mg , accurately weighed, of USP Methylparaben RS in 1 mL of the Test solution, and dilute with acetone to 10 mL (Standard solution $B$ ).

Procedure-Separately apply $2 \mu \mathrm{~L}$ of the Test solution and $2 \mu \mathrm{~L}$ of each Standard solution to a thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ), coated with a $0.25-\mathrm{mm}$ layer of chromatographic octadecylsilanized silica gel mixture. Develop the chromatogram in a solvent system consisting of a mixture of methanol, water, and glacial acetic acid ( $70: 30: 1$ ) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Examine the plate under short-wavelength UV light, and compare the intensities of any secondary spots observed in the chromatogram of the Test solution with that of the principal spot in the chromatogram of Standard solution $A$ : the intensity of any individual secondary spot in the chromatogram of the Test solution is not greater than that of the principal spot obtained in the chromatogram of Standard solution $A(0.5 \%)$. The test is not valid unless the chromatogram obtained with Standard solution $B$ shows two clearly separated principal spots.

Organic volatile impurities, Method $I V\langle 467\rangle$ : meets the requirements.

Assay-Transfer about 1.000 g of Ethylparaben, accurately weighed, to a flask fitted with a ground-glass stopper. Add 20.0 mL of 1 N sodium hydroxide VS, and heat at about $70^{\circ}$ for 1 hour. Cool rapidly in an ice bath. Carry out the titration of the solutions at room temperature. Titrate the excess sodium hydroxide with 1 N sulfuric acid VS, continuing the titration until the second point of inflection and determining the endpoint potentiometrically (see Titrimetry $\langle 541\rangle$ ). Perform a blank determination (see Residual Titrations under Titrimetry $\langle 541\rangle$ ). Each mL of 1 N sodium hydroxide is equivalent to 166.2 mg of $\mathrm{C}_{9} \mathrm{H}_{10} \mathrm{O}_{3 \cdot \text {-1 }}$ (NF23)

Briefing

Methylparaben, NF 22 page 2896 and page 575 of $P F$ 28(2) [Mar.-Apr. 2002]. The European Pharmacopoeia, a member of the Pharmacopoeial Discussion Group, is the coordinating pharmacopoeia in the efforts toward the international harmonization of compendial standards for this monograph. The presented text represents the ADOPTION STAGE 6 draft in the harmonization process.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Appearance of <br> solution | + | + | + |
| Acidity | + | + | + |
| Related substances* | + | + | + |
| Sulphated ash | + | + | + |
| Assay | + | + | + |

* JP will not include the system suitability requirement and consequently will not include reference solution (b).

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Identification by infrared spectrophotometry, Storage.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.

Local requirements: JP: Heavy metals ( 20 ppm ); USP: Organic volatile impurities.

Differences between the ADOPTION STAGE 6 document and the current $N F$ monograph include the following:
(1) In the opening paragraph (the Definition)-Calculations using the dried substance are deleted, as the Loss on drying test is deleted. The acceptance range has been widened.
(2) Packaging and storage-No change.
(3) USP Reference standards-No change.
(4) Identification-The test for Melting range has been moved under Identification. Other Identification tests have been omitted, as they are not needed with the Infrared Absorption and Melting range tests.
(5) Color of solution-This test is added to comply with EP standards.
(6) Melting range-Moved under Identification.
(7) Acidity-The EP test method has replaced the current USP method.
(8) Loss on drying-Deleted.
(9) Residue on ignition-A sample weight of 1.0 g is added.
(10) Organic volatile impurities-No change.
(11) Related substances-This test is modified to include one related substance, ethylparaben, for system suitability requirements.
(12) Assay-The sample amount and the amount of 1 N sodium hydroxide has changed, and the heating process has changed to a specific temperature and does not include refluxing.
(EMC: J. Lane) RTS-41235-4

## Change to read:

## Methylparaben



## $\mathrm{E}_{8} \mathrm{H}_{8} \mathrm{O}_{3} \quad 152.15$

Benzoic acid, 4 hydroxy, methyl ester.
Methyl $p$ hydroxybenzonte $[99-76-3]$.

H-Methylparaben contains not less than-99.0 percent and not more than 100.5 percent of $\mathrm{C}_{8} \mathrm{H}_{8} \Theta_{3}$.

Packaging and storage- Preserve in well closed containers.
USP Referenee-standards- $\langle H\rangle$-USP Methylparaben RS. USP Ethylpaben RS.

## Identifiention-

A: Infrated Absorption- 197 M$\rangle$ =
B: The principal spet obtained in the chrematogram- of Test solution B prepared as directed in the test for Chromatographic purity correspends in size and $R_{+}$value to that of the principal sper ebtrined from Standed solution- $B$.

C: Transfer about 10 mg to a tube, add 1 mL of sodium earbonate TS, mix, beil for 30 seconds, and cool (Test solution - 4). Transfer about 10 mg to seend test tube, add 1 mL of sodimm earbenate TS, and mix (Test solution B). [NOTE-The Methylparaben partly dissolves in Test solution B.]-Prepare a solution of 4 aminountipyrine in pH 9.0 alkaline berate buffer containing 4 mes per mL . Simultaneously add 5 mL of the- 4 amineantipyrine solution and 0.5 mL of potassium ferricyanide TS to Test solution $A$ and Test solution $B$, and mix: Test solution $B$ beemer yellow to erange brown and Test solution $A$ beeomes orange to red, with the coler of Test solution $A$ being clearly more intense than any similar color that may be obtained with Test solution $B$.
Color of solution Dissolve 1 g in alcohol, dilute with aleohol to 10 mL , and mix (Methylparaben solution). This solution is clear and not more intensely colored than a solution prepared immediately before use by mixing 2.4 mL of ferric chloride $\mathrm{CS}, 1.0 \mathrm{~mL}$ of eobaltous chloride $C S$, and 0.4 mL of eupric sulfate $C S$ with -0.3 N hydrechloric acid to make 10 mL , and diluting 5 mL of this solttion with 0.3 N hydrechlorie acid to make 100 mL . Make the eom parisen by viewing the solutions downward in matehed color emparisen tubes ggainst a white surface (see Color and Achromieif $\langle 634$ ) ).
Aeidity To 2 mL of Methylparable prepared in the Cot Or of solution test add 3 mL of aleohel, 5 mL of earben dioxidefree water, and 0.1 mL of bromoresol green TS, and titratewith 0.10 N sodium hydroxide: not more than 0.1 mL is required to produee ablue coler.
Residmeon-ignition- $\langle z 81\rangle$ : not mere than $0.1 \%$.

## Ghromatographie ptrity -

Fest solutions. Prepare a solution of Methylparaben in acetone eontaining 10 mg per mL (Test solution A). Transfer 1.0 mL of this solution to a 10 mL velumetric flack, dilute with acetone to vol the, and mix (Test soltion B).

Standard solutions. Transfer 0.5 mL of Test solution A to a 100 mL volumetric flask, dilute with acetone to volume, and mix (Stan dard solion 4). Dissolve an aceurately weighed quantity of USP Methylparaben PS in aeetone, and mix tobtain a solution having a known concentration of about 1 mg per mb (Standard solution B). Transfer about 10 mg of USP Ethylparaben-RS, aeeurately weighed, to a 10 mL volumetric flack, dissolve in- 1 mL of Test solution A, dilute with neetone to velume, and mix (Standeted solution $C$ ).
Preedure Separately apply $2 \mu \mathrm{~L}$ of each Test solution and 2 $\mu$ L of each Standard solution to a hin layer ehrematographic plate (seeChromtograpy $\langle 624$ ) ) matographic octadecylsilanized siliea gel mixtare. Pevelop the ehromatogram in a solvent system consisting of a mixture of methanol, water, and glacial acetic acid ( $70: 30: 1$ ) until the sol vent front has moved about three fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Examine the plate under short wavelength UV light, and eompare the intensities of any seeondary spots observed in the chrematogram of Test solution $A$ with that of the prineipal spet in the chromatogram of Stand solution A: the intensity of any individual secondary spot in the chromatogram-of Test solution $A$ is not greater than that of the prineipal spot obtained in the chromatogram of Standed solution $4(0.5 \%)$. The test is not valid unless the ehromatogram obtained with Standerd solution $-G$ shows two clearly separated principal-spets.
Melting range $\langle 744\rangle$ : be $125^{\circ}$ and $128^{\circ}$.
Organie volatile impurities, Methed $I V\langle 467\rangle$ : meets the requirements.
Assay Transfer about 2 gof Methylparaben, aceuraty weighed, to a flack fitted with a ground glass stopper and equipped for refluxing under a water cooled condenser. Add -40.0 mL of $1 \mathrm{~N}-\mathrm{se}$ dium hydroxide VS, and reflux for 1 hour. Cool to reom temperature, and rinse the condenser with water. Titrate the exeess sodium hydroxide with-1N sulfuric acid VS, continuing the titration until the second point of inflection and determining the end peint petentiometrieally (see Titrimetry $\langle 544$ ) ). Perform a blank determination (see Residual Titrations under Titrimetry (544)). Each mL of 1 N soditm hydroxide is equivalent to 152.2 mg of $\mathrm{G}_{8} \mathrm{H}_{8} \mathrm{O}_{3}=$

## Methylparaben

$\mathrm{C}_{8} \mathrm{H}_{8} \mathrm{O}_{3} \quad 152.15$

Benzoic acid, 4-hydroxy-, methyl ester.

Methyl p-hydroxybenzoate [99-76-3].

## » Methylparaben contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{8} \mathrm{H}_{8} \mathrm{O}_{3}$.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle$ —USP Ethylparaben RS. USP Methylparaben RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$.
B: Melting range $\langle 741\rangle$ : between $125^{\circ}$ and $128^{\circ}$.
Color of solution-Dissolve 1 g in alcohol, dilute with alcohol to 10 mL , and mix (Methylparaben solution). This solution is clear and not more intensely colored than alcohol or a solution prepared immediately before use by mixing 2.4 mL of ferric chloride CS, 1.0 mL of cobaltous chloride CS, and 0.4 mL of cupric sulfate CS with 0.3 N hydrochloric acid to make 10 mL , and diluting 5 mL of this solution with 0.3 N hydrochloric acid to make 100 mL . Make the comparison by viewing the solutions downward in matched colorcomparison tubes against a white surface (see Color and Achromicity $\langle 631\rangle$ ).

Acidity-To 2 mL of Methylparaben solution prepared in the Color of solution test add 3 mL of alcohol, 5 mL of carbon dioxide-free water, and 0.1 mL of bromocresol green TS, and titrate with 0.10 N sodium hydroxide: not more than 0.1 mL is required to produce a blue color.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on 1.0 g .

## Related substances-

Test solution-Prepare a solution of Methylparaben in acetone containing 10 mg per mL .

Standard solutions-Transfer 0.5 mL of the Test solution to a $100-\mathrm{mL}$ volumetric flask, dilute with acetone to volume, and mix (Standard solution A). Dissolve 10 mg , accurately weighed, of USP Ethylparaben RS in 1 mL of the Test solution, and dilute with acetone to 10 mL (Standard solution $B)$.

Procedure-Separately apply $2 \mu \mathrm{~L}$ of the Test solution and $2 \mu \mathrm{~L}$ of each Standard solution to a thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ), coated with a $0.25-\mathrm{mm}$ layer of chromatographic octadecylsilanized silica gel mixture. Develop the chromatogram in a solvent system consisting of a mixture of methanol, water, and glacial acetic acid ( $70: 30: 1$ ) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Examine the plate under short-wavelength UV light, and compare the intensities of any secondary spots observed in the chromatogram of the Test solution with that of the principal spot in the chromatogram of Standard solution $A$ : the intensity of any individual secondary spot in the chromatogram of the Test solution is not greater than that of the principal spot obtained in the chromatogram of Standard solution $A(0.5 \%)$. The test is not valid unless the chromatogram obtained with Standard solution $B$ shows two clearly separated principal spots.

Organic volatile impurities, Method $I V\langle 467\rangle$ : meets the requirements.

Assay-To about 1.000 g of Methylparaben, accurately weighed, add 20.0 mL of 1 N sodium hydroxide VS, and heat at about $70^{\circ}$ for 1 hour. Cool rapidly in an ice bath. Carry out the titration on the solutions at room temperature. Titrate the excess sodium hydroxide with 1 N sulfuric acid VS, continuing the titration until the second point of inflection and determining the endpoint potentiometrically (see Titrimetry $\langle 541\rangle$ ). Perform a blank determination (see Residual Titrations under Titrimetry $\langle 541\rangle$. Each mL of 1 N sodium hydroxide is equivalent to 152.1 mg of $\mathrm{C}_{8} \mathrm{H}_{8} \mathrm{O}_{3 \cdot \boldsymbol{\square}}$ 1S (NF23)

## BRIEFING

Propylparaben, NF 22 page 2924 and page 1970 of $P F$ 28(6) [Nov.-Dec. 2002]. The European Pharmacopoeia, a member of the Pharmacopoeial Discussion Group, is the coordinating pharmacopoeia in the efforts toward the international harmonization of compendial standards for this monograph. The presented text represents the ADOPTION STAGE 6 draft in the harmonization process.

## Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Appearance of <br> solution | + | + | + |
| Acidity | + | + | + |
| Related substances* | + | + | + |
| Sulphated ash | + | + | + |
| Assay | + | + | + |

* JP will not include the system suitability requirement and consequently will not include reference solution (b).

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Identification by infrared spectrophotometry, Storage.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.

Local requirements: JP: Heavy metals (20 ppm); USP: Organic volatile impurities.

Differences between the ADOPTION STAGE 6 document and the current $N F$ monograph include the following:
(1) In the opening paragraph (the Definition)-Calculations using the dried substance are deleted because the Loss on drying test is deleted. The acceptance range has been widened.
(2) Packaging and storage-No change.
(3) USP Reference standards-The reference standard for Ethylparaben has been added for the Related substances test.
(4) Identification-The test for Melting range has been moved under Identification.
(5) Color of solution-This test is added to comply with EP standards.
(6) Melting range-Moved under Identification.
(7) Acidity-The EP test method has replaced the current USP method.
(8) Loss on drying-Deleted.
(9) Residue on ignition-The limits are increased to not more than $0.1 \%$ to comply with EP standards.
(10) Organic volatile impurities-No change.
(11) Related substances-This test is added to comply with EP standards.
(12) Assay-The sample amount and the amount of 1 N sodium hydroxide has changed and the heating process has changed to a specific temperature and does not include refluxing.
(EMC: J. Lane) RTS-41235-2

## Change to read:

## Propylparaben


$\mathrm{E}_{10} \mathrm{H}_{42} \mathrm{O}_{2} \quad 180.20$
Benzoic acid, 4 hydroxy, propyl ester.
Propylp hydroxybenzoate [94-13-3].
H-Propylparaben contains not less than 99.0 percent and not more than 100.5 percent of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{O}_{3}$, calet tated on the dried basis.
Paeknging and-storage-Preserve in well closed containers.
USP Referenee standards $\langle H\rangle$-USP Propylpat RS.
Identifiention, Infrated Absorption- $\langle 197 \mathrm{M}\rangle$ )=
Melting range $\langle 744\rangle$ :- berween $95^{\circ}$ and $98^{\circ}$.
Organie volatile impurities, Methed $\mathrm{H}\langle 467\rangle$ : meets the requirements.
Other requirements It meets the requirements of the tests for Aeidity, Loss on drying, and Residue on ignition under Butl paraben.
Assay Proceed with Propylparaben as directed in the Assay under Buthlparaben. Each mL of 1 N sodium hydroxide is equivalent $180.2 \mathrm{mg}_{5}$ of $\mathrm{G}_{40} \mathrm{H}_{42} \mathrm{O}_{3}=$

## Propylparaben

$\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{O}_{3} \quad 180.20$
Benzoic acid, 4-hydroxy-, propyl ester.
Propyl $p$-hydroxybenzoate [94-13-3].
» Propylparaben contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{O}_{3}$.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle$ —USP Ethylparaben RS. USP Propylparaben RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{M}\rangle$.
B: Melting range $\langle 741\rangle$ : between $96^{\circ}$ and $99^{\circ}$.
Color of solution-Dissolve 1 g in alcohol, dilute with alcohol to 10 mL , and mix (Propylparaben solution). This solution is clear and not more intensely colored than alcohol or a solution prepared immediately before use by mixing 2.4 mL of ferric chloride $\mathrm{CS}, 1.0 \mathrm{~mL}$ of cobaltous chloride CS , and 0.4 mL of cupric sulfate CS with 0.3 N hydrochloric acid to make 10 mL , and diluting 5 mL of this solution with 0.3 N hydrochloric acid to make 100 mL . Make the comparison by viewing the solutions downward in matched col-or-comparison tubes against a white surface (see Color and Achromicity $\langle 631\rangle$ ).
Acidity-To 2 mL of Propylparaben solution prepared in the Color of solution test add 3 mL of alcohol, 5 mL of carbon dioxide-free water, and 0.1 mL of bromocresol green TS, and titrate with 0.10 N sodium hydroxide: not more than 0.1 mL is required to produce a blue color.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on 1.0 g .

## Related substances-

Test solution-Prepare a solution of Propylparaben in acetone containing 10 mg per mL .

Standard solutions-Transfer 0.5 mL of the Test solution to a $100-\mathrm{mL}$ volumetric flask, dilute with acetone to volume, and mix (Standard solution A). Dissolve 10 mg , accurately weighed, of USP Ethylparaben RS in 1 mL of the Test solution, and dilute with acetone to 10 mL (Standard solution B).

Procedure-Separately apply $2 \mu \mathrm{~L}$ of the Test solution and $2 \mu \mathrm{~L}$ of each Standard solution to a thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ) coated with a $0.25-\mathrm{mm}$ layer of chromatographic octadecylsilanized silica gel mixture. Develop the chromatogram in a solvent system consisting of a mixture of methanol, water, and glacial acetic acid $(70: 30: 1)$ until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Examine the plate under shortwavelength UV light, and compare the intensities of any secondary spots observed in the chromatogram of the Test solution with that of the principal spot in the chromatogram of Standard solution $A$ : the intensity of any individual secondary spot in the chromatogram of the Test solution is not greater than that of the principal spot obtained in the chromatogram of Standard solution $A(0.5 \%)$. The test is not valid unless the chromatogram obtained with Standard solution $B$ shows two clearly separated principal spots.

Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

Assay-Transfer about 1.000 g of Propylparaben, accurately weighed, to a flask fitted with a ground-glass stopper. Add 20.0 mL of 1 N sodium hydroxide VS, and heat at about $70^{\circ}$ for 1 hour. Cool rapidly in an ice bath. Carry out the titration of the solutions at room temperature. Titrate the excess sodium hydroxide with 1 N sulfuric acid VS, continuing the titration until the second point of inflection and determining the endpoint potentiometrically (see Titrimetry $\langle 541\rangle$ ). Perform a blank determination (see Residual Titrations under Titrimetry $\langle 541\rangle$ ). Each mL of 1 N sodium hydroxide is equivalent to 180.2 mg of $\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{O}_{3}$. 1 IS (NF23)

## Briefing

Saccharin, $N F 22$ page 2825 and page 1711 of $P F 29(5)$ [Sept.Oct. 2003]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Saccharin monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based in part on comments from the European and Japanese Pharmacopoeias in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the United States Pharmacopeia.

## Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Loss on drying | + | + | + |
| Readily carbonizable <br> substances | + | + | + |
| Residue on ignition | + | + | + |
| Limit of benzoate <br> and salicylate | - | + | + |
| Assay | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Heavy metals, Melting range, Clarity of solution, Limit of toluenesulfonamides, Identification (IR), Packaging and storage.

Specific local attributes: USP: Organic volatile impurities; JP: Description.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.

Differences between the ADOPTION STAGE 6 document and
the current $N F$ monograph include the following:
(1) In the opening paragraph (the Definition)-The lower limit is changed from not less than 98.0 percent to not less than 99.0 percent.
(2) Packaging and storage-No change.
(3) USP Reference standards-A reference for Saccharin is added for use in the Identification test.
(4) Clarity of solution-This test is added to comply with EP standards.
(5) Color of solution-This test is added to comply with EP standards.
(6) Identification-Identification tests $A$ and $B$ are replaced with a more definitive IR absorption test.
(7) Melting range-No change.
(8) Loss on drying-No change.
(9) Readily carbonizable substances-No change.
(10) Residue on ignition-No change.
(11) Limit of toluenesulfonamides-The test method and limits are changed to those of the European Pharmacopoeia, which include a more modern test method.
(12) Selenium-This test is deleted because it is unnecessary for this compound.
(13) Heavy metals-No change.
(14) Limit of benzoate and salicylate-No change.
(15) Organic volatile impurities-No change.
(16) Assay-No change.
(EMC: J. Lane) RTS-41235-6

## Change to read:

## Saceharin


$\mathrm{E}_{2} \mathrm{H}_{5} \mathrm{NO}_{3} \mathrm{~S} \quad 183.19$
1,2 Benzisethiazol-3(2H) one, 1,1 dioxide.
1,2 Benzisothiazolin 3-one-1,1 dioxide [81-07-2].
HSaceharin contains net less than 98.0 percent and net more than 101.0 pereent of $\mathrm{C}_{7} \mathrm{H}_{5} \mathrm{NO}_{3} \mathrm{~S}$, ealeulated on the dried basis.

Packaging and-storage- Preserve in well closed containers.
USP Reference standards- $\langle 4\rangle$-USP - Toltenesulfonnide RS. USP $P_{p}$ Tolterndfande RS.

## Identifieation-

A: Dissolveabent 100 mg in 5 mL of sodium hydroxide solution ( 1 in 20), evaporate the solution to drymess, and gently fuse the residue over a small flame until it no lenger evolves ammenia. A1 tow the residue to eol, dissolve it in 20 mL of water, neutralize the solution with 3 N hydrechloric acid, and filter: the addition of a drop of ferric chloride TS to the filtrate produces a violet coler.

B: Mix 20 mg with 40 mg of resoreinel, add 10 dreps of sul furie acid, and heat the mixture in a suitable liquid bath at $200^{\circ}$ for 3 minttes. Allow it to cool, and add 10 mL of water and an exeess of 1 N sodium hydroxide: a flureseent green liquid results.
Melting range $\langle 744\rangle$ :- be $226^{\circ}$ and $230^{\circ}$.
Lossondrying $\left\langle 734\right.$ ) - Dry it at $105^{\circ}$ for 2 hems: it loses not mere than $1.0 \%$ of its weight.
Readily earbonizable substanees- $\langle 274\rangle$ - Dissolve 200 mg in 5 mL of sulftrie acid TS, and keep at a temperature of $48^{\circ}$ to $50^{\circ}$ for 10 minutes: the solution has no more color than Matehing Flaid A.

Residue-0n ignition- $\langle 284\rangle$ : net mere than $0.2 \%$.
Toluenesulfonamides-
mernal stand solution Place 10 mg of n-tricosane in a 10 mL volumetric flask, dissolve in $n$ heptane, dilute with $n$ heptane to valume, and mix.

Standard stock solution Transfer 20 me weighed, of USP o Toluenesulfonamide RS and of USP $p$ - Toluenesulfenamide RS to a 10 mL volumetric flask, dissolve in methylene chloride, dilute with methylene chloride to volume, and mix.

Stan Transfer 100, 150, 200, and $250 \mu \mathrm{~L}$, re spectively, of Standard stoek solution to each of four 10 mL velt metric flasks. Add $250 \mu \mathrm{~L}$, aceurately measured, of Internat standerd solution to each flask, dilute each with methylene-chle-
ride to volume, and mix. These preparations contain, in each mL , $25 \mu \mathrm{~g}$ of $n$-trieosane and, respectively, $20,30,40$, and 50 - g of each toluenesulfonamide isomer.

Test preparation- Prepare as direeted under Column Partition Chromatography (see Chrematography ( 624 ) , employing a chromatographie tube fitted with a porous glass disk in its base, a plas tie stopeock on the delivery tube, and a reservir at the top. Add a mixture consisting of 12 g of Solid Support and a solution of 2.0 ह\%, aceurately weighed, of Saceharin with 12 mL of filtered soditm biearbenate solution ( 1 in 11). Add about 200 mg of sodium biear benate to effect complete solution of the saceharin. Pack the com tents of the tube by tapping the column on a padeled surface, and then by tamping firmly from the top. Place 100 mL of methylene ehloride in the reserveir, and adjust the stopeock so that 50 mL of eluate is collected in 20 to 30 minter. To the eluate add $25 \mu \mathrm{\mu}$ of Internal standard solution, mix, and concentrate the solution, by suitable means, to a volume of 1.0 mL .

Chromagre syist (see-Chromegraphy $\langle 624$ )) Under ypieal conditions, the instrument is equipped with a flame-ionization detector, and contains a $1.8 \mathrm{~m} \times 3.2 \mathrm{~mm}$ glass columm packed with $10 \%$ liquid phase 63 on 100 to 120 mesh suppert S1AB, utilizing a glass lined sample introduction system or on cellumn injection. The injector pert, column, and detector block are maintained at temperatures of about $225^{\circ}, 210^{\circ}$, and $250^{\circ}$, re spectively, and diry helium is used as the earrier ges at a flow rate of about 30 mL per minute.

Procedure Inject pertions (about $2.5 \mu \mathrm{~L}$ ) of the Stated pre parations, suceessively, into a gas chrematograph, and recordeach ehromatogram so as to obtain at least $50 \%$ of maximum recerder respense. Measure the areas under the first ( 8 toltenesulfenamide), second ( $p$-toluenesulfonamide), and third ( $n$ trieosane) peaks, and fer each chromatogram record the values as $A_{o}, A_{t}$, and $A_{A}$, respec tively. Caleulate the ratios $R_{0}$, and $R_{p}$ taken by the equations:

$$
R_{\theta}=A_{\theta}+A_{\#} \text { and } R_{F}=A_{p}+A_{\#} ;
$$

and prepare standard curves by plotting the concentrations, in $\mu \mathrm{g}$ per mL, of USP $\&$ Toluenesulfonamide RS and of USP $p$-Toluenesulfonamide $R S$ in the Stethedrd preparations versus $R_{s}$ and $R_{p}$, re spectively. [NOTE-Relative retention times are, approximately, $\theta .39$ for $\theta$ tolthenesulfonamide, 0.46 for $p$ toltenesulfonamide, and 1.0 for $n$ trieosane.] Similarly inject a pertion (about $2.5 \mu \mathrm{~L}$ ) ef the Test preparation, and record the chromatogram. Measure the areas under the first (o-toluenesulfonamide), second ( $p$-tolthenesut fonamide), and third (n tricosane) peaks, and record the values as $t_{s}, t_{p}$, and $t_{A}$, respectively. Caleulate the ratios - , and + , taken by the equations:-

$$
f_{0}=A_{0}+A_{t}-\text { and } r_{p}=a_{p}+A_{A_{*}} ;
$$

and, from the standard-urve, determine the concentration, in $\mu \mathrm{g}$ per mL , of each toluenesulfonamide isomer in the Test prepara tion: the total amount of toluenesulfonamides in the specimen taken is not more than $0.0025 \%$.
Selenium- $\langle 294\rangle: \quad 0.003 \%$, a 100 mg specimen, mixed with 100 mg of magnesitm oxide, being used.
Heary metals, Method $H\langle Z 34\rangle: \quad 0.001 \%$.
Benzoie and salieylic aeids To 10 mL of a hot, satrated solth tion of it add ferric chloride TS, dropwise: no precipitate or violet color appears in the liquid.
Organic volatile impurities, Method $V\langle 467\rangle$ : meets the requirements.

Solvent Use dimethyl sulfoxide.
Assay Aceurately weigh about 500 mg of Saceharin, dissolve in 40 mL of aleohel, add 40 mL of water, mix, add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Perform a blank determination, and make any nee ssary correction. Each mL of 0.1 N sodium hydroxide is equivalent to $18.32 \mathrm{mg}_{5}$ of $\mathrm{C}_{7} \mathrm{H}_{5} \mathrm{NO}_{3} \mathrm{~S}$.

## ■Saccharin


$\mathrm{C}_{7} \mathrm{H}_{5} \mathrm{NO}_{3} \mathrm{~S} \quad 183.19$
1,2-Benzisothiazol-3(2H)-one, 1,1-dioxide.
1,2-Benzisothiazolin-3-one 1,1-dioxide [81-07-2].
» Saccharin contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{7} \mathrm{H}_{5} \mathrm{NO}_{3} \mathrm{~S}$, calculated on the dried basis.

Packaging and storage-Preserve in well-closed containers. Store at room temperature.

USP Reference standards $\langle 11\rangle —$ USP Saccharin RS. USP $o$-Toluenesulfonamide RS. USP p-Toluenesulfonamide RS.

Clarity of solution-[NOTE-The Test solution is to be compared to Reference suspension $A$ and to water in diffused daylight 5 minutes after preparation of Reference suspension A.]

Hydrazine solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Methenamine solution-Transfer 2.5 g of methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension-[NOTE-This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before
use.] Transfer 25.0 mL of Hydrazine solution to the Methenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension A. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension B.

Test solution-Dissolve 5.0 g of test material in about 20 mL of a 200 g per L solution of sodium acetate, dilute with the same solution to 25 mL , and mix.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Reference suspension $A$, Reference suspension $B$, water, and a 200 g per L solution of sodium acetate to separate matching test tubes. Compare the Test solution, Reference suspension $A$, Reference suspension $B$, water, and a 200 g per L solution of sodium acetate in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and Light-Scattering 〈851〉). [NOTEThe diffusion of light must be such that Reference suspension $A$ can readily be distinguished from water and that Reference suspension $B$ can readily be distinguished from Reference suspension A.] The Test solution shows the same clarity as that of water, or the 200 g per L solution of sodium acetate, or its opalescence is not more pronounced than that of Reference suspension $A$.

## Color of solution-

Standard stock solution-Combine 3.0 mL of ferric chloride $\mathrm{CS}, 3.0 \mathrm{~mL}$ of cobaltous chloride $\mathrm{CS}, 2.4 \mathrm{~mL}$ of cupric sulfate CS , and 1.6 mL of dilute hydrochloric acid ( 10 g per L).

Standard solution-[NOTE—Prepare the Standard solution immediately before use.] Transfer 1.0 mL of Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix.
Test solution-Use the Test solution from Clarity of solution.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of the Standard solution, a 200 g per L solution of sodium acetate, and water to separate matching test tubes. Compare the Test solution, the Standard solution, a 200 g per L solution of sodium acetate, and water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). The Test solution has the appearance of water or the 200 g per L solution of sodium acetate, or is not more intensely colored than the Standard solution.

Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
Melting range $\langle 741\rangle$ : between $226^{\circ}$ and $230^{\circ}$.
Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 2 hours: it loses not more than $1.0 \%$ of its weight.

Readily carbonizable substances $\langle 271\rangle$-Dissolve 200 mg in 5 mL of sulfuric acid (between $94.5 \%$ and $95.5 \%$ [w/w] of $\mathrm{H}_{2} \mathrm{SO}_{4}$ ), and keep at a temperature of $48^{\circ}$ to $50^{\circ}$ for 10 minutes: the solution has no more color than Match$\operatorname{ing}$ Fluid $A$, when viewed against a white background.

Residue on ignition $\langle 281\rangle$ : not more than $0.2 \%$. Ignition temperature: $600 \pm 50^{\circ}$.

Heavy metals, Method II $\langle 231\rangle$ : $\quad 0.001 \%$.

## Limit of toluenesulfonamides-

Internal standard solution-Dissolve 25 mg of caffeine in methylene chloride, and dilute with the same solvent to 100 mL .

Reference solution-Dissolve 20.0 mg of USP $o$-Toluenesulfonamide RS and 20.0 mg of USP $p$-Toluenesulfonamide RS in methylene chloride, and dilute with the same solvent to 100.0 mL . Dilute 5.0 mL of the solution with methylene chloride to 50.0 mL . Evaporate 5.0 mL of the final solution to dryness in a stream of nitrogen. Dissolve the residue in 1.0 mL of the Internal standard solution.

Test solution-Suspend 10.0 g of the substance to be examined in 20 mL of water, and dissolve using 5 mL to 6 mL of 10 N sodium hydroxide. If necessary adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 7 to 8 , and dilute with water to 50 mL . Shake the solution with four quantities each of 50 mL of methylene chloride. Combine the lower layers, dry over anhydrous sodium sulfate, and filter. Wash the filter and the sodium sulfate with 10 mL of methylene chloride. Combine the solution and the washings, and evaporate almost to dryness in a water bath at a temperature not exceeding $40^{\circ}$. Using a small quantity of methylene chloride, quantitatively transfer the residue into a suitable 10 mL tube, evaporate to dryness in a stream of nitrogen, and dissolve the residue in 1.0 mL of the Internal standard solution.

Blank solution-Evaporate 200 mL of methylene chloride to dryness in a water bath at a temperature not exceeding $40^{\circ}$. Dissolve the residue in 1 mL of methylene chloride.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The instrument is equipped with a flame-ionization detector and contains a $0.53-\mathrm{mm} \times 10-\mathrm{m}$ fused silica column, coated with G3 phase (film thickness $2 \mu \mathrm{~m}$ ). The injector port, column, and detector temperatures are maintained at
about $250^{\circ}, 180^{\circ}$, and $250^{\circ}$, respectively; and nitrogen is used as the carrier gas at a flow rate of about 10 mL per minute. The injector employs a split ratio of $1: 2$.

Procedure-Inject about $1 \mu \mathrm{~L}$ of the Reference solution. Adjust the sensitivity of the detector so that the height of the peak due to caffeine is not less than $50 \%$ of the full scale of the recorder. The substances are eluted in the following order: $o$-toluenesulfonamide, $p$-toluenesulfonamide, and caffeine. The test is not valid unless the resolution between the peaks due to $o$-toluenesulfonamide and $p$-toluenesulfonamide is at least 1.5 . Inject about $1 \mu \mathrm{~L}$ of the Blank solution. In the chromatogram obtained, verify that there are no peaks with the same retention times as the internal standard, $o$-toluenesulfonamide, and $p$-toluenesulfonamide. Inject about $1 \mu \mathrm{~L}$ of the Test solution and $1 \mu \mathrm{~L}$ of the Reference solution. If any peaks due to $o$-toluenesulfonamide, and $p$ toluenesulfonamide appear in the chromatogram obtained with the Test solution, the ratio of their areas to that of the internal standard is not greater than the corresponding ratio in the chromatogram obtained with the Reference solution ( 10 ppm of $o$-toluenesulfonamide and 10 ppm of $p$-toluenesulfonamide).

Limit of benzoate and salicylate-To 10 mL of a hot, saturated solution of it add ferric chloride TS, dropwise: no precipitate or violet color appears in the liquid.

Organic volatile impurities, Method $V\langle 467\rangle$ : meets the requirements.

Solvent-Use dimethyl sulfoxide.
Assay-Accurately weigh about 500 mg of Saccharin, dissolve in 40 mL of alcohol, add 40 mL of water, mix, add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide. Perform a blank titration, if necessary, and make the appropriate correction. Each mL of 0.1 N sodium hydroxide is equivalent to 18.32 mg of $\mathrm{C}_{7} \mathrm{H}_{5} \mathrm{NO}_{3} \mathrm{~S}$.■1S (NF23)

## Briefing

Sodium Starch Glycolate, $N F 22$ page 2933 and page 3202 of PF 22(6) [Nov.-Dec. 1996]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Sodium Starch Glycolate monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based on the corresponding monograph for Sodium Starch Glycolate that was prepared by the U.S. Pharmacopeia. This draft was based in part on comments from the European and Japanese Pharmacopoeias in response to the Provisional Harmonized Text Stage 5 A and 5 B drafts.

## Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Identification B | + | + | + |
| pH | + | + | + |
| Loss on drying | + | + | + |
| Limit of iron | + | + | + |
| Limit of sodium <br> chloride | + | + | + |
| Limit of sodium <br> glycolate | + | + | + |
| Assay | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Packaging and storage, Labeling, Microbial limits, Heavy metals, Identification by IR absorption.

Specific local attributes: Appearance of solution (EP).
Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Differences between the Adoption Stage 6 document and the current $N F$ monograph include the following:

1. Definition-Modified to be more specific in terms of Type A and Type B.
2. Packaging and storage-No change.
3. Labeling-Requirements to label indicating Type A or Type $B$, the botanical source of the starch from which it was derived, and the cross-linking agent are added.
4. USP Reference standards-Reference standards for sodium starch glycolate Type A and Type B are added for use with Identification test $A$.
5. Identification - An IR absorption test and a test for sodium are added.
6. Microbial limits-No change.
7. $p H$-Clarification of the requirements for Type A and Type B is added.
8. Loss on drying-No change.
9. Limit of iron-The test from the EP is adopted.
10. Heavy metals-No change.
11. Limit of sodium chloride-A simpler procedure using a silver nitrate titration is adopted.
12. Limit of sodium glycolate-This test is added to comply with EP standards.
13. Assay-No change.
(EMC: J. Lane) RTS-41235-1

## Change to read:

## Soditm-Starch-Glycolate

## Stareh earboxymethyl ether, soditm salt.

\#Sodium Stareh Glyeolate is the sodium salt of a carbexymethyl ether of stareh. It contains not less than 2.8 pereent and not more than 4.2 percent of sodium. (Na) on the dried, aleohol-washed basis. It may contain not more than 7.0 percent of Sodium Chloride.

Packaging and-storage-Preserve-in well-clesed containers, preferably protected from wide-variations in temperature and hamidity, whieh may catse caking.
Eabeling The labeling indieates the pHrange.
Itentifieation A slightly acidified-solution of it is colored blue by iodine and petassiam iodide-TS.
Mierobial limits- $\langle 64$ - It meets the requirements of the tests for absenee of Salmenella species and Escherichia ooli.
$\mathrm{pH}\langle 794\rangle$-Disperse 1 gin 30 mL of water: the pH of the resulting suspension is either between 3.0 and 5.0 or between 5.5 and 7.5 .
Loss ondrying $\left\langle 734\right.$ ) - Dry it at $130^{\circ}$ for 90 mintutes: it loses net more than $10.0 \%$ of its weight.
Iron $\langle 244\rangle \div \quad 0.002 \%$, the Test preparation being prepared as directed for Test preparation under Heaw metals, Method IIT 〈z34); a- $0.5-5$ test specimen being used and the final solution being dilated with water to -47 mL .

Heary metals, Meth $\Psi\langle 234\rangle$ : $0.002 \%$.
Sodium ehboride- Weigh aceurately about 1 g, transfer to acenieal flask, add 20 mL of $80 \%$ aleohol, 0.1 mL of phenolphthalein TS, and 1 N soditm hydroxide solution until the-suspension beeomes faintly pink, stir for 10 mintutes, and filter. Repeat the extraction until chloride has been completely extracted, as shown by a test with silver nitrate TS. Dry the insoluble pertion at $105^{\circ}$ to cen stant weight ( 4 mg ), and reserve it for the 4 ssay. Evaporate the eombined filtrates, and dry the residue at $105^{\circ}$ to constant weight. The weight of the dried residue is not greater than $15 \%$ of the weight of Sodium Stareh Glye ${ }^{\text {ant ataken. If the weight of the dried }}$ residue is not more than $7.0 \%$ of the weight of Sodimm Stareh Gly colate taken, the requirement is met. If the weight is greater than $7.0 \%$ of the weight of Sodium Starch Glycolate taken, transfer it with the aid of water to a 200 mL volumetric flask, add 5 mL of nitric acid and 40.0 mL of 0.1 N silver nitrate $V \mathrm{~S}$, mix, and dilute with water to volume. Allow it to stand in the dark for 30 mintutes, and filter. To 100.0 mL of the filtrate add 5 mL of ferric ammenitum
sulfate TS , and titrate with 0.1 N ammenium thiocyanate VS (see Residual Titrations under Titnimetry (544) ). Caleulate the percentage of sodium chloride by the formma:-

$$
5.844\left(40 N_{4}-2 H N_{z}\right) / W
$$

in which $N_{+}$and $N_{2}$ are the normalities of the silver nitrate VS and the ammenium thio yanate VS, respectively, $V$ is the volume, in mL, of ammenium thierymate VS used in the titration, and $W$ - is the weight, in of, of Sodium Stareh Glyeolate taken.
Assay Transfer an aceurately weighed pertion, $B$, (about 700 mg) of the dried $80 \%$ aleohel insoluble pertion obtained in the test for Soditn chloride, to a suitable flask, add 80 mL of glacial acetic acid, heat the mixture under reflux, on a beiling water bath, for 2 hours, cool to room temperature, and titrate with 0.1 N perehloric acid VS, determinimg the endpoint potentiometrically. Cateulate the percentage of sodium combined in the form of sodium stareh glyeolate by the formula:
$100(22.99) H_{3} \mathrm{Al}_{3}+B$,
in which $V_{2}$ is the volume, in mL , of the perchloric acid $\mathrm{VS}, \mathrm{N}_{3}$ is the normality of the perchloric acid VS, and $B$ is the weight, in mo, of the dried aleohol insoluble residue taken for the Assety.

## ■Sodium Starch Glycolate

Starch carboxymethyl ether, sodium salt.
» Sodium Starch Glycolate is the sodium salt of a carboxymethyl ether of starch or of a cross-linked carboxymethyl ether of starch. It may contain not more than 7.0 percent of Sodium Chloride. The pH and assay requirements for Type A and Type $B$ are set forth in the accompanying table.

|  |  |  | \% Sodium, com- <br> bined as sodium <br> starch glycolate |  |
| :---: | :---: | :---: | :---: | :---: |
|  |  | pH |  | Max. |
| Type | Min. | Min. | Max. |  |
| A | 5.5 | 7.5 | 2.8 | 4.2 |
| B | 3.0 | 5.0 | 2.0 | 3.4 |

Packaging and storage-Preserve in well-closed containers, preferably protected from wide variations in temperature and humidity, which may cause caking.

Labeling-Label it to indicate the botanical source of the starch from which it was derived, the cross-linking agent (if used), the pH range, and whether it is Type A or Type B.

USP Reference standards $\langle 11\rangle$ —USP Sodium Starch Glycolate Type A RS. USP Sodium Starch Glycolate Type B RS

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: A slightly acidified solution of it is colored blue to violet by the addition of iodine and potassium iodide TS 1 .

C: A 2-mL portion of the solution prepared for the test for Limit of iron meets the requirements of the potassium carbonate-potassium pyroantimonate test for Sodium $\langle 191\rangle$.

Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli.
$\mathbf{p H}\langle 791\rangle$-Disperse 1 g in 30 mL of water: the pH of the resulting suspension is either between 5.5 and 7.5 for Type A or between 3.0 and 5.0 for Type B.

Loss on drying $\langle 731\rangle$ —Dry it at $130^{\circ}$ for 90 minutes: it loses not more than $10.0 \%$ of its weight.

Heavy metals, Method II $\langle 231\rangle$ : $0.002 \%$.

## Limit of iron-

Standard solution-Dissolve 863.4 mg of ferric ammonium sulfate $\left[\mathrm{FeNH}_{4}\left(\mathrm{SO}_{4}\right)_{2} \cdot 12 \mathrm{H}_{2} \mathrm{O}\right]$ in water, add 25 mL of 2 N sulfuric acid, dilute with water to 500.0 mL , and mix. Pipet 10 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Pipet 5 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of $1.0 \mu \mathrm{~g}$ of iron per mL .

Test solution-[NOTE-Save a portion of this solution for Identification test $C$.] Place 2.5 g in a silica or platinum crucible, and add 2 mL of 10 N sulfuric acid. Heat on a water bath, then cautiously raise the temperature progressively over an open flame. Ignite, preferably in a muffle furnace, at $600 \pm 25^{\circ}$. Continue heating until all black particles have disappeared. Cool, add a few drops of 2 N sulfuric acid, and heat and ignite as above. Add a few drops of 2 M ammonium carbonate, evaporate to dryness, and ignite as above. Cool, dissolve the residue in 50 mL of water, and mix.

Procedure-Treat the Test solution and the Standard solution as follows. Transfer 10 mL of the solution to a suitable beaker, add 2 mL of citric acid solution ( 1 in 5 ) and 0.1 mL of thioglycolic acid, and mix. Render the solution alkaline, using litmus paper as an external indicator, by the addition of ammonium hydroxide, dilute with water to 20 mL , and mix. Allow the solutions to stand for 5 minutes: the color of the solution from the Test solution is a shade of pink no deeper than that of the solution from the Standard solution ( $0.002 \%$ ).

Limit of sodium chloride-Transfer to a beaker about 500 mg of Sodium Starch Glycolate, accurately weighed, and suspend in 100 mL of water. Add 1 mL of nitric acid. Titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically, using a suitable silver-based indicator electrode and a double-junction reference electrode containing a $10 \%$ potassium nitrate filling solution in the outer jacket and a standard filling solution in the inner jacket. Each mL of 0.1 N silver nitrate is equivalent to 5.844 mg of sodium chloride.

Limit of sodium glycolate-[NOTE-Conduct this test without exposure to daylight. Use low-actinic glassware.]

Standard solution-Transfer 310 mg of glycolic acid, previously dried over phosphorus pentoxide in a desiccator at room temperature overnight, to a $500-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume. Transfer 5.0 mL of this solution to a $100-\mathrm{mL}$ beaker, add 4 mL of 6 N acetic acid, and allow to stand for about 30 minutes. Add 50 mL of acetone and 1 g of sodium chloride, mix, and pass through fast filter paper moistened with acetone into a $100-\mathrm{mL}$ volumetric flask. Rinse the beaker and filter paper with acetone. Combine the filtrate and washings, dilute with acetone to volume, and mix. Allow to stand for 24 hours without shaking. Use the clear supernatant as the Standard solution.

Test solution-Transfer 200 mg , accurately weighed, to a $100-\mathrm{mL}$ beaker. Add 4 mL of 6 N acetic acid and 5 mL of water. Stir until dissolution is complete (about 10 minutes). Add 50 mL of acetone and 1 g of sodium chloride, mix, and pass through fast filter paper moistened with acetone into a $100-\mathrm{mL}$ volumetric flask. Rinse the beaker, and filter with acetone. Combine the filtrate and washings, dilute with acetone to volume, and mix. Allow to stand for 24 hours without shaking. Use the clear supernatant as the Test solution.

Procedure-Treat the Test solution and the Standard solution as follows. Heat 2.0 mL of the solution on a water bath for 20 minutes to remove acetone. Cool to room temperature. Prepare a 2,7 -dihydroxynaphthalene solution as follows. Dissolve 10 mg of 2,7-dihydroxynaphthalene in 100 mL of sulfuric acid, allow to stand until decolorized, and use within 2 days. Add 20.0 mL of this 2,7-dihydroxynaphthalene solution to the solution under test, mix, and heat on a water bath for 20 minutes. Cool under running water, and transfer quantitatively to a $25-\mathrm{mL}$ volumetric flask. Maintain the flask under running water, and dilute with sulfuric acid to volume. Within 10 minutes determine the absorbance of the solution at 540 nm with a suitable spectropho-
tometer, using water as the blank: the absorbance of the solution from the Test solution is not more than that of the solution from the Standard solution (2.0\%).

Assay-Weigh about 1 g , transfer to a conical flask, add 20 mL of $80 \%$ alcohol, stir for 10 minutes, and filter. Repeat the extraction until the chloride has been completely extracted, as shown by a test with silver nitrate. Dry the insoluble portion at $105^{\circ}$ to constant weight, and transfer an accurately weighed portion (about 700 mg ) of the dried $80 \%$ alco-hol-insoluble portion to a suitable flask, add 80 mL of glacial acetic acid, heat the mixture under reflux on a boiling water bath for 2 hours, cool to room temperature, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Calculate the percentage of sodium combined in the form of sodium starch glycolate by the formula:

$$
100(22.99) V N / W,
$$

in which $V$ is the volume, in mL , of the perchloric acid consumed; $N$ is the normality of the perchloric acid; and $W$ is the weight, in mg , of the dried alcohol-insoluble residue taken for the Assay.■1S (NF23)

## BRIEFING

Corn Starch, page 715 of PF 30(2) [Mar.-Apr. 2004]; Potato Starch, page 718 of PF 30(2) [Mar.-Apr. 2004]; Wheat Starch, page 723 of $P F 30(2)$ [Mar.-Apr. 2004]. It is proposed to revise Identification test $C$ to reflect the use of a new test solution, Iodine and potassium iodide TS 2, which appears in the section Reagents, Indicators, and Solutions in this issue of $P F$.
(EMC: J. Lane) RTS-41144-2

## Add the following:

## ${ }^{\Delta}$ Corn Starch

» Corn Starch consists of the starch granules separated from the mature grain of corn [Zea mays Linné (Fam. Gramineae)].

Packaging and-storage-Preserve in well-closed containers.

Labeling-Where Corn Starch is intended for use in preparing Absorbable Dusting Powder, it is so labeled and the label states that it must be subjected to further processing during the preparation of Absorbable Dusting Powder.

## Change to read:

## Identification-

A: Under a microscope, using not less than $20 \times$ magnification and using a mixture of glycerin and water $(1: 1)$ as a mounting agent, it appears as either angular polyhedral granules of irregular sizes with diameters ranging from about $2 \mu \mathrm{~m}$ to about $23 \mu \mathrm{~m}$ or as rounded or spheroidal granules of irregular sizes with diameters ranging from about $25 \mu \mathrm{~m}$ to about $35 \mu \mathrm{~m}$. The central hilum consists of a distinct cavity or two- to five-rayed cleft, and there are no concentric striations. Between crossed nicol prisms, the starch granules show a distinct black cross intersecting at the hilum.

B: Suspend 1 g of it in 50 mL of water, boil for $1 \mathrm{~min}-$ ute, and cool: a thin, cloudy mucilage is formed.

C: To 10 mL of the meteilage obtained in Identification
test $B$, add 0.04 mL of iodine and potassitm iodide TS: an erange red to dark blue color is produced, which disappears en heating.

C: To 1 mL of the mucilage obtained in Identification test $B$, add 0.05 mL of $\mathbf{m i n d i n e}^{\text {iodine }}$ and potassium iodide TS 2:1S (NF23) an orange-red to dark blue color is produced, which disappears on heating.

## Iodinesolution Dissolve 12.7gofiodine and 20gofpe-

 fassiumiodide-in water, and dilute with water to 1000.0 mL. Fe 10.0 mL of this seltion, ade 0.6 of petassium iodide, and dilute with water to 100.0 mL . Prepare immediately be fore use: ■is (NF23)Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed 1000 cfu per g , the total combined molds and yeasts count does not exceed 100 cfu per g , and it meets the requirements of the test for the absence of Escherichia coli. Where it is intended for use in preparing Absorbable Dusting Powder, it also meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.
$\mathbf{p H}\langle 791\rangle$ —Prepare a slurry by weighing 5.0 g of Corn Starch, transferring to a suitable nonmetallic container, and adding 25.0 mL of freshly boiled and cooled water. Agitate continuously at a moderate rate for 1 minute. Stop the agitation, and allow to stand for 15 minutes. Determine the pH to the nearest 0.1 unit: the pH , determined potentiometrically, is between 4.0 and 7.0.

Loss on drying $\langle 731\rangle$ —Dry about 1 g , accurately weighed, at $130^{\circ}$ for 90 minutes: it loses not more than $15.0 \%$ of its weight.

## Change to read:

Residue on ignition $\langle 281\rangle$ : not more than $0.6 \%$, determined on a $1.0-\mathrm{g}$ test specimen. Ignition temperature


Limit of iron-Shake 1.5 g of Corn Starch with 15 mL of 2 N hydrochloric acid, and filter. Transfer 10 mL of the filtrate to a test tube, add 2 mL of citric acid solution (2 in 10), 0.1 mL of thioglycolic acid, and mix. Add 10 N ammonium hydroxide until the solution is distinctly alkaline to litmus, dilute with water to 20 mL , and mix (Test Solution). Prepare a Standard Iron Solution containing the equivalent of $10 \mu \mathrm{~g}$ of iron per mL as directed under Iron $\langle 241\rangle$. Immediately before use, quantitatively dilute an accurately measured volume of this solution with water to obtain a Diluted Standard Iron Solution containing the equivalent of $1 \mu \mathrm{~g}$ of iron per mL . Prepare the Standard Solution by transferring 10 mL of the Diluted Standard Iron Solution to a test tube and proceeding in the same manner as directed for the preparation of the Test Solution, beginning with "add 2 mL of citric acid solution (2 in 10)." After 5 minutes, any pink color in the Test Solution is not more intense than that in the Standard Solution, corresponding to a limit of $10 \mu \mathrm{~g}$ of iron per g .

Limit of oxidizing substances-Transfer 4.0 g to a glassstoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate is required ( $20 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ).

Limit of sulfur dioxide—Not more than $50 \mu \mathrm{~g}$ per g . REAGENTS-

Carbon dioxide-Use carbon dioxide, with a flow regulator that will maintain a flow of $100 \pm 10 \mathrm{~mL}$ per minute.

Bromophenol blue indicator solution-Dissolve 100 mg of bromophenol blue in 100 mL of dilute alcohol (1 in 5), and filter if necessary.

Hydrogen peroxide solution-Dilute 30\% hydrogen peroxide with water to obtain a $3 \%$ solution. Just before use, add 3 drops of Bromophenol blue indicator solution, and neutralize to a violet-blue endpoint with 0.01 N sodium hydroxide. Do not exceed the endpoint.

APPARATUS-In this test, the sulfur dioxide is released from the test specimen in a boiling acid medium and is removed by a stream of carbon dioxide. The separated gas is collected in a dilute hydrogen peroxide solution where the sulfur dioxide is oxidized to sulfuric acid and titrated with standard alkali. The apparatus consists essentially of a 500mL three-neck, round-bottom, boiling flask, a separatory funnel having a capacity of 100 mL or greater, a gas inlet tube of sufficient length to permit introduction of the carbon dioxide within 2.5 cm of the bottom of the boiling flask, a reflux condenser having a jacket length of 200 mm , and a delivery tube connecting the upper end of the reflux condenser to the bottom of a receiving test tube. Apply a thin film of stopcock grease to the sealing surfaces of all of the joints except the joint between the separatory funnel and the boiling flask, and clamp the joints to ensure tightness.

PROCEDURE-Add 150 mL of water to the boiling flask. Close the stopcock of the separatory funnel, and begin the flow of carbon dioxide at a rate of $100 \pm 5 \mathrm{~mL}$ per minute through the Apparatus. Start the condenser coolant flow. Add 10 mL of Hydrogen peroxide solution to a receiving test tube. After 15 minutes, without interrupting the flow
of carbon dioxide, remove the separatory funnel from the boiling flask, and transfer 25.0 g of test specimen into the boiling flask with the aid of 100 mL of water. Apply stopcock grease to the outer joint of the separatory funnel, and replace the separatory funnel in the boiling flask. Close the stopcock of the separatory funnel, and add 80 mL of 2 N hydrochloric acid to the separatory funnel. Open the stopcock of the separatory funnel to permit the hydrochloric acid solution to flow into the boiling flask, guarding against the escape of sulfur dioxide into the separatory funnel by closing the stopcock before the last few mL of hydrochloric acid drain out. Position the Apparatus in a water bath, and Boil the mixture for 1 hour. Remove the receiving test tube, and transfer its contents to a $200-\mathrm{mL}$ wide-necked, conical flask. Rinse the receiving test tube with a small portion of water, add the rinsing to the $200-\mathrm{mL}$ conical flask, and mix. Heat on a water bath for 15 minutes, and allow to cool. Add 0.1 mL of Bromophenol blue indicator solution, and titrate the contents with 0.1 N sodium hydroxide VS until the color changes from yellow to violet-blue, with the color change lasting for at least 20 seconds. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Calculate the content, in $\mu \mathrm{g}$ per g , of sulfur dioxide in the test specimen taken by the formula:

$$
1000(32.03) V N / W,
$$

in which 32.03 is the milliequivalent weight of sulfur dioxide; $V$ is the volume, in mL , of titrant consumed; $N$ is the normality of the titrant; and $W$ is the weight, in g , of test specimen taken.

Organic volatile impurities, Methol $H\langle\langle 467\rangle$ : meets the requirements.:ANF23

## Briefing

Potato Starch, page 718 of PF 30(2) [Mar.-Apr. 2004]—See briefing under Corn Starch.
(EMC: J. Lane) RTS-41144-3

## Add the following:

## © Potato Starch

» Potato Starch is obtained from the tuber of Solanum tuberosum $L$.

Packaging and-storage-Preserve in well-closed containers.

## Change to read:

## Identification-

A: Under a microscope, using a mixture of glycerin and water $(1: 1)$ as a mounting agent, it presents granules, either irregularly shaped, ovoid, or pear-shaped, usually $30 \mu \mathrm{~m}$ to $100 \mu \mathrm{~m}$ in size, but occasionally exceeding $100 \mu \mathrm{~m}$, or rounded, $10 \mu \mathrm{~m}$ to $35 \mu \mathrm{~m}$ in size. There are occasional compound granules having two or four components. The ovoid and pear-shaped granules have an eccentric hilum and the rounded granules acentric or slightly eccentric hilum. All granules show clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum.

B: Suspend 1 g of it in 50 mL of water, boil for $1 \mathrm{~min}-$ ute, and cool: a thin, cloudy mucilage is formed.

C: To 1 mL of the mucilage obtained in Identification test $B$, add 0.05 mL of iodine and potassium iodide TS
 duced, which disappears on heating.

Microbial limits $\langle 61\rangle$ —The total aerobic microbial count does not exceed 1000 cfu per $g$, the total combined molds and yeasts count does not exceed 100 cfu per g , and it meets the requirements of the test for the absence of Escherichia coli.
$\mathbf{p H}\langle 791\rangle$ —Prepare a slurry by weighing 5.0 g of Potato Starch, transferring to a suitable nonmetallic container, and adding 25.0 mL of freshly boiled and cooled water. Agitate continuously at a moderate rate for 1 minute. Stop the agitation, and allow to stand for 15 minutes. Determine the pH to the nearest 0.1 unit: the pH , determined potentiometrically, is between 5.0 and 8.0.
Loss on drying $\langle 731\rangle$-Dry about 1 g , accurately weighed, at $130^{\circ}$ for 90 minutes: it loses not more than $20.0 \%$ of its weight.

## Change to read:

Residue on ignition $\langle 281\rangle$ : not more than $0.6 \%$, determined on a $1.0-\mathrm{g}$ test specimen. Ignition temperature $600 \pm 50^{\circ} \cdot$ ■. $_{\text {1S (NF23) }}$

Limit of iron-Shake 1.5 g of Potato Starch with 15 mL of 2 N hydrochloric acid, and filter. Transfer 10 mL of the filtrate to a test tube, add 2 mL of citric acid solution (2 in 10), 0.1 mL of thioglycolic acid, and mix. Add 10 N ammonium hydroxide until the solution is distinctly alkaline to litmus, dilute with water to 20 mL , and mix (Test Solution). Prepare a Standard Iron Solution containing the equivalent of $10 \mu \mathrm{~g}$ of iron per mL as directed under Iron $\langle 241\rangle$. Immediately before use, quantitatively dilute an accurately measured vol-
ume of this solution with water to obtain a Diluted Standard Iron Solution containing the equivalent of $1 \mu \mathrm{~g}$ of iron per mL . Prepare the Standard Solution by transferring 10 mL of the Diluted Standard Iron Solution to a test tube and proceeding in the same manner as directed for the preparation of the Test Solution, beginning with "add 2 mL of citric acid solution (2 in 10)." After 5 minutes, any pink color in the Test Solution is not more intense than that in the Standard Solution, corresponding to a limit of $10 \mu \mathrm{~g}$ of iron per g .

Limit of oxidizing substances-Transfer 4.0 g to a glassstoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate is required ( $20 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ).

Limit of sulfur dioxide: not more than $50 \mu \mathrm{~g}$ per g . REAGENTS-

Carbon dioxide-Use carbon dioxide, with a flow regulator that will maintain a flow of $100 \pm 10 \mathrm{~mL}$ per minute.

Bromophenol blue indicator solution-Dissolve 100 mg of bromophenol blue in 100 mL of dilute alcohol (1 in 5), and filter if necessary.

Hydrogen peroxide solution-Dilute $30 \%$ hydrogen peroxide with water to obtain a $3 \%$ solution. Just before use, add 3 drops of Bromophenol blue indicator solution, and neutralize to a violet-blue endpoint with 0.01 N sodium hydroxide. Do not exceed the endpoint.

APPARATUS-In this test, the sulfur dioxide is released from the test specimen in a boiling acid medium and is removed by a stream of carbon dioxide. The separated gas is collected in a dilute hydrogen peroxide solution where the sulfur dioxide is oxidized to sulfuric acid and titrated with standard alkali. The apparatus consists essentially of a 500mL three-neck, round-bottom boiling flask, a separatory funnel having a capacity of 100 mL or greater, a gas inlet tube of sufficient length to permit introduction of the carbon dioxide within 2.5 cm of the bottom of the boiling flask, a reflux condenser having a jacket length of 200 mm , and a delivery tube connecting the upper end of the reflux condenser to the bottom of a receiving test tube. Apply a thin film of stopcock grease to the sealing surfaces of all of the joints, except the joint between the separatory funnel and the boiling flask, and clamp the joints to ensure tightness.

PROCEDURE-Add 150 mL of water to the boiling flask. Close the stopcock of the separatory funnel, and begin the flow of carbon dioxide at a rate of $100 \pm 5 \mathrm{~mL}$ per minute through the Apparatus. Start the condenser coolant flow. Add 10 mL of Hydrogen peroxide solution to a receiving test tube. After 15 minutes, without interrupting the flow of carbon dioxide, remove the separatory funnel from the boiling flask, and transfer 25.0 g of test specimen into the boiling flask with the aid of 100 mL of water. Apply stopcock grease to the outer joint of the separatory funnel, and replace the separatory funnel in the boiling flask. Close the stopcock of the separatory funnel, and add 80 mL of 2 N hydrochloric acid to the separatory funnel. Open the stopcock of the separatory funnel to permit the hydrochloric acid
solution to flow into the boiling flask, guarding against the escape of sulfur dioxide into the separatory funnel by closing the stopcock before the last few mL of hydrochloric acid drain out. Position the Apparatus in a water bath, and Boil the mixture for 1 hour. Remove the receiving test tube, and transfer its contents to a $200-\mathrm{mL}$ wide-necked, conical flask. Rinse the receiving test tube with a small portion of water, add the rinsing to the $200-\mathrm{mL}$ conical flask, and mix. Heat on a water bath for 15 minutes, and allow to cool. Add 0.1 mL of Bromophenol blue indicator solution, and titrate the contents with 0.1 N sodium hydroxide VS until the color changes from yellow to violet-blue, with the color change lasting for at least 20 seconds. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Calculate the content, in $\mu \mathrm{g}$ per g , of sulfur dioxide in the test specimen taken by the formula:

$$
1000(32.03) \mathrm{VN} / W,
$$

in which 32.03 is the milliequivalent weight of sulfur dioxide; $V$ is the volume, in mL, of titrant consumed; $N$ is the normality of the titrant; and $W$ is the weight, in g , of test specimen taken.

Organie volatile imptrities, Method $W\langle\langle 467\rangle$ : meets the requirements._NF23

## BRIEFING

> Wheat Starch, page 723 of $P F 30(2)$ [Mar.-Apr. 2004]-See briefing under Corn Starch.
> (EMC: J. Lane) $\quad$ RTS-41144-1

## Add the following:

## © Wheat Starch

» Wheat Starch is obtained from the caryopsis of Triticum aestivum L. (T. vulgare Vill.).

Packaging and-storage-Preserve in well-closed containers.

## Change to read:

## Identification-

A: Under a microscope, using a mixture of glycerin and water ( $1: 1$ ) as a mounting agent, it presents large and small granules, and very rarely, intermediate sizes. The large granules, usually $10 \mu \mathrm{~m}$ to $60 \mu \mathrm{~m}$ in diameter, are discoid or, more rarely, reniform when seen face-on. The central hilum and striations are invisible or barely visible and the granules sometimes show cracks on the edges. Seen in profile, the granules are elliptical and fusiform and the hilum appears as a slit along the main axis. The small granules, rounded or polyhedral, are $2 \mu \mathrm{~m}$ to $10 \mu \mathrm{~m}$ in diameter. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum.
B: Suspend 1 g of it in 50 mL of water, boil for $1 \mathrm{~min}-$ ute, and cool: a thin, cloudy mucilage is formed.

6: To 1 mL of the mutilage obtained in Itentification
test $B$, add 0.05 mL of iodine and potassium iodide TS: a

## dark blue color is produced, which disappears on heating.

C: To 1 mL of the mucilage obtained in Identification test $B$, add 0.05 mL of foline $\mathbf{m}_{\text {iodine }}$ and potassium iodide TS 2:-1S (NF23) an orange-red to dark blue color is produced, which disappears on heating.

## Iodine solution Dissolve 12.7 g of iodine and 20 g of pe-

tassitm iodide in water, and dilute with water to 1000.0 mL .
Fe 10.0 mL of this solution, add 0.6 g of petassitum iodide,
and dilute with water to 100.0 mL . Prepare-immediately be
fore use:-1.1S(NF23)
Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed 1000 cfu per g , the total combined molds and yeasts count does not exceed 100 cfu per g , and it meets the requirements of the test for the absence of Escherichia coli.
$\mathbf{p H}\langle 791\rangle$ —Prepare a slurry by weighing 5.0 g of Wheat Starch, transferring to a suitable nonmetallic container, and adding 25.0 mL of freshly boiled and cooled water. Agitate continuously at a moderate rate for 1 minute. Stop the agitation, and allow to stand for 15 minutes. Determine the pH to the nearest 0.1 unit: the pH , determined potentiometrically, is between 4.5 and 7.0.

Loss on drying $\langle 731\rangle$-Dry about 1 g , accurately weighed, at $130^{\circ}$ for 90 minutes: it loses not more than $15.0 \%$ of its weight.

## Change to read:

Residue on ignition $\langle 281\rangle$ : not more than $0.6 \%$, determined on a $1.0-\mathrm{g}$ test specimen. Ignition temperature $600 \pm 50^{\circ} \square 1 \mathrm{C}($ NF23 $)$

Total protein: not more than $0.3 \%$ of total protein (corresponding to $0.048 \% \mathrm{~N}_{2}$, conversion factor: 6.25).

Procedure-Accurately weigh 6.0 g of test substance containing about 2 mg of nitrogen, transfer to a combustion flask, and add 4 g of a powdered mixture of 100 g of potassium sulfate, 5 g of cupric sulfate, and 2.5 g of selenium, and three glass beads. Wash any adhering particles from the
neck into the flask with 5 mL of sulfuric acid, allowing it to run down the sides of the flask, and mix the contents by rotation. Close the mouth of the flask loosely (e.g., by means of a glass bulb with a short stem) to avoid excessive loss of sulfuric acid. Heat gradually at first, then increase the temperature until there is vigorous boiling with condensation of sulfuric acid in the neck of the flask. [Note-Precautions should be taken to prevent the upper part of the flask from becoming overheated.] Continue the heating for 30 minutes, unless otherwise directed. Cool, dissolve the solid material by cautiously adding to the mixture 25 mL of water, cool again, and place in a steam distillation apparatus. Add 30 mL of sodium hydroxide solution (42 in 100), and distill immediately by passing steam through the mixture. Collect about 40 mL of distillate in 20.0 mL of 0.01 N hydrochloric acid and enough water to cover the tip of the condenser. Towards the end of the distillation, lower the receiver so that the tip of the condenser is above the surface of the acid. [NOTE-Take precautions to prevent any water on the outer surface of the condenser from reaching the contents of the receiver.] Titrate the distillate with 0.01 N sodium hydroxide, using methyl purple TS as indicator ( $n_{1} \mathrm{~mL}$ of 0.01 N sodium hydroxide).
Repeat the test using about 50 mg of glucose in place of the substance to be examined ( $n_{2} \mathrm{~mL}$ of 0.01 N sodium hydroxide).

$$
\text { Content of nitrogen }=\left(0.01401\left(n_{2}-n_{1}\right)\right) / m,
$$

where $m$ is the amount of test substance weighed, in g .
Limit of iron-Shake 1.5 g of Wheat Starch with 15 mL of 2 N hydrochloric acid, and filter. Transfer 10 mL of the filtrate to a test tube, add 2 mL of citric acid solution (2 in 10),
0.1 mL of thioglycolic acid, and mix. Add 10 N ammonium hydroxide until the solution is distinctly alkaline to litmus, dilute with water to 20 mL , and mix (Test Solution). Prepare a Standard Iron Solution containing the equivalent of $10 \mu \mathrm{~g}$ of iron per mL as directed under Iron $\langle 241\rangle$. Immediately before use, quantitatively dilute an accurately measured volume of this solution with water to obtain a Diluted Standard Iron Solution containing the equivalent of $1 \mu \mathrm{~g}$ of iron per mL . Prepare the Standard Solution by transferring 10 mL of the Diluted Standard Iron Solution to a test tube and proceeding in the same manner as directed for the preparation of the Test Solution, beginning with "add 2 mL of citric acid solution (2 in 10)." After 5 minutes, any pink color in the Test Solution is not more intense than that in the Standard Solution, corresponding to a limit of $10 \mu \mathrm{~g}$ of iron per g .

Limit of oxidizing substances-Transfer 4.0 g to a glassstoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate is required ( $20 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ).

Limit of sulfur dioxide: not more than $50 \mu \mathrm{~g}$ per g . REAGENTS-

Carbon dioxide-Use carbon dioxide, with a flow regulator that will maintain a flow of $100 \pm 10 \mathrm{~mL}$ per minute.

Bromophenol blue indicator solution-Dissolve 100 mg of bromophenol blue in 100 mL of dilute alcohol (1 in 5), and filter if necessary.

Hydrogen peroxide solution-Dilute 30\% hydrogen peroxide with water to obtain a $3 \%$ solution. Just before use, add 3 drops of Bromophenol blue indicator solution, and neutralize to a violet-blue endpoint with 0.01 N sodium hydroxide. Do not exceed the endpoint.

APPARATUS-In this test, the sulfur dioxide is released from the test specimen in a boiling acid medium and is removed by a stream of carbon dioxide. The separated gas is collected in a dilute hydrogen peroxide solution where the sulfur dioxide is oxidized to sulfuric acid and titrated with standard alkali. The apparatus consists essentially of a 500mL three-neck, round-bottom, boiling flask, a separatory funnel having a capacity of 100 mL or greater, a gas inlet tube of sufficient length to permit introduction of the carbon dioxide within 2.5 cm of the bottom of the boiling flask, a reflux condenser having a jacket length of 200 mm , and a delivery tube connecting the upper end of the reflux condenser to the bottom of a receiving test tube. Apply a thin film of stopcock grease to the sealing surfaces of all of the joints, except the joint between the separatory funnel and the boiling flask, and clamp the joints to ensure tightness.
PROCEDURE-Add 150 mL of water to the boiling flask. Close the stopcock of the separatory funnel, and begin the flow of carbon dioxide at a rate of $100 \pm 5 \mathrm{~mL}$ per minute through the Apparatus. Start the condenser coolant flow.

Add 10 mL of Hydrogen peroxide solution to a receiving test tube. After 15 minutes, without interrupting the flow of carbon dioxide, remove the separatory funnel from the boiling flask, and transfer 25.0 g of test specimen into the boiling flask with the aid of 100 mL of water. Apply stopcock grease to the outer joint of the separatory funnel, and replace the separatory funnel in the boiling flask. Close the stopcock of the separatory funnel, and add 80 mL of 2 N hydrochloric acid to the separatory funnel. Open the stopcock of the separatory funnel to permit the hydrochloric acid solution to flow into the boiling flask, guarding against the escape of sulfur dioxide into the separatory funnel by closing the stopcock before the last few mL of hydrochloric acid drain out. Position the Apparratus in a water bath, and Boil the mixture for 1 hour. Remove the receiving test tube, and transfer its contents to a $200-\mathrm{mL}$ wide-necked, conical flask. Rinse the receiving test tube with a small portion of water, add the rinsing to the $200-\mathrm{mL}$ conical flask, and mix. Heat on a water bath for 15 minutes, and allow to cool. Add 0.1 mL of Bromophenol blue indicator solution, and titrate the contents with 0.1 N sodium hydroxide VS until the color changes from yellow to violet-blue, with the color change lasting for at least 20 seconds. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Calculate the content, in $\mu \mathrm{g}$ per g , of sulfur dioxide in the test specimen taken by the formula:

$$
1000(32.03) \mathrm{VN} / W,
$$

in which 32.03 is the milliequivalent weight of sulfur dioxide; $V$ is the volume, in mL , of titrant consumed; $N$ is the normality of the titrant; and $W$ is the weight, in g , of test specimen taken.

Organie volatile impurities, Method $I V\langle 467$ ): meets the requirements._ANF23

## GENERAL CHAPTERS

General Tests and Assays

## General Requirements for Tests and Assays

## Briefing

$\langle 846\rangle$ Specific Surface Area, USP 27 page 2385. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the Specific Surface Area General Chapter, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following text represents the ADOPTION STAGE 6 document. The EP draft was based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the EP.

There are very few differences between the international harmonization ADOPTION STAGE 6 document for Specific Surface Area and the current USP General Chapter, $\langle 846\rangle$ Specific Surface Area. The fundamental principles have not changed.
(EMT: J. Lane) RTS-41202-1

## Change to read:

## <846>-SPECIFIC SURFACE AREA

Introduetion The specifie surface are of a powder is deter mined by physieal adsorption of a gas on the suface of the selid and by measuring the amount of adsorbate gas corresponding to a single layer (menolayer) on the surface. Physieal adserption results from relatively weak forees (van der Wanls forees) between the ad sorbategas molecules and the adsorbent surface of the test powder. The ameunt of gas adsorbed can be measured by a gravimetric, volumetric, or continturus flow procedure. Since the amount of gas adsorbed under a given pressure tends to increase on decreas ing the temperature, adsorption measurements are ustally made at
a low temperature. Measurement is performed at 77 K , the beiling point of liquid nitrogen. The data are treated according to the Bru nater, Emmett, and Teller (BET) adsorption isotherm equation:-


Where $P$, in mm of mereury, is the partial vapor pressure of adsor bate gas in equilibrium with the surface at $77 \mathrm{~K}, P_{s}$, in mmof mer emy, is the satwated pressure of the adserbate gas, $K_{s}$, in mL, is the volume of gas adsorbed at standard temperature and pressure(STP, 273.15 K and 760 mm of mereury), $Y_{m}$, in mL , is the volume of gas adsorbed at STP to produce an apparent monolayer on the sample surface, and $C$ is a dimensionless constant that is related to the en thalpy of adserption of the adsorbate gas on the pewder sample. $A$ value of $Y_{\text {s }}$ is measured a a Then the BET value-

is pletted against $P / P$, necording to equation (1). This plet should yield a straight line. The data are considered aceeptable if the cor relation coefficient, $r$, of the linear regression is not less than 0.9975; that is, $r^{2}$ is not less than 0.995 . From the resulting linear plot, the slope, which is equal to $(C, 1) / Y_{.} C$, and the intereept, which is equal to $1 H Y_{m} \in$, are evaluated by linear regression analy sis. Frem these values, $V_{\text {m }}$-is caleulated as $1 /($ slope + intereept $)$, while- $C$ is ealeulated as (slopelintereept) +1 . From the value of
 tated by the equation:
in which $N$ is the Avogadre constant $\left(6.023 \times 10^{23}\right.$ mole $\left.{ }^{-4}\right), a$ is the effective cross sectional area of one adsorbate molecule ( 0.162 $* 10^{-18} \mathrm{~m}^{2}$ for nitregen or $0.195 \times 10^{-18} \mathrm{~m}^{2}$ for krypten), m is the mass, in f , of test pewder, and 22400 is the volume, in mb, veet pied by 1 mole of the adsorbate gas at STP, allowing for miner departares from-ideality.

Some caleulations and procedures, deseribed below, require the absolute value of $P_{a}$, defined above, and of the baremetric pressure, $B$, in mmof mercury. For liquid nitrogen open to the atmosphere in a Dewar vessel, $P$, and $B$ are taken to be equal to the measured atmospheric pressure (i.e., baremetric pressure) plus 10 mam of mereury. Seme instruments automatically perform the above mea strements and comptatations. The upward correction of $P_{2}$ and $B$ allows for the elevation of the beiling peint of nitrogen eatnsed by impurities, such as oxygen, dissolvedin the liquid nitrogen-in the-open Dewar vessel. This chapter deseribes the dynamic flow gas adsorption teehnique (Methed I) and the volumetric gas ad serption technique (Method II).

## $\theta$ thgassing

Before the specifie surface area the sample can be determined, it is necessary to remove gases and vapers that may have beeme physically adserbe ont the surface after manufacture and during treatment, handling, and storage. If outgassing is not achieved, the specific surface area may be reduced or may be variable beeatese an intermediate area of the strface is covered with molecules of the previously adsorbed gases-or vapors.

Conditions The outgassing conditions must be demenstrated to yield reprodurible BET plots, as diseussed under Introduction, a eonstant weight of test powder, and no-detectable physical or ehemieal changes in the test powder. The outgassing conditions are-critical for obtaining the required precision and aceuracy of specific surface area measurements on phamacentienls beeause of the sensitivity of the surface of the materials. The outgassing eonditions define by the temperature, pressure, and time should be so chosen that the original surface of the solid is reproduced as closely as possible. Outgassing of many substances is often achieved by applying a vacumm or by purging the sample in a flow ing stream of a nemreactive gas. In either ease, elevated temperatures are-sometimes applied to increase the rate at whieh the contaminants leave the surface. Outgassing by heating the test powder may change the nature-of the-surface and should be avoided unless specifieally indieated in the individual monograph. The outgassing conditions stated in the menograph for each material have been derived where possible from studies of several mat terials from various manufacturers. If henting is employed, the ree emmended temperature and time of outgossing are as low as pes sible so as to achieve reproduribly high measures of specific sur face are within an acceptable time span. For outgassing sensitive specimens the deserption adsorption cyeling method may be employed.

Procedure-To outgas the test specimen by the desorption ad sorption cyeling method, proceed as follows. Allow the test pow der to equilibrate with the adsorbate gas, nitrogen at $P / P_{\theta}=0.30$-r krypen at $P / P=1.038 \times 10^{-3}$, for at least one minte. Raise the Dewar vessel containing liquid nitrogen at 77 K up-to a defined point on the sample cell. This level should be high enough above the level of the sample to enstre that the temperature drops to 77 K yet below any connections, such as 0 rings in the cell holder, which could leak if cooled. At least one minute after vigorous boil ing of liquid nitrogen has subsided, recordor zero the gas detector integrator signal according to Method I, or record the pressure sig anl aceording to Meth $\Psi$ (adsorption-signal). Lower the Dewar vessel from the sample cell, and surround the sample cell with a beaker of water at room temperature. Record the gas detector integrator signal according to Method I, or record the pressure signat according to the Method $I$ (deserption signal) when the signal has become constant. Repent the cooling heating eycle until three suc eessive desorption signals differ by not more than $3 \%$. If possible, reweigh the sealed sample cell containing the test powder and subtract the mass of the empty sample eell to obtain the actual mass, m, of the test powder. The sealed sample cell containing the test pow der may be weighed after the meastrement of the specific surface area, if neessayy.

## Standard Materials

The method employed for the determination of the specific sur face are of the samples should be tested using reference-standards ef known surface area, such as alpha alumina, purchased together with a certificate of analysis from a seientifieally aceredited source.*The chosen reference standard should have a specific sur face area as simitar as possible to that of the porder sample and should be treated with the utmost care. If the measured specific sur face area of the reference material does not fall within the range specified on the eertifient of analysis from an aceredited seuree, the same adsorbate gas being used, the elements of the methed and the gas adsorption apparatus should be carefully examined to iden tify the ense of the diserepaney, whieh should then be eliminated.

[^186]
## МЕТНӨФ Т ТНЕ ФУNAMHC FLOW MЕТНӨР

Prineiples of the Method- In the dynamic flow method, the recommended adsorbate gas, is nitrogen or krypton, while helitm is mployed as a diluent gas, which is not adsorbed under the ree emmended conditions. For powder samples of surface area less than about $0.3 \mathrm{~m}^{3}$ (or of specific surface area less than about 0.5 $\mathrm{m}^{2}-\frac{8}{5}$ 1) krypton is the preferred adsorbate gas, while for samples of greater surface area, nitrogen is preferred. $\Lambda$ minimmen of three mixtures of the appropriate adsorbate gas with helium are required within the $P / P$, range 0.05 to 0.30 , such as $0.100,0.200$, and 0.300 mole fraction of nitrogen or $3.46 \times 10^{-4}, 6.92 \times 10^{-4}$, and $1.038 \times 10^{-3}$ mole fraction of krypten, where $P / P$ is the relative pressure of the adsorbate gas, $P$ being the partial vaper pressure and $P_{\text {a }}$-being the suturated vapor pressure of the adsorbate gas. These mixtures should be certified to within $1 \%$ (absolute) or may be obtained by using a suitable apparatus to mix the appropriate adsorbate gas with helimm in propertions aceurate to $1 \%$. Nitro gen or krypton, at least 99.9 mole pereent, is also required for ealibrating the gas detector integrator employed for measuring the velume or mass of the gas adsorbed, or desorbed, by the test powder. The gas detector integrator should provide a signal that is approximately proportional to the volume of the gas passing through it under defined conditions of temperature and pressure. For this purpese, a thermal conductivity detector with an electromic integrator is one ameng various suitable types. A minimmmof three data peints within the recommended range of 0.05 to 0.30 for $P / P_{\text {o }}$ should be determined.

Procedure Aceurately weigh a quantity of the test powder, such that the 1 surface area is at least $1 \mathrm{~m}^{2}$, if pessible, in a tared gas adsorption flow eell. [NOTE-Transfer the test powder earefully int the flow eell so that aclear path is provided for the flow of the gas. An approximate value of the mass, $m$, of the test powder to be taken may be caleulated from the mean particle diameter, $d$, and the tre or crystal density, $\rho$, assuming spherieal partieles by the equa-tion:-

$$
m=A d \rho / 6
$$

in which $A$ is the sufface are desired. Because of the assumptions en which it is based, this equation must not be mployed to caleu tate the actual surface area.] Outgas the powder sample.

Pass the gas mixture eontaining the largest mole fraction of the adsorbate gas, nitrogen or krypton, within the recommended range over the test powder for at least 30 seconds. Raise the Dewar vessel eontaining liquid nitrogen at 77 K up to a defmed point on the flow eell. As mentioned above, this level should be high enough above the level of the sample to ensure that the temperature dreps to 77 K ye below any connections, such as 0 rings in the cell holder, which could leak if cooled. Record or zero the gas detector integrator signal (adserption signal) at least one minute after vigorous beiling of liquid nitrogen has subsided. Lower the Dewar vessel from the flow cell, and surround the flow cell with a beaker of water at room temperature. Pecord the gas detector integrater sif fal (desorption signal) when the signal becomes constant. Repeat the cooling heating eycle until three suecessive desorption sighals differ by not mere than $3 \%$. The data for the first peint may be derived from the desorption adsorption cyeling method, provided that this method is employed for outgossing the powder sample.

Record the last thre desorption values at the largest mole frac tion of the adsorbate gas, and caleulate the arithmetic mean. Calibrate the gas detector integrator by injecting, from a gas tight syringe, a known volume of adsorbate gas, measured to $\pm 2 \%$,
so as to give a signal within $15 \%$ of the last three desorption sig nals. Caleulate the correspending volume of adsorbate gas, $K_{\text {t }}$ (im mm-of mereury), at standard temperature and pressure (STP, 273.15 K and 760 mm of mereury), frem the alibrater integrator signal by the equation:-

in which $Y_{\text {e }}$ is the volume, in mL, of gas injected for calibration, $A_{4}$ is the detector integrator respense for the gas desorbed from the test powder, $A_{\text {e }}$ is the detector integrator signal respense for the ealibration volume, $B$ is the measured barometric pressure, in mm-of mereury without the eorrection (deseribed above under In moturn), and $T$, in $K$, is the temperattre of volume meastrement (room temperatre). If possible, weigh the sealed flow celleontain ing the test powder, and subtract the mass of the empty flow cell from this mass to obtain the aetual mass, m, of the powder taken.

Prepare at least two other mixtures of the appropriate adsorbate gas with helium, as described above. For each of these gas mix tares, repeat the above cooling heating cycle, beginning with "Pass the gas mixture." Repeat the measurements for each of the gas mixtures until three sureessive desorption signals differ by not more than $3 \%$. Immediately after recording each gas mix tere signal, calibrate the gas detector integrator, and caleulate $-{ }_{\text {a }}^{\text {a }}$ as directed in the previeus paragraph.

If the BET plot is not linear, when using nitrogen as the adsor bate gas, or if the measured amounts of nitrogen adsorbed are not repeatable to within $\pm 30$, lack of striet propertionality between the meastred values and the actual amounts of nitrogen adsorbed may be suspeeted, perhaps becatse of the thermat diffusion effect of nitrogen. The magnitude of this effeet inereases, and the aecu ray and precision of the measurements decrease, with decreasing specific surface area the pewder specimen. Under these cireumt stanees, and especially if the surface area of the powder sample is tess than $0.3 \mathrm{~m}^{2}$ or if the specifie surface area of the powder sample is less than $0.5 \mathrm{~m}^{2} \mathrm{~m}^{+}$, as mentioned above, the thermal diffusion effect may be considerably redueed or eliminated by using an ad serbate gas that has a lower vaper pressure, such as krypten, in stead of nitrogen. Since-for krypton the saturated vapor pressure at 77 K is only 2.63 mm of mereury, the required mole fractions of kryptan in the three mixtures of krypten with helimm are less than those of nitrogen in its mixtures with helimm by a factor of 2.63/760-0.00346. Sinee the eross sectional are of the kypton moleeule is not well defined, it is reemmended that the standard value, $a=0.195 \mathrm{~mm}^{2}$, be used in equation (2) when caleulating the specific surface area, and that the name of the adsorbate gas em ployed be stated, if it is not nitregen, when reporting the value of the specific surface area.

## МЕТНӨФ- THE VOLUMETRIC METHOР

Prineiples of the Method-In the volumetric method, the ree emmended adsorbate gas is nitrogen which is admitted into the evacuated space above the previously outgassed powder sample to give a deffned equilibritm pressure, $P$, of the gas. The use of a diluent gas, sueh as helium, is therefore unnecessary, although helium may be employed for other purposes, such as to measure the void volume. Sinee only pure adsorbate gas, instead of a gas mixture, is employed, interfering effeets of thermal diffusion are avoided in this method. Consequently, the use of an adsorbate
gas possessing a low vaper pressure at 77 K , such as krypton, is unnecessary. Some instruments employ a balance tube to offse the effects of free space, thermal gradients, and non ideal gas behavior. Other instruments claim other advantages. The use of equipment from any partieular manufacturer is not specifieally endorsed.

The volume of nittrogen admitted into the sample tube of give the equilibrium pressure, $P$, is equal to the sum of the volume of gas aetually adsorbed, $I$, plus the volume of gas in the free space around and above the sample, $V_{f}$, which must be either corrected for by suitable adjustment of the instrument or balaneed out. $Y$ is then converte by the following equation to the volume, $Y_{\text {a }}$, -recu pied by the same amount of ges at standard temperature and pressure (STP, 273.15 K and 760 mm of mereury):

$$
\begin{aligned}
& \left.\hline V_{\alpha}=[V \times B \times(2) \quad \mathrm{mmHg})\right] . \quad \text { (5) }
\end{aligned}
$$

Several instruments attomatieally perform the above measurements and computations. The instrument mantal should always beconsulted for guridanee and for a complete description of the proeedures for data aequisition and computation. $A$ value of $K_{4}$-is meastred at each of not less than three values of $P / P$, and the data are plotted so as to provide a value of the specific surface area as deseribed above under Introduction.

Procedure Aceurately weigh a quantity of the test powder, such that the total surface area is at least $1 \mathrm{~m}^{2}$, if possible, in a tared gas adsorption tube. [To caleulate an approximate value of the mass of the test powder to be taken, use equation (3).] Admit a small amount of dry nitregen into the sample tube to provent con amination of the clean surface, remove the sample tube, insert the stopper, and weigh it. Caleulate the weight of the sample. Attach the sample tube to the dynamic volumetric apparatus. Cautiously evactate the sample down to a presstre of 0.02 mm of meretry or tess.

If the prineiple of operation of the instrument requires the deter mination of the void volume in the sample tabe, for example, by the admission of a nonadsorbed gas, such as helium, this procedure is carried out at this point, followed by evacuation of the sample down to 0.02 mm of mereury or less. The adsorption of nitrogen gas is then meastred as described below.

Raise a Dewar vessel containing liquid nitrogen at 77 K up to a defined peint on the sample cell as directed under Meth $I$. Admit a sufficient valume of nitrogen gen to give relative pressure, $P / P_{s}$; equal to $0.10 \pm 0.02$. Measure the volume adsorbed, $Y_{4}$. Repent the measurement of $K_{\text {H }}$ at $P / P_{\text {e }}$ values of $0.20 \pm 0.02$ and $0.30 \pm 0.02$. A minimum of three points is required. Additional meacure ments may be carried out, especially on these rare oecasions when nemlinearity is obtained at a $P / P$, value close to 0.3 . Since nenlinearity is often obtained at $P / P$, at or below 0.05 , values in this res ion are not recommended. The test for linearity, the treatment of the data, and the calleulation of the specific surface area of the sample are described above under Introduction.

## Single-Point Measurement

Normally, at least three measurements of $Y_{\text {a }}$, each at a different value of $P / P$, are required for the determination of specific surface area by Meth I Or Meth IH. However, under certain cireumstances it may be aceeptable to determine the specific surface area ef a powder from a single value of $F_{\text {s }}$ meastred at a single value of
$P / P_{s}$, such as 0.300 (correspending to 0.300 mole of nitrogen or 0.001038 mole fraction of krypton), using the following equation for calculating $Y_{m}$ :-


The specific-surface area is caleulated from the value-of $H_{. . .}$by eqution (2) stated above.

The single peint methed may be employed directly for a series of powder samples of a given material for which the material con stant, $C$, is much greater than unity. This cireumstance may be veriffed by comparing value of speciffe surface area determined by the single point method with that detemined by the multiple point method for the series of powder samples. Close similarity between the single point values and multiple point values suggests that $1 / \mathrm{C}$ approaches zero:

The single peint method may be employed indirectly for a series of very similar powder samples of a given material for which the material constant, $C$, is not infinite but may be assumed to be in variant. Under this cireumstanee, the error associated with the sin gle point method can be redured of eliminated by using the multiple peint method to evaluate $C$ for one of the samples of the series from the BET plet, from which $C$ is caleulated as $(1+$ stope intereept). Then $Y_{\text {w }}$ is caleulated from the single value of $F_{*}$ measured at a single value of $P / P$, by the equation::


The specific suffee area is calculated from- $Y_{\text {m }}$ by equation (2) stat ed above.

## - $<846\rangle$ SPECIFIC SURFACE AREA

## INTRODUCTION

The specific surface area of a powder is determined by physical adsorption of a gas on the surface of the solid and by calculating the amount of adsorbate gas corresponding to a monomolecular layer on the surface. Physical adsorption results from relatively weak forces (van der Waals forces) between the adsorbate gas molecules and the adsorbent surface of the test powder. The determination is usually carried out at the temperature of liquid nitrogen.

The amount of gas adsorbed can be measured by a volumetric or continuous flow procedure.

## BRUNAUER, EMMETT AND TELLER (BET)

THEORY AND SPECIFIC SURFACE AREA DETERMINATION

## Multipoint Measurement

The data are treated according to the Brunauer, Emmett and Teller (BET) adsorption isotherm equation:

$$
\begin{equation*}
\frac{1}{\left[V_{a}\left(\frac{P_{o}}{P}-1\right)\right]}=\frac{C-1}{V_{m} C} \times \frac{P}{P_{o}}+\frac{1}{V_{m} C} \tag{1}
\end{equation*}
$$

$P=$ partial vapor pressure of adsorbate gas in equilibrium with the surface at 77.4 K (b.p. of liquid nitrogen), in Pa ,
$P_{o}=$ saturated pressure of adsorbate gas, in Pa ,
$V_{a}=$ volume of gas adsorbed at standard temperature and pressure (STP) [273.15 K and atmospheric pressure $\left.\left(1.013 \times 10^{5} \mathrm{~Pa}\right)\right]$, in mL ,
$V_{m}=$ volume of gas adsorbed at STP to produce an apparent monolayer on the sample surface, in mL ,
$C=$ dimensionless constant that is related to the enthalpy of adsorption of the adsorbate gas on the powder sample.
A value of $V_{a}$ is measured at each of not less than three values of $P / P_{o}$.

Then the BET value

$$
\frac{1}{\left[V_{a}\left(\frac{P_{o}}{P}-1\right)\right]}
$$

is plotted against $P / P_{o}$, according to equation (1). This plot should yield a straight line usually in the approximate relative pressure range 0.05 to 0.3 . The data are considered acceptable if the correlation coefficient, $r$, of the linear regression is not less than 0.9975 ; that is, $r^{2}$ is not less than 0.995 . From the resulting linear plot, the slope, which is equal to $(C-1) / V_{m} C$, and the intercept, which is equal to $1 / V_{m} C$, are evaluated by linear regression analysis. From these values, $V_{m}$ is calculated as $1 /($ slope + intercept ), while $C$ is calculated as (slope/intercept) +1 . From the value of $V_{m}$ so determined, the specific surface area, $S$, in $\mathrm{m}^{2} \cdot \mathrm{~g}^{-1}$, is calculated by the equation:

$$
\begin{equation*}
S=\frac{V_{m} N a}{m \times 22400} \tag{2}
\end{equation*}
$$

$N=$ Avogadro constant $\left(6.023 \times 10^{23} \mathrm{~mol}^{-1}\right)$,
$a=$ effective cross-sectional area of one adsorbate molecule, in square meters ( $0.162 \mathrm{~nm}^{2}$ for nitrogen and $0.195 \mathrm{~nm}^{2}$ for krypton),
$m=$ mass of test powder, in g ,
$22400=$ volume, in mL, occupied by one mole of the adsorbate gas at STP allowing for minor departures from the ideal.

A minimum of three data points is required. Additional measurements may be carried out especially when nonlinearity is obtained at a $P / P_{o}$ value close to 0.3 . Because nonlinearity is often obtained at a $P / P_{o}$ value below 0.05 , values in this region are not recommended. The test for linearity, the treatment of the data, and the calculation of the specific surface area of the sample are described above.

## Single-Point Measurement

Normally, at least three measurements of $V_{a}$, each at different values of $P / P_{o}$, are required for the determination of specific surface area by the dynamic flow gas adsorption technique (Method I) or by volumetric gas adsorption (Method II). However, under certain circumstances described below, it may be acceptable to determine the specific surface area of a powder from a single value of $V_{a}$ measured at a single value of $P / P_{o}$ such as 0.300 (corresponding to 0.300 mole of nitrogen or 0.001038 mole fraction of krypton), using the following equation for calculating $V_{m}$ :

$$
\begin{equation*}
V_{m}=V_{a}\left(1-\frac{P}{P_{o}}\right) \tag{3}
\end{equation*}
$$

The specific surface area is then calculated from the value of $V_{m}$ by equation (2) given above.

The single-point method may be employed directly for a series of powder samples of a given material for which the material constant $C$ is much greater than unity. These circumstances may be verified by comparing values of specific surface area determined by the single-point method with that determined by the multipoint method for the series of powder samples. Close similarity between the single-point values and multipoint values suggests that $1 / C$ approaches zero.

The single-point method may be employed indirectly for a series of very similar powder samples of a given material for which the material constant $C$ is not infinite but may be assumed to be invariant. Under these circumstances, the error associated with the single-point method can be reduced or eliminated by using the multipoint method to evaluate $C$ for one of the samples of the series from the BET plot, from
which $C$ is calculated as $(1+$ slope/intercept $)$. Then $V_{m}$ is calculated from the single value of $V_{a}$ measured at a single value of $P / P_{o}$, by the equation:

$$
\begin{equation*}
V_{m}=V_{a}\left(\frac{P_{o}}{P}-1\right)\left[\frac{1}{C}+\frac{C-1}{C} \times\left(\frac{P}{P_{o}}\right)\right] \tag{4}
\end{equation*}
$$

The specific surface area is calculated from $V_{m}$ by equation (2) given above.

## EXPERIMENTAL TECHNIQUES

This section describes the methods to be used for the sample preparation, the dynamic flow gas adsorption technique (Method I) and the volumetric gas adsorption technique (Method II).

## Sample Preparation

## OUTGASSING

Before the specific surface area of the sample can be determined, it is necessary to remove gases and vapors that may have become physically adsorbed onto the surface after manufacture and during treatment, handling, and storage. If outgassing is not achieved, the specific surface area may be reduced or may be variable because an intermediate area of the surface is covered with molecules of the previously adsorbed gases or vapors. The outgassing conditions are critical for obtaining the required precision and accuracy of specific surface area measurements on pharmaceuticals because of the sensitivity of the surface of the materials.

The outgassing conditions must be demonstrated to yield reproducible BET plots, a constant weight of test powder, and no detectable physical or chemical changes in the test powder.

The outgassing conditions defined by the temperature, pressure, and time are chosen so that the original surface of the solid is reproduced as closely as possible. Outgassing of many substances is often achieved by applying a vacuum by purging the sample in a flowing stream of a nonreactive, dry gas or by applying a desorption-adsorption cycling method. In either case, elevated temperatures are sometimes applied to increase the rate at which the contaminants leave the surface. Caution should be exercised when outgassing powder samples using elevated temperatures to avoid affecting the nature of the surface and the integrity of the sample.

If heating is employed, the recommended temperature and time of outgassing are as low as possible to achieve reproducible measurement of specific surface area in an acceptable time. For outgassing sensitive samples, other outgassing methods such as the desorption-adsorption cycling method may be employed.

## ADSORBATE

The standard technique is the adsorption of nitrogen of analytical quality at liquid nitrogen temperature.

For powders of low specific surface area ( $<0.2 \mathrm{~m}^{2} \mathrm{~g}^{-1}$ ) the proportion adsorbed is low. In such cases, the use of krypton at the liquid nitrogen temperature is preferred because the low vapor pressure exerted by this gas greatly reduces error. The use of larger sample quantities, where feasible (equivalent to $1 \mathrm{~m}^{2}$ or greater total surface area using nitrogen), may compensate for the errors in determining low surface areas.

All gases used must be free from moisture.

## QUANTITY OF SAMPLE

A quantity of the test powder is accurately weighed such that the total surface of the sample is at least $1 \mathrm{~m}^{2}$ when the adsorbate is nitrogen and $0.5 \mathrm{~m}^{2}$ when the adsorbate is krypton.

Lower quantities of sample may be used after appropriate validation.

## Measurements

Because the amount of gas adsorbed under a given pressure tends to increase when the temperature is decreased, adsorption measurements are usually made at a low temperature. Measurement is performed at 77.4 K , the boiling point of liquid nitrogen.

## Method I: The Dynamic Flow Method

## PRINCIPLE

In the dynamic flow method (see Figure 1), the recommended adsorbate gas is dry nitrogen or krypton, while helium is employed as a diluent gas, which is not adsorbed under the recommended conditions.

A minimum of three mixtures of the appropriate adsorbate gas with helium are required within the $P / P_{o}$ range 0.05 to 0.30 .

The gas detector-integrator should provide a signal that is approximately proportional to the volume of the gas passing through it under defined conditions of temperature and pressure. For this purpose, a thermal conductivity detector with an electronic integrator is one among various suitable types. A minimum of three data points within the recommended range of 0.05 to 0.30 for $P / P_{o}$ is determined.


Fig. 1. Schematic diagram of the dynamic flow method apparatus.

## PROCEDURE

A known mixture of the gases, usually nitrogen and helium, is passed through a thermal conductivity cell, through the sample again, through the thermal conductivity cell, and then to a recording potentiometer.

The sample cell is immersed in liquid nitrogen, and the sample adsorbs nitrogen from the mobile phase. This unbalances the thermal conductivity cell, and a pulse is generated on a recorder chart.

The sample is removed from the coolant; this gives a desorption peak equal in area and in the opposite direction to the adsorption peak. Because this is better defined than the adsorption peak, it is the one used for the determination.

To effect the calibration, a known quantity of adsorbate, sufficient to give a peak of similar magnitude to the desorption peak, is injected into the system, and the proportion of gas volume per unit peak area is obtained.

A mixture of nitrogen and helium is used for a singlepoint determination; and several such mixtures or premixing two streams of gas are used for a multipoint determination.

The calculation is the same as the volumetric method.

## Method II: The Volumetric Method

PRINCIPLE

In the volumetric method (see Figure 2), the recommended adsorbate gas is nitrogen, which is admitted into the evacuated space above the previously outgassed powder sample to give a defined equilibrium pressure, $P$, of the gas. The use of a diluent gas, such as helium, is therefore unnecessary, although helium may be employed for other purposes, such as to measure the dead volume.

Because only pure adsorbate gas, instead of a gas mixture, is employed, interfering effects of thermal diffusion are avoided in this method.


Fig. 2. Schematic diagram of the volumetric method apparatus.

## PROCEDURE

A small amount of dry nitrogen is admitted into the sample tube to prevent contamination of the clean surface, the sample tube is removed, a stopper is inserted, the tube is weighed, and the weight of the sample is calculated. Then the sample tube is attached to the volumetric apparatus. The sample is cautiously evacuated down to the specified pressure (e.g., between 2 Pa and 10 Pa ). Alternately, some instruments are operated by evacuating to a defined rate of pressure change (e.g., less than $13 \mathrm{~Pa} / 30 \mathrm{~s}$ ) and by holding for a defined period of time before commencing the next step.

If the principle of operation of the instrument requires the determination of the dead volume in the sample tube, for example, by the admission of a nonadsorbed gas, such as helium, this procedure is carried out at this point, followed by evacuation of the sample. The determination of dead vol-
ume may be avoided using difference measurements: that is, by means of reference and sample tubes connected by a differential transducer. The adsorption of nitrogen gas is then measured as described below.

Raise a Dewar vessel containing liquid nitrogen at 77.4 K up to a defined point on the sample cell. Admit a sufficient volume of adsorbate gas to give the lowest desired relative pressure. Measure the volume adsorbed, $V_{a}$. For multipoint measurements, repeat the measurement of $V_{a}$ at successively higher $P / P_{o}$ values. When nitrogen is used as the adsorbate gas, $P / P_{o}$ values of $0.10,0.20$, and 0.30 are often suitable.

## Reference Materials

Periodically verify the functioning of the apparatus using appropriate reference materials of known surface area that has a specific surface area similar to that of the sample to be examined.■1S (USP28)

## Briefing

＜905〉 Uniformity of Dosage Units，USP 27 page 2396 and page 1587 of $P F$ 28（5）［Sept．－Oct．2002］．The United States Phar－ macopeia is the coordinating pharmacopeia in the efforts toward international harmonization of the specifications provided in this general test chapter．The Stage 5B text for this chapter has been signed－off by the Pharmacopeial Discussion Group members． The text presented herein represents a merger of the Stage 5B text and the national $U S P$ text．This combined text，which is being pub－ lished in this issue of $P F$ for information only，not for public com－ ment，is scheduled for publication in USP 28－NF 23，with a scheduled implementation date of 1 April 2006．Earlier implemen－ tation by individual companies may be done at their discretion．

Major differences between this current text and that of the
STAGE 4 ＂merged＂draft that was published on pages 1595－ 1599 of PF 28（5）［Sept．－Oct．2002］are listed below．
（1）The text discussing harmonization in the first paragraph of the STAGE 4 draft has been deleted in this current draft because the revised chapter will not officially be harmonized until the EP adopts the global text in the European Pharmacopoeia， Supplement 5．2，official December 2004 and the JP adopts the global text in the $J P X V$ ，official April 2006．At that time USP will republish this text with the addition of symbols for the national text throughout and with the explanatory intro－ ductory text，＂Portions of this general chapter have been har－ monized with the corresponding texts of the European Pharmacopoeia or the Japanese Pharmacopoeia．Those por－ tions that are not harmonized are marked with symbols（＊）to specify this fact．＂
（2）The term＂active ingredient＂in the STAGE 4 draft has been replaced globally by the preferred term＂drug substance＂．
（3）In the current listing of dosage forms that require testing by Content Uniformity（see item C3 in the text），suspensions or emulsions or gels in unit－dose containers or in soft capsules that are intended for systemic administration only are distin－ guished from those that are intended for external，cutaneous administration．
（4）A new Table 1 ，linking the various dosage forms to the appro－ priate Uniformity of Dosage Units test procedure，has been added to the current text．
（5）The text listing those dosage forms for which Weight Varia－ tion is applicable has been revised for clarity．
（6）The definition for the reference value $M$ in Table 2 has been revised to indicate coverage of cases where the target test sample amount（amount of drug substance）at time of manu－ facture，$T$ ，is either（a）less than or equal to $101.5 \%$ ，or（b） greater than 101．5\％．
（7）The variable $U$ ，an overage factor that was indicated for use in cases where the drug product was formulated with an overage of drug substance to compensate for stability losses during product shelf life，has been deleted from the current text． The addition of such overages is no longer considered to be acceptable．
（8）The text regarding the term Acceptance Value，$A V$ ，has been expanded for clarity．
（9）The text relating to the variables $L 1$ and $L 2$ in Table 2 has been expanded，and the values＂ 0.75 M ＂and＂ 1.25 M ＂have been replaced by formulas that clarify how the computations are made．
（10）The first paragraph in the Weight Variation section of the cur－ rent text contains new text for clarity．This text indicates that the assay results，designated as $A$ ，are to be expressed as＂$\%$ of label claim＂．
（11）Revised text stating that the drug substance concentration is assumed to be uniform（throughout the batch）has been added to the first paragraph under Weight Variation．For the purpose
of this chapter，tablet concentration，unlike tablet content，is assumed to be independent of individual dosage unit weight when Weight Variation is applicable．．
（PDF：W．L．Paul）RTS－41183－1

## Change to read：

## 〈905〉UNIFORMITY OF DOSAGE UNITS

NOTE－In this chapter，unit and dosage mit are－synomymous． The uniformity of destige units can be demenstrated by either of we methods，weight variation or centent unifermity．The require－ ments of this chapter apply beth to dosage units containing a single active ingredient and to dosage units containing fwor mere active ingredients；unless otherwise－specifled in the individual mene－ graph，they apply individually to each active ingredient in the product．

Content Unifermity requirements may be applied in all eases． The test for Content Uniformity is required for：－
（1）coated ablets，other than film coated tablets containing 50 mg or more of an active－ingredient that comprises $50 \%$ or more（by weight）of one tablet；
（2）transdermal systems；
（3）suspensions in single unit containers－or in soft capsules；
（4）inhalations（other than solutions for inhalation packaged inglass or plastic ampuls，intended for use in nebulizers） packaged in premetered dosage units（For inhalers and premetered desage units labeled for use with a mamed in halation deviee，alse see Aerosols，Metered Dese Inhat ers，and Dry Powder Intaters $\langle 6 \theta 1\rangle$ ；；
（5）solids（including sterile solids）that are packaged in unit dose containers and that contain active or inactive added substances，except that the test for Weight Variation may be－applied in the－special－situations－stated below；and
（6）suppesitories．
When the test for Content Uniformity is not required，the test for Weight Variation may be applied in any of the following sitations：
（1）products containing 50 mg or mereof an active ingredient eomprising $50 \%$ or more，by weight，of the dosage unit $\theta$ ，in the ease of hard capsules，the capsule contents，ex eept that uniformity of other aetive ingredients present in lesser propertions is demenstrated by meeting Centent Uniformity requirements；
（2）liqutid filled soft eapsules other than soft eapsules con－ faining suspensions；
（3）solids（including sterile－selids）that are packaged in sin gle unit containers and contain no added substances， whether active－or inactive；
（4）solids（ineluding sterile－solids）that are－packaged in sin gle unit containers，with or without added substances， whether active or inactive，that have been prepared frem true－solutions and freeze－dried in the fanaleontainers and are－labeled to indieate this methed of preparation；and
（5）solations for inhalation packaged in glass or plastic am puls，intended for use in nebulizers，oral solutions，and syrups when these artieles are packaged in single unit eontainers．

## WEHGHT VARझATHON

For the determination of dosage unit uniformity by weight var iation, select not fewer than 30 units, and proced as follows for the dosage form designated. [NOTE-Specimens other than these test units may be drawn frem the same bateh for Assay determinations.]

Uneanted and Film-Conted Tablets-Weigh aceurately 10 tab lets individually. From the result of the Assay, obtained as directed in the individual menograph, calculate the content of active ingre dient in each of the 10 tablets, assuming homegeneous distribution of the active ingredient.

Hard-Capsules Weigh aecurately 10 eapsules individually, taking are to preserve the identity of each capsule. Remove the eontents of each eapsule by a suitable means. Weigh aceuraty the emptied shells individually, and caleulate for each eapsule the net weight of its contents by subtrating the weight of the shell from the respective gross weight. From the results of the Assay, ebtained as direeted in the individual menegraph, caleulate the entent of active ingredient in each of the eapsules, assuming homogeneous distribution of the active ingredient.

Soft-Capstules Determine the net weight of the content of in dividual capsules as follows. Weigh aceurately the 10 intact eap sules individually to obtain their gross weights, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as seis sers or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the oceluded solvent to evaporate from the shells at room temperature over a period of about 30 min utes, taking precautions to avoid uptake or less of meisture. Weigh the individual shells, and caleulate the net contents. From the results of the Assety, obtained as directed in the individual menegraph, caleulate the content of active ingredient in each of the eqpoules, assuming hemegeneous distribution of the active ingredient.

Solids (Ineluding Sterile-Solids) in-Single-Unit ContainersProeed as direeted for Hard Capsules, treating each unit as deseribed therein.

Solutions for Inhalation-Packnged in-Glass-or Plastic Ampuls, Intended for Use in Nebulizers Proeed as directed for Hard Capsules, treating each unit as described therein.

Oral Solutions and Syrups Packaged in-Single-Unit Containers Weigh accurately the amount of liquid that drains in not more than 5 seeonds from each of 10 -individual containers. If nee ssary, compute the equivalent volume after determining the apparent density. Frem the result of the Assay, obtained as direeted in the individual monograph, caleulate the content of active ingredient in the liquid drained from ach of the 10 units.

## CONTENT UNHFORMHTY

For the determination of dosage unit uniformity by assay of in dividual units, select not fewer than 30 units, and proced as fot tows for the dosage form designated.

UNCOATED AND COATED TABLETS, HARD AND SOFT CAPSULES, SUP POSITORLES, TRANSPERMAL SYSTEMS, ORAL SOLUTЮNS IN SINGLE UNHT CONTAINERS, SUSPENSIONS IN SINGLE UNHT CONTAINERS, SYR UPS IN SINGLE UNHT CONTAINERS, INHALATMNS PACKAGED IN PREME TERED-DOSAGE UNHTS, AND SOLIDS (INCLUDING STERHE SOLISS) IN SINGLE UNHT CONTAINERS, Assay 10 maits individually as direeted in the Assay in the individual menegraph, unless otherwise specifred in the Procedure for content uniformity. For oral solutions, suspensions, and syrups in single unit containers, eonduct the Assay en the ameant of well mixed material that drains frem an individ walcentainer in not mere than 5 seeonds, andexpress the results as delivered dese. Where the amount of active-ingredient in a single desage unit differs from that required in the Assty, adjust the de gree of dilution of the selutions and/or the volume-of aliquets-se that the concentration of the active ingredients in the final solution
is of the same order as that obtained in the Assay procedure; or, in the case of a titrimetric assay, use a titrant of a different concentration, if necessary, so that an adequate volume of titrant is required (see Titrinetry $(544$ )); see alse Preedures under Tests and Assays in the General Notices and Requirements. If any such modifiea tions are made in the Assay procedure set forth in the individunt monegraph, make the appropriate corresponding changes in the ealeulation formula and titration factor:

Where a special Procedure for content uniformity is specified in the test for Uniformity of dosege units in the individual meno graph, make any necessary correction of the results obtained as fol tows.
(1) Prepare - composite-specimen of a sufficient number of dosage units to provide the amoun of specimencalled for in the Assay in the individual monograph plus the amount required for the special Proe dure for eontent uniformity in the monograph by finely powdering tablets or mixing the contents of eapsules or oral solutions, syrups, suspen sions, or solids in single unit enntainers to obtain a hemegeneous mixture. If a hemogeneous mixture cannet be obtained in this manner, use suitable solvents or other procedures to prepare a solution containing all of the at tive ingredient, and use appropriate aliquet pertions of this solution for the specified procedures.
(2) Assay separate, aecurately measured portions of the eom pesite-specimen of eapsules or tablets or suspensions-or inhalations or solids in single mit containers, both (a) as direeted in the Assety, and (b) using the special Proedure for content uniformity in the menegraph.
(3) Caleulate the weight of active ingredient equivalent to-1 average dosage unit, by (a) using the results obtained by the Assay procedure, and by (b) using the results obtained by the special procedure.
(4) Caleulate the correction factor, $F$, by the formula:-

$$
F=A / P
$$

in which $A$ is the weight of active ingredient equivalent to 1 over age dosage unit obtained by the Assety procedure; and $P$ is the weight of active ingredient equivalent to 1 average dosage mit obtained by the special procedure. If

is greater than 10 , the use of a correction factor is net valid.
(5) A valideorrection may be appliedonly if $F$ is not less than 1.030 nor greater than 1.100 , or, not less than 0.900 nor greater than 0.970 , and if $F$ is between 0.970 and 1.030 no correction is required.
(6) If $F$ lies between 1.030 and 1.100 , or between 0.900 and 0.970 , caleulate the weight of active ingredient in each dosage unit by multiplying each of the weights found using the special procedure by $F$.

## Galeulation of the Relative Standard Periation

The use of preprogrammed ealeulators or computers is aeeepta ble. A manual mathematical method is as follows:
s-smple-standard deviation:
$R S D$ - relative standard deviation (the sample standard devia tion expressed as a percentage of the mean).
$\bar{X}$ - mean of the values obtained from the units tested, ex pressed as a pereentage of the label claim.
$\#-$ number of units tested.
$x_{4}, x_{2}, x_{2} \ldots x_{4}=$ individual values $\left(x_{i}\right)$ of the units tested, ex pressed as a percentage of the label claim.


## Griteria

Apply the following criteria, unless othervise specified in the individual menegraph.
(4) If the Average of the Limits Specified in the Potency Defini tion in the Individual Monograph is 100.0 Pereent or Less-

GOMPRESSED TABLETS (COATED OR UNCOATED), SUPPOSITORIES, ORAL SOLUTONS IN SINGLE UNT CONTAINERS, SYRUPS IN SINGLE UNIT CONTANERS, SUSPENSONS IN SNNGLE UNT CONTAINERS, SOLIDS (HNCLUDNG STERHE SOLIDS) IN SNNGLE UNIT CONTANHERS, ANDSTER HESOLIDS FOR PARENTERAL USE-Unless therwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the active ingredient in each of the 10 dosage units as determined from the Weight Variation or the Content Uni fomity method lies within the range of $85.0 \%$ to $115.0 \%$ of the tabelclaim and the Relative standed devion is less than-or equal - $6.0 \%$.

If 1 unit is outside the range of $85.0 \%$ to $115.0 \%$ of label claim and no mit is outside the range of $75.0 \%$ to $125.0 \%$ of label claim, or if the Relative standard deviation is greater than $6.0 \%$, or if both enditions prevail, test 20 -additional units. The requirements are met if not more than 1 unit of the 30 is outside the range of $85.0 \%$ to $115.0 \%$ of label claim and no unit is outside the range of $75.0 \%$ 125.0\% of labelelaim and the Relative stateder tion of the 30 dosage units does not $7.8 \%$

GAPSULES, TRANSDERMAL SYSTEMS, INHALATYNS PACKAGED-IN PREMETERED DOSAGE UNITS, AND MOLDED TABLETS-Unless other wise specified in the individual monegraph, the requirements for dosage uniformity are met if the amount of the active ingredient in not less than 9 of the 10 dosage units as determined from the Height Variation or the Content Uniformity method lies within the range of $85.0 \%$ to $115.0 \%$ of label clam and no unit is outside the range of $75.0 \%$ to $125.0 \%$ of label claim and the Relative stan dad devion the 10 dosage uits is less than or equal to $6.0^{\circ} \%$.

If 2 or 3 dosage units are outside the range of $85.0 \%$ to $115.0 \%$ of label claim, but not outside the range of $75.0 \%$ to $125.0 \%$ of tabel claim, or if the Relative standed devian is greater than $6.0 \%$ or if beth conditions prevail, test 20 additional units. The requirements are met if not more than 3 units of the 30 are outside the range of $85.0 \%$ to $115.0 \%$ of label claim and no wit is outside the range of $75.0 \%$ to $125.0 \%$ flabelelaim, and the Relative standed devien of the 30 desage units does not exeed $7.8 \%$
(B) If the Average of the Limits Specified in the Poteney Defini tion in the Individual Monograph is Greater than 100.0 Percent-
(1) If the average value of the dosage units tested is 100.0 pereent or less, the requirements are as in (A).
(2) If the average value of the dosage units tested is greater than or equal to the average of the limits speciffed in the potency definition in the individual monograph, the requirements are as in ( 4 ), exeept that the words "label elaim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency def inition in the menegraph divided by 100 ".
(3) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as in ( 4 ), exeept that the-words "label elaim" are replace by the werds "labelclaim multiplied by the average value of the dosage units tested (expressed as a pereent of label claim) divided by 100 ".

## ^ $\langle 905\rangle$ UNIFORMITY OF DOSAGE UNITS

[NOTE-In this chapter, unit and dosage unit are synonymous.]

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit.

The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified in the individual monograph.

The uniformity of dosage units can be demonstrated by either of two methods, Content Uniformity or Weight Variation (see Table 1). The test for Content Uniformity is based on the assay of the individual content of drug substance(s) in a number of individual dosage units to determine whether the individual content is within the limits set. The Content Uniformity method may be applied in all cases. The test for Content Uniformity is required for those dosage forms described in (C1)-(C6) below:
(C1) coated tablets, other than film-coated tablets
containing 25 mg or more of a drug substance that comprises $25 \%$ or more (by weight) of one tablet;
(C2) transdermal systems;
(C3) suspensions or emulsions or gels in unit-dose containers or in soft capsules that are intended for systemic administration only (not for those drug products that are intended for external, cutaneous administration);
(C4) inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers) packaged in premetered dosage units. For inhalers and premetered dosage units labeled for use with a named inhalation device, also see Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers $\langle 601\rangle$;
(C5) solids (including sterile solids) that are packaged in single-unit containers and that contain active or inactive added substances, except that the test for Weight Variation may be applied in the special situations stated in (W2) and (W3) below; and
(C6) suppositories.

The test for Weight Variation is applicable for the following dosage forms:
(W1) solutions for inhalation that are packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules; solids (including sterile solids) that are packaged in single-unit containers and contain no added substances, whether active or inactive; hard capsules, uncoated tablets, or filmcoated tablets, containing 25 mg or more of a drug substance comprising $25 \%$ or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting Content Uniformity requirements.

The test for Content Uniformity is required for all dosage forms not meeting the above conditions for the Weight Variation test. Alternatively, products listed in item (W4) above that do not meet the $25 \mathrm{mg} / 25 \%$ threshold limit may be tested for uniformity of dosage units by Weight Variation instead of the Content Uniformity test if the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than $2 \%$, based on process validation data and development data. The concentration RSD is the RSD of the concentration per dosage unit ( $\mathrm{w} / \mathrm{w}$ or $\mathrm{w} / \mathrm{v}$ ), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in Table 2.

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

| Dosage Form | Type | Subtype | Dose \& Ratio of Drug Substance |  |
| :---: | :---: | :---: | :---: | :---: |
|  |  |  | $\begin{aligned} & \geq 25 \mathrm{mg} \& \\ & \quad \geq 25 \% \end{aligned}$ | $\begin{gathered} <25 \mathrm{mg} \& \\ <25 \% \end{gathered}$ |
| Tablets | Uncoated |  | WV | CU |
|  | Coated | Film | WV | CU |
| Capsules |  | Others | CU | CU |
|  | Hard |  | WV | CU |
|  | Soft | Suspension, emulsion, or gel | CU | CU |
| Solids in single-unit containers |  | Solutions | WV | WV |
|  | Single component |  | WV | WV |
|  | Multiple components | Solution freeze-dried in final container | WV | WV |
|  |  | Others | CU | CU |
| Suspension, emulsion, or gel for systemic use only packaged in single-unit containers |  |  | CU | CU |
| Solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules |  |  | WV | WV |
| Inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers) packaged in premetered dosage units |  |  | CU | CU |

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms (Continued)

|  |  |  | Dose \& Ratio of Drug <br> Substance |  |
| :--- | :--- | :--- | :---: | :---: |
| Dosage Form |  |  | $\geq 25 \mathrm{mg} \mathrm{\&}$ <br> $\geq 25 \%$ | $<25 \mathrm{mg} \&$ <br> $<25 \%$ |
| Transdermal systems | Type |  |  | CU |
| Suppositories |  |  | CU | CU |
| Others |  |  | CU | CU |

## CONTENT UNIFORMITY

Select not less than 30 units, and proceed as follows for the dosage form designated. Where the amount of drug substance in a single dosage unit differs from that required in the Assay, adjust the degree of dilution of the solutions and/or the volume of aliquots so that the concentration of the drug substances in the final solution is of the same order as that obtained in the Assay procedure; or, in the case of a titrimetric assay, use a titrant of a different concentration, if necessary, so that an adequate volume of titrant is required (see Titrimetry $\langle 541\rangle$ ); see also Procedures under Tests and Assays in the General Notices and Requirements. If any such modifications are made in the Assay procedure set forth in the individual monograph, make the appropriate corresponding changes in the calculation formula and titration factor.

Where a special Procedure for content uniformity is specified in the test for Uniformity of dosage units in the individual monograph, make any necessary correction of the results obtained as follows.
(1) Prepare a composite specimen of a sufficient number of dosage units to provide the amount of specimen called for in the Assay in the individual monograph plus the amount required for the special Procedure for content
uniformity in the monograph by finely powdering tablets or mixing the contents of capsules or oral solutions, suspensions, emulsions, gels, or solids in single-unit containers to obtain a homogeneous mixture. If a homogeneous mixture cannot be obtained in this manner, use suitable solvents or other procedures to prepare a solution containing all of the drug substance, and use appropriate aliquot portions of this solution for the specified procedures.
(2) Assay separate, accurately measured portions of the composite specimen of capsules or tablets or suspensions or inhalations or solids in single-unit containers, both (a) as directed in the Assay, and (b) using the special Procedure for content uniformity in the monograph.
(3) Calculate the weight of drug substance equivalent to 1 average dosage unit, by (a) using the results obtained by the Assay procedure, and by (b) using the results obtained by the special procedure.
(4) Calculate the correction factor, $F$, by the formula:

$$
F=W / P,
$$

in which $W$ is the weight of drug substance equivalent to 1 average dosage unit obtained by the Assay procedure, and $P$ is the weight of drug substance equivalent to 1 average dosage unit obtained by the special procedure. If

$$
\frac{100|W-P|}{W}
$$

is greater than 10 , the use of a correction factor is not valid.
(5) The correction factor is to be applied only if $F$ is not less than 1.030 nor greater than 1.100 , or not less than 0.900 nor greater than 0.970 . If $F$ is between 0.970 and 1.030 , no correction is required.
(6) If $F$ lies between 1.030 and 1.100 , or between 0.900 and 0.970 , calculate the weight of drug substance in each dosage unit by multiplying each of the weights found using the special procedure by $F$.

Uncoated, Coated, or Molded Tablets, Capsules, Oral Solutions in Single-Unit Containers, Oral Suspensions or Oral Emulsions or Oral Gels in Single-Unit Containers, and Solids (including Sterile Solids) in SingleUnit Containers-Assay 10 units individually as directed in the Assay in the individual monograph, unless otherwise specified in the Procedure for content uniformity in the individual monograph. Calculate the acceptance value as directed below.

For oral solutions, oral suspensions, oral emulsions, or oral gels in single-unit containers, conduct the Assay on the amount of well-mixed material that drains from an individual container in not more than 5 seconds, or for highly viscous products, conduct the Assay on the amount of well-mixed material that is obtained by quantitatively removing the contents from an individual container, and express the results as the delivered dose.

Calculation of Acceptance Value-Calculate the acceptance value by the formula:

$$
|M-\bar{X}|+k s,
$$

in which the terms are as defined in Table 2.

Table 2

| Variable | Definition | Conditions | Value |
| :--- | :--- | :--- | :--- |
| $\bar{X}$ | Mean of individual contents $\left(\chi_{1}\right.$, <br> $\left.\chi_{2}, \ldots, \chi_{n}\right)$, expressed as a per- <br> centage of the label claim |  |  |
| $\chi_{1}, \chi_{2}, \ldots, \chi_{n}$ | Individual contents of the units <br> tested, expressed as a percentage <br> of the label claim |  |  |

Table 2 (Continued)

| Variable | Definition | Conditions | Value |
| :---: | :---: | :---: | :---: |
| $n$ | Sample size (number of units in a sample) |  |  |
| $k$ | Acceptability constant | If $n=10$, then $k=$ | 2.4 |
|  |  | If $n=30$, then $k=$ | 2.0 |
| $s$ | Sample standard deviation |  | $\left[\frac{\sum_{i=1}^{n}\left(\chi_{i}-\bar{X}\right)^{2}}{n-1}\right]^{\frac{1}{2}}$ |
| RSD | Relative standard deviation (the sample standard deviation expressed as a percentage of the mean) |  | $\frac{100 s}{\bar{X}}$ |
| $M$ (case 1) to be applied when $T \leq 101.5$ | Reference value | $\begin{aligned} & \text { If } 98.5 \% \leq \bar{X} \\ & \leq 101.5 \% \text {, then } \end{aligned}$ | $\begin{gathered} M=\bar{X} \\ (A V=k s) \end{gathered}$ |
|  |  | If $\bar{X}<98.5 \%$, then | $\begin{gathered} M=98.5 \% \\ (A V=98.5-\bar{X}+k s) \end{gathered}$ |
|  |  | If $\bar{X}>101.5 \%$, then | $\begin{gathered} M=101.5 \% \\ (A V=\bar{X}-101.5+k s) \end{gathered}$ |
| $M$ (case 2) to be applied when $T>101.5$ | Reference value | If $98.5 \leq \bar{X} \leq T$, then | $\begin{gathered} M=\bar{X} \\ (A V=k s) \end{gathered}$ |
|  |  | If $\bar{X}<98.5 \%$, then | $\begin{gathered} M=98.5 \% \\ (A V=98.5-\bar{X}+k s) \end{gathered}$ |
|  |  | If $\bar{X}>\mathrm{T}$, then | $\begin{gathered} M=T \% \\ (A V=\bar{X}-T+k s) \end{gathered}$ |

Table 2 (Continued)

| Variable | Definition | Conditions | Value |
| :---: | :---: | :---: | :---: |
| Acceptance value ( $A V$ ) |  |  | general formula: $\|M-\bar{X}\|+k s$ <br> (Calculations are specified above for the different cases.) |
| L1 | Maximum allowed acceptance value |  | $L 1=15.0$ unless otherwise specified in the individual monograph |
| L2 | Maximum allowed range for deviation of each dosage unit tested from the calculated value of $M$ | On the low side, no dosage unit result can be less than (1$L 2 * 0.01) M$, while on the high side no dosage unit result can be greater than (1 + $L 2 * 0.01$ ) $M$. (This is based on an $L 2$ value of 25.0 .) | $L 2=25.0$ unless otherwise specified in the individual monograph |
| $T$ | Target test sample amount at time of manufacture. For purposes of this Pharmacopeia, unless otherwise specified in the individual monograph, $T$ is $100.0 \%$, and for manufacturing purposes, $T$ is the manufacturer's approved target test amount value at the time of manufacture. |  |  |

Suppositories, Transdermal Systems, and Inhalations Packaged in Premetered Dosage Units-[NOTE-Acceptance value calculations are not required for these dosage forms.] Assay 10 units individually as directed in the Assay in the individual monograph, unless otherwise specified in the Procedure for content uniformity.

## WEIGHT VARIATION

Select not less than 30 dosage units, and proceed as follows for the dosage form designated. The result of the $A s$ say, obtained as directed in the individual monograph, is designated as result $A$, expressed as \% of label claim (see Calculation of the Acceptance Value). Assume that the concentration (weight of drug substance per weight of dosage unit) is uniform. [NOTE-Specimens other than these test units may be drawn from the same batch for assay determinations.]

Uncoated or Film-Coated Tablets-Accurately weigh 10 tablets individually. Calculate the drug substance content, expressed as $\%$ of label claim, of each tablet from the weight of the individual tablet and the result of the $A s$ say. Calculate the acceptance value.

Hard Capsules-Accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by a suitable means. Accurately weigh the emptied shells individually, and calculate for each capsule the net weight of its contents by subtracting the weight of the shell from the respective gross weight. Calculate the drug substance content, expressed as $\%$ of label claim, of each capsule from the net weight of the individual capsule content and the result of the Assay. Calculate the acceptance value.

Soft Capsules-Accurately weigh 10 intact capsules individually to obtain their gross weights, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the drug substance content, expressed as $\%$ of label claim, in each capsule from the net weight of product removed from the individual capsules and the result of the Assay. Calculate the acceptance value.

Solids (Including Sterile Solids) in Single-Unit Con-tainers-Proceed as directed for Hard Capsules, treating each unit as described therein. Calculate the acceptance value.

Oral Solutions Packaged in Single-Unit ContainersAccurately weigh the amount of liquid that drains in not more than 5 seconds from each of 10 individual containers. If necessary, compute the equivalent volume after determining the density. Calculate the drug substance content, expressed as \% of label claim, in the liquid drained from each unit from the net weight of the individual container content and the result of the Assay. Calculate the acceptance value.

Calculation of Acceptance Value-Calculate the acceptance value as shown in Content Uniformity, except that the individual contents of the units are replaced with the individual estimated contents defined below.

$$
\begin{aligned}
\chi_{1}, \chi_{2}, \ldots, \chi_{n}= & \text { the individual estimated contents } \\
& \text { of the units tested, where } \\
& =w_{i} \times A / \bar{W}
\end{aligned}
$$

$$
\begin{array}{ll}
w_{1}, w_{2}, \ldots, w_{n}= & \begin{array}{r}
\text { individual weights of the units } \\
\\
\\
\text { tested, }
\end{array} \\
A & \quad \text { content of drug substance }(\% \text { of } \\
\text { label claim) determined as } \\
& \\
& \\
& \text { described in the Assay, and } \\
\bar{W} & \text { mean of individual weights } \\
& \left(w_{1}, w_{2}, \ldots, w_{n}\right) .
\end{array}
$$

Solutions for Inhalation Packaged in Glass or Plastic Ampuls and Intended for Use in Nebulizers-[NOTEAcceptance value calculations are not required for these dosage forms.] Accurately weigh 10 containers individually, taking care to preserve the identity of each container. Remove the contents of each container by a suitable means. Accurately weigh the emptied containers individually, and calculate for each container the net weight of its contents by subtracting the weight of the container from the respective gross weight. From the results of the Assay, obtained as directed in the individual monograph, calculate the drug substance content, expressed as \% of label claim, in each of the containers.

## CRITERIA

Apply the following criteria, unless otherwise specified in the individual monograph.

Uncoated, Coated, or Molded Tablets, Capsules, Oral Solutions in Single-Unit Containers, Oral Suspensions or Oral Emulsions or Oral Gels in Single-Unit Containers, and Solids (Including Sterile Solids) in SingleUnit Containers-The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to $L 1 \%$. If the acceptance value is greater than $L 1 \%$, test the next 20 units and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to $L 1 \%$, and no individual content of any dosage unit is less than (1-
$L 2 * 0.01) M$ nor more than $(1+L 2 * 0.01) M$ as specified in the Calculation of Acceptance Value under Content Uniformity or under Weight Variation. Unless otherwise specified in the individual monograph, $L 1$ is 15.0 and $L 2$ is 25.0.

## Suppositories-

Limit $A$ (if the average of the limits specified in the potency definition in the individual monograph is 100.0 percent or less)-Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in each of the 10 dosage units as determined from the Content Uniformity method lies within the range of $85.0 \%$ to $115.0 \%$ of the label claim, and the RSD is less than or equal to $6.0 \%$.
If 1 unit is outside the range of $85.0 \%$ to $115.0 \%$ of label claim, and no unit is outside the range of $75.0 \%$ to $125.0 \%$ of label claim, or if the RSD is greater than $6.0 \%$, or if both conditions prevail, test 20 additional units. The requirements are met if not more than 1 unit of the 30 is outside the range of $85.0 \%$ to $115.0 \%$ of label claim, and no unit is outside the range of $75.0 \%$ to $125.0 \%$ of label claim and the RSD of the 30 dosage units does not exceed $7.8 \%$.

Limit $B$ (if the average of the limits specified in the potency definition in the individual monograph is greater than 100.0 percent)-
(1) If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under Limit $A$, except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100 ".
(2) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual
monograph, the requirements are as specified under Limit A, except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100 ".

Transdermal Systems and Inhalations Packaged in

## Premetered Dosage Units-

Limit $A$ (if the average of the limits specified in the potency definition in the individual monograph is 100.0 percent or less)-Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in not less than 9 of the 10 dosage units as determined from the Content Uniformity method (or, in the case of solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers, from either the Content Uniformity or the Weight Variation method) lies within the range of $85.0 \%$ to $115.0 \%$ of label claim, and no unit is outside the range of $75.0 \%$ to $125.0 \%$ of label claim, and the RSD of the 10 dosage units is less than or equal to $6.0 \%$.

If 2 or 3 dosage units are outside the range of $85.0 \%$ to $115.0 \%$ of label claim, but not outside the range of $75.0 \%$ to $125.0 \%$ of label claim, or if the RSD is greater than $6.0 \%$ or if both conditions prevail, test 20 additional units. The requirements are met if not more than 3 units of the 30
are outside the range of $85.0 \%$ to $115.0 \%$ of label claim and no unit is outside the range of $75.0 \%$ to $125.0 \%$ of label claim, and the RSD of the 30 dosage units does not exceed 7.8\%.

Limit $B$ (if the average of the limits specified in the potency definition in the individual monograph is greater than 100.0 percent)-
(1) If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under Limit $A$, except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100 ".
(2) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under Limit $A$, except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by $100 "$. $\triangle$ USP28
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## PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the Staff Directory to find the contact information).

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PHARMACOPEIAL PREVIEWS ..... 1487
GENERAL INFORMATION CHAPTERS ..... 1489
〈1073〉 Effusivity ..... 1489

# GENERAL CHAPTERS <br> General Information 

## BRIEFING

$\langle\mathbf{1 0 7 3}\rangle$ Effusivity. A new general chapter for effusivity, designated Efflusivity $\langle 1073\rangle$, is being previewed. Effusivity is a heat transfer property present in all materials in all formats-solids, liquids, pastes, powders, and gases. As such, this property has many potential uses in the production of pharmaceuticals for controlling product consistency, homogeneity, and final product quality. This chapter provides general information on this technique, which may have application in certain cases as a manufacturing real-time control technique.
(PDF: G. Ritchie; PDF: W. Paul) RTS-41237-1

## Add the following:

## 〈1073〉 EFFUSIVITY

## INTRODUCTION

Effusivity (thermal effusivity) is a thermal property present in materials of all formats-solid, liquid, paste, powder, and gas. Effusivity measures the rate at which a material can absorb heat and is defined as the square root of the product of the thermal conductivity, density, and specific heat capacity. Specifically, effusivity is the thermal property that dictates the interfacial temperature when two semi-infinite bodies meet (see Sample Thickness). [NOTE-See the final section of this chapter, Definition of Terms and Symbols, for the terms and symbols referred to in this chapter and commonly employed in effusivity technology.]

Every material has a specific thermal effusivity value. Effusivity is sensitive to composition because materials differ in effusivity value $\left(W_{s}^{1 / 2} / m^{2} \cdot K\right)$ from 5 for air to 1600 for water to several thousand for advanced composites. As a result, effusivity can differentiate between materials in solid, liquid, and powder formats. In the application of blend evaluation, the blending endpoint can then be identified when the effusivities of samples at different positions in the blender give minimum variation (see Definition of Terms and Symbols). The effusivity of a powder sample is driven by the properties of the particles and the interparticle material (typically air). Because effusivities of pharmaceutical solid materials (typically 150 to $800 \mathrm{Ws}^{1 / 2} / \mathrm{m}^{2} \cdot K$ ) are much higher than that of air, effusivity technology can also identify particle size distribution and density of powders. Because the effusivity of liquids (i.e., water is $1600 \mathrm{Ws}^{1 / 2} / \mathrm{m}^{2} \cdot K$ ) is so much greater than powder, effusivity technology can be used to monitor wet granulation and drying.

A big advantage of effusivity technology is that accurate measurements can be made rapidly and nondestructively. Furthermore, effusivity sensors only require brief contact with any materials investigated. As a result, effusivity technology allows in situ measurements and on-line monitoring of processes in challenging environments. If the material is in motion during the measurement but makes periodic contact with the sensor (as in blending), the measurement is taken only during the periods of contact.

## MODIFIED HOT WIRE (MHW) INTERFACIAL HEAT REFLECTANCE

A fast, nondestructive and accurate effusivity measurement can be performed using a transient heat interfacial reflectance MHW technique (see Definition of Terms and Symbols).

The sample is tested by placing the heating elements of the sensor of the apparatus against the surface of the sample (see Definition of Terms and Symbols). A known quantity of electrical current is passed through the heating elements of the sensor for a known time, which results in a temperature rise (less than 5 K ) at the sensor/sample interface. The size of the temperature increase is measured, and because the temperature rise of the element is inversely proportional to the ability of the sample to transfer heat, a relationship between the change in temperature and material characteristics can be developed. This relationship is created through the use of a calibration equation using well-characterized samples (see Definition of Terms and Symbols). The value of effusivity can then be measured by inputting the appropriate sample test data into the calibration equation.

During the transient measurement, the heat flows into the sample. The longer the test duration, the further the heat wave penetrates into the sample based on the Einstein equation:

$$
d=(4 \alpha t)^{1 / 2}
$$

where:

$$
\begin{aligned}
& d=\text { distance traveled by } 1 \% \text { of the heat wave (m) } \\
& \alpha=\text { the thermal diffusivity of the material }\left(\mathrm{m}^{2} / \mathrm{s}\right)
\end{aligned}
$$

$$
t=\text { the time }(\mathrm{s})
$$

Tests with a longer duration cause heat to travel further into the sample, and, therefore, the resulting effusivity measurement represents a larger volume of material, or a larger scale
of scrutiny. It is important to balance the scale of scrutiny appropriately with the expectations of homogeneity and consistency in the material evaluated.

For powder samples, the effusivity varies with packing conditions because air has an effusivity of $5 \mathrm{Ws}^{1 / 2} / \mathrm{m}^{2} \cdot \mathrm{~K}$. As the material is compressed, air is removed and the effusivity value increases. After a user-defined nominal pressure of 15 Pa is applied for most materials, the effusivity measurement reaches a plateau when it is plotted against applied pressure. This is referred to as the threshold pressure and should be independently determined for materials that are tested offline. Alternately, if a sensor used for effusivity measurements weighs at least 500 g and has a surface area equal to or less than a $6.4-\mathrm{cm}(2.5-\mathrm{inch})$ diameter, adequate pressure is supplied. During on-line testing, the column of powder above a sensor face provides adequate pressure if the sensor is at least 20 cm below the powder surface.
Although the scale of scrutiny is only 200 to 500 mg , in off-line blend evaluation, each sample should be 25 g or more to establish reproducible compression and consistency in sample treatment. It is recommended that samples be placed in a container whose inner diameter is in close proximity to the outer diameter of the sensor. This prevents additional movement and spreading of the sample and results in improved reproducibility. In the case of a $6.4-\mathrm{cm}$ diameter sensor, a $250-\mathrm{mL}$ beaker makes an excellent single, sample holder. On the other hand, the threshold pressure will not affect evaluation results in on-line blend evaluation as long as the sensors are placed at a level well below the fill line in order for the downward pressure of the powder above the sensor to generate the equivalent pressure (see Definition of Terms and Symbols).

## Other Factors Affecting Effusivity Quantification

Moisture-Effusivity values are sensitive to the amount of moisture contained in a sample. It is, therefore, important to maintain consistent sample moisture during calibrations and sample testing, unless it is the moisture variations that are the desired measurement. Because water has an effusivity of $1600 \mathrm{Ws}^{1 / 2} / \mathrm{m}^{2} \cdot K$, the content of $1 \%$ water increases the effusivity of a typical powder by $3 \%$.

Environmental Temperature-The variation of environmental temperature may jeopardize the target precision and accuracy (see Definition of Terms and Symbols). It is recommended that the variation of the environmental temperature should be less than $\pm 1 \mathrm{~K}$ to achieve absolute effusivity measurements with accuracies of $1 \%$ to $2 \%$. If the environmental temperature cannot be controlled, then it should be measured and recorded. The temperature data then provide a basis upon which a suitable correction for temperature effects can be formulated. Because the major application of effusivity is the relative effusivity or determination of effusivity plateaus rather than absolute effusivity (e.g., blend evaluation and drying), and each set of measurements is taken at the same environmental temperature, this factor typically has little or no affect on the final results.

Sample Thickness-Because heat is applied and detected on the same side of the material, if the sample is completely penetrated during a test, the material on the other side of the sample will be factored into the test results, producing a false representation of the effusivity value of the sample. Therefore, any off-line sample that is tested should be thicker than the depth of heat penetration during the test. In blend evaluation, a typical 2 -second test penetrates into the powders approximately 0.5 mm , which is why a $25-\mathrm{g}$ sample placed in a container with sides matching the sensor dimensions is recommended. In an on-line measurement, the thickness of sample has no significance, because the
sample is semi-infinite and the heat never reaches the far side of the sample. The worst-case scenario for minimum sample thickness would be to use the longest test time of 10 seconds and a high effusivity material (crystalline material with high moisture). In this scenario, a minimum sample thickness of 5 mm would be required.

Sensor/Sample Interface Temperature-The differences in test results caused by variability in the starting temperature are not negligible. It is, therefore, critical to monitor the sensor/sample interface temperature and ensure that the temperature is the same at the start of each test. To achieve this, a cooling time may be used between two successive experiments (see Definition of Terms and Symbols). Otherwise, the temperature of the sensor/sample interface should be measured and recorded. The temperature data then provide a basis upon which a suitable correction for the effects of starting sensor/sample interface temperature can be formulated.
(In)homogeneity-Effusivity at the surface of a sample may or may not represent the effusivity of the bulk of the sample. The extent of regional differences in effusivity will depend on the homogeneity or inhomogeneity of the sample. As a result, differences in homogeneity or inhomogeneity can be detected by regional differences in effusivity values. In pharmaceutical analysis, this characteristic enables effusivity technology to be an efficient, effective tool for blend evaluation. The limiting factor is the range of effusivities of the components in the mixture. If all the materials had effusivities with a span of $10 \mathrm{Ws}^{1 / 2} / \mathrm{m}^{2} \cdot K$, the technique would not be able to differentiate between blended and unblended material because the relative standard deviation (RSD) between sensors at different locations in the powder bed would start at a maximum of $1.25 \%$.

Power Supply-Accuracy and precision of the test results depend directly on the accuracy and precision of the power supply for heating elements. Therefore, it is desirable to use a high-precision, constant current and voltage power supply in the constant current and voltage configuration, respectively. Also, the power supply should be capable of delivering sufficient current to the heating elements such that the sensor generates a statistically significant temperature rise at the sensor/sample interface. The ideal temperature rise at the sensor/sample interface ranges from statistically significant to less than 5 K .

## APPARATUS

The sensor of the apparatus is based on the modified transient hot wire technique, which means that the heating elements are supported on a backing that provides mechanical support and electrical and thermal insulation (see Definition of Terms and Symbols). Such a modification eliminates the intrusive nature of hot wire technique, thereby allowing solids to be tested without melting, or otherwise modifying the sample to conform to the geometry of the test cell.

The sensor of this apparatus consists of three parallel wires mounted on a piece of thermally and electrically insulating backing. The parallel wires function as heating and guarding elements to generate a measurable rectangular one-dimensional heat flow. The constant current or voltage electrical source supplies power to the heating elements. The two outer wires are guard heaters, preventing the undesired lateral spread of heat from the heating elements and generating rectangular one-dimensional heat flow. The sensor of this apparatus functions by measuring the temperature rise at the sensor/sample interface. The temperature rise at the sensor/sample interface is measured as the voltage rises over time in a constant current configuration, or as the current rises over time in a constant voltage configuration. An

ADC (analog/digital converter) with suitable input range and resolution should be connected to the sensor. The temperature rise is recorded using an appropriate data acquisition rate.

In on-line blend evaluation, the effusivity sensors can be retrofitted onto a blender. It is recommended to retrofit the sensors onto the covers of the blender for reasons of flatness and economics as well as for constant applied load of the material on top of the sensors. The measurement is taken while the blender is inverted. The number of sensors placed depends on the system and the size of the blenders, but typically it is four to eight sensors. For bin blenders with flat surfaces, the volume limitation on the lower end is related to the surface area of the bin so that no fewer than two sensor ferrules can be retrofitted on each side of the blender.

## FACTORY/VENDOR CALIBRATION

MHW technique is a comparative (secondary) method of measurement and the sensor must be calibrated with standards, which have known effusivity values. This calibration is conducted at the factory. The MHW instruments are factory calibrated with four calibration standards in triplicate. [NOTE-Calibration standards should be selected from or traceable to a recognized source of national standards.] During calibration, the test time and cooling time are established.

The highest/lowest effusivity of the sample must be less/ greater than the highest/lowest effusivity of the calibration standard. The heating elements of the sensor must be completely covered by the standard. Handling the standard should be minimized. Avoid touching the sample/standard with bare hands or fingers because such touching can lead to significant disruption of thermal equilibrium.

Relatively stable thermal equilibrium must exist between the sensor and the sample in order for accurate and precise measurements to be made. Thermal equilibrium is disrupted during each test because the temperature of the sensor/sample interface increases during a test. As a result, it is desirable to employ a cooling time between two successive experiments to allow the system to (1) re-establish thermal equilibrium between the sensor and the sample and (2) ensure that the temperature of the sensor/sample interface is the same at the start of the each test. Depending on thermal diffusivity of the sample and sensor power, the cooling time needed may vary from a few seconds to several minutes or more. An acceptable cooling time should make temperature or voltage differences from the beginning to end of a test sequence less than 0.5 K or 0.9 mV . In blend evaluation, the typical cooling time is 1 to 3 minute(s). This is a factor that is set during factory calibration and is directly proportional to the test time. If the tests are conducted without cooling, the temperature of the sensor/sample interface should be recorded. The apparatus should be corrected for the difference in the initial sensor/sample interface temperature.

Test time may vary from less than 1 second to a few minutes, depending on the sample's thermal diffusivity (see Definition of Terms and Symbols). The lower the sample's thermal diffusivity, the shorter the test time, and vice versa. In blend evaluation, the typical test time is 1 to 10 seconds.

Data collection rates should be fast enough to provide statistical confidence in the test results. Shorter test times will require faster data collection rates. The data collection rate is determined such that at least 100 data points can be collected at each test. In blend evaluation, the typical data collection rate is 100 to 400 Hz .

The factory calibration is acceptable when the squared correlation coefficient resulting from the least-square correlation between raw instrument response and known thermal effusivities of the standards is greater than or equal to 0.990 ( $R^{2} \geq 0.990$ ). Other correlation techniques should result in equivalent precision and bias in the tests after an acceptable calibration (see Definition of Terms and Symbols). Upon an acceptable calibration, both precision and bias estimates are less than $\pm 3 \%$ RSD between sensors and less than $\pm 1 \%$ RSD within a single sensor. Appropriateness and accuracy of the calibration are proven when a reference standard is tested and the effusivity value is within $\pm 5 \%$.

An effusivity reference material should be checked daily to ensure that the calibration has not drifted. The absolute effusivity value should be maintained within acceptance criteria at all times. Aside from that, the calibration should be carried out when the testing environment changes or when a need arises to change operating parameters such as test time and sampling frequency.

## DEFINITION OF TERMS AND SYMBOLS

ABSOLUTE EFFUSIVITY is the numerical value of effusivity. ACCURACY is the closeness of test results obtained to the true value.

BACKING is a piece of thermally and electrically insulating material to provide mechanical support for heating elements, to help generate one-dimensional heat flow, and to avoid a short circuit.

BIAS, also referred to as systematic error, is a fixed deviation that is inherent in every measurement.

BLEND ENDING POINT is a blend status when the blend uniformity is reached.

CALIBRATION is the process by which standard materials are used to determine the settings of instruments that correspond to particular values of voltage, current, frequency, or other output.

CALIBRATION EQUATION is an equation used to convert raw instrument response to effusivity values.

CALIBRATION STANDARD is a sample having known thermal effusivity value and selected from or traceable to a recognized library of national standards.

COOLING TIME is the time interval between two successive experiments, in seconds (s).

DATA ANALYSIS WINDOW is a calculation method to select part of data instead of whole data collected to determine the effusivity of samples tested.

DENSITY is the mass per unit volume of the material, in kg / $\mathrm{m}^{3}$ 。

ENDING TIME is the time point counted as the last valid data for the calculation of effusivity. It defines the ending point of the data analysis window.

HEATING ELEMENT is a thin material with high electrical resistance to generate a measurable temperature increase at the sensor/sample interface.

INTERFACIAL HEAT REFLECTANCE is a reflectance measurement technique where the sensors supply the heat source to samples and detect the heat flow reflected from the samples. PRECISION is the degree of agreement among individual test results when the method is applied repeatedly to multiple samplings of a homogeneous sample. It is important to distinguish between within sensor and between sensor precisions in all reports.

RELATIVE EFFUSIVITY is the effusivity value of a specific sample relative to the mean effusivity of a group of such samples.

SAMPLING FREQUENCY is the frequency of testing during each set of test.

SPECIFIC HEAT CAPACITY is the quantity of heat required to raise the temperature of a unit of mass of a substance by a unit change in temperature, in $J /(\mathrm{kg} \cdot \mathrm{K})$.

START TIME is the elapsed time from the beginning of the test to the time point counted as the first valid data for the calculation of effusivity. It defines the start point of the data analysis window, in s .

TEST TIME is the elapsed time from start to finish of passing current through the heating elements to perform a single test, in s .

THERMAL CONDUCTIVITY is the time rate of steady state heat flow through a unit area of a homogeneous material induced by a unit temperature gradient in a direction perpendicular to that unit area, in $W / m \cdot K$.

THERMAL DIFFUSIVITY is the ratio of thermal conductivity of a substance to the product of its density and specific heat, in $m^{2} / s$.

THERMAL EFFUSIVITY, $e$, also referred to as effusivity or thermal inertia, is the square root of the product of the thermal conductivity, density, and specific heat capacity, in $W s^{1 / 2} / m^{2} \cdot K$. In the MHW technique, $e$, is calculated using the following formula:

$$
1 / e \infty(d \Delta T / d t)
$$

in which, $\Delta T$ is the temperature rise at the sensor/sample interface, and $d t$ is the time period corresponding to this temperature rise.

## STIMULI TO THE REVISION PROCESS

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- reports or statements of authoritative committees
- original research reports
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# Determination of the Hydroxypropoxy Content in Hydroxypropyl Cellulose by ${ }^{1} \mathrm{H}$ NMR 

T. Andersson ${ }^{1}$, S. Richardson ${ }^{1}$, and M. Erickson ${ }^{1,2}$


#### Abstract

The authors describe the use of ${ }^{1} \mathrm{H}$ NMR for determination of molar substitution and hydroxypropoxy content in hydroxypropyl cellulose. The method is developed as a possible alternative to the present pharmacopeial methods (GC and titration). The method is shown to be robust and gives a good correlation to the titration procedure described in the USP monograph, Hydroxypropyl Cellulose.


## INTRODUCTION

The hydroxypropoxy (HP) content of high-substituted hydroxypropyl cellulose (HPC) is determined by different methods in the United States Pharmacopeia (USP) (1) and the Japanese Pharmacopeia (JP) (2). USP uses chromic acid oxidation followed by titration, whereas $J P$ utilizes a treatment with hydroiodic acid followed by a gas chromatographic method (Zeissel-GC) for the HP content analysis. The USP assay has been reported to be more accurate than the $J P$ method. The $J P$ method is, however, more reproducible but gives consistently lower results compared to the USP method (3). A proposal for a harmonized monograph for HPC using chromic acid oxidation as the assay was published in Pharmeuropa 14.2 (4). However, chromic acid is considered a hazardous material by $J P$.

This report describes an alternative method for determination of the HP content in HPC by ${ }^{1} \mathrm{H}$ NMR based on the paper of Tezuka et al. (5). In this method HPC is acetylated (see Figure 1), which allows direct determination of the molar substitution of the polymer.


Fig. 1. The structure of acetylated HPC.
The areas from the ${ }^{1} \mathrm{H}$ NMR signals from the methyl group in the introduced acetyl group (signal a) and from the methyl group in the HP group (signal b) are used to determine the molar substitution (MS) (see Figure 2).


Fig. 2. The ${ }^{1} \mathrm{H}$ NMR spectrum of acetylated HPC.

The weight percentage of HP groups accordingly is calculated by the following formula:

$$
\mathrm{HP}(\mathrm{w} / \mathrm{w} \%)=75 \times \mathrm{MS} \times 100 /(58 \times \mathrm{MS}+162)
$$

$$
\mathrm{MS}=3 \mathrm{~b} / \mathrm{a}
$$

It also has been reported by Ho et al. (6) that ${ }^{1} \mathrm{H}$ NMR was used to determine HP content in HPC without derivatization. This method (i.e., by dissolving the HPC directly in $\mathrm{CDCl}_{3}$ ) was also evaluated. However, this method gave integrals with low reproducibility and was therefore abandoned.

[^187]
## EXPERIMENTAL

Two HPC samples from different manufacturers were investigated, HPC L from Nippon Soda Company (Tokyo, Japan) and HPC LF (Klucel) from Hercules (Wilmington, DE, USA). The HPC samples were acetylated according to the method of Tezuka et al. (5) in order to acetylate all hydroxyl groups in the polymer, which also makes it soluble in common NMR solvents. Acetylation was carried out by dissolving 150 mg of HPC in acetic anhydride ( 2.25 mL ) and pyridine $(0.75 \mathrm{~mL})$. The mixture was then allowed to reflux for 3 h .

The acetylated products were dialyzed against water in Spectra/Por dialysis membranes (Spectrum Laboratories, Rancho Dominguez, CA, USA) with a molecular weight cutoff of 10 kDa for 24 h and finally freeze-dried overnight. Typically, $8-12 \mathrm{mg}$ of this material was transferred to a $5-$ mm NMR tube. DMSO- $d_{6}(0.7 \mathrm{~mL})$ was added to the tube, which dissolved the acetylated HPC after heating.

The ${ }^{1} \mathrm{H}$ NMR spectra were recorded on a Varian 500 Inova spectrometer operating at a magnetic field of 11.7 T , equipped with a $5-\mathrm{mm}{ }^{1} \mathrm{H}\{\mathrm{X}\}$ inverse detection gradient probe. The probe had a maximum working temperature of $80^{\circ} \mathrm{C}$.

The FID was recorded with at least 16 scans, and the spectral window was at least between -2 and 10 ppm referring to the solvent signal of DMSO ( 2.49 ppm ). A $45^{\circ}$ pulse was used with an acquisition time of 5 seconds and a delay time of 5 seconds between each pulse. The total time for obtaining one FID using these parameters is less than 5 minutes. The acquisition data were zero filled at least twofold, and the transformation was made using a line-broadening factor of 0.3 . The spectra were phased correctly prior to the integration. The signal area of a was integrated between 2.20 ppm and 1.60 ppm , and $\mathbf{b}$ was integrated between 1.50 ppm and 0.70 ppm . Usually the ${ }^{1} \mathrm{H}$ NMR spectra were recorded both at $25^{\circ} \mathrm{C}$ and at $78{ }^{\circ} \mathrm{C}$.

## RESULTS AND DISCUSSION

Three different acetylations were made on two different samples using the reported acetylation time, 3 h (5). To check if the acetylation had been driven to completeness, acetylation for 1 h and 6 h was also carried out. For results, see Table 1. The ${ }^{1} \mathrm{H}$ NMR data were compared with the results obtained by a determination of the HP content according to the $U S P$ method.

Table 1. Assay of HP groups, HP (w/w\%)

| Sample | $\begin{gathered} \text { HP, w/w\% } \\ \left(\begin{array}{c} \text { (H NMR, } \\ \left.\mathbf{3} \mathbf{h}^{\mathrm{a}}\right) \end{array}\right. \\ \hline \end{gathered}$ | $\begin{gathered} \text { HP, w/w\% } \\ \left({ }^{\mathbf{1}} \mathrm{H} \text { NMR },\right. \\ \left.1 \mathrm{~h}^{\mathrm{a}}\right) \end{gathered}$ | $\begin{gathered} \text { HP, w/w\% } \\ \left({ }^{( }{ }^{\prime} \mathrm{H} N \mathrm{NR},\right. \\ \left.6 \mathrm{~h}^{2}\right) \end{gathered}$ | HP, w/w\% (USP) |
| :---: | :---: | :---: | :---: | :---: |
| HPC L | 73.7 | 74.4 | 73.8 | 74.5 |
|  | 73.8 | 74.7 |  |  |
|  | 73.8 |  |  |  |
| HPC LF | 77.4 | 77.6 | 77.4 | 73.6 |
|  | 76.8 | 77.7 |  |  |
|  | 76.5 |  |  |  |

${ }^{\text {a }}$ Acetylation time

The results were in reasonably good agreement with the USP method. The ${ }^{1} \mathrm{H}$ NMR method seems to be reproducible and robust with respect to acetylation time. Other magnetic field strengths ( 300 and 600 MHz ) and higher temperatures $\left(78{ }^{\circ} \mathrm{C}\right)$ have been used for the NMR determinations with no significant changes in the results.

In order to verify that the method also works for HPC of different molecular weights, a series of determinations were made on samples from Klucel that were kindly supplied by

Hercules. The average molecular weights of these samples cover the range from 80 kDa to $>1000 \mathrm{kDa}$ (7). In Table 2 the results of these NMR determinations are shown together with data provided by Hercules on the HP content obtained by $U S P$ and $J P$ methodology.

Table 2. Determination of the HP content in HPC with different viscosity grades (Klucel) by ${ }^{1}$ H NMR spectroscopy.

|  | HP content (w/w\%) |  |  |  |
| :--- | :---: | :---: | :---: | :---: |
| Sample | $1 \mathrm{H}^{\prime} \mathrm{H} \mathrm{NMR}$ <br> $\left(25{ }^{\circ} \mathrm{C}\right)$ | 1 <br> ${ }^{1} \mathrm{H} \mathrm{NMR}$ <br> $\left(78{ }^{\circ} \mathrm{C}\right)$ | $\boldsymbol{J P}$ | $\boldsymbol{U S P}$ |
| EF 7926 | 75.9 | 75.6 | 59.3 | 72.5 |
| LF 8056 | 76.1 | 75.9 | 59.7 | 74.2 |
| JF 8865 | 76.1 | 75.5 | 60.2 | 74.3 |
| GF 8271 | 77.2 | 76.2 | 60.3 | 76.6 |
| MF 8810 | $78.0^{*}$ | 78.1 | 60.6 | 75.7 |
| HF 8679 | $79.2^{*}$ | 78.9 | 61.0 | 76.1 |

* The ${ }^{1} \mathrm{H}$ NMR spectra were poorly resolved.

For the highest molecular weight samples (MF and HF sample designations) viscous solutions containing small gel particles were obtained upon dissolution of the acetylated samples in DMSO- $d_{6}$ at room temperature. In order to increase solubility, the samples were also run at $78{ }^{\circ} \mathrm{C}$. In Table 2, data from both $25^{\circ} \mathrm{C}$ and $78^{\circ} \mathrm{C}$ are reported. In general, the spectra obtained at $78^{\circ} \mathrm{C}$ showed a higher resolution (sharper NMR signals) compared with $25^{\circ} \mathrm{C}$, in particular for the MF and HF samples. No significant difference was, however, observed in the determination of the molar substitution of any of the samples.

It can thus be concluded that the NMR determination also works for high-substituted HPC of different molecular weights that are available on the market.

For low-substituted HPC ( $14.7 \mathrm{w} / \mathrm{w} \%$ HP by the $J P$ method) the acetylation did not yield a soluble material that was useful for NMR determination.

## CONCLUSION

NMR is a versatile method for determining the molar substitution of HPC and thus for calculating the HP content. It is applicable to high-substituted HPC of different molecular weights. No hazardous material is used in the method. The determination, when made on an acetylated sample, is not dependent on the use of any external (or internal) standard
and seems quite insensitive (robust) to experimental conditions, in contrast to the currently used pharmacopeial methods. An appropriately executed NMR determination can be expected to give the true value for the molar substitution of the polymer, and the determination is not dependent on exact experimental conditions.

The NMR method is proposed as an alternative to, or a replacement for, the present pharmacopeial methods in a harmonized monograph for hydroxypropyl cellulose. It may, alternatively, be used as a reference method.

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# Improving Sensitivity and Robustness of Chromatographic Assays for Netilmicin 

Yaqi Cai, Jun Cheng, Shifen Mou, and Petr Jandik*


#### Abstract

This article discusses the optimization of a chromatographic method for the determination of netilmicin sulfate. The performance of a polymeric column is compared with that of a silica-based column. The total run time with the silicabased column was only 15 minutes vs. 45 minutes that were required with the polymeric column. The signal-to-noise ratio was also improved with the silica-based column. Also described is the optimization of the integrated amperometric detection. A quadruple potential waveform originally introduced for the detection of carbohydrates was optimized for netilmicin and its accompanying impurities. The authors explain the importance of completely reporting all parameters influencing the performance of electrochemical detection.


## INTRODUCTION

Two recent publications $(1,2)$ describe a technique for chromatographic assays of netilmicin and impurities frequently accompanying netilmicin in pharmaceutical formulations. The technique is based on a separation in conjunction with integrated amperometric detection.

The first of the two reports offers a thorough description of an optimization of mobile phase composition. The influence of pH on retention time and peak symmetry was evaluated between pH 2 and 7. Acetonitrile, 2-methyl-2propanol, dimethyl sulfoxide, acetone, and tetrahydrofuran were evaluated as organic modifiers. A 4-factorial design process was utilized to determine the optimum concentrations of tetrahydrofuran, sodium sulfate, and sodium octanesulfonate in conjunction with optimizing the column temperature.

According to both reports, the ion-pair separation worked best if carried out on a polymeric stationary phase (styrenedivinylbenzene). However, no comparison or references to comparisons by other authors are provided to support the claim. Although the studies mention the exact flow rate and concentration of sodium hydroxide added post-column to enable the electrode reaction of the aminoglycosides on a gold electrode, neither of the two reports provides any information about the size of the detection electrode or the geometry of the gasket inside the detection cell. The gasket geometry determines the size of the fluid channel inside the cell and is thus, together with the size of the working electrode, one of the essential parameters required for successful reproduction of the reported method. Similar problems exist in the description of the amperometric waveform. Only one of the reports (1) provides both the electrode potentials and time intervals. The second report gives only the poten-

[^188]tial values without specifying any time intervals. Because the first report is not referenced in the second publication, interested readers will not be able to reproduce the method without their own optimization or access to the first of the two reports. In this article, we compare separation results obtained for netilmicin and accompanying impurities with the polymeric and silica-based columns. We also discuss the influence of essential electrode cell parameters on the detection results. A new waveform for the detection of aminoglycosides is presented and compared with the previously recommended waveform.

## EXPERIMENTAL

## Separation of Netilmicin and of Related Impurities

In addition to the polymeric reversed-phase column described in the previous two reports $(1,2)(8 \mu \mathrm{~m}$ particle size, 100 nm pore size, styrene-divinylbenzene, column diameter 4.6 mm , column length 250 mm ), we used a silica-based re-versed-phase column incorporating a polar group near the surface of the silica particle for improved hydrolytic stability. This phase consists of a C16 functional group bonded to the surface of silica using a sulfonamide group coupled to an ether linkage. The particle size was $5 \mu \mathrm{~m}$ and pore size 12 nm . The column diameter and length were 4.6 and 150 mm , respectively.

For the separations with the silica-based reversed-phase column, the mobile phase composition was as described previously (1, 2): $35 \mathrm{~g} / \mathrm{L}$ anhydrous sodium sulfate, $0.5 \mathrm{~g} /$ L sodium octane sulfonate, $10 \mathrm{~mL} / \mathrm{L}$ tetrahydrofuran, and $50 \mathrm{~mL} / \mathrm{L}$ of 0.2 M potassium dihydrogenphosphate previously adjusted to pH 3.0 with a dilute solution of phosphoric acid. In order to reproduce the separation of reference 1 with the polymeric column, we had to modify the reported eluent composition to the following: $38 \mathrm{~g} / \mathrm{L}$ anhydrous so-
dium sulfate, $0.4 \mathrm{~g} / \mathrm{L}$ sodium octane sulfonate, $13 \mathrm{~mL} / \mathrm{L}$ tetrahydrofuran, and $50 \mathrm{~mL} / \mathrm{L}$ of 0.2 M potassium dihydrogenphosphate previously adjusted to pH 3.0 .

All chemicals used for the preparation of this mobile phase were of reagent-grade purity or better.

## Apparatus

A typical system for reversed-phase separations and integrated amperometric detection of aminoglycosides such as netilmicin and its accompanying impurities includes an autosampler, dual-piston pump with a built-in eluent degasser, a column thermostat (column temperature of $40^{\circ} \mathrm{C}$ was used in all experiments discussed here), a pressurized vessel for post-column addition of 0.5 M sodium hydroxide (a dual-piston pump can also be utilized; see Experimental Considerations below), and an electrochemical detector. The eluent and post-column addition flow rates were 1.0 and $0.3 \mathrm{~mL} / \mathrm{min}$, respectively, in all our experiments. A suitable electrochemical detector must be able to produce amperometric waveforms presented in Tables $1 a$ and $1 b$. Additionally, it must include a three-electrode amperometric cell containing a gasket defining the flow path, a gold working electrode, a suitable counter electrode, and a silver-silver chloride reference electrode. The cell gaskets in our system had the following dimensions (thickness $\times$ fluid channel width $\times$ fluid channel length) gasket A: $0.140 \times$ $3.5 \times 14 \mathrm{~mm}$; gasket B: $0.050 \times 1.8 \times 14 \mathrm{~mm}$. Gasket A was used with a gold electrode having a diameter of 3 mm and gasket B with a gold electrode having a diameter of 1.4 mm .

Table 1a. Waveform of reference (1)

| Time (s) | Potential vs. <br> $\mathbf{A g - A g C l ~ ( V ) ~}$ | Integration of <br> Electrode <br> Current |
| :---: | :---: | :---: |
| 0.0 | 0.05 |  |
| 0.2 | 0.05 | Start |
| 0.4 | 0.05 | Stop |
| 0.41 | 0.75 |  |
| 0.60 | 0.75 |  |
| 0.61 | -0.15 |  |
| 1.0 | -0.15 |  |

Table 1b. Optimized waveform

| Time (s) | Potential vs. <br> Ag-AgCl (V) | Integration of <br> Electrode <br> Current |
| :---: | :---: | :---: |
| 0.00 | 0.05 |  |
| 0.24 | 0.05 | Start |
| 0.50 | 0.05 | Stop |
| 0.51 | -2.0 |  |
| 0.52 | -2.0 |  |
| 0.53 | 0.6 |  |
| 0.54 | -0.15 |  |
| 0.60 | -0.15 |  |

## Preparation of Standards and Test Solutions

We prepared the following final dilutions of standards in the chromatographic mobile phase according to the protocol from Reference 2 :
$1 \mu \mathrm{~g} / \mathrm{mL}$ netilmicin sulfate
$10 \mu \mathrm{~g} / \mathrm{mL}$ each netilmicin sulfate, sisomicin sulfate, and $1-\mathrm{N}$ ethylgaramine sulfate
$0.97 \mathrm{mg} / \mathrm{mL}$ of "the substance to be examined."
The "substance to be examined (STBE)" was a netilmicin formulation obtained from a pharmaceutical manufacturing facility in China (No. 2 Drug Manufacturer of Wuxi City).
Injection volume for all standard and STBE chromatograms was $25 \mu \mathrm{~L}$.

# OPTIMIZATION OF CHROMATOGRAPHIC METHOD 

## General Comments

On the one hand, Reference 1 describes a well-designed and complete optimization of the chromatographic mobile phase. On the other hand, some additional improvements are possible by evaluating different types of reversed-phase columns (polymer-based vs. silica-based) and by an optimization of detection parameters for integration amperometry (electrode size, gasket geometry, waveform, etc.).

## Column Evaluation

We compared the analytical performance of two types of reversed-phase columns. The first of the two columns was a polymeric reversed-phase type specified in References 1 and 2 (see Experimental for additional details). The second of the two columns was a new type containing silica-based reversed-phase spherical particles made more hydrolytically stable by inclusion of a polar group in the otherwise hydrophobic alkyl chain. The new type of reversed-phase tolerates long-term rinsing with pure water better than do reversed-phase packings without any polar groups and exhibits improved long-term stability over the pH range of 2.0 to 8.0 (see additional description in Experimental). When
comparing the two different columns we used the optimized detection conditions discussed in the following section of our report.

Injecting the standard solution containing $10 \mu \mathrm{~g} / \mathrm{mL}$ of netilmicin sulfate, sisomicin sulfate, and 1-N-ethylgaramine sulfate onto both types of columns, using identical flow rates for the eluent and post-column 0.5 M hydroxide ( 1.0 and $0.3 \mathrm{~mL} / \mathrm{min}$ respectively), we obtained the chromatograms of Figure 1. The corresponding peak resolution data are presented in Table 2. Our resolution results with the polymeric reversed-phase column exceed those reported in Reference 1 and are also better than the values required by Reference 2. This validates the results of our column evaluation. The peak resolution of $R>2$ observed with the silicabased column is generally considered as sufficient (3) for two peaks exhibiting extreme peak height ratios (e.g., peak height ratios $>100$ ) as in the case of chromatographic assays of netilmicin formulations. Resolution achieved on the sili-ca-based column can thus be considered adequate for netilmicin assays.

In the next experiment, we compared the signal-to-noise ratio for the same amount of netilmicin ( 25 picograms) using the same mobile phase and identical optimized detection conditions.
The signal (peak height in nC ) to noise (peak-to-peak noise in nC ) ratios were 12.86 and 31.75 for the polymeric and silica-based columns, respectively. The observed sig-nal-to-noise value with the polymeric column is thus better than that specified in Reference 2. On the other hand, the signal-to-noise ratio of the silica-based column is improved by a factor of two in comparison with the polymeric column.
Another point in favor of the silica-based reversed-phase column was the shorter run time for running of unknown samples. Our observed retention times of netilmicin were approximately 5.0 and 15 minutes for the silica-based and polymeric column, respectively. Applying the formula for the total run time from Reference 2 ( 3 times the retention time of netilmicin), we obtain a total run time of 45 minutes for the polymeric column and 15 minutes for the silicabased column.


Fig. 1. Chromatograms of a standard solution containing $10 \mu \mathrm{~g} / \mathrm{mL}$ each netilmicin sulfate, sisomicin sulfate, and 1-N-ethylgaramine sulfate. Injection volume: $25 \mu \mathrm{~L}$. Trace a: silica-based reversed-phase column. Trace b: polymeric reversed-phase column. Peak identities, 1: 1-N-ethylgaramine, 2: sisomicin, 3: netilmicin. See text for additional details.

Table 2. Chromatographic resolution
\(\left.$$
\begin{array}{lcc}\hline & \begin{array}{c}\mathbf{R} \\
\mathbf{1 - N}-\end{array} & \begin{array}{c}\mathbf{R} \\
\text { Ethylgaramin- } \\
\text { Sisomicin }\end{array}\end{array}
$$ \begin{array}{c}Sisomicin- <br>

Netilmicin\end{array}\right]\)| Column Type | 5.64 | 4.38 |
| :--- | :---: | :---: |
| Polymeric reversed- <br> phase | 2.79 | 4.19 |
| Silica-based <br> reversed-phase |  |  |

## Optimization of Integrated Amperometric Detection

As discussed in the Introduction, the two original references $(1,2)$ specify neither the size of the working electrode nor the geometry of the cell gasket. There are two available gasket-electrode combinations for the detector type utilized in Reference 1: Gasket A with a $3-\mathrm{mm}$ Au electrode and gasket B with a $1.4-\mathrm{mm}$ Au electrode (see Experimental). For the two available electrode-gasket combinations, we compared the peak heights of the major peak in the chromatograms of the $0.97 \mathrm{mg} / \mathrm{mL}$ STBE solution under otherwise identical conditions (identical eluent composition and flow rate, identical post-column hydroxide concentration and flow rate, silica-based column, and Table $1 b$ waveform). The peak height of the major peak (netilmicin, retention time approximately 5 min .) observed with the $3-\mathrm{mm}$ electrode was approximately 1.9 times higher than that obtained with the $1.4-\mathrm{mm}$ electrode.

It should be noted that the waveform of Reference 1 ( Ta ble $1 a$ ) is essentially a so-called triple-potential waveform recommended for the detection of another aminoglycoside in 1991 (4). The relatively long period of high positive potentials of that waveform was observed to cause a slow dissolution of the working electrode material, making the surface of that electrode recede below the level of its plastic housing. That in turn led to a gradual decrease of detection signal. Frequently, it was difficult to obtain comparable results between two or more electrodes due to a different degree of electrode recession. This observation prompted the development and introduction of a so-called quadruple-potential waveform that minimizes the problem of electrode corrosion by employing post-detection electrode cleaning at a negative instead of a positive potential (5). A detailed discussion of practical considerations for the use of the two types of waveform is offered in Reference 6.

The quadruple potential waveform was optimized for the detection of carbohydrates but not for the detection of aminoglycosides such as netilmicin. Keeping the cleaning ( -2.0 and +0.6 V ) potentials of the quadruple waveform un-
changed, the authors experimented with several different values for the detection and re-equilibration potentials for netilmicin, also making adjustments of the duration of the detection and re-equilibration intervals. The waveform that was found to give a maximum response for netilmicin is presented in Table $1 b$. Comparing the detection response obtained with the Table la and Table $1 b$ waveforms under otherwise identical conditions ( $25 \mu \mathrm{~L}$ of $10 \mu \mathrm{~g} / \mathrm{mL}$ netilmicin, identical eluent composition and flow rate, identical post-column hydroxide concentration and flow rate, silicabased reversed-phase column, and $3-\mathrm{mm}$ Au electrode with gasket A), we observed a 10 times higher signal with the newer of the two waveforms.

## Summary of Optimization Results

The silica-based reversed-phase column made possible shorter run times than did the polymeric reversed-phase column. Detection sensitivity also improved on the silica-based column due to the improvement of the signal-to-noise ratio. Comparing two different commercially available Au elec-trode-gasket combinations, we observed superior results with the Au electrode having a diameter of 3 mm and the gasket of matching geometry.
A new type of waveform, originally optimized for carbohydrates, was shown to significantly improve the sensitivity of netilmicin detection after only a minor adjustment of potentials and timing periods.

## APPLICATION

The optimized separation and detection method was applied to an analysis of a real pharmaceutical netilmicin sample. Unlike the sample of Reference 1, the netilmicin sample available to us contained only three instead of five unknown impurities in addition to $N^{\prime}$-ethylgaramine and sisomicin. The number of unknown impurity peaks was the same for both the polymeric and silica-based columns. Peaks 7 and 8 of Figure 2 in Reference 1 were missing in all chromatograms of our netilmicin sample.
The chromatographic results obtained with the silicabased column are shown in the overlay of six injections presented in Figure 2. Actual levels of impurities relative to the main ingredient netilmicin are shown in Table 3. The examined substance is thus in full compliance with the requirements and limits of Reference 2. The last column of Table 3 shows the $\%$ RSD value calculated from six repeat injections for each of the impurities. All of the RSD values are less than $5 \%$.


Fig. 2. Chromatograms of six repeat injections of a solution containing $0.97 \mathrm{mg} / \mathrm{mL}$ of a pharmaceutical netilmicin formulation. Injection volume: $25 \mu \mathrm{~L}$. Column: silica-based reversed-phase. Peak identities: S: unretained impurities, $1: 1-N$-ethylgaramine, 2 : sisomicin, 3 : unknown impurity 1,4 : netilmicin, 5 : unknown impurity 2,6 : unknown impurity 3 . See text for additional details.

Table 3. Analytical results from six injections of a netilmicin formulation

| Component | Analytical <br> Result (\%) | \%RSD <br> $(n=6)$ |
| :--- | :---: | :---: |
| S (unretained im- | 0.210 | 2.10 |
| $\quad$ purities) |  |  |
| 1- $N$-ethylgaramine | 0.550 | 1.60 |
| Sisomicin | 0.110 | 4.10 |
| Impurity 1 | 0.650 | 3.40 |
| Impurity 2 | $<0.1$ | 3.40 |
| Impurity 3 | 0.170 | 3.90 |

## EXPERIMENTAL CONSIDERATIONS

A relatively large body of scientific literature (1,2, and 716) contains an in-depth discussion of method validation for various antibiotics following the relevant regulatory guidelines (17). This allows us to limit our discussion of relevant parameters to those that are important in the context of the optimization of netilmicin assays discussed in this report.

## Chromatographic System

Stainless steel surfaces are known to contaminate chromatographic eluents with trace concentrations of metals. Although such contamination remains invisible in UV and visible detection, it causes spurious peaks, fluctuating background levels, and electrode poisoning in amperometric detection. In a system for netilmicin assays such as the one discussed here, inertness of surfaces (PEEK, titanium, Teflon, etc.) exposed to the eluent is beneficial. Although the inertness of the liquid-swept surfaces between the main pump and the separation column outlet is merely recommended, the inertness of the fluid path for post-column addition of hydroxide is essential.

At present, a pressurized vessel is the most frequent mode of delivery of post-column sodium hydroxide. If complete automation of a system is required, attempts are made to substitute the pressurized pump with a more suitable one that is capable of becoming a part of an automated system. Accumulated experience shows single-piston pumps to be unsuitable for additions of purely aqueous fluids (such as 0.5 M NaOH ) into a stream of a chromatographic mobile phase containing a certain percentage of an organic solvent (such as the eluent of Reference 1). Large oscillations of baseline are observed if a single-piston pump is employed for post-column hydroxide addition in a system utilizing integrated amperometric detection. On the other hand, dual-
piston pumps employed for post-column addition do not cause any comparable problems under the same conditions (18).

Integrated amperometric detection with gold working electrodes is sensitive to the oxygen content in eluents. Dissolved oxygen can cause large negative peaks at one or more retention time intervals of a chromatogram. For this reason, optimization of a waveform always includes an attempt to minimize the effects caused by oxygen. This can be achieved to a varying degree depending on the actual eluent composition and the presence of on-line eluent degassing inside the main chromatographic pump. For that reason, most of the widely used waveforms (4-6) work best if used in a system that includes an on-line eluent degasser.

## Integrated Amperometric Detection

A description of an amperometric method that does not include electrode size and flow path geometry (gasket thickness, along with width and length of the cutout defining the flow path) is incomplete. It is not possible to reproduce a method knowing only the material of the working electrode and not its dimension. Even if the electrode dimension is given but the gasket geometry remains unknown, it is still impossible or very difficult to achieve comparable results.

Fluctuations of possible results with several commercially available electrode-gasket combinations are illustrated in Table 4. Applying a mathematical model (equation 5 in Reference 19), one uses gasket thickness, flow path
width, and electrode lengths as parameters in calculations of coulombic efficiency. Coulombic efficiency is a fraction (\%) of an electroactive compound that actually reacts at the working electrode during its passage through the detection cell. With everything else being equal, chromatographic peak heights will follow the same relationship as their corresponding coulombic efficiencies. Normalized coulombic efficiencies are included in the last column for easier comparison. All calculations were made for the same total volume flow rate of $1.3 \mathrm{~mL} / \mathrm{min}$. utilized by the technique under discussion. The linear flow rate differences are caused by differences in flow path cross sections defined by gasket thickness and the cutout width.

From all combinations in Table 4, the 3-mm cell used with a $125-\mu \mathrm{m}$ thick gasket delivers the highest peaks. The smaller electrode ( 1.4 mm ) available for the same cell in combination with a $50-\mu \mathrm{m}$ gasket produces peak heights that are lower by a factor of 1.5 . Note that the actual comparison for the same two sets of conditions confirmed a lower peak height for the $1.4-\mathrm{mm}$ electrode and $50-\mu \mathrm{m}$ gasket by a factor of 1.9 (see Optimization of Integrated Amperometric Detection above). This represents a good validation of the mathematical model used to generate the theoretical data in Table 4.
It should be noted that for the relatively few electrodegasket combinations listed in Table 4, possible peak height results may differ by more than a factor of 10 .

In conclusion, electrode size and gasket geometry must be included in all reports dealing with amperometric detection.

Table 4. Predicted relative signal size from the mathematical model of amperometric detection (19)

| Linear <br> Flow <br> Rate <br> $(\mathbf{c m} / \mathbf{s e c})$ | Gasket <br> Thickness <br> $(\mathbf{c m})$ | Electrode <br> Length <br> $(\mathbf{c m})$ | Flow Path <br> Width <br> $(\mathbf{c m})$ | Coulombic <br> Efficiency <br> $(\%)$ | Normalized <br> Efficiency <br> $(\%)$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 68.24 | 0.00250 | 0.10 | 0.127 | 0.57 | 66.62 |
| 4.50 | 0.01375 | 0.30 | 0.35 | 0.85 | 100.00 |
| 24.07 | 0.00500 | 0.14 | 0.18 | 0.56 | 66.10 |
| 10.14 | 0.0125 | 0.14 | 0.19 | 0.26 | 31.05 |
| 2.85 | 0.04000 | 0.14 | 0.19 | 0.07 | 8.74 |

## Reference Electrode Care and Monitoring

Actual potentials applied to the working electrode are only as correct as the actual potential of the reference electrode relative to the hydrogen electrode. It is not uncommon for the potential of silver-silver chloride reference electrodes to increase by 60 mV or more when those electrodes are exposed to alkaline pH as, for example, in the method under discussion. In the worst case, lack of monitoring of reference electrode potential may cause passivation or corrosion of the gold working electrode. It is possible that the perceived "lack of stability" (1) of the electrochemical detection is at least partly caused by too infrequent or missing monitoring of reference electrode potentials by the majority
of users. The monitoring of reference electrodes can be easily accomplished by measuring the potential of an alkalineexposed electrode vs. another electrode that was never exposed to alkaline pH (stored in 3 M KCl ). For the monitoring measurement, both electrodes are immersed in the same 0.1 M KCl solution and connected to the leads of a suitable voltmeter. The authors recommend replacing any reference electrode exhibiting more than 30 mV of shift by a new or reconditioned reference electrode. Reference electrodes that have not been allowed to drift by more than approximately 30 mV can always be restored by several weeks of soaking in a solution containing 0.1 M HCl and 3 M KCl .

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# Manufacturers' Market Containers and Closures Study II: Proposed Revisions to $\langle 671\rangle$ Containers-Permeation 

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#### Abstract

This article is the second in a series intended to provide meaningful data to aid in the establishment of specifications and functional test procedures for container-closure systems for solid oral dosage forms. The containerclosure systems tested in this study are in common use, and the laboratory that conducted the study is an FDA-registered facility that commonly conducts these studies. Several different closure, innerseal, and liner configurations are used to package drug products. In a departure from the previous study, the container-closure system in the present series consists of a bottle with an innerseal, liner, and screw closure. The innerseal is designed to be removed and discarded once the container is opened.


## INTRODUCTION

The functional/performance requirements and standards for $U S P-N F$ "tight" and "well-closed" are being reevaluated. The $U S P-N F$ contains standards for pharmaceutical bottles and for prescription vials, but $\langle 671\rangle$ ContainersPermeation standards do not apply to manufacturers' con-tainer-closure systems. In many cases, the smallest con-tainer-closure configuration for a solid oral dosage form is designed for dispensing or for consumer use and is provided with a child-resistant closure. At the present time, the manufacturer's unopened multiple-unit package is exempt from the $U S P$ general chapter $\langle 671\rangle$ test. In the past, only the moisture permeation data for the manufacturer's unopened market container was considered by FDA as part of the approval process for a drug application. The permeation of this container-closure system under actual conditions of use by the consumer was ignored. FDA has started to question manufacturers about the permeation data for the container once the innerseal is removed. This issue has been of concern to USP as well.

## BACKGROUND

Since the 1970s, USP general chapters $\langle 661\rangle$ Containers and $\langle 671\rangle$ Containers-Permeation have provided standards for container-closure systems (1, 2). When USP general chapter $\langle 671\rangle$ was originally written, no limits were provided for manufacturers' containers. FDA was to determine the standards for containers used by commercial manufacturers and packagers after USP published this section. FDA has been applying the $U S P$ general chapter $\langle 671\rangle$ standards to the containers in which drug companies package their drugs. FDA also has implemented a policy that if certain market containers meet $U S P-N F$ standards and the con-

[^189]tainer-closure system provides the same degree of protection, then the firm can change from one system to another and report the change in an annual report (3).

The $U S P-N F$ limits and tests should provide a standard for manufacturers' containers that would support FDA policy. Based on the information at hand, USP attempted to implement standards for market containers (4). On 4 May 2000, SETCO wrote to USP to comment on the revisions to USP general chapter $\langle 671\rangle$ as published in the First Supplement to USP 24-NF 19. After careful consideration, USP decided to withdraw the standard until additional information could be provided (5).

The section reads as follows:
$\ldots$ and containers utilized by manufacturers or distributors for products that are repackaged by the dispenser prior to distribution or sale . . . For multiple-unit containers used by manufacturers or distributors where the products are repackaged prior to distribution or sale, the containers so tested are tight containers if not more than 1 of the test containers exceeds 10 $\mathrm{mg} /$ day $/ \mathrm{L}$ in moisture permeability and none exceeds $25 \mathrm{mg} /$ day/L.
This wording states that manufacturers' market containers (not for dispensing) must meet $10 \mathrm{mg} / \mathrm{day} / \mathrm{L}$ to be "tight" containers if sold to a pharmacist for dispensing. Manufacturers' containers not meeting $10 \mathrm{mg} /$ day $/ \mathrm{L}$ would be in violation of this chapter. This section also states that if the container manufacturer or distributor packages in a container to be used for dispensing, this section does not apply.

The proposed revisions to this chapter should be written in the spirit of the law and regulations and incorporate less ambiguous language. Specifications should be based upon data from testing conducted on approved commercial container systems. USP recently published data on the test results multiple for a range of bottle sizes using alternate liners, closure designs, and closures manufactured with multiple sources of polypropylene (6). The data demonstrated that the closure size, design, and particularly the liner
had an effect on the permeation, but the use of polypropylene from alternative manufacturers to mold the closures had an insignificant impact.

The comments received on the proposal to test with and without innerseals in place were predictable (7, 8). For drug companies not yet asked to provide this data to FDA, the ultimate fear is that firms will be requested to conduct additional stability studies. It is also a given that removing the foil innerseal can yield greater variability in test data, but the same conditions exist when a consumer removes the seal. To some extent this can be corrected by adding a tab to the innerseal to make it easier to remove. This configuration already exists on food commodities, and makes it easier to remove the seal and leaves less foil on the bottle.

The liner and innerseal play an important role in protecting the product from moisture. Industry rushed to add foil innerseals when the ICH stability guidance mandated humidity requirements in room temperature stability studies (9). Practitioners did not consider protection of the drug product once the seal was broken. However, it is not the intention of these articles to support the need for additional stability studies but rather to demonstrate the need for permeation studies and reliable standards for protection of the drug once the container has been opened.

Some new drug applications and abbreviated new drug applications were approved for solid oral drugs that were packaged in containers that used a pressure-sensitive tack seal with a compressible liner. Because stability was demonstrated in these containers, the firms did not change to foil
induction seals. Some drug companies and repackagers have continued to use these liners and pressure-sensitive seals.
In order to establish meaningful specifications, it is important to consider these seals and liners as well as others currently approved for use with these dosage forms. In assisting USP and responding to the request for information, the following data are provided.

## PROCEDURE

To conduct this study, USP general chapter $\langle 661\rangle$ Containers testing was first performed on bottles (see Test Methods below). USP general chapter $\langle 671\rangle$ ContainersPermeation as modified was then used to test the bottles with the seal in place. Then the seals were removed, the bottles were opened and closed 30 times, and then they were retested. For this study, commercial pressure-sensitive innerseals were used. The tests reported here include the following variables:

- The same bottles, closures, and closure liners,
- One bottle size, and
- Testing before and after innerseals were removed.

All the materials used in these studies have been approved by CDER for use in packaging solid oral dosage forms. They all have market history and Drug Master Files that have been reviewed by CDER and have been found to be satisfactory.

Table 1. Components

| Component | Identification | Manufacturer |
| :--- | :--- | :--- |
| Bottles | White 75 cc high-density | SETCO |
|  | polyethylene bottles | Attn: Upendra Mehta |
|  | with a 33-mm neck finish | 4875 E. Hunter Avenue |
|  |  | Anaheim, CA 92617-0808 |
|  |  | 714.777 .5315 |
| Closures | 33-mm Saf-Cap III | Van Blarcom Closures, Inc. |
|  | plastic child-resistant closure | 156 Sanford Street |
|  |  | Brooklyn, NY 11205 |
|  |  | 718.855 .3810 |
| Liners and |  | Tekni-Plex ${ }^{\circledR}$ |
| innerseals | 0.030 Polystyrene | 201 Industrial Parkway |
|  | foam liner | Somerville, NJ 08876 |
|  |  | 908.722 .4800 |
|  |  | Tri-Seal ${ }^{\circledR}$ |
|  |  | 900 Bradley Hill Road |
|  |  | Blauvelt, NY 10913 |
|  |  | 845.353 .3300 |

## RESULTS

As provided in Figure 1 and Table 2, the testing of the bottles was first conducted according to USP general chapter $\langle 661\rangle$ as written without closures. The results are well within the limits of $10 \mathrm{mg} / \mathrm{day} / \mathrm{L}$. In the middle column are the test results for the bottles with the pressure-sensitive seal, liner, and child-resistant closure, which would represent the permeation expected for the unopened packaged product. Using this configuration, certain solid oral dosage forms have been tested and demonstrated to be stable for 24 months.

Table 2. Permeation mg/day/liter

|  | $U S P$ general chapter <br> $\langle 661\rangle$ test results <br> with foil seals | $U S P$ general chapter <br> $\langle 671\rangle$ tack seal <br> and cap in place | USP general chapter <br> $\langle 671\rangle$ same container <br> with tack seal removed, opened <br> and closed 30 times |
| :---: | :---: | :---: | :---: |
| Bottle | 3.1 | 9.7 | 62.2 |
| 1 | 2.2 | 10.6 | 61.2 |
| 2 | 2.5 | 9.7 | 53.0 |
| 3 | 2.7 | 19.7 | 60.0 |
| 4 | 3.0 | 13.1 | 56.7 |
| 5 | 3.1 | 9.4 | 57.5 |
| 6 | 3.4 | 9.8 | 58.4 |
| 7 | 3.1 | 12.4 | 47.7 |
| 8 | 3.0 | 11.6 | 48.0 |
| 9 | 3.0 | 14.2 | 59.9 |
| 10 |  | 12.0 |  |
|  | 2.9 | 3.16 | 56.5 |
| Avg | 0.348 | 9.4 to 19.7 | 5.22 |
| Std Dev | 2.2 to 3.4 |  | 47.7 to 62.2 |



Fig. 1 Water vapor permeation ( $\mathrm{mg} /$ day $/ \mathrm{liter}$ )

## CONCLUSIONS

The limits and requirements placed on manufacturers' and distributors' containers should be scientifically justified, and the limits should be consistent with and independent of the person packaging the drug. The standards with the associated expiration dates, discard dates, or beyond-use dates should be based on the protection afforded by the materials and the requirements provided by the manufacturer or listed in the $U S P-N F$ monograph. USP should establish limits for "well-closed" containers for drugs that do not require "tight" containers.

The manufacturer's multiple-unit container-closure system should be tested as marketed and as it appears in actual conditions of use in the hands of the consumer. If the market container employs an innerseal, the container should be tested for the two-week period as marketed with the innerseal in place, without opening and closing 30 times. The container should then be retested with the innerseal removed and the container opened and closed 30 times. Pharmacy prescription vials and consumer containers should continue to be closed and opened 30 times. The standards for containers under actual conditions for use in the hands of the consumer should be the same for the market container (with the seal removed) and the prescription vial. For the purpose of this article the limit proposed for "tight" market container permeation is $20 \mathrm{mg} /$ day/L.

Many prescription vials and containers do meet the standard of $20 \mathrm{mg} /$ day $/ \mathrm{L}$. It would seem logical that the acceptability for use of a particular container for a moisturesensitive drug should be based on the permeation and the storage time; shorter storage times should be allowed for more permeable containers. It may also be appropriate to consider some new class of protection between that of "tight" and "well-closed."

The following points are provided for consideration:

1. The commercial market container-closure system from which the product is removed and repackaged for dispensing usually holds the product for a short period of time. If the product is dispensed in the market container, there is no limit for permeation in the $U S P-N F$ or imposed by FDA. The prescription vial into which it is repackaged uses a beyond-use date of up to one year and permeation rates of 100 to $2000 \mathrm{mg} / \mathrm{day} / \mathrm{L}$. The rates for unit dose are uncontrolled at this time. The be-yond-use time periods are under review.
2. There are no market container provisions for "wellclosed containers" for drugs that do not require "tight" containers.
3. When tablets and capsules are repackaged, the repackager can use a container-closure system tested using USP standards and determined to be equivalent to those of the manufacturer, and the repackager can use the same expiration period as the manufacturer. In some cases, the repackager can enter into an agreement with the manufacturer to obtain container-closure and stability information. Alternatively, the repackager can conduct its own testing of containers and product, and assign an expiration date based upon these studies.
4. Manufacturers can use testing in USP general chapter $\langle 661\rangle$ and $U S P$ general chapter $\langle 671\rangle$ on container-closure systems to provide acceptability data to FDA in support of their proposed systems. These tests also can be used to support changes to alternative systems. The containers so tested should be equivalent to or better than those on which stability studies have been based in order to use the same expiration period.

## TEST METHOD: MULTIPLE-UNIT CONTAINERS FOR CAPSULES AND TABLETS

## Phase 1

## Desiccant

Place a quantity of 4- to 8-mesh, anhydrous calcium chloride in a shallow container, taking care to exclude any fine powder; then dry at $110^{\circ}$ for 1 hour and cool in a desiccator.

## Procedure

Select 12 containers of a uniform size and type, and clean the sealing surfaces with a lint-free cloth. Add Desiccant to 10 of the designated test containers, filling each to within 13 mm of the closure. The layer of Desiccant in such a container shall be not less than 5 cm in depth. Close each immediately after adding Desiccant, applying the torque designated in the USP general chapter $\langle 671\rangle$ table, Torque Applicable to Screw-Type Container.

NOTE-The tack seal and liner are provided in the closures as supplied. To each of the remaining 2 containers (designated controls) add a sufficient number of glass beads to attain a weight approximately equal to that of each of the test containers, and close, applying the torque designated in the USP general chapter $\langle 671\rangle$ table, Torque Applicable to Screw-Type Container.
Record the weight of the individual containers so prepared to the nearest 0.1 mg if the container volume is less than 20 mL ; to the nearest mg if the container volume is 20 mL or more but less than 200 mL ; or to the nearest 10 mg if the container volume is 200 mL or more; and store at $75 \pm$ $3 \%$ relative humidity and a temperature of $23 \pm 2^{\circ}$.
After $336 \pm 1$ hour ( 14 days), record the weight of the individual containers in the same manner. Completely fill 5 empty containers of the same size and type as the containers under test with water or a noncompressible, freeflowing solid such as well-tamped fine glass beads, to the level indicated by the closure surface when in place. Trans-
fer the contents of each to a graduated cylinder, and determine the average container volume, in mL . Calculate the rate of moisture permeability, in mg per day per L , by the formula:

$$
(1000 / 14 V)\left[\left(T_{f}-T_{i}\right)-\left(C_{f}-C_{i}\right)\right]
$$

in which $V$ is the volume, in mL , of the container; $\left(T_{f}-T_{i}\right)$ is the difference, in mg , between the final and initial weights of each test container; and $\left(C_{f}-C_{i}\right)$ is the difference, in mg , between the average final and average initial weights of the 2 controls.

## Phase 2

Open each individual bottle, and remove the innerseal. Open and close each bottle 30 times, applying the torque designated in the USP general chapter $\langle 671\rangle$ table when closing the screw-capped containers. Record the weight of the individual containers so prepared to the nearest 0.1 mg if the container volume is less than 20 mL ; to the nearest mg if the container volume is 20 mL or more but less than 200 mL ; or to the nearest 10 mg if the container volume is 200 mL or more; and store at $75 \pm 3 \%$ relative humidity and a temperature of $23 \pm 2^{\circ}$. Repeat the calculation as provided above.

## ACKOWLEDGEMENT

The authors wish to acknowledge the contributions of Judith Haber and Joanne M. Deskus, STR Laboratories.

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## NOMENCLATURE

This section includes supplements to the latest edition of the USP Dictionary of USAN and International Drug Names that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

# USP Dictionary of USAN and International Drug Names 2004 USP DICTIONARY SUPPLEMENT 2 

IMPORTANT-Save this Supplement. This and all supplements appearing in $P F$ are needed to keep the 2004 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2004) edition will be included in the next complete edition of the Dictionary.

## New United States Adopted Names (USAN)

The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of $P F$ for other new USAN to supplement the Dictionary main volume.

Dabuzalgron Hydrochloride [2004] (da bue zal' gron).
$\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{ClN}_{3} \mathrm{O}_{3} \mathrm{~S} . \mathrm{HCl}$ 354.26. (1) Methanesulfonamide, $N$ - $[6-$ chloro-3-[(4,5-dihydro-1 H-imidazol-2-yl)methoxy]-2-methylphenyl]-, monohydrochloride; (2) N -[6-Chloro-3-[(4,5-dihydro-1 H -imidazol-2-yl)methoxy]-2-methylphenyl]methanesulfonamide hydrochloride. CAS-219311-43-0. Treatment of stress urinary incontinence. (Hoffmann-LaRoche) $\langle R O 115-1240 / 190$


Pegamotecan [2004] (peg am oh tee' kan). $\mathrm{C}_{50} \mathrm{H}_{44} \mathrm{~N}_{6} \mathrm{O}_{13}$ $\left[\mathrm{C}_{2} \mathrm{H}_{4} \mathrm{O}\right]_{n}$. (1) L-Alanine, (4S)-4-ethyl-3,4,12,14-tetrahydro-3,14-dioxo-1H-pyrano[ $3^{\prime}, 4^{\prime}: 6,7$ ]indolizino [1,2-b]quinolin-4yl ester, mono(trifluoroacetate), reaction products with polyethylene glycol bis (carboxymethyl) ether; (2) Derivative of camptothecin and polyethylene glycol produced by amide formation between $[(4 S)$-4-ethyl-3,14-dioxo-3,4,12,14-tetra-hydro-1 $H$-pyrano [ $3^{\prime}, 4^{\prime}: 6,7$ ]indolizino [1,2-b]quinolin-4-yl] (2S)-2-aminopropanoate (camptothecin L-alaninate) and $\alpha$ -(carboxymethyl)- $\omega$-(carboxymethoxy)poly(oxyethylene). CAS-581079-18-7. Treatment of gastric and gastroesophageal junction adenocarcinoma. Prothecan (Enzon) $\langle E Z-246$


Ranolazine [2004] (ra noe la zeen). $\mathrm{C}_{24} \mathrm{H}_{33} \mathrm{~N}_{3} \mathrm{O}_{4}$. 427.54. (1) 1Piperazineacetamide, $N$-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-; (2) ( $\pm$ )- $N$-(2,6-Dimethyl-phenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazineacetamide; (3) 1-Piperazineacetamide, $N$-(2,6-
dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)pro-pyl]-, ( $\pm$ )-. CAS-95635-55-5. INN. Anti-anginal; anti-ischemic. Ranexa (Dow Chemical) [Note-The trivial names, Ran D and Ran4, have appeared in literature.] $\diamond R S$-43285-003; CVT-303


Rotigotine [2004] (roe' ti goe tine). $\mathrm{C}_{19} \mathrm{H}_{25}$ NOS. 315.48. (1) 1-
Naphthalenol, 5,6,7,8-tetrahydro-6-[propyl [2-(2-thieny-1)ethyl]amino-(6S)-; (2) (-)-(S)-5,6,7,8-Tetrahydro-6-[pro-pyl[2-(2-thienyl)ethyl]amino]-1-naphthol; (3) (6S)-6-[Propyl(2-(2-thienyl)ethyl)amino]-5,6,7,8-tetrahydro-1-naphthalenol.CAS-99755-59-6. INN. Treatment of early and advanced Parkinson's disease and restless leg syndrome. (Cambrex Karlskoga AB, Sweden) $\diamond S P M 962$


Tefibazumab [2004] (tef ee ba' zoo mab). Immunoglobulin G1, anti-(Staphylococcus aureus protein ClfA (clumping factor A)) (human-Mus musculus monoclonal Aurexis heavy chain), disulfide with human-Mus musculus monoclonal Aurexis $\kappa$-chain, dimer. Molecular weight is approximately 147,590 daltons. CAS-521079-87-8. Treatment of Staphylococcus aureus infections. Aurexis (Avid Bioservices) $\checkmark$ INH-H2002

Tocilizumab [2004] (toe si liz' oo mab). Immunoglobulin G1, anti(human interleukin 6 receptor) (human-mouse monoclonal MRA heavy chain), disulfide with human-mouse monoclonal MRA $\kappa$-chain, dimmer. Molecular weight is approximately 144,986 daltons. CAS-375823-41-9. Treatment of Castelman's disease; treatment of multiple myeloma; treatment of systemic lupus erythematosus; treatment of Crohn's disease; treatment of rheumatoid arthritis; treatment of systemic juvenile idiopathic arthritis. (A. Christiaens S.A., Belgium) $\checkmark M R A$

Trabectedin [2004] (tra bek' te din). $\mathrm{C}_{39} \mathrm{H}_{43} \mathrm{~N}_{3} \mathrm{O}_{11} \mathrm{~S} .761 .84$. (1) Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3dioxolo $[7,8]$ isoquino $[3,2-b][3]$ benzazocine- $20,1^{\prime}\left(2^{\prime} H\right)$-iso-quinolin]-19-one, 5-(acetyloxy)-3' $4^{\prime}, 6,6 \mathrm{a}, 7,13,14,16$-octahy-dro-6', 8,14 -trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, ( $1^{\prime} R, 6 R, 6$ a $R, 7 R, 13 S, 14 S, 16 R$ ) - ; (2) ( $1^{\prime} R, 6 R, 6 \mathrm{a} R, 7 R, 13 S, 14 S, 16 R$ )-6',8,14-Trihydroxy-7',9-di-methoxy-4,10,23-trimethyl-19-oxo-3', $4^{\prime}, 6,7,12,13,14,16$-oc-tahydrospiro[6,16-(epithiopropanooxymethano)-7,13-imino6 a $H$-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine20, 1'(2'H)-isoquinolin]-5-yl acetate. CAS-114899-77-3. INN. Anticancer, antineoplastic and antitumoral. Yondelis (Pharmacia \& Upjohn) $\diamond E T-743$


Valrocemide [2004] (val roe' se mide). $\mathrm{C}_{10} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{O}_{2}$. 200.28. (1) Pentanamide, N -(2-amino-2-oxoethyl)-2-propyl-; (2) N -(Car-bamoylmethyl)-2-propylvaleramide; (3) $N$-(2-Amino-2-ox-oethyl)-2-propylpentanamide. CAS-92262-58-3. INN. Antiepileptic; anticonvulsant. (Teva, Israel) $>T V-1901$


## Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

## Apafant

Change the chemical structure to read:


## Acetyltriethyl Citrate

Change the chemical structure to read:


## Suggested United States Adopted Names

The United States Adopted Names (USAN) program is the specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs while the drugs are still in the investigational stages. The American Medical Association (AMA), the American Pharmaceutical Association (APhA), and the United States Pharmacopeial Convention (USPC) jointly sponsor the USAN program with representation from the FDA.

Each U.S. Adopted Name is chosen with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official United States Pharmacopeia or National Formulary. A measure of the prestige and recognition of the value of the USAN program can be found in the following regulations published by the Commissioner of Food and Drugs and the Secretary of Health and Human Services in the Federal Register of February 1988.

All who are concerned with the prescription, dispens-
ing, use, sale or manufacture of drugs may, in the absence of the designation of an official name by the FDA, rely on the current compendial name or the U.S. Adopted Name (USAN) listed in this volume as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act.
A formal procedure ${ }^{1}$ is followed by the USAN Council in selecting an established name for a drug. The USAN Council Secretary is also an ex officio member of the International Nonproprietary Names (INN) Committee. USAN Guiding Principles are concordant with World Health Organization (WHO) principles, and all

| Suggested USAN | Category |
| :--- | :--- |
| Abacumab | Treatment of anthrax infection |
| Abbacumab |  |
| Agobacumab |  |
| Aribacumab |  |
| Raxibacumab | Prevention of chronic solid or- |
| Abubucol | gan transplant rejection |
| Abucolide |  |
| Elsibucol |  |
| Lebucolimus |  |
| Libobucol |  |
| Lidabucol |  |
| Lobucolide |  |
| Resibucol |  |
| Acalcidiol |  |
| Acalcisecodiol |  |
| Becocalcidiol |  |
| Nobicalcidiol |  |
| Secocalcidiol |  |
| Advapladib | Treatment of psoriasis |
| Arapladib | matic management of arthritis |
| Avapladib |  |
| Efipladib |  |

[^190]USANs for substances also named by the INN Committee are systematically processed through the INN Committee. This ensures that, with very rare exceptions, USANs are identical to INNs and available for world-wide use.
A suggestion for a USAN originates usually from a firm or an individual who has developed a substance of potential therapeutic utility to the point where there is a distinct possibility of its being marketed in the United States of America. Occasionally, the initiative is taken by the USAN Council in the form of a request to parties interested in a substance for which a nonproprietary name appears to be lacking.

Submissions to the USAN Council are expected to conform to the established Guiding Principles ${ }^{2}$ and to be reasonably free from conflict with other names, including both trademarks and nonproprietary names. An effort is made to discourage the occasional, undesirable practice of incorporating in trademarks the syllables used in an established nonproprietary name, or syllables recommended for USAN. Such trademarks may act as a bar to the subsequent adoption of appropriate nonproprietary names for closely related drugs.

The suggested nonproprietary names for the drugs described in the following list are under consideration by the USAN Council. The name(s) being considered for each drug substance, and the applicable category, are separated by double spacing from the name(s) and category for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Suggested USAN | Category |
| :--- | :--- |
| Afrexagliptin | Treatment of type 2 diabetes <br> Axagliptin <br> Cedagliptin |
| Cideptagliptin |  |
| Saxagliptin metabolic syn- |  |
| Afatacib |  |
| Afenatacib | Treatment of rheumatoid ar- |
| Afenatastat |  |
| Fanatacib |  |
| Fapenatacib |  |
| Fapenetacib |  |
| Pratacib |  |
| Rafatacib |  |
| Rafenatacib |  |
| Rafutastat | Treatment of type 2 diabetes |
| Tratacib | and associated cardiovascular |
| Agglitazar | indications |
| Avaglitazar |  |
| Cabaglitazar |  |
| Navaglitazar |  |
| Naveglitazar |  |
| Naviglitazar |  |
| Neloglitazar |  |

[^191]| Suggested USAN | Category |
| :--- | :--- |
| Alaglumetad Hydrochloride | Treatment of anxiety and stress <br> Eglumetad Alanine <br> Hydrochloride |
| Talaglumetad Hydrochloride |  |
| Xalaglumetad Hydrochloride |  |
| Alkarginine Acetate | Treatment of cardiogenic shock |
| Arloginine Acetate | complicating acute myocardial |
| Marginine Acetate |  |
| infarction |  |


| Suggested USAN | Category |
| :---: | :---: |
| Atamcimod Acetate Binamcimod Acetate Delamcimod Acetate Delamgatide Acetate Delmitide Acetate | Treatment of chemotherapyinduced diarrhea (CID) |
| Atebineuzumab Bapneuzumab Pasineuzumab | Treatment or prevention of Alzheimer's disease |
| Atilmotide Atilmotin Atilmotrec Atimotilin Prozomotin Tilemcitide Zilmotisin | Stimulation of gastrointestinal motility (GI prokinetic agent) |
| Avanafil <br> Tyanafil <br> Vatanafil <br> Vitanafil <br> Xyanafil | Treatment of erectile dysfunction |
| Becatecarin <br> Becotecarin <br> Bectcarin <br> Effectecarin <br> Eftecarin <br> Nebetecarin <br> Neotecarin | Antineoplastic |
| Bioctadekin Iboctadekin Immunoctadekin Munoctadekin | Antineoplastic |
| Bisatrizole <br> Bisoctrizole <br> Bistriazole <br> Bitrisorb <br> Microtriazol <br> Mirometrizole | Topical sunscreen active ingredient for OTC use |
| Brifospofol Disodium <br> Fospropofol Disodium <br> Prefospofol Disodium <br> Profospofol Disodium <br> Propofol Phosphate Disodium | Intravenous sedative-hypnotic solution in conscious sedation for brief surgical and diagnostic procedures |
| Caremtorib <br> Carolistat <br> Casorolimus <br> Emtorolimus <br> Macitorstat <br> Macrociclistat <br> Mactinistat <br> Mactorolimus <br> Saticrolimus <br> Sirolimus Bidproate <br> Temsirolimus | Antineoplastic; cytostatic |
| Cinacalcet | Treatment of hyperparathyroidism and related disorders, such as hypercalcemia |


| Suggested USAN | Category |
| :---: | :---: |
| Cimtuzumab Ozogamicin | Treatment of cancer |
| Cintuzumab Ozogamicin |  |
| Cituzumab Ozogamicin |  |
| Inotuzumab Ozogamicin |  |
| Intuzumab Ozogamicin |  |
| Tamatuzumab Ozogamicin |  |
| Closafupermin | Treatment of immune thrombo- |
| Karyopermin | cytopenic purpura |
| Megapermin |  |
| Rocafupermin |  |
| Tegafupermin |  |
| Tegafuplermin |  |
| Chlorsalbutrozate Sodium | Oral absorption promoter |
| Closalbuzate Sodium |  |
| Salchlorbutrozate Sodium |  |
| Salclobuzate Sodium |  |
| Contafocon A | Hydrophobic contact lens ma- |
| Disilfocon A | terial |
| Disilofocon A |  |
| Roflufocon A |  |
| Roflusifocon A |  |
| Contafocon B | Hydrophobic contact lens ma- |
| Roflufocon B terial |  |
| Contafocon C | Hydrophobic contact lens ma- |
| Roflufocon C | terial |
| Contafocon D Roflufocon D | Hydrophobic contact lens ma- |
|  | terial |
| Contafocon E Roflufocon E | Hydrophobic contact lens ma- |
|  | terial |
| Corstat Hydrochloride Forodesine Hydrochloride | Treatment of T-cell malignan- |
|  | cies such as acute lymphoblas- |
| Polastat Hydrochloride | tic leukemia (ALL) and |
| Senistat Hydrochloride | cutaneous T-cell lymphoma |
| Zenstat Hydrochloride | $(C T C L)$ |
| Cynostumab | Prevention and treatment of all |
| Cynotumumab | forms of osteoporosis or bone |
| Denostumab | loss |
| Denotumumab |  |
| Genostumab |  |
| Synostumab |  |
| Darifenacin | Treatment of overactive bladder |
| Decripentoc | Antiviral; CCR5 antagonist; |
| Dicripentoc | treatment of autoimmune con- |
| Vicripentoc | ditions |
| Deferamin | Treatment of patients with |
| Deferatrimine | chronic iron overload who re- |
| Deferitrin | quire iron chelation therapy |
| Deferitrine |  |
| Triferamin |  |


| Suggested USAN | Category |  |
| :---: | :---: | :---: |
| Dinamostat | Anticancer; hematopoietic |  |
| Dynamostat | stimulant |  |
| Falamostat |  |  |
| Oramostat |  |  |
| Talabostat |  |  |
| Talamostat |  |  |
| Toramostat |  |  |
| Valamostat |  |  |
| Dronedarone Hydrochloride | Antiarrhythmic |  |
| Edratide | Treatment of systemic lupus erythematosus |  |
| Eriforan Tetrasodium | Treatment of sepsis |  |
| Eriquaran Tetrasodium |  |  |
| Eritolforan Tetrasodium |  |  |
| Eritolimod Tetrasodium |  |  |
| Eritoran Tetrasodium |  |  |
| Ipoforan Tetrasodium |  |  |
| Lipoforan Tetrasodium |  |  |
| Etemucret | Treatment of dry eye (stimu- |  |
| Idroxicotrent | lates glycoprotein secretion) | 9 |
| Etosirolimus | Prevention of human coronary | 产 |
| Tetrazolimus | artery restenosis following | 言 |
| Tetrolimus | stent replacement |  |
| Tetrosirolimus |  |  |
| Tezolimus |  |  |
| Zolimus |  |  |
| Ferric Ferrocyanide | Antidote indicated for the treat- |  |
| Ferric Hexacyanoferrate (II) | ment of patients with known or |  |
| Ferric Hexacyanoferrate III | suspected internal contamina- |  |
| Insoluble Prussian Blue | tion with radioactive cesium |  |
| Prussian Blue | and/or radioactive or nonra- |  |
| Prussian Blue Insoluble | dioactive thallium to increase their rates of elimination |  |
| Glutatrexed Ammonium | Antineoplastic |  |
| Gretopterin Ammonium |  |  |
| Loropterin Ammonium |  |  |
| Oropterin Ammonium |  |  |
| Orotrexed Ammonium |  |  |
| Talopterin Ammonium |  |  |
| Idraparinux Sodium | Antithrombotic |  |
| Inkinesib Mesylate | Antineoplastic |  |
| Iskinesib Mesylate |  |  |
| Ispinesib Mesylate |  |  |
| Kispinesib Mesylate |  |  |
| Tokinesib Mesylate |  |  |
| Tominesib Mesylate |  |  |
| Levalbuterol Tartrate | Anti-asthmatic and bronchodilator |  |
| Liritrexate | Treatment of patients with ma- |  |
| Panatrexate | lignancies |  |
| Piritrexate |  |  |
| Pralatrexate |  |  |
| Travitrexate |  |  |
| Nebivolol Hydrochloride | Antihypertensive |  |


| Suggested USAN | Category |
| :--- | :--- |
| Necapimod <br> Tenifimod | Immunomodulator <br> Panglitazar <br> Peliglitazar <br> Periglitazar <br> Puliglitazar |
| Pemetrexed Disodium | Treatment of type 2 diabetes <br> mellitus, mixed dyslipidemia, <br> atherosclerosis and metabolic <br> syndrome |
| Perflutan | Antineoplastic (thymidylate <br> synthase inhibitor; inhibitor of <br> dihydrofolate reductase and <br> glycinamide ribonucleotide |
| formyl tranferase) |  |


| Yttrium Y90 EpratuzumabDOTA | A chelating agent used to conjugate radioisotope to mono- |
| :---: | :---: |
| Yttrium Y90 Epratuzumab Dotetate | clonal antibody in radioimmunotherapy (RAIT) for |
| Yttrium Y90 Epratuzumab Dotetran | non-Hodgkin's $B$-Cell lymphoma |
| Yttrium Y90 Epratuzumab Itraterate |  |
| Yttrium Y90 Epratuzumab Itrateric |  |
| Yttrium Y90 Epratuzumab Itratertan |  |
| Yttrium Y90 Epratuzumab Itraxetan |  |
| Yttrium Y90 LabetuzumabDOTA | Radioimmunotherapy (RAIT) of CEA-expressing tumors in |
| Yttrium Y90 Labetuzumab Tetraxetan | colorectal, pancreatic, lung, breast, ovarian, and medullary thyroid cancer |
| Yttrium Y90 Labetuzumab Tetraxetan | Radioimmunotherapy (RAIT) of CEA-expressing tumors in colorectal, pancreatic, lung, breast, ovarian, and medullary thyroid cancer |
| Yttrium Y90 Lecratuzumab | Tumor eradication |
| Yttrium Y90 Tacatuzumab |  |
| Yttrium Y90 Tactuzumab |  |
| Yttrium Y90 Vintuzumab |  |

## Suggested International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO). INNs for substances originating within the United States are applied for through the USAN Council. INN and USAN Guiding Principles are concordant, which assures that, with very few exceptions, INNs and USANs are identical.

Under its charter, the WHO is empowered simply to recommend specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as proposals ("Proposed International Nonproprietary Names"). A period of four months from the date of publication in WHO Drug Information is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event
that no objection is received, the WHO proceeds with listing and publishing the names so devised as recommendations ("Recommended International Nonproprietary Names"), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

The names for the drugs that are categorized in the following list are under consideration for the selection of new Proposed International Nonproprietary Names. The name(s) being considered for each drug substance, and the applicable category, are separated by double spacing from the name(s) and category for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Suggested INN | Category | Suggested INN | Category |
| :---: | :---: | :---: | :---: |
| Alsufatase | Treatment of Maroteaux-Lamy syndrome (mucopolysaccharidosis [MPS]) | Deferitrin | Treatment of patients with chronic iron overload who require iron chelation therapy |
| Angenemid | Gene therapy for peripheral ar- | Delamcimod Acetate | Treatment of chemotherapy- |
| Perminamid | terial disease | Delmitide Acetate | induced diarrhea |
| Pulermid |  |  |  |
| Apilimumab | Treatment of oncological diseases and HIV infection | Efipladib | Treatment of pain and symptomatic management of arthritis |
| Atilmotin | Stimulation of gastrointestinal motility (GI prokinetic agent) | Elomotecan | Anticancer agent; topoisomerase type I and II inhibitor |
| Avanafil | Treatment of erectile dysfunction | Elsibucol | Prevention of chronic solid organ transplant rejection |
| Becatecarin | Antineoplastic | Emaglitazar | Treatment of hyperglycemia of patients with type 2 diabetes and related lipid abnormalities |
| Becocalcidiol | Treatment of psoriasis |  | (hypertriglyceridemia and/or low HDL cholesterol) |
| Bemotrizinol | Topical sunscreen active ingredient for OTC use | Eriforan | Endotoxin antagonist for the |
| Bisoctrizole | Topical sunscreen active ingredient for OTC use | Eritoran | treatment of sepsis and other diseases due to reaction to bacterial endotoxin |
| Caremtorib | Antitumor agent; cytostatic | Etagoloxan | Antineoplastic |
| Casorolimus | agent (cell cycle inhibitor) | Etagolukib |  |
| Sirolimus |  | Etalocib |  |
| Temsirolimus |  |  |  |
| Cedratide | Treatment for systemic lupus | Etemucret | Treatment of dry eye (stimulates glycoprotein secretion) |
| Edratide | erythematosus |  |  |
| Leptide |  | Forodesine | Treatment of T-cell malignan- |
| Sletide |  |  | cies such as acute lymphoblastic leukemia (ALL) and |
| Cinacalcet | Treatment of hyperthyroidism |  | cutaneous T-cell lymphoma |
| Cincalcept | and related disorders, such as hypercalcemia |  | (CTCL) |
|  |  | Iboctadekin | Antineoplastic |
| Contusugene (p53 adenovirus) | Treatment of head and neck cancer | Idraparinux | Antithrombotic |


| Suggested INN | Category |
| :---: | :---: |
| Inotropine | Inotropic agent; Na-KATPase |
| Taucor | inhibitor |
| Inotuzumab Ozogamicin | Oncologic treatment |
| Ispinesib | Antineoplastic |
| Lactofertide Alfa Talactoferrin Alfa Teractoferrin Alfa | Anti-infective; anti-inflammatory, antineoplastic |
| Medirazole <br> Neorazole <br> Reserazole | Antifungal agent for treatment of diseases caused by fungi and yeast |
| Navaglitazar <br> Naveglitazar <br> Naviglitazar <br> Neloglitazar | Treatment of type 2 diabetes and associated cardiovascular indications |
| Nibacatin Selcapsin Selcatin | Treatment of osteoporosis (Cathepsin $K$ inhibitor) |
| Oxybate Sodium | Treatment of cataplexy in patients with narcolepsy |
| Peliglitazar | Treatment of type 2 diabetes mellitus, mixed dyslipidemia, atherosclerosis and metabolic syndrome |
| Perflisobane Perflisobutane Perflisobute Perflisotane | Diagnostic aid; ultrasound contrast agent (intravenous) |
| Pralatrexate | Treatment of patients with malignancies |


| Suggested INN | Category |
| :---: | :---: |
| Pratacib | Treatment of rheumatoid arthritis |
| Raxibacumab | Treatment of anthrax infection |
| Remofovir | Synthetic nucleotide antiviral agent |
| Salclobuzate | Facilitates and/or enables the oral delivery of a drug |
| Saxagliptin | Treatment of type 2 diabetes mellitus and metabolic syndrome |
| Talabostat Talamostat | Anti-cancer; hematopoietic stimulant |
| Talaglumetad | Treatment of anxiety and stress disorders (metabotropic glutamate [mGlu] agonist) |
| Targinine Acetate | Treatment of cardiogenic shock complicating acute myocardial infarction (MI) |
| Tegafuplermin | Treatment of immune thrombocytopenic purpura (ITP) |
| Tetraxetan | Radical |
| Yttrium Y 90 Epratuzumab Itraxetan | Radioimmunotherapy for nonHodgkin's B-cell lymphoma |
| Yttrium Y 90 Epratuzumab <br> Tetraxetan <br> Yttrium Y 90 Labetuzumab Tetraxetan | Radioimmunotherapy (RAIT) for non-Hodgkin's B-cell lymphoma patients |
| Yttrium Y 90 Tacatuzumab | Tumor eradication |

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| Cat. <br> No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1048619 | Benazepril Hydrochloride (125 mg) | F0C250 | \$156 |
| 1048620 | Benazepril Related Compound A ( 15 mg ) | F0C252 | \$487 |
| 1048630 | Benazepril Related Compound B ( 15 mg ) | F0C256 | \$487 |
| 1048641 | Benazepril Related Compound C ( 50 mg ) | F0C425 | \$487 |
| 1071439 | Positive Bioreaction (3 strips; $10 \mathrm{~cm} \times 1$ cm) | F0D014 | \$325 |
| 1098118 | Cefpiramide ( 300 mg ) | F0C203 | \$156 |
| 1098027 | Cefpodoxime Proxetil ( 350 mg ) | F0C192 | \$156 |
| 1105009 | Powdered Chaste Tree Extract (1.5 g) | F0C406 | \$520 |
| 1111001 | Chlorhexidine ( 200 mg ) | F0C306 | \$156 |
| 1111103 | Chlorhexidine Acetate ( 500 mg ) | F0C281 | \$156 |
| 1111307 | Chlorhexidine Related Compounds $(50 \mathrm{mg})$ | F0D017 | \$487 |
| 1115545 | Chlorogenic Acid (50 mg) | F0C420 | \$156 |
| 1140349 | Clonazepam Related Compound C $(25 \mathrm{mg})$ | F0C340 | \$487 |
| 1140393 | Clonidine ( 200 mg ) | F0C401 | \$156 |
| 1140418 | Clonidine Related Compound A ( 25 mg ) | F0C373 | \$487 |
| 1140429 | Clonidine Related Compound B ( 25 mg ) | F0C403 | \$487 |
| 1152701 | Cyclandelate ( 200 mg ) | F0C384 | \$156 |
| 1171900 | Desflurane ( 0.5 mL ) | F0C187 | \$156 |
| 1179708 | Dextran 40 (50 mg) | F0C247 | \$156 |
| 1179741 | Dextran 70 ( 50 mg ) | F0C260 | \$156 |
| 1224959 | Dolasetron Mesylate ( 200 mg ) | F0C319 | \$156 |
| 1224960 | Dolasetron Mesylate Related Compound A $(25 \mathrm{mg})$ | F0C321 | \$487 |
| 1231728 | Powdered Echinacea Purpurea Extract $(1 \mathrm{~g})$ | F0D018 | \$520 |
| 1231706 | Powdered Echinacea Angustifolia Extract (1 g) | F0D019 | \$520 |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | \$520 |
| 1269414 | Fenbendazole Related Compound A ( 30 mg ) | F0D009 | \$487 |
| 1269425 | Fenbendazole Related Compound B ( 30 mg ) | F0D008 | \$487 |
| 1272204 | Fludarabine Phosphate ( 300 mg ) | F0C374 | \$156 |
| 1273808 | Flumazenil ( 200 mg ) | F0C305 | \$780 |
| 1279837 | $\underset{(15 \mathrm{mg})}{\text { Fluoxetine Related Compound C }}$ $(15 \mathrm{mg})$ | F0C352 | \$487 |
| 1288306 | Ganciclovir (200 mg) | F0C287 | \$364 |
| 1288317 | Ganciclovir Related Compound A $(15 \mathrm{mg})$ | F0C288 | \$624 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 | \$156 |
| 1305507 | 2E, 4E-Hexadienoic Acid Isobutylamide $(25 \mathrm{mg})$ | F0C353 | \$540 |
| 1311306 | Homopolymer Polypropylene (3 Strips) | F0C096 | \$156 |
| 1349014 | Isoflurane Related Compound A (0.1 mL ) | F0C232 | \$487 |


| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1349025 | Isoflurane Related Compound B (0.1 mL ) | F0C233 | \$487 |
| 1355753 | Kawain (200 mg) | F0C160 | \$208 |
| 1356836 | Lamivudine ( 200 mg ) | F0C361 | \$156 |
| 1356847 | Lamivudine Resolution Mixture A ( 10 mg ) | F0D024 | \$487 |
| 1358503 | Leuprolide Acetate (200 mg) | F0C430 | \$1,525 |
| 1367708 | Linoleoyl Polyoxylglycerides (100 mg) | F0C283 | \$156 |
| 1370270 | Loratadine ( 200 mg ) | F0C414 | \$260 |
| 1378012 | Medroxyprogesterone Acetate Related Compound A ( 25 mg ) | F0C427 | \$500 |
| 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution CII ( 0.5 mL ) | F0C368 | \$560 |
| 1441232 | Metoprolol Related Compound A $(20 \mathrm{mg})$ | F0C343 | \$520 |
| 1441243 | Metoprolol Related Compound B ( 50 mg ) | F0C377 | \$520 |
| 1441254 | Metoprolol Related Compound C ( 20 mg ) | F0C344 | \$520 |
| 1441265 | Metoprolol Related Compound D ( 50 mg ) | F0C378 | \$520 |
| 1441298 | Metoprolol Succinate ( 200 mg ) | F0C415 | \$156 |
| 1445211 | Mitoxantrone System Suitability Mixture $(0.3 \mathrm{mg})$ | F0D010 | \$500 |
| 1457469 | Naratriptan Hydrochloride (125 mg) | F0C360 | \$208 |
| 1460714 | Nevirapine Hemihydrate ( 100 mg ) | F0D034 | \$156 |
| 1460725 | Nevirapine Related Compound A ( 15 mg ) | F0D035 | \$487 |
| 1460736 | Nevirapine Related Compound B ( 15 mg ) | F0D033 | \$487 |
| 1478152 | Oleoyl Polyoxylglycerides (100 mg) | F0C313 | \$156 |
| 1478629 | Ondansetron Related Compound D ( 50 mg ) | F0C226 | \$487 |
| 1483301 | Oxfendazole ( 200 mg ) | F0C128 | \$156 |
| 1485125 | Oxybutynin Related Compound B $(20 \mathrm{mg})$ | F0D061 | \$487 |
| 1485136 | $\begin{array}{\|l} \hline \text { Oxybutynin Related Compound C } \\ (20 \mathrm{mg}) \end{array}$ | F0D062 | \$487 |
| 1500251 | Paroxetine Related Compound D $(15 \mathrm{mg})$ | F0C228 | \$487 |
| 1535020 | Phenytoin Related Compound B ( 50 mg ) | F0C157 | \$487 |
| 1548134 | Potassium Bicarbonate (1 g) (AS) | F0D074 | \$156 |
| 1599500 | Powdered Red Clover Extract (500 mg) | F0C188 | \$260 |
| 1601102 | Residual Solvent Mixture - Class 1 ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C407 | \$156 |
| 1601146 | Residual Solvent Class 1 - Benzene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C408 | \$156 |
| 1601168 | Residual Solvent Class 1 - Carbon Tetrachloride ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C409 | \$156 |
| 1601180 | Residual Solvent Class 1-1,2Dichloroethane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C412 | \$156 |
| 1601204 | Residual Solvent Class 1-1,1Dichloroethene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C411 | \$156 |
| 1601226 | Residual Solvent Class 1-1,1,1Trichloroethane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C410 | \$156 |
| 1601340 | Residual Solvent Class 2 - Acetonitrile ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D049 | \$156 |

## New Items at a Glance (Continued)

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :--- | :--- | :--- | :--- |
| 1601361 | Residual Solvent Class 2 - <br> Chlorobenzene (1.2 mL/ampule; <br> 3 ampules) | F0D048 | $\$ 156$ |
| 1601420 | Residual Solvent Class 2 - 1,2- <br> Dichloroethene (1.2 mL/ampule; <br> 3 ampules) | F0D040 | $\$ 156$ |
| 1601521 | Residual Solvent Class 2 - 1,4-Dioxane <br> $(1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D050 | $\$ 156$ |
| 1601623 | Residual Solvent Class 2 - Methanol <br> $(1.2$ mL/ampule; 3 ampules) | F0D045 | $\$ 156$ |
| 1601441 | Residual Solvent Class 2 - Methylene <br> Chloride (1.2 mL/ampule; 3 ampules) | F0D046 | $\$ 156$ |
| 1601770 | Residual Solvent Class 2 - <br> Tetrahydrofuran (1.2 mL/ampule; <br> 3 ampules) | F0D043 | $\$ 156$ |
| 1601805 | Residual Solvent Class 2 - Toluene <br> $(1.2$ mL/ampule; 3 ampules) | F0D042 | $\$ 156$ |
| 1601849 | Residual Solvent Class 2 - Xylenes <br> $(1.2$ mL/ampule; 3 ampules) | F0D041 | $\$ 156$ |
| 1604508 | Rimantadine Hydrochloride (300 mg) | F0C266 | $\$ 156$ |
| 1610090 | Scopoletin (20 mg) | F0C329 | $\$ 156$ |
| 1612540 | Sevoflurane (1 mL) |  |  |


| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :--- | :--- | :--- | :--- |
| 1612550 | Sevoflurane Related Compound A $(0.2$ <br> mL) | F0C261 | $\$ 487$ |
| 1617408 | Sotalol Hydrochloride (300 mg) | F0C234 | $\$ 182$ |
| 1617419 | Sotalol Related Compound A $(50 \mathrm{mg})$ | F0C235 | $\$ 487$ |
| 1617420 | Sotalol Related Compound B $(50 \mathrm{mg})$ | F0C236 | $\$ 487$ |
| 1617430 | Sotalol Related Compound C $(50 \mathrm{mg})$ | F0C237 | $\$ 487$ |
| 1621507 | Stearoyl Polyoxyglycerides $(100 \mathrm{mg})$ | F0C286 | $\$ 156$ |
| 1642223 | Sumatriptan Succinate Related <br> Compound C $(50$ mg) | F0C230 | $\$ 624$ |
| 1643463 | Terazosin Related Compound A $(50 \mathrm{mg})$ | F0C245 | $\$ 487$ |
| 1643474 | Terazosin Related Compound B $(50 \mathrm{mg})$ | F0C218 | $\$ 487$ |
| 1643485 | Terazosin Related Compound C $(25 \mathrm{mg})$ | F0C257 | $\$ 487$ |
| 1667290 | Tiamulin Fumarate (250 mg) | F0C327 | $\$ 156$ |
| 1667337 | Tiamulin Related Compound A (50 mg) | F0C328 | $\$ 494$ |
| 1708762 | Valsartan (350 mg) | F0C147 | $\$ 156$ |
| 1711155 | Vecuronium Bromide (60 mg) | F0C367 | $\$ 156$ |
| 1714506 | Vinorelbine Tartrate (200 mg) | F0C243 | $\$ 156$ |
| 1714528 | Vinorelbine Related Compound A <br> $(25$ mg) | F0C242 | $\$ 487$ |

## USING AND ORDERING USP REFERENCE STANDARDS

## Official Reference Standards

USP Reference Standards are required for use in pharmacopeial assays and tests in the official standards publication, the United States Pharmacopeia-National Formulary (USP-NF). USP Reference Standards help to ensure compliance with the official, FDA-enforceable quality requirements in the $U S P-N F$. The Reference Standards also lend themselves to many other applications, including measurements required to attain accurate and reproducible results in modern chromatographic and spectrophotometric methods.

## Rigorous Testing and Quality Control

USP Reference Standards are selected for their high purity, critical characteristics, and suitability for the intended purpose. Unless a USP Reference Standard label states a specific potency or content, the USP Reference Standard is taken as being $100 \%$ pure for the USP purposes for which it is provided. As a service to our customers, labeled purity values for Reference Standards and Authentic substances released after January 1, 2004 are listed in this catalog. See p. 9 for explanation of how values are calculated.

Heterogeneous substances, of natural origin, are also designated "Reference Standards" where needed. Usually these are the counterparts of international standards.

USP Reference Standards are established through a process of rigorous testing, evaluation, and quality control. They are independently tested in three or more laboratories-USP, FDA, and academic and industrial laboratories throughout the United States. The Reference Standards are released under the authority of USP's Board of Trustees, on the recommendation of the USP Reference Standards Expert Committee, which approves selection and suitability of each lot.

## Reference Standards Categories

USP offers more than 1,560 Reference Standards for pharmaceuticals, excipients, and dietary supplements. On pages 12-56 of this catalog, you'll find a full list of available USP and NF Reference Standards, with information updated through May 2004. The list includes:

- Reference Standards required by the current official edition of $U S P-N F$.
- Reference Standards not required in the current $U S P-N F$, but for which sufficient demand remains.
- Reference Standards specified in the current edition of the Food Chemicals Codex (FCC).
- Authentic Substances (AS)-highly purified samples of chemicals, including substances of abuse, required by analytical, clinical, pharmaceutical, and research laboratories.

The distribution of controlled substances is subject to the regulations and licensing provisions of the Drug Enforcement Administration (DEA) of the U.S. Department of Justice.

USP also collaborates with the World Health Organization in its program to provide international biological standards and chemical reference materials for antibiotics, biologicals, and chemotherapeutic agents. Some USP Reference Standards are standardized in terms of the corresponding international standards.

## Proper Use of USP Reference Standards

USP Reference Standards are provided primarily for quality control use in conducting the pharmacopeial assays and tests described in the $U S P-N F$. Neither Reference Standards nor Authentic Substances are intended for use as drugs, dietary supplements, or medical devices.

To serve its intended purpose, each USP Reference Standard must be properly stored, handled, and used. Users of USP Reference Standards should refer to General Chapter $\langle 11\rangle$ in the $U S P-N F$ :

## Listing and directions in USP-NF

- Refer to the list of revisions, additions, and deletions of individual USP Reference Standards in USP 27-NF 22. Individual $U S P$ or $N F$ monographs specify the USP Reference Standard(s) required for assay and test procedures. The USP 27-NF 22 General Test Chapter $\langle 11\rangle$ USP Reference Standards provides additional information and instructions for proper use and storage. Note that if specific instructions for use appearing on the label of a USP Reference Standard differ from the instructions in Chapter $\langle 11\rangle$, the instructions on the label take precedence.
- Consult the cumulative updates to Reference Standards information provided in $U S P-N F$ Supplements and also in $U S P-N F$ Interim Revision Announcements, which are published in USP's bimonthly journal, Pharmacopeial Forum.


## Suitability for use

- The user must ascertain that the Reference Standards they are using are an official lot.


## USING AND ORDERING USP REFERENCE STANDARDS

- The user must determine the suitability of Reference Standards for applications and uses not in the $U S P-N F$.


## Storing

- Ensure that the USP Reference Standards are stored in their original stoppered containers, according to any special label directions, away from heat and humidity, and protected from light.


## Weighing

- Ensure that Reference Standard substances are accurately weighed-taking due account of relatively large errors potentially associated with weighing small masses-where it is directed that a standard solution or a standard preparation be prepared for a quantitative determination. See USP 27-NF 22 General Chapters $\langle 41\rangle$ Weights and Balances and $\langle 31\rangle$ Volumetric Apparatus, and USP-NF General Notices, for information regarding appropriate use of USP Reference Standards.


## Drying

- Use a clean and dry vessel, and not the original container, as the drying vessel where a USP Reference Standard is required to be dried before use.
- Make sure not to dry a specimen repeatedly at temperatures above 25 degrees.
- Follow any special drying requirements specified on the Reference Standards label or in specific sections of USP or NF monographs (note that any specific instructions on the label or in the monograph supersede the usual instructions in Procedures under Tests and Assays in $U S P-N F$ General Notices).
- Follow Method I under USP-NF General Chapter $\langle 921\rangle$ Water Determination where the titrimetric determination of water is required at the time a Reference Standard is to be used. Instrumental or microanalytical methods are acceptable for this purpose. When using typical amounts, users must titrate about 50 mg of the Reference Standard with a fourfold dilution of the reagent.


## ORDERING USP REFERENCE STANDARDS

## Four convenient ways to order

1. Phone: Call USP with your requirements: (800) 227-8772 from the U.S. or Canada and (301) 881-0666 from other countries. Please note that DEA controlled substances cannot be placed over the phone.

Hours of operation:

Monday-Friday
8:30AM-5:00PM
Fax: Fax your orders to (301) 816-8148.
Online: Order through the World Wide Web at http://store.usp.org. Please note that DEA controlled substances cannot be ordered online.
Mail: Send all mail orders to:
USP
Customer Service Department
12601 Twinbrook Parkway
Rockville, MD 20852, USA

## Important Order/Policy Information

For fax and mail orders, please use the order form at the back of this catalog. Official purchase orders on company letterhead may also be used to order USP Reference Standards. The purchase orders must have billing and shipping addresses and should include the catalog number, the name of the official Reference Standard, and the number of units ordered. Lot numbers need not be specified on written purchase orders as USP only ships current official lots. Confirmation orders may be sent and must clearly be designated as such. The USP does not assume responsibility for duplication of orders not clearly marked as confirmation orders.

## Pricing

USP Reference Standards must be ordered in whole units. Please note that one unit may include several individual containers.

Reference Standards unit prices included in the product listings from pages 12-56 of this catalog are effective until December 31, 2004. Please note that prices and package sizes are subject to change without notice.

## No Returns or Exchanges

USP Reference Standards may not be returned or exchanged for refund.

## Quantity Discounts

A 5\% discount is allowed for 5-24 units of any one Reference Standard in a single order, and a $10 \%$ discount for 25 or more units of any one Reference Standard in a single order. These discounts are subject to change without notice.

## Shipping

## USING AND ORDERING USP REFERENCE STANDARDS

- Reference Standards orders can only be shipped to a street address and not to P.O. boxes.
- Orders to the U.S. and Ontario, Canada are shipped via air courier of USP's choice at a charge of $\$ 11$ or via air courier of the customer's choice at an additional $\$ 25$ charge.
- Non-controlled substance orders to Canadian provinces other than Ontario are shipped via air courier of USP's choice at a charge of U.S. $\$ 70$. Carriers of the customer's choice incur an additional $\$ 25$ charge.
- Non-controlled substance orders to be shipped outside the U.S. and Canada are accepted directly by USP only when customs forms related to export are not required. They are shipped via air courier of USP's choice at a charge of U.S. $\$ 70$. Carriers of the customer's choice incur an additional $\$ 25$ charge.
- Shipping in cold pack can be done at customer request for an extra charge of $\$ 25$.
- Controlled substance orders to anywhere outside the U.S. are shipped via air courier of USP's choice with a charge of U.S. $\$ 220$.
- An additional shipping charge may be assessed for dangerous goods shipments.
- An additional shipping charge of $\$ 75$ will be assessed for rush/ same-day shipments.
- Customers may provide their shipping account numbers to have shipping charged directly.


## Payment

- Full payment in advance, in U.S. dollars, is required for all U.S. orders unless open account status has been granted by USP's Finance Department. To apply for open account status, an application can be requested by calling (301) 816-8177.
- Full payment in advance, in U.S. dollars, is required for all non-U.S. orders.
- Payment may be made by check, money orders, credit cards (VISA, MasterCard, American Express), and electronic wire transfer (please call (301) 816-8177 to get bank information for wire transfers). The customer is responsible for any bank fees and must include it in the payment. The customer is also responsible for any other fees such as customs duties, taxes, or tariffs.


## List Chemicals

The following Reference Standards are "List Chemicals": Dihydroergotamine Mesylate
*Ephedrine Sulfate
Ergonovine Maleate
Ergotamine Tartrate
Methylergonovine Maleate
Phenylpropanolamine Bitartrate
Phenylpropanolamine HCl
Pseudoephedrine HCl
Pseudoephedrine Sulfate

An organization in the United States seeking to purchase a List Chemical Reference Standard for resale to another customer must have a DEA registration (either a controlled substance or List Chemical registration). If an organization in the United States is purchasing the List Chemical Reference Standard for its own analytical use, it must provide USP with a letter on company letterhead describing the reason for the purchase.

## CONTROLLED DRUG SUBSTANCE ORDER

## DEA Requirements (U.S. Orders)

For all orders for controlled drug substances-regulated by the U.S. Drug Enforcement Administration (DEA)-to be shipped within the U.S., a copy of the customer's current DEA Registration Certificate must be on file with USP. To order Schedule I and II standards, customers must submit, with their order forms or purchase orders, a DEA Form 222-C, properly completed. In addition, customers ordering DEA Schedules III and IV must provide appropriate DEA registration numbers for those schedules on their order forms or purchase orders.

## DEA Requirements (International Orders)

For all international controlled drug substance orders, please contact Julie Smith at (301) 816-8164 or foreigncontrols@ usp.org.

All orders for controlled drug substances-regulated by the U.S. Drug Enforcement Administration (DEA)-to be shipped outside the U.S. must be accompanied by:

1. Full payment.
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## USING AND ORDERING USP REFERENCE STANDARDS

2. An import permit (in English or with an English translation attached) valid at least 6 months from the date of its receipt by USP Customer Service.
3. A statement of non-reexport and use for medical or scientific purposes (in English or with an English translation attached).
4. Purchase Order or Price Quote given by USP.

On receiving the order, USP takes 2-3 business days to:

- Review all documents to make sure they are adequate and appropriate.
- Complete and legally approve the required DEA forms.
- Forward the forms to the DEA office to obtain the necessary Export Permits.

USP cannot ship items without an Export Permit. While it typically takes 6-10 weeks to get the permit from the DEA, USP has no control over the time in which permits are issued. On receiving the Export Permit, USP completes processing of the order in 1-3 days and ships out the materials through its freight forwarder.

Controlled substances (CI, CII, CIII, CIV, CV) and List Chemicals shipped to an international address, including Canada, add $\$ 25$ per unit.

For controlled substance orders to be shipped to Mexico, in addition to the DEA processing period, an additional week is required to obtain a certificate from the Mexican Embassy, authorizing the shipment to enter the country. Customers will pay an additional $\$ 114$ to cover the fee charged by the Mexican Embassy per import permit.

## Back Orders

USP will ship a back-ordered item if that item becomes available within 30 days of the date the order is placed if there is a valid open P.O. or payment for the item. If the order is more than 30 days old when the item becomes available, the customer will receive a Notice of Availability (NOA), indicating that the item is available. Such items will be shipped only after USP receives written authorization by the customer. The order will be canceled if the Reference Standard does not become available within six months of the original order. NOAs not replied to within 45 days of generation will be cancelled, and the customer account will be credited appropriately.

Customers may send confirmation orders for back-ordered Reference Standards that subsequently become available. They must clearly designate the confirmation orders as such-USP is not responsible for duplication of orders not clearly designated.

## HOW TO READ PRODUCT LISTINGS

Column 1 (Catalog Number): Catalog number currently assigned to each Reference Standard and Authentic Substance. Please include this number in your orders.

Column 2 (Description): Product description as designated in $U S P-N F$, the product label, and / or the Drug Enforcement Administration Control Schedule, as applicable. The quantity of material per container follows the name in parentheses (all materials are in single containers unless otherwise specified).

Column 3 (Current Lot): Current lot designation of each official item being distributed as of the date of this catalog. If the current lot is blank, the item is not in distribution.

Column 4 (Purity Values) Assigned purity value as it appears on the RS or AS label. Code interpretations for the basis of purity assignments are as follows:
Basis Interpretation

## Code

| (ai) | as is |
| :--- | :--- |
| (dr) | dried |
| (an) | anhydrous |
| (fb) | free base |

Column 5 (Change Code): Codes that identify any change in USP Reference Standards status or information since the May/June 2004, official Catalog. Code interpretations are as follows:

| Change <br> Code | Interpretation |
| :---: | :--- |
| 1 | New Reference Standard |
| 2 | New lot |
| 3 | Change in package size or description |
| 4 | Correction of typographical error |
| 5 | New catalog number-use for all orders |
| 6 | Previous lot no longer official; only <br> current lot to be used |
| 7 | Valid use date of previous lot extended <br> Change in catalog number and / or name, <br> 8 |
| see cross-reference section <br> Discontinued |  |

Column 6 (Previous Lot/Valid Use Date): Lot designations for recent lots no longer being distributed. The indicated month and year in parenthesis indicates the date (last day of the month) through which that lot was valid as an official USP Reference Standard. (e.g. "F-1 (06/00)" means lot F-1 is no longer being distributed, but was considered official through June 30, 2000.)

Column 7 (CAS Number)*: Chemical Abstracts Service number, when available, for USP Reference Standards and Authentic Substances. In case of mixtures, typically, the CAS number of the analyte of interest is listed.

Column 8 (Price) List price of the reference standard.

[^193]New Lots in Distribution

| Cat. No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | $\begin{aligned} & \text { CAS } \\ & \text { No. } \end{aligned}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1098027 | Cefpodoxime Proxetil ( 350 mg ) | F0C192 | $736 \mathrm{ug} / \mathrm{mg}$ (an) | 1 |  | [87239-81-4] | \$156 |
| 1269414 | Fenbendazole Related Compound A ( 30 mg ) (Methyl (1H-benzimidazole-2-yl)carbamate) | F0D009 | $0.99 \mathrm{mg} / \mathrm{mg}$ (ai) | 1 |  | [10605-21-7] | \$487 |
| 1269425 | Fenbendazole Related Compound B ( 30 mg ) (Methyl [5(6)-chlorobenzimidazole-2-yl]carbamate) | F0D008 | $0.99 \mathrm{mg} / \mathrm{mg}$ (ai) | 1 |  | n/f | \$487 |
| 1311306 | Homopolymer Polypropylene (3 Strips) | F0C096 |  | 1 |  | [9003-07-0] | \$156 |
| 1356847 | Lamivudine Resolution Mixture A (10 mg) | F0D024 |  | 1 |  | [134678-17-4] | \$487 |
| 1358503 | Leuprolide Acetate (200 mg) | F0C430 | $0.907 \mathrm{mg} / \mathrm{mg}$ (an,fb) | 1 |  | [74381-53-6] | \$1,525 |
| 1367708 | Linoleoyl Polyoxylglycerides ( 100 mg ) | F0C283 |  | 1 |  | n/f | \$156 |
| 1460714 | Nevirapine Hemihydrate ( 100 mg ) | F0D034 |  | 1 |  | [129618-40-2] | \$156 |
| 1460725 | Nevirapine Related Compound A (15 mg) (5,11-Dihydro-6H-11-ethyl-4-methyl-dipyrido[3,2-b2',3'-e][1,4]diazepin-6-one) | F0D035 |  | 1 |  | n/f | \$487 |
| 1460736 | Nevirapine Related Compound B ( 15 mg ) ( $5,11-$ Dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one) | F0D033 |  | 1 |  | n/f | \$487 |
| 1478152 | Oleoyl Polyoxylglycerides ( 100 mg ) | F0C313 |  | 1 |  | n/f | \$156 |
| 1485125 | Oxybutynin Related Compound B ( 20 mg ) (Cyclohexyl mandelic acid methyl ester) | F0D061 |  | 1 |  | [10399-13-0] | \$487 |
| 1485136 | Oxybutynin Related Compound C (20 mg) (4(Ethylmethyamino) but-2-ynyl (+/-)-2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride) | F0D062 |  | 1 |  | n/f | \$487 |
| 1548134 | Potassium Bicarbonate (1 g) (AS) | F0D074 | 99.9\% (dr) | 1 |  | [298-14-6] | \$156 |
| 1601340 | Residual Solvent Class 2 - Acetonitrile ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D049 | $2.00 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601361 | Residual Solvent Class 2-Chlorobenzene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D048 | $1.81 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601420 | Residual Solvent Class 2 - 1,2-Dichloroethene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D040 | $9.2 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601521 | Residual Solvent Class 2-1,4-Dioxane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D050 | $1.89 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601623 | Residual Solvent Class 2 - Methanol ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D045 | $14.8 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601441 | Residual Solvent Class 2 - Methylene Chloride ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D046 | $2.90 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601770 | Residual Solvent Class 2 - Tetrahydrofuran ( $1.2 \mathrm{~mL} /$ /ampule; 3 ampules) | F0D043 | $3.49 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601805 | Residual Solvent Class 2 - Toluene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D042 | $4.39 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601849 | Residual Solvent Class 2 - Xylenes ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D041 | $10.7 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1034002 | Amprolium ( 200 mg ) | G0C317 | $0.991 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{aligned} & \text { F-1 (04/05) } \\ & F(04 / 02) \\ & \hline \end{aligned}$ | [121-25-5] | \$156 |
| 1046307 | Aztreonam E-Isomer ( 50 mg ) | F1D056 |  | 2 | F (04/05) | n/f | \$156 |
| 1046409 | Open Ring Aztreonam ( 25 mg ) | G0D071 |  | 2,3 | F (12/04) | [87500-74-1] | \$156 |
| 1083100 | 3-tert-Butyl-4-hydroxyanisole (200 mg) | K0C239 |  | 2 |  | [121-00-6] | \$156 |
| 1097603 | Cefazolin (400 mg) | L0C345 |  | 2 | $\begin{aligned} & \hline \mathrm{K}(04 / 05) \\ & \mathrm{J}(06 / 00) \end{aligned}$ | [25953-19-9] | \$156 |
| 1134051 | Cilastatin Ammonium Salt (100 mg) | G0C334 | $945 \mathrm{ug} / \mathrm{mg}$ (ai) | 2 | $\begin{aligned} & \text { F-1 (05/05) } \\ & \text { F }(07 / 00) \\ & \hline \end{aligned}$ | n/f | \$156 |
| 1135000 | Clidinium Bromide (2 g) | H0B115 |  | 2 | G (03/05) | [3485-62-9] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

New Lots in Distribution

| Cat. <br> No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1138405 | Clobetasol Propionate (200 mg) | F2C309 | 980 ug/mg (ai) | 2 | $\begin{array}{\|l\|} \hline \text { F-1 (03/05) } \\ \text { F (10/01) } \\ \hline \end{array}$ | [25122-46-7] | \$156 |
| 1156000 | Cyclopentolate Hydrochloride ( 300 mg ) | 10 C 424 | $0.999 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{aligned} & \mathrm{H}(03 / 05) \\ & \mathrm{G}(04 / 00) \\ & \hline \end{aligned}$ | [5870-29-1] | \$156 |
| 1180004 | Dextroamphetamine Sulfate CII (500 mg) | 10C311 | $1.000 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{array}{\|l\|} \hline H(05 / 05) \\ G(08 / 03) \\ \text { F-6 (12/99) } \\ \hline \end{array}$ | [51-63-8] | \$216 |
| 1269389 | Felodipine (200 mg) | G0D065 | $0.999 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | $\begin{array}{\|l} \hline \text { F-1 (04/05) } \\ \text { F (09/02) } \\ \hline \end{array}$ | [72509-76-3] | \$156 |
| 1430305 | Methyl Laurate ( 500 mg ) | G0C356 | $0.998 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | F (03/05) | [111-82-0] | \$156 |
| 1431501 | Methyl Myristate ( $300 \mathrm{mg} \mathrm{)}$ | G0C357 | $0.998 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | F (03/05) | [124-10-7] | \$156 |
| 1433008 | Methylphenidate Hydrochloride CII (125 mg) | I1C241 |  | 2 | $\begin{aligned} & \text { I (04/05) } \\ & \text { H (05/01) } \\ & \hline \end{aligned}$ | [298-59-9] | \$165 |
| 1448005 | Morphine Sulfate CII (500 mg) | M0D016 | 0.999 mg/mg (an) | 2 | $\begin{array}{\|l\|} \hline \text { LOB056 (04/05) } \\ \text { K (06/03) } \\ \mathrm{J}-1(07 / 00) \\ \hline \end{array}$ | [6211-15-0] | \$332 |
| 1448923 | Mupirocin Lithium (100 mg) | H0C176 | 926 ug/mg (ai) | 2 | $\begin{array}{\|l\|} \hline G(03 / 05) \\ F(02 / 01) \\ \hline \end{array}$ | [73346-79-9] | \$156 |
| 1465503 | Nitrofurfural Diacetate ( 100 mg ) | G0D066 | $0.99 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | F-1 (12/04) | [92-55-7] | \$487 |
| 1468501 | Norepinephrine Bitartrate ( 125 mg ) | I0C381 |  | 2 | H (04/05) | [69815-49-2] | \$124 |
| 1500240 | Paroxetine Related Compound C ( 15 mg ) ((+)-trans-Paroxetine hydrochloride) | G0D053 | $0.96 \mathrm{mg} / \mathrm{mg}$ (ai) | 2,3 | F0B192 (05/05) | [130855-30-0] | \$487 |
| 1533002 | Phenylephrine Hydrochloride ( 125 mg ) | K1C290 |  | 2 | $\begin{aligned} & \mathrm{K}(03 / 05) \\ & \mathrm{J}(02 / 99) \end{aligned}$ | [61-76-7] | \$124 |
| 1551300 | Potassium Trichloroammineplatinate ( $20 \mathrm{mg} \mathrm{)}$ | IOD022 | $0.84 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{aligned} & \text { H0B149 (12/04) } \\ & \text { G-1 (01/03) } \\ & \text { G (07/99) } \end{aligned}$ | [13820-91-2] | \$487 |
| 1602706 | Ribavirin (200 mg) | H1C335 |  | 2 | $\begin{array}{r} \mathrm{H}(03 / 05) \\ \mathrm{G}(08 / 01) \\ \hline \end{array}$ | [36791-04-5] | \$289 |
| 1614308 | Sodium Lactate (200 mg) | 10C299 |  | 2 | $\begin{aligned} & \mathrm{H}(04 / 05) \\ & \mathrm{G}(06 / 00) \end{aligned}$ | [867-56-1] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1000601 | Acebutolol Hydrochloride ( 125 mg ) | F-1 |  |  |  | [34381-68-5] | \$156 |
| 1001003 | Acenocoumarol (200 mg) | F |  |  |  | [152-72-7] | \$156 |
| 1001502 | Acepromazine Maleate ( $250 \mathrm{mg} \mathrm{)}$ | F-2 |  |  | F-1 (05/02) | [3598-37-6] | \$156 |
| 1002505 | Acesulfame Potassium ( 200 mg ) | F0C136 |  |  |  | [55589-62-3] | \$260 |
| 1003009 | Acetaminophen ( 400 mg ) | J-1 |  |  | $\begin{array}{\|l\|l\|} \hline J(05 / 02) \\ I(05 / 99) \\ \hline \end{array}$ | [103-90-2] | \$124 |
| 1004001 | Acetanilide Melting Point Standard ( 500 mg ) (Approximately 114 degrees) | M0A029 |  |  | $\begin{aligned} & \hline \text { L (06/04) } \\ & \text { K (02/00) } \end{aligned}$ | [103-84-4] | \$75 |
| 1005004 | Acetazolamide (2 g) | J |  |  |  | [59-66-5] | \$156 |
| 1006007 | Acetohexamide ( 250 mg ) | H |  |  | G-1 (06/99) | [968-81-0] | \$156 |
| 1006506 | Acetohydroxamic Acid ( 200 mg ) | F-1 |  |  | F (03/03) | [546-88-3] | \$156 |
| 1007000 | Acetophenazine Maleate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  |  | [5714-00-1] | \$156 |
| 1008002 | alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphe-nyl-3-methylbutane ( 125 mg ) | G-3 |  |  |  | n/f | \$487 |
| 1008501 | Acetylcholine Chloride ( 200 mg ) | G |  |  |  | [60-31-1] | \$156 |
| 1009005 | Acetylcysteine ( 200 mg ) | H1B169 |  |  | H (01/04) | [616-91-1] | \$156 |
| 1009901 | Acetyltributyl Citrate ( 500 mg ) | G0C120 |  |  | F (05/04) | [77-90-7] | \$156 |
| 1009923 | Acetyltriethyl Citrate ( 500 mg ) | F-1 |  |  | F (05/02) | [77-89-4] | \$156 |
| 1012065 | Acyclovir (300 mg) | JoC149 |  |  | $1(06 / 04)$ | [59277-89-3] | \$197 |
| 1012101 | Adenine ( 200 mg ) | G-1 |  |  | G (06/00) | [73-24-5] | \$156 |
| 1012123 | Adenosine (200 mg) | G0C295 |  |  | $\begin{aligned} & \text { F1B058 (01/05) } \\ & \text { F (04/03) } \end{aligned}$ | [58-61-7] | \$156 |
| 1012145 | Agigenin ( 25 mg ) | F |  |  |  | n/f | \$156 |
| 1012509 | L-Alanine ( 200 mg ) | F-2 |  |  | F-1 (04/01) | [56-41-7] | \$156 |
| 1012553 | Albendazole ( 200 mg ) | G |  |  | F-1 (01/00) | [54965-21-8] | \$156 |
| 1012600 | Albuterol ( 200 mg ) | 1 |  |  | H (12/00) | [18559-94-9] | \$156 |
| 1012633 | Albuterol Sulfate ( 200 mg ) | J |  |  | I (04/00) | [51022-70-9] | \$156 |
| 1012757 | Alclometasone Dipropionate ( 300 mg ) | H |  |  | G (01/00) | [66734-13-2] | \$156 |
| 1012780 | Alendronate Sodium (200 mg) | F0B315 |  |  |  | [121268-17-5] | \$156 |
| 1012906 | Alfentanil Hydrochloride CII (500 mg) | F0B016 |  |  |  | [70879-28-6] | \$207 |
| 1012939 | Allantoin (200 mg) | F0C169 |  |  |  | [97-59-6] | \$156 |
| 1012950 | Alliin (25 mg) | F |  |  |  | [556-27-4] | \$1,525 |
| 1013002 | Allopurinol ( 250 mg ) | J0C186 |  |  | $\begin{aligned} & \hline \text { I-1 (01/05) } \\ & \text { I (07/02) } \\ & \hline \end{aligned}$ | [315-30-0] | \$156 |
| 1013024 | Allopurinol Related Compound A ( 50 mg ) (3-Amino-4-carboxamidopyrazole Hemisulfate) | G |  |  | $\begin{aligned} & \text { F-3 }(05 / 02) \\ & \text { F-2 }(04 / 99) \end{aligned}$ | n/f | \$487 |
| 1013057 | S-Allyl-L-Cysteine (25 mg) | F |  |  |  | n/f | \$487 |
| 1014005 | Alphaprodine Hydrochloride CII (250 mg) | F |  |  |  | [561-78-4] | \$207 |
| 1015008 | Alprazolam CIV (200 mg) | H |  |  |  | [28981-97-7] | \$207 |
| 1016000 | Alprostadil ( 25 mg ) | H |  |  |  | [745-65-3] | \$1,525 |
| 1017105 | Altretamine ( 500 mg ) | F |  |  |  | [645-05-6] | \$156 |
| 1017502 | Dried Aluminum Hydroxide Gel ( 200 mg ) | F2B120 |  |  | F-1 (01/04) | [21645-51-2] | \$156 |
| 1018505 | Amantadine Hydrochloride (200 mg) | H |  |  | G (04/01) | [665-66-7] | \$156 |
| 1019202 | Amcinonide (200 mg) | G0B260 |  |  | F-1 (03/04) | [51022-69-6] | \$156 |
| 1019417 | Amifostine Disulfide ( 25 mg ) | F0C152 |  |  |  | [112901-68-5] | \$487 |
| 1019508 | Amikacin (200 mg) | 1 |  |  | H (08/00) | [37517-28-5] | \$156 |
| 1019701 | Amiloride Hydrochloride ( 500 mg ) | H |  |  |  | [17440-83-4] | \$156 |
| 1019756 | Aminobenzoate Potassium (200 mg) | F-1 |  |  | F (06/01) | [138-84-1] | \$156 |
| 1019767 | Aminobenzoate Sodium (200 mg) | F |  |  |  | [55-06-6] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1019803 | Aminobenzoic Acid ( 200 mg ) (p-aminobenzoic acid) | H1C083 |  |  | $\begin{aligned} & \mathrm{H}(10 / 04) \\ & \mathrm{G}(10 / 00) \\ & \hline \end{aligned}$ | [150-13-0] | \$156 |
| 1020008 | Aminobutanol (500 mg) | G-1 |  |  | G (06/99) | [13054-87-0] | \$389 |
| 1021000 | Aminocaproic Acid (200 mg) | F-4 |  |  |  | [60-32-2] | \$156 |
| 1021703 | N -(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methy-lene)-amino]-glycine ( 25 mg ) | F-1 |  |  |  | n/f | \$487 |
| 1022808 | 2-Amino-5-chlorobenzophenone ( 25 mg ) | 1 |  |  | H-1 (01/03) | [719-59-5] | \$487 |
| 1025205 | Aminoglutethimide (200 mg) | F |  |  |  | [125-84-8] | \$156 |
| 1025307 | m -Aminoglutethimide ( 100 mg ) | G |  |  | F (05/01) | n/f | \$487 |
| 1025351 | Aminohippuric Acid (200 mg) | F-1 |  |  |  | [61-78-9] | \$156 |
| 1025806 | 2-[3-Amino-5-(n-methylacetamido)-2,4,6-triiodo-benzamido]-2-deoxy-d-glucose ( 25 mg ) | F |  |  |  | n/f | \$487 |
| 1025908 | Aminopentamide Sulfate (200 mg) | F0B273 |  |  |  | [60-46-8] | \$156 |
| 1026004 | m-Aminophenol ( 300 mg ) | F |  |  |  | [591-27-5] | \$487 |
| 1026401 | Aminosalicylic Acid (125 mg) | F-1 |  |  | F (03/99) | [65-49-6] | \$124 |
| 1026605 | 3 -Amino-2,4,6-triodobenzoic Acid ( 50 mg ) | G |  |  |  | [3119-15-1] | \$487 |
| 1027007 | 5-Amino-2,4,6-triiodo-N-methylisophthalamic Acid ( 50 mg ) | F-1 |  |  |  | [2280-89-9] | \$487 |
| 1028000 | Amitraz (200 mg) | FOC042 |  |  |  | [33089-61-1] | \$156 |
| 1029002 | Amitriptyline Hydrochloride (200 mg) | J0A004 |  |  | 1 (03/03) | [549-18-8] | \$156 |
| 1029909 | Ammonio Methacrylate Copolymer Type A ( 100 mg ) | F-1 |  |  | F (06/01) | [33434-24-1] | \$156 |
| 1029910 | Ammonio Methacrylate Copolymer Type B ( 100 mg ) | F-1 |  |  | F (05/00) | [33434-24-1] | \$156 |
| 1029953 | Ammonium Chloride (200 mg) | F0C134 |  |  |  | [12125-02-9] | \$156 |
| 1030001 | Amobarbital CII (200 mg) | F-2 |  |  |  | [57-43-2] | \$207 |
| 1031004 | Amodiaquine Hydrochloride ( 500 mg ) | H0B238 |  |  | G-1 (04/03) | [6398-98-7] | \$156 |
| 1031401 | Amoxapine ( 200 mg ) | G |  |  | F-1 (04/02) | [14028-44-5] | \$156 |
| 1031503 | Amoxicillin (200 mg) | J0C043 |  |  | I (07/04) | [61336-70-7] | \$156 |
| 1032007 | Amphotericin B (125 mg) | J3C246 | 1009 ug/mg (dr) |  | $\begin{array}{\|l} \hline \mathrm{J}-2(01 / 05) \\ \mathrm{J}-1(07 / 02) \\ \hline \end{array}$ | [1397-89-3] | \$124 |
| 1033000 | Ampicillin (200 mg) | J-1 |  |  | $J(12 / 01)$ | [69-53-4] | \$156 |
| 1033203 | Ampicillin Sodium ( 125 mg ) | G-1 |  |  | G (10/99) | [69-52-3] | \$124 |
| 1033407 | Ampicillin Trihydrate (200 mg) | G |  |  |  | [7177-48-2] | \$156 |
| 1034002 | Amprolium (200 mg) | G0C317 | $0.991 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{array}{\|l} \hline \text { F-1 (04/05) } \\ \text { F (04/02) } \\ \hline \end{array}$ | [121-25-5] | \$156 |
| 1034308 | Amrinone ( 500 mg ) | G |  |  |  | [60719-84-8] | \$156 |
| 1034320 | Amrinone Related Compound A (100 mg) (5-carboxamide[3,4'-bipyridin]-6(1H)-one) | F |  |  |  | [62749-46-6] | \$487 |
| 1034341 | Amrinone Related Compound B ( 100 mg ) ( N -(1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-yl)-2-hydroxypropanamide) | F-1 |  |  | F (03/00) | n/f | \$487 |
| 1034363 | Amrinone Related Compound C ( 50 mg ) (1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-carbonitrile) | F-1 |  |  | F (05/00) | n/f | \$487 |
| 1036008 | Anileridine Hydrochloride CII (250 mg) | F |  |  |  | [126-12-5] | \$207 |
| 1036507 | 3-Anilino-2-(3,4,5-trimethoxybenzyl) acrylonitrile ( 25 mg ) | G-1 |  |  |  | [30078-48-9] | \$487 |
| 1038003 | Antazoline Phosphate (200 mg) | H |  |  | G-1 (04/02) | [154-68-7] | \$156 |
| 1039006 | Anthralin (200 mg) | IOB221 |  |  | H (11/02) | [1143-38-0] | \$156 |
| 1040005 | Antipyrine (200 mg) | G |  |  | F-4 (09/01) | [60-80-0] | \$156 |
| 1040708 | Apigenin-7-glucoside ( 30 mg ) | F |  |  |  | n/f | \$487 |

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| 1041008 | Apomorphine Hydrochloride ( 250 mg ) | H |  |  | G (01/03) | [41372-20-7] | \$162 |
| 1041609 | Apraclonidine Hydrochloride ( 100 mg ) | H0B112 |  |  | G (06/03) | [73218-79-8] | \$479 |
| 1042000 | Aprobarbital CIII (200 mg) (AS) | F-1 |  |  |  | [77-02-1] | \$207 |
| 1042500 | L-Arginine (200 mg) | G-1 |  |  | G (09/00) | [74-79-3] | \$156 |
| 1042601 | Arginine Hydrochloride ( 125 mg ) | G0B060 |  |  | F-1 (05/03) | [1119-34-2] | \$124 |
| 1042703 | Arsanilic Acid (25 mg) | F |  |  |  | [98-50-0] | \$156 |
| 1043003 | Ascorbic Acid (1 g) (Vitamin C) | Q0B012 |  |  | P (04/03) | [50-81-7] | \$156 |
| 1043706 | Aspartame ( 200 mg ) | H1B125 |  |  | H (05/03) | [22839-47-0] | \$156 |
| 1043750 | Aspartame Acesulfame (200 mg) | F0C137 |  |  |  | [106372-55-8] | \$156 |
| 1043728 | Aspartame Related Compound A ( 75 mg ) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid) | H |  |  | G-1 (10/99) | [5262-10-2] | \$487 |
| 1043819 | Aspartic Acid (100 mg) | F0B087 |  |  |  | [6899-03-2] | \$156 |
| 1044006 | Aspirin ( 500 mg ) | H |  |  | G-1 (11/02) | [50-78-2] | \$156 |
| 1044301 | Astemizole ( 200 mg ) | F |  |  |  | [68844-77-9] | \$156 |
| 1044403 | Atenolol ( 200 mg ) | H1C320 | 998 ug/mg (dr) |  | $\begin{aligned} & \mathrm{H}(01 / 05) \\ & \mathrm{G}(08 / 01) \\ & \hline \end{aligned}$ | [29122-68-7] | \$156 |
| 1044651 | Atovaquone (200 mg) | FOB190 |  |  |  | [95233-18-4] | \$156 |
| 1044662 | Atovaquone Related Compound A ( 25 mg ) (cis-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4naphthoquinone) | FOB188 |  |  |  | n/f | \$487 |
| 1044800 | Atracurium Besylate ( 100 mg ) | FOB143 |  |  |  | [64228-81-5] | \$156 |
| 1045009 | Atropine Sulfate ( 500 mg ) | M0B098 |  |  | L-2 (04/03) <br> L-1 (06/02) <br> L (10/00) | [5908-99-6] | \$156 |
| 1045337 | Avobenzone ( 500 mg ) | G0B280 |  |  | F (09/03) | [70356-09-1] | \$156 |
| 1045508 | Aurothioglucose (100 mg) | H0B224 |  |  | $\begin{aligned} & \hline G(10 / 03) \\ & F(12 / 01) \\ & \hline \end{aligned}$ | [12192-57-3] | \$156 |
| 1045600 | Azaerythromycin A (100 mg) | G |  |  | $\begin{array}{\|l} \hline \text { F-1 (02/02) } \\ \text { F (02/99) } \\ \hline \end{array}$ | [76801-85-9] | \$156 |
| 1045756 | Azaperone ( 200 mg ) | F |  |  |  | [1649-18-9] | \$156 |
| 1045803 | Azatadine Maleate (200 mg) | G0B300 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (04/04) } \\ \text { F (06/00) } \\ \hline \end{array}$ | [3978-86-7] | \$156 |
| 1046001 | Azathioprine (200 mg) | H |  |  | G-1 (02/00) | [446-86-6] | \$156 |
| 1046056 | Azithromycin (100 mg) | H0C212 |  |  | $\begin{aligned} & \hline G(11 / 04) \\ & F(06 / 00) \\ & \hline \end{aligned}$ | [117772-70-0] | \$156 |
| 1046103 | Azlocillin Sodium (200 mg) | F |  |  |  | [37091-65-9] | \$156 |
| 1046147 | Azo-aminoglutethimide ( 100 mg ) | F |  |  |  | n/f | \$487 |
| 1046205 | Aztreonam ( 200 mg ) | G0C077 |  |  | F-1 (03/04) | [78110-38-0] | \$156 |
| 1046307 | Aztreonam E-Isomer ( 50 mg ) | F1D056 |  | 2 | F (04/05) | n/f | \$156 |
| 1046409 | Open Ring Aztreonam ( 25 mg ) | G0D071 |  | 2,3 | F (12/04) | [87500-74-1] | \$156 |
| 1047300 | Bacampicillin Hydrochloride ( 200 mg ) | G0B053 |  |  | F (11/02) | [37661-08-8] | \$156 |
| 1047503 | Bacitracin (1 g) (Susceptibility disk standard) | G1C254 |  |  | G (07/04) | [1405-87-4] | \$156 |
| 1048007 | Bacitracin Zinc (200 mg) | N0A024 |  |  | $\begin{aligned} & \mathrm{M}-1(11 / 02) \\ & \mathrm{M}(02 / 00) \\ & \hline \end{aligned}$ | [1405-89-6] | \$156 |
| 1048200 | Baclofen ( 500 mg ) | 1 |  |  |  | [1134-47-0] | \$156 |
| 1048222 | Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone) | H1C289 |  |  | H (11/04) | n/f | \$389 |
| 1048506 | Beclomethasone Dipropionate ( 200 mg ) | K |  |  | $J(12 / 00)$ | [5534-09-8] | \$156 |
| 1048619 | Benazepril Hydrochloride ( 125 mg ) | F0C250 |  |  |  | [86541-74-4] | \$156 |

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| 1048620 | Benazepril Related Compound A (15 mg) ((3R)-3-[[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]ami-no]-2,3,4,5-tetrahydro-2-oxo-1H-1-benazapine-1-acetic acid, monohydrochloride) | F0C252 |  |  |  | n/f | \$487 |
| 1048630 | Benazepril Related Compound B ( 15 mg ) ((3S)-3-[[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]ami-no]-2,3,4,5-tetrahydro-2-oxo-1H-1-benazapine-1-acetic acid, monohydrochloride) | F0C256 |  |  |  | n/f | \$487 |
| 1048641 | Benazepril Related Compound C (50 mg) ((3S)-3-[[(1S)-1-carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1H-1-benazepine]-1acetic acid) | FOC425 | $1.00 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | [86541-78-8] | \$487 |
| 1049000 | Bendroflumethiazide ( $200 \mathrm{mg} \mathrm{)}$ | G-1 |  |  |  | [73-48-3] | \$156 |
| 1050009 | Benoxinate Hydrochloride ( 200 mg ) | F-2 |  |  | F-1 (10/99) | [5987-82-6] | \$124 |
| 1051001 | Benzalkonium Chloride ( 5 mL of approx. 10\% aqueous solution) | K0B151 |  |  | J (06/03) | [8001-54-5] | \$156 |
| 1054000 | Benzocaine ( 500 mg ) | J0C130 |  |  | I (12/04) | [94-09-7] | \$156 |
| 1055002 | Benzoic Acid (300 mg) | F6B173 |  |  | $\begin{aligned} & \hline \text { F-5 (03/04) } \\ & \text { F-4 (07/01) } \\ & \hline \end{aligned}$ | [65-85-0] | \$156 |
| 1056005 | Benzonatate (1 g) | 10B003 |  |  | H (01/03) | [104-31-4] | \$156 |
| 1056504 | 1,4-Benzoquinone (200 mg) | G1B145 |  |  | $\begin{aligned} & \hline \text { G (01/04) } \\ & \text { F-1 (11/01) } \\ & F(09 / 00) \\ & \hline \end{aligned}$ | [106-51-4] | \$156 |
| 1057507 | Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide) | H0B069 |  |  | G-4 (03/03) | [121-30-2] | \$487 |
| 1059003 | $\begin{aligned} & \begin{array}{l} \text { Benzphetamine Hydrochloride CIII }(200 \mathrm{mg}) \\ \text { (AS) } \end{array} \\ & \hline \end{aligned}$ | F-1 |  |  |  | [5411-22-3] | \$207 |
| 1060002 | Benzthiazide (200 mg) | F |  |  |  | [91-33-8] | \$156 |
| 1061005 | Benztropine Mesylate (200 mg) | 10 C 038 |  |  | H (09/04) | [132-17-2] | \$156 |
| 1061901 | Benzyl Alcohol ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | G0B306 |  |  | F0B106 (10/03) | [100-51-6] | \$156 |
| 1062008 | Benzyl Benzoate (5 g) | J0C060 |  |  | I (05/04) | [120-51-4] | \$156 |
| 1064003 | 1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride ( 25 mg ) | F-1 |  |  |  | n/f | \$487 |
| 1065006 | Bephenium Hydroxynaphthoate ( 500 mg ) | F |  |  |  | [3818-50-6] | \$156 |
| 1065618 | Betahistine Hydrochloride ( 200 mg ) | F0C105 |  |  |  | [5579-84-0] | \$156 |
| 1065709 | Betaine Hydrochloride (200 mg) | F-1 |  |  | F (11/02) | [590-46-5] | \$156 |
| 1066009 | Betamethasone (200 mg) | K2C204 |  |  | $\begin{aligned} & \hline \text { K-1 (10/04) } \\ & \text { K (11/02) } \\ & \hline \end{aligned}$ | [378-44-9] | \$156 |
| 1067001 | Betamethasone Acetate ( 500 mg ) | J0B079 |  |  | I (08/03) | [987-24-6] | \$156 |
| 1067307 | Betamethasone Benzoate ( 200 mg ) | F-1 |  |  |  | [22298-29-9] | \$156 |
| 1067704 | Betamethasone Dipropionate (125 mg) | K0C229 |  |  | $\begin{array}{\|l\|} \hline J(04 / 04) \\ \text { I (03/99) } \\ \hline \end{array}$ | [5593-20-4] | \$124 |
| 1068004 | Betamethasone Sodium Phosphate (500 mg) | J0B043 |  |  | $\begin{aligned} & \hline \text { I-1 (02/03) } \\ & \text { I (01/01) } \\ & \hline \end{aligned}$ | [151-73-5] | \$156 |
| 1069007 | Betamethasone Valerate ( $200 \mathrm{mg} \mathrm{)}$ | $J$ |  |  | $1(05 / 00)$ | [2152-44-5] | \$156 |
| 1069903 | Betaxolol Hydrochloride (200 mg) | G |  |  | F-1 (06/00) | [63659-19-8] | \$156 |
| 1070006 | Betazole Hydrochloride ( 200 mg ) | H |  |  |  | [138-92-1] | \$156 |
| 1071009 | Bethanechol Chloride (200 mg) |  |  |  | $\begin{aligned} & \hline \text { G (03/05) } \\ & \text { F-3 }(07 / 01) \\ & \hline \end{aligned}$ | [590-63-6] | \$156 |
| 1071304 | Bile Salts (10 g) | $10 \mathrm{C003}$ |  |  | $\begin{aligned} & \mathrm{H}-1(05 / 04) \\ & \mathrm{H}(05 / 99) \\ & \hline \end{aligned}$ | [145-42-6] | \$124 |
| 1071439 | Positive Bioreaction (3 strips; $10 \mathrm{~cm} \times 1 \mathrm{~cm}$ ) | F0D014 |  |  |  | n/f | \$325 |

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## USP Reference Standards and Authentic Substances

| Cat. No. | Description | Curr. Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \text { CAS } \\ \text { No. } \\ \hline \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1071508 | Biotin (200 mg) | H1B019 |  |  | H (04/03) | [58-85-5] | \$156 |
| 1072001 | Biperiden (200 mg) | F2B080 |  |  | F-1 (02/04) | [514-65-8] | \$156 |
| 1073004 | Biperiden Hydrochloride (200 mg) | F-3 |  |  | F-2 (06/99) | [1235-82-1] | \$156 |
| 1074007 | Bisacodyl (125 mg) | 11B162 |  |  | $\begin{aligned} & \text { I (01/04) } \\ & \mathrm{H}-1(02 / 99) \\ & \hline \end{aligned}$ | [603-50-9] | \$124 |
| 1074700 | 2,5-Bis(D-arabino-1,2,3,4-tetrahydroxybutyl)pyrazine ( 25 mg ) | F |  |  |  | n/f | \$487 |
| 1075203 | Bis(2-ethylhexyl)maleate ( 250 mg ) | F-2 |  |  | F-1 (01/01) | [142-16-5] | \$487 |
| 1075509 | p-Bis(di-n-propyl)carbamylbenzenesulfonamide $(50 \mathrm{mg})$ | F |  |  |  | n/f | \$487 |
| 1075531 | Bismuth Citrate (100 mg) | F |  |  |  | [813-93-4] | \$156 |
| 1075553 | Bismuth Subsalicylate ( 100 mg ) | F |  |  |  | [14882-18-9] | \$156 |
| 1075757 | Bisoprolol Fumarate ( $200 \mathrm{mg} \mathrm{)}$ | FOB038 |  |  |  | [104344-23-2] | \$156 |
| 1076002 | 4,4'-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimi-dazolinyl)-1-pyridyl]butyrophenone ( 25 mg ) |  |  |  | G (05/03) | n/f | \$487 |
| 1076308 | Bleomycin Sulfate ( 15 mg ) | J0B213 |  |  | 1 (01/04) | [9041-93-4] | \$307 |
| 1076352 | Bretylium Tosylate (200 mg) | F-1 |  |  |  | [61-75-6] | \$156 |
| 1076363 | Brinzolamide (200 mg) | F0C034 |  |  |  | [138890-62-7] | \$156 |
| 1076374 | Brinzolamide Related Compound A (50 mg) ((S)-(-)-4-ethylamino-2,3-dihydro-2-(3-methoxy-propyl)-4H-thieno-[3,2,e]-thiazine-6-sulfona-mide-1,1-dioxide) | F0C033 |  |  |  | n/f | \$487 |
| 1076385 | Brinzolamide Related Compound B ( 50 mg ) ((R)-4-amino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide ethanedioate) | F0C035 |  |  |  | n/f | \$487 |
| 1076501 | Bromocriptine Mesylate ( 150 mg ) | I1C197 |  |  | I (09/04) | [22260-51-1] | \$156 |
| 1077005 | Bromodiphenhydramine Hydrochloride ( 200 mg ) | F-1 |  |  |  | [1808-12-4] | \$156 |
| 1077708 | 8-Bromotheophylline ( 400 mg ) | G |  |  | F (07/02) | [10381-75-6] | \$156 |
| 1078008 | Brompheniramine Maleate (125 mg) | 11A036 |  |  | $\begin{aligned} & \hline \mathrm{I}(01 / 03) \\ & \mathrm{H}-1(04 / 99) \end{aligned}$ | [980-71-2] | \$124 |
| 1078303 | Bumetanide (250 mg) | 10 C 111 |  |  | $\begin{aligned} & \text { HOBO30 (05/04) } \\ & \text { G (03/03) } \end{aligned}$ | [28395-03-1] | \$156 |
| 1078325 | Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid) | F-2 |  |  | F-1 (05/00) | n/f | \$487 |
| 1078336 | Bumetanide Related Compound B (25 mg) (3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid) | F-2 |  |  | F-1 (01/03) | [28328-53-2] | \$487 |
| 1078507 | Bupivacaine Hydrochloride (1 g) | H |  |  | $\begin{aligned} & \text { G-2 (03/03) } \\ & \text { G-1 (08/02) } \end{aligned}$ | [14252-80-3] | \$156 |
| 1078700 | Buprenorphine Hydrochloride CIII ( 50 mg ) | F-1 |  |  | F (02/99) | [53152-21-9] | \$207 |
| 1078711 | Buprenorphine Related Compound A ( 50 mg ) (21-[3-(1-propenyl)]-7-alpha-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine) | F1C076 |  |  | F (04/04) | n/f | \$487 |
| 1078733 | Bupropion Hydrochloride (200 mg) | F0C123 |  |  |  | [31677-93-7] | \$208 |
| 1078802 | Buspirone Hydrochloride (200 mg) | G |  |  |  | [33386-08-2] | \$156 |
| 1079000 | Butabarbital CIII (200 mg) | H0C007 |  |  | G (03/04) | [125-40-6] | \$207 |
| 1080000 | Butacaine Sulfate ( 600 mg ) | F |  |  |  | [149-15-5] | \$156 |
| 1081002 | Butalbital CIII (200 mg) | H0C054 |  |  | $\begin{aligned} & \hline \text { G2B077 (07/04) } \\ & \text { G-2 (06/03) } \\ & \text { G (05/02) } \\ & \hline \end{aligned}$ | [77-26-9] | \$207 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1081501 | Butamben (200 mg) | F |  |  |  | [94-25-7] | \$156 |
| 1082300 | Butoconazole Nitrate (200 mg) | F1B097 |  |  | F (03/03) | [64872-77-1] | \$156 |
| 1082504 | Butorphanol Tartrate CIV (500 mg) | J |  |  | I (06/00) | [58786-99-5] | \$207 |
| 1082800 | Monotertiary-butyl-p-benzoquinone ( 100 mg ) (FCC) | F |  |  |  | [3602-55-9] | \$156 |
| 1082901 | Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate ( 25 mg ) | F-1 |  |  |  | n/f | \$487 |
| 1083008 | 2-tert-Butyl-4-hydroxyanisole (200 mg) | L0C028 |  |  | K (09/03) | [88-32-4] | \$156 |
| 1083100 | 3-tert-Butyl-4-hydroxyanisole (200 mg) | K0C239 |  | 2 | $\begin{aligned} & \hline J(03 / 05) \\ & \text { I-1 }(09 / 01) \end{aligned}$ | [121-00-6] | \$156 |
| 1084000 | Butylparaben (200 mg) | 10C139 |  |  | $\begin{aligned} & \text { H-1 (03/04) } \\ & \text { H (09/01) } \\ & \hline \end{aligned}$ | [94-26-8] | \$156 |
| 1085003 | Caffeine ( 200 mg ) | $J$ |  |  | I (06/02) | [58-08-2] | \$156 |
| 1086006 | Caffeine Melting Point Standard (1 g) (Approximately 236 degrees) | JOB204 |  |  | I (03/04) | [58-08-2] | \$92 |
| 1086108 | Calcifediol ( 75 mg ) | G |  |  |  | [63283-36-3] | \$156 |
| 1086356 | Calcium Ascorbate (200 mg) | F-1 |  |  | F (08/01) | [5743-28-2] | \$156 |
| 1086800 | Calcium Gluceptate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | F (09/00) | [29039-00-7] | \$156 |
| 1086902 | Calcium Lactobionate ( 200 mg ) | G0B138 |  |  | $\begin{array}{\|l} \hline \text { F-1 (01/04) } \\ \text { F (11/01) } \\ \hline \end{array}$ | [110638-68-1] | \$156 |
| 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) | N-1 |  |  | N (06/00) | [137-08-6] | \$156 |
| 1087202 | Calcium Saccharate ( 200 mg ) | F |  |  |  | [5793-89-5] | \$156 |
| 1088001 | Candicidin (200 mg) | F |  |  |  | [1403-17-4] | \$156 |
| 1089004 | Cannabidiol Cl (25 mg) (AS) | F-2 |  |  |  | [13956-29-1] | \$207 |
| 1090003 | Cannabinol CI ( 25 mg ) (AS) |  |  |  | F-2 (05/02) | [521-35-7] | \$207 |
| 1091006 | Capreomycin Sulfate (200 mg) | G |  |  | F (06/01) | [1405-37-4] | \$156 |
| 1091108 | Capsaicin (100 mg) | G-1 |  |  | $\begin{aligned} & \text { G (03/02) } \\ & \text { F-1 (06/00) } \\ & \text { F (03/99) } \\ & \hline \end{aligned}$ | [404-86-4] | \$156 |
| 1091200 | Captopril (200 mg) | H |  |  |  | [62571-86-2] | \$156 |
| 1091221 | Captopril Disulfide ( 100 mg ) | G1B066 |  |  | G (01/04) | [64806-05-9] | \$487 |
| 1092009 | Carbachol (200 mg) | G |  |  |  | [51-83-2] | \$156 |
| 1093001 | Carbamazepine (100 mg) | $J$ |  |  | 1-1 (02/00) | [298-46-4] | \$156 |
| 1093205 | Carbarsone ( 200 mg ) | F |  |  |  | [121-59-5] | \$156 |
| 1093500 | Carbenicillin Indanyl Sodium ( 300 mg ) | G |  |  |  | [26605-69-6] | \$156 |
| 1094004 | Carbenicillin Monosodium Monohydrate ( 200 mg ) | G-2 |  |  |  | n/f | \$156 |
| 1095506 | Carbidopa ( 400 mg ) | 1 |  |  | H (10/99) | [38821-49-7] | \$156 |
| 1095517 | Carbidopa Related Compound A (50 mg) (3-OMethylcarbidopa) | H0B121 |  |  | G (04/03) | n/f | \$487 |
| 1096000 | Carbinoxamine Maleate ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  | G-1 (11/02) | [3505-38-2] | \$156 |
| 1096407 | Carboplatin ( 100 mg ) | H0C240 |  |  | $\begin{aligned} & \mathrm{G}(07 / 04) \\ & \mathrm{F}(03 / 00) \\ & \hline \end{aligned}$ | [41575-94-4] | \$159 |
| 1096509 | Carboprost Tromethamine ( 25 mg ) | F-1 |  |  | F (02/01) | [58551-69-2] | \$487 |
| 1096600 | Carisoprodol (1 g) | G |  |  | F-2 (05/02) | [78-44-4] | \$156 |
| 1096757 | Carteolol Hydrochloride (200 mg) | F-1 |  |  | F (11/00) | [51781-21-6] | \$156 |
| 1096804 | Cathinone Hydrochloride $\mathbf{C I}(50 \mathrm{mg})$ (alphaAminopropiophenone Hydrochloride) | 1 |  |  |  | [76333-53-4] | \$560 |
| 1096906 | Cefaclor ( 400 mg ) | H |  |  |  | [70356-03-5] | \$156 |
| 1096917 | Cefaclor, Delta-3-Isomer ( 30 mg ) | G |  |  | F-1 (02/00) | n/f | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1097104 | Cefadroxil ( 125 mg ) | 11B319 | 935 ug/mg (ai) |  | $\begin{array}{\|l\|} \hline I(01 / 05) \\ H(04 / 99) \\ \hline \end{array}$ | [66592-87-8] | \$124 |
| 1097308 | Cefamandole Lithium (200 mg) | H |  |  |  | n/f | \$156 |
| 1097400 | Cefamandole Nafate ( 200 mg ) | H |  |  |  | [42540-40-9] | \$156 |
| 1097501 | Cefamandole Sodium ( 250 mg ) | F |  |  |  | [30034-03-8] | \$156 |
| 1097603 | Cefazolin ( 400 mg ) | L0C345 |  | 2 | $\begin{aligned} & \mathrm{K}(04 / 05) \\ & \mathrm{J}(06 / 00) \end{aligned}$ | [25953-19-9] | \$156 |
| 1097636 | Cefepime Hydrochloride ( 500 mg ) | F0C063 |  |  |  | [123171-59-5] | \$156 |
| 1097647 | Cefepime Hydrochloride System Suitability (25 mg) | F0C095 |  |  |  | n/f | \$156 |
| 1097658 | Cefixime ( 500 mg ) | F |  |  |  | [79350-37-1] | \$156 |
| 1097771 | Cefmenoxime Hydrochloride ( 350 mg ) | F |  |  |  | [75738-58-8] | \$156 |
| 1097782 | Cefmetazole (200 mg) | F-1 |  |  | F (04/02) | [56796-20-4] | \$156 |
| 1097750 | Cefonicid Sodium (1 g) | G |  |  |  | [61270-78-8] | \$156 |
| 1097705 | Cefoperazone Dihydrate (200 mg) | H |  |  | G (12/99) | [62893-19-0] | \$156 |
| 1097807 | Ceforanide ( 200 mg ) | F-1 |  |  | F (07/00) | [60925-61-3] | \$156 |
| 1097909 | Cefotaxime Sodium ( 250 mg ) | J0C189 | 901 ug/mg (ai) |  | I (11/04) | [64485-93-4] | \$124 |
| 1097975 | Cefotetan ( 500 mg ) | H0C175 |  |  | $\begin{array}{\|l\|} \hline G(07 / 04) \\ F(09 / 00) \\ \hline \end{array}$ | [69712-56-7] | \$156 |
| 1098005 | Cefotiam Hydrochloride ( 325 mg ) | G0B050 |  |  | F (01/03) | [66309-69-1] | \$156 |
| 1098107 | Cefoxitin ( 500 mg ) | I |  |  | H (05/00) | [35607-66-0] | \$156 |
| 1098118 | Cefpiramide ( 300 mg ) | F0C203 |  |  |  | [70797-11-4] | \$156 |
| 1098027 | Cefpodoxime Proxetil ( 350 mg ) | F0C192 | $736 \mathrm{ug} / \mathrm{mg}$ (an) | 1 |  | [87239-81-4] | \$156 |
| 1098049 | Cefprozil E-Isomer ( 50 mg ) | F2C284 |  |  | $\begin{aligned} & \hline \text { F-1 (10/04) } \\ & \text { F (05/01) } \\ & \hline \end{aligned}$ | [121123-17-9] | \$156 |
| 1098050 | Cefprozil Z-Isomer (200 mg) | G0C037 |  |  | F (12/03) | [121123-17-9] | \$156 |
| 1098129 | Ceftazidime, Delta-3-Isomer ( 25 mg ) | G |  |  | F (03/00) | n/f | \$208 |
| 1098130 | Ceftazidime Pentahydrate ( $300 \mathrm{mg} \mathrm{)}$ | H |  |  | G (12/99) | [78439-06-2] | \$156 |
| 1098173 | Ceftizoxime ( 200 mg ) | H |  |  |  | [68401-81-0] | \$156 |
| 1098184 | Ceftriaxone Sodium ( 350 mg ) | G0B264 |  |  | F (08/03) | [104376-79-6] | \$156 |
| 1098195 | Ceftriaxone Sodium E-Isomer (25 mg) | IOC190 |  |  | $\begin{array}{\|l\|} \hline \mathrm{H}(07 / 04) \\ \mathrm{G}(08 / 01) \\ \mathrm{F}-1(02 / 00) \\ \hline \end{array}$ | n/f | \$208 |
| 1098209 | Cefuroxime Sodium ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  | G-1 (05/00) | [56238-63-2] | \$156 |
| 1098220 | Cefuroxime Axetil ( 500 mg ) | G |  |  | F-1 (05/02) | [64544-07-6] | \$156 |
| 1098231 | Cefuroxime Axetil Delta-3-Isomers ( 35 mg ) | H0B160 |  |  | G (03/03) | n/f | \$156 |
| 1098300 | Cellulose Acetate ( 125 mg ) | F-1 |  |  | F (11/99) | [9004-35-7] | \$124 |
| 1098355 | Cellulose Acetate Phthalate ( 125 mg ) | F-1 |  |  | F (03/99) | [9004-38-0] | \$124 |
| 1098708 | Cephaeline Hydrobromide ( 200 mg ) | G-1 |  |  |  | n/f | \$487 |
| 1099008 | Cephalexin ( 250 mg ) | I-2 |  |  | I-1 (03/00) | [23325-78-2] | \$156 |
| 1102000 | Cephalothin Sodium ( 200 mg ) | 1 |  |  |  | [58-71-9] | \$156 |
| 1102408 | Cephapirin Benzathine ( 100 mg ) | F |  |  |  | [97468-37-6] | \$156 |
| 1102500 | Cephapirin Sodium ( 200 mg ) | I-1 |  |  | I (07/02) | [24356-60-3] | \$156 |
| 1102805 | Cephradine ( 200 mg ) | J |  |  | I (04/00) | [58456-86-3] | \$156 |
| 1103003 | Cetyl Alcohol ( 100 mg ) | 1 |  |  | H (03/99) | [36653-82-4] | \$156 |
| 1103105 | Cetyl Palmitate ( 50 mg ) | FOB241 |  |  |  | [540-10-3] | \$156 |
| 1104006 | Cetylpyridinium Chloride ( 500 mg ) | 1 |  |  | $\begin{array}{\|l\|} \hline \mathrm{H}-1(06 / 01) \\ \mathrm{H}(08 / 99) \\ \hline \end{array}$ | [6004-24-6] | \$156 |
| 1105009 | Powdered Chaste Tree Extract (1.5 g) | F0C406 |  |  |  | [91722-47-3] | \$520 |
| 1106001 | Chlorambucil (125 mg) (FOR U.S. SALE ONLY) | G |  | 3 | F-1 (02/99) | [305-03-3] | \$124 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1107004 | Chloramphenicol (200 mg) | N1C074 |  |  | $\begin{array}{\|l\|} \hline N(10 / 04) \\ M(03 / 00) \\ \hline \end{array}$ | [56-75-7] | \$156 |
| 1107300 | Chloramphenicol Palmitate ( 200 mg ) | G-1 |  |  |  | [530-43-8] | \$156 |
| 1107401 | Chloramphenicol Palmitate Nonpolymorph A ( 200 mg ) | F-1 |  |  |  | [530-43-8] | \$487 |
| 1107503 | Chloramphenicol Palmitate Polymorph A ( 200 mg ) | G |  |  | F (08/99) | [530-43-8] | \$487 |
| 1109000 | Chlordiazepoxide CIV (200 mg) | 10B063 |  |  | H-1 (03/03) | [58-25-3] | \$207 |
| 1110009 | Chlordiazepoxide Hydrochloride CIV (200 mg) | G-4 |  |  |  | [438-41-5] | \$207 |
| 1110020 | Chlordiazepoxide Related Compound A (25 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide) | G |  |  |  | [963-39-3] | \$487 |
| 1111001 | Chlorhexidine ( 200 mg ) | F0C306 |  |  |  | [55-56-1] | \$156 |
| 1111103 | Chlorhexidine Acetate ( 500 mg ) | F0C281 |  |  |  | [56-95-1] | \$156 |
| 1111307 | Chlorhexidine Related Compounds ( 50 mg ) | F0D017 |  |  |  | n/f | \$487 |
| 1112503 | Chlorobutanol ( 200 mg ) | G |  |  | F-3 (12/01) | [6001-64-5] | \$156 |
| 1115545 | Chlorogenic Acid ( 50 mg ) | F0C420 | $0.97 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | [327-97-9] | \$156 |
| 1115556 | beta-Chlorogenin ( $20 \mathrm{mg} \mathrm{)}$ | F |  |  |  | n/f | \$156 |
| 1117008 | Chloroprocaine Hydrochloride (200 mg) | GOB285 |  |  | $\begin{aligned} & \hline \text { F-3 (01/04) } \\ & \text { F-2 (03/99) } \\ & \hline \end{aligned}$ | [3858-89-7] | \$156 |
| 1118000 | Chloroquine Phosphate ( 500 mg ) | 1 |  |  | H (10/99) | [50-63-5] | \$156 |
| 1121005 | Chlorothiazide (200 mg) | H0B161 |  |  | G (04/03) | [58-94-6] | \$156 |
| 1122008 | Chlorotrianisene (1 g) | F |  |  |  | [569-57-3] | \$156 |
| 1122700 | Chloroxylenol (125 mg) | F2C259 |  |  | $\begin{aligned} & \hline \text { F-1 (07/04) } \\ & \text { F (10/99) } \end{aligned}$ | [88-04-0] | \$124 |
| 1122722 | Chloroxylenol Related Compound A (25 mg) (2-chloro-3,5-dimethylphenol) | G0C275 |  |  | F-1 (07/04) | [5538-41-0] | \$487 |
| 1123000 | Chlorpheniramine Maleate ( 125 mg ) | M0B020 |  |  | L-1 (06/03) | [113-92-8] | \$124 |
| 1123102 | Chlorpheniramine Maleate Extended-Release Tablets (Drug Release Calibrator, Single Unit) ( 60 Tablets) | G0B259 |  |  | F (06/03) | [113-92-8] | \$156 |
| 1124003 | Chlorphenoxamine Hydrochloride ( 200 mg ) | F-1 |  |  |  | [562-09-4] | \$156 |
| 1125006 | Chlorpromazine Hydrochloride (200 mg) | J |  |  | I (04/99) | [69-09-0] | \$156 |
| 1126009 | Chlorpropamide (200 mg) | H |  |  |  | [94-20-2] | \$156 |
| 1127001 | Chlorprothixene (200 mg) | F-1 |  |  |  | [113-59-7] | \$156 |
| 1129007 | Chlortetracycline Hydrochloride ( 200 mg ) | K0C185 | 1008 ug/mg (ai) |  | $\begin{aligned} & \hline \mathrm{J}-1(12 / 04) \\ & \mathrm{J}(02 / 02) \\ & \hline \end{aligned}$ | [64-72-2] | \$156 |
| 1130006 | Chlorthalidone (200 mg) | 10C255 |  |  | $\begin{aligned} & \mathrm{H}-1(11 / 04) \\ & \mathrm{H}(07 / 99) \end{aligned}$ | [77-36-1] | \$156 |
| 1119309 | Chlorthalidone Related Compound A ( 25 mg ) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid) | G0C376 |  |  | F-3 (07/04) | n/f | \$487 |
| 1130505 | Chlorzoxazone ( 500 mg ) | 1 |  |  | H (07/01) | [95-25-0] | \$156 |
| 1130527 | Chlorzoxazone Related Compound A (50 mg) (2-Amino-4-chlorophenol) | G-1 |  |  | G (11/00) | [95-85-2] | \$487 |
| 1131009 | Cholecalciferol ( $30 \mathrm{mg} / \mathrm{ampule} ; 5$ ampules) (Vitamin D3) | M0B157 |  |  | $\begin{array}{\|l\|} \hline \text { L (10/03) } \\ \text { K (09/99) } \\ \hline \end{array}$ | [67-97-0] | \$159 |
| 1131803 | Delta-4,6-cholestadienol ( $30 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [14214-69-8] | \$156 |
| 1132001 | Cholesteryl Caprylate ( 200 mg ) | F |  |  |  | [1182-42-9] | \$156 |
| 1133004 | Cholestyramine Resin ( 500 mg ) | 1 |  |  |  | [11041-12-6] | \$124 |
| 1133503 | Cholic Acid (2 g) (AS) | F3B159 |  |  | F-2 (01/03) | [81-25-4] | \$156 |
| 1133536 | Choline Bitartrate (200 mg) | F0C057 |  |  |  | [87-67-2] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1133547 | Choline Chloride ( $200 \mathrm{mg} \mathrm{)}$ | F0C058 |  |  |  | [67-48-1] | \$156 |
| 1133570 | Chondroitin Sulfate Sodium ( 300 mg ) | FOB256 |  |  |  | [39455-18-0] | \$156 |
| 1133638 | Chromium Picolinate ( 100 mg ) | F |  |  |  | [14639-25-9] | \$156 |
| 1134007 | Chymotrypsin ( 300 mg ) | I |  |  | H (06/01) | [9004-07-3] | \$156 |
| 1134030 | Ciclopirox Olamine ( 125 mg ) | H0C207 |  |  | G (05/03) | [41621-49-2] | \$124 |
| 1134051 | Cilastatin Ammonium Salt (100 mg) | G0C334 | $945 \mathrm{ug} / \mathrm{mg}$ (ai) | 2 | $\begin{aligned} & \text { F-1 (05/05) } \\ & \text { F (07/00) } \\ & \hline \end{aligned}$ | n/f | \$156 |
| 1134062 | Cimetidine (200 mg) | 11C081 |  |  | 1 (05/04) | [51481-61-9] | \$156 |
| 1134073 | Cimetidine Hydrochloride ( 200 mg ) | F |  |  |  | [70059-30-2] | \$156 |
| 1134109 | Cinoxacin (200 mg) | F |  |  |  | [28657-80-9] | \$156 |
| 1134313 | Ciprofloxacin (125 mg) | G-1 |  |  | G (05/01) | [85721-33-1] | \$124 |
| 1134324 | Ciprofloxacin Ethylenediamine Analog (25 mg) | J0A030 |  |  | $\begin{aligned} & \hline \mathrm{I}(01 / 03) \\ & \mathrm{H}-1(02 / 99) \\ & \hline \end{aligned}$ | n/f | \$208 |
| 1134335 | Ciprofloxacin Hydrochloride ( 400 mg ) | 10C265 |  |  | $\begin{aligned} & \mathrm{H}(02 / 05) \\ & \mathrm{G}(04 / 00) \\ & \hline \end{aligned}$ | [86393-32-0] | \$156 |
| 1134357 | Cisplatin ( 100 mg ) | H |  |  | $\mathrm{G}(03 / 01)$ | [15663-27-1] | \$156 |
| 1134368 | Citric Acid (200 mg) | F1B092 |  |  | $\begin{aligned} & \text { F-1 (01/04) } \\ & \text { F (07/02) } \\ & \hline \end{aligned}$ | [77-92-9] | \$156 |
| 1134379 | Clarithromycin (75 mg) | F4B183 |  |  | $\begin{aligned} & \hline \text { F-3 }(01 / 04) \\ & \text { F-2 }(09 / 01) \\ & \hline \end{aligned}$ | [81103-11-9] | \$156 |
| 1134380 | Clarithromycin Related Compound A ( 50 mg ) (6,11-di-O-methylerythromycin A) | G |  |  | F (04/01) | n/f | \$208 |
| 1134404 | Clavam-2-carboxylate Potassium (1 Pellet) | H0C089 |  |  | $\begin{aligned} & \hline \text { GOB225 (12/03) } \\ & F(10 / 03) \\ & \hline \end{aligned}$ | n/f | \$487 |
| 1134426 | Clavulanate Lithium ( 200 mg ) | 11C270 | $0.952 \mathrm{mg} / \mathrm{mg}$ (ai) |  | $\begin{aligned} & \text { I (02/05) } \\ & \text { H (09/02) } \end{aligned}$ | n/f | \$156 |
| 1134506 | Clemastine Fumarate (250 mg) | 1 |  |  | H (10/00) | [14976-57-9] | \$156 |
| 1135000 | Clidinium Bromide ( 2 g ) | H0B115 |  | 2 | G (03/05) | [3485-62-9] | \$156 |
| 1135021 | Clidinium Bromide Related Compound A ( 250 mg ) (3-Hydroxy-1-methylquinuclindinium Bromide) | 1 |  |  |  | [76201-95-1] | \$487 |
| 1136002 | Clindamycin Hydrochloride ( 200 mg ) | G4A017 |  |  | $\begin{aligned} & \text { G-3 (07/03) } \\ & \text { G-2 (05/99) } \\ & \hline \end{aligned}$ | [58207-19-5] | \$428 |
| 1137005 | Clindamycin Palmitate Hydrochloride ( 200 mg ) | F-2 |  |  |  | [25507-04-4] | \$428 |
| 1138008 | Clindamycin Phosphate (125 mg) | IOC165 |  |  | $\begin{aligned} & \hline \mathrm{H}-3(04 / 04) \\ & \mathrm{H}-2(07 / 03) \\ & \mathrm{H}-1(02 / 99) \\ & \hline \end{aligned}$ | [24729-96-2] | \$214 |
| 1138201 | Clioquinol ( 500 mg ) | M |  |  | L-1 (01/03) | [130-26-7] | \$156 |
| 1138405 | Clobetasol Propionate ( 200 mg ) | F2C309 | 980 ug/mg (ai) | 2 | $\begin{aligned} & \hline \text { F-1 (03/05) } \\ & \text { F (10/01) } \\ & \hline \end{aligned}$ | [25122-46-7] | \$156 |
| 1138427 | Clobetasol Propionate Related Compound A ( 50 mg ) (9-alpha-fluoro-11-beta-hydroxy-16-beta-methyl-3-oxo-androsta-1,4-diene-17(R)-spiro-2'-[4'-chloro-5'-ethylfuran-3'(2'H)-one]) | F-1 |  |  | F (01/03) | n/f | \$208 |
| 1138507 | Clocortolone Pivalate (200 mg) | G |  |  |  | [34097-16-0] | \$156 |
| 1138904 | Clofazimine ( 200 mg ) | F |  |  |  | [2030-63-9] | \$156 |
| 1139000 | Clofibrate (1 g) | 1 |  |  | H (04/01) | [637-07-0] | \$156 |
| 1140000 | Clomiphene Citrate ( 500 mg ) | H |  |  | G-1 (10/99) | [50-41-9] | \$156 |
| 1140101 | Clomiphene Related Compound A ( 100 mg ) ((E,Z)-2-[4-(1,2-diphenylethenyl)phenoxy]-N,Ndiethylethanamine Hydrochloride) | F1B206 |  |  | F (09/03) | n/f | \$208 |
| 1140247 | Clomipramine Hydrochloride ( 200 mg ) | F0C075 |  |  |  | [17321-77-6] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1140305 | Clonazepam CIV (200 mg) | G1B175 |  |  | $\begin{array}{\|l\|} \hline G(01 / 04) \\ \text { F-2 }(01 / 00) \\ \hline \end{array}$ | [1622-61-3] | \$207 |
| 1140327 | Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril) | G2B110 |  |  | $\begin{aligned} & \text { G-1 (01/04) } \\ & \text { G (02/99) } \\ & \hline \end{aligned}$ | n/f | \$487 |
| 1140338 | Clonazepam Related Compound B ( 25 mg ) (2-Amino-2'-chloro-5-nitrobenzophenone) | H |  |  | G (04/01) | [2011-66-7] | \$487 |
| 1140349 | Clonazepam Related Compound C ( 25 mg ) (2-Bromo-2'-(2-chlorobenzoyl)-4'-nitroacetanilide) | F0C340 |  |  |  | n/f | \$487 |
| 1140393 | Clonidine ( 200 mg ) | F0C401 |  |  |  | [4205-90-7] | \$156 |
| 1140407 | Clonidine Hydrochloride (200 mg) | G |  |  |  | [4205-91-8] | \$156 |
| 1140418 | Clonidine Related Compound A ( 25 mg ) (Acetylclonidine) | F0C373 |  |  |  | [54707-71-0] | \$487 |
| 1140429 | Clonidine Related Compound B ( 25 mg ) ( $2-[(\mathrm{E})-$ 2,6-Dichlorophenylimino]-1-(1-\{2-[(E)-2,6-di-chlorophenylimino]-imidazolidin-1-yl\}-ethyl)-imidazolidine) | F0C403 | $0.99 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | n/f | \$487 |
| 1140509 | Clorazepate Dipotassium CIV (125 mg) | G0B027 |  |  | $\begin{array}{\|l} \hline \text { F-1 (06/03) } \\ \text { F (12/99) } \\ \hline \end{array}$ | [57109-90-7] | \$207 |
| 1140702 | Clorsulon (200 mg) | F1B084 |  |  | F (01/04) | [60200-06-8] | \$156 |
| 1141002 | Clotrimazole (200 mg) | K0C282 |  |  | $\begin{array}{\|l\|} \hline J(02 / 05) \\ I(05 / 99) \\ \hline \end{array}$ | [23593-75-1] | \$124 |
| 1141024 | Clotrimazole Related Compound A ( 25 mg ) ( $(0-$ chlorophenyl)diphenylmethanol) | 1 |  |  | $\begin{aligned} & \hline \text { H }(10 / 01) \\ & \text { G-1 }(02 / 99) \end{aligned}$ | [66774-02-5] | \$487 |
| 1141909 | Cloxacillin Benzathine ( 200 mg ) | F-1 |  |  | F (03/02) | [23736-58-5] | \$156 |
| 1142005 | Cloxacillin Sodium (200 mg) | LOB086 |  |  | K (01/04) | [7081-44-9] | \$156 |
| 1142107 | Clozapine ( 100 mg ) | F0C032 |  |  |  | [5786-21-0] | \$260 |
| 1143008 | Cocaine Hydrochloride CII (250 mg) | 10B074 |  |  | $\begin{array}{\|l\|l} \hline \mathrm{H}-2(01 / 04) \\ \mathrm{H}-1 & (02 / 99) \\ \hline \end{array}$ | [53-21-4] | \$207 |
| 1143802 | Codeine N-Oxide Cl (50 mg) | G0A034 |  |  | F-1 (11/02) | [3688-65-1] | \$207 |
| 1144000 | Codeine Phosphate CII (100 mg) | J0C200 |  |  | $\begin{array}{\|l} \hline \mathrm{I}-1(10 / 04) \\ \mathrm{I}(09 / 02) \\ \mathrm{H}-1(01 / 00) \\ \hline \end{array}$ | [41444-62-6] | \$207 |
| 1145003 | Codeine Sulfate CII (250 mg) | H-2 |  |  | $\mathrm{H}-1$ (01/02) | [6854-40-6] | \$207 |
| 1146006 | Colchicine ( 300 mg ) | J |  |  | I (05/02) | [64-86-8] | \$156 |
| 1146505 | Colestipol Hydrochloride (200 mg) | F-1 |  |  |  | [37296-80-3] | \$156 |
| 1147009 | Colistimethate Sodium ( 200 mg ) | H |  |  |  | [8068-28-8] | \$156 |
| 1148001 | Colistin Sulfate (200 mg) | G-1 |  |  | G (09/99) | [1264-72-8] | \$156 |
| 1148500 | Copovidone ( 100 mg ) | FOC194 |  |  |  | [2586-89-9] | \$156 |
| 1149004 | Corticotropin (5.6 Units/vial; 5 vials) | M |  |  | L (06/99) | [9002-60-2] | \$124 |
| 1150003 | Cortisone Acetate ( 150 mg ) | 1 |  |  |  | [50-04-4] | \$156 |
| 1150353 | Creatinine ( 100 mg ) | F |  |  |  | [60-27-5] | \$156 |
| 1150502 | Cromolyn Sodium ( 500 mg ) | $J$ |  |  | I (06/00) | [15826-37-6] | \$156 |
| 1150706 | Crospovidone ( 200 mg ) | G1C273 |  |  | G (12/04) | [9003-39-8] | \$156 |
| 1151006 | Crotamiton ( 200 mg ) | H-1 |  |  | H (07/00) | [483-63-6] | \$156 |
| 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) | N |  |  | M-3 (08/99) | [68-19-9] | \$156 |
| 1152508 | Cyclacillin (200 mg) | G |  |  |  | [3485-14-1] | \$156 |
| 1152701 | Cyclandelate (200 mg) | F0C384 |  |  |  | [456-59-7] | \$156 |
| 1154004 | Cyclizine Hydrochloride ( 200 mg ) | G |  |  |  | [303-25-3] | \$156 |
| 1154503 | Cyclobenzaprine Hydrochloride ( 200 mg ) | G0A013 |  |  | F-3 (07/03) | [6202-23-9] | \$156 |
| 1154558 | Alpha Cyclodextrin ( 50 mg ) | F-1 |  |  | F (10/00) | [10016-20-3] | \$156 |
| 1154569 | Beta Cyclodextrin (250 mg) | G |  |  | F-1 (12/02) | [7585-39-9] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1154707 | Cyclomethicone 4 (200 mg) | F-2 |  |  | F-1 (06/02) | [69430-24-6] | \$156 |
| 1154809 | Cyclomethicone 5 (125 mg) | F-2 |  |  | F-1 (09/99) | [69430-24-6] | \$124 |
| 1154900 | Cyclomethicone 6 (200 mg) | F2B024 |  |  | F-1 (03/03) | [69430-24-6] | \$156 |
| 1156000 | Cyclopentolate Hydrochloride ( 300 mg ) | 10C424 | $0.999 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{aligned} & \text { H (03/05) } \\ & \text { G (04/00) } \end{aligned}$ | [5870-29-1] | \$156 |
| 1157002 | Cyclophosphamide ( 500 mg ) (FOR U.S. SALE ONLY) | J1B200 |  | 3 | $J$ (02/05) | [6055-19-2] | \$124 |
| 1157501 | 2-Cyclopropylmethylamino-5-chlorobenzophenone ( 50 mg ) | F |  |  |  | n/f | \$487 |
| 1158005 | Cycloserine ( 200 mg ) | G |  |  |  | [68-41-7] | \$156 |
| 1158504 | Cyclosporine ( 50 mg ) | H-1 |  |  | $\begin{aligned} & \hline \text { H (11/02) } \\ & \text { G-2 }(03 / 00) \\ & \hline \end{aligned}$ | [59865-13-3] | \$479 |
| 1158650 | Cyclosporine Resolution Mixture (25 mg) | F |  |  |  | $\begin{aligned} & {[108027-45-8]} \\ & \text { (U) } \end{aligned}$ | \$412 |
| 1159008 | Cyclothiazide (200 mg) | F-1 |  |  |  | [2259-96-3] | \$156 |
| 1161000 | Cyproheptadine Hydrochloride ( 500 mg ) | G |  |  | F-4 (11/02) | [41354-29-4] | \$156 |
| 1161509 | L-Cysteine Hydrochloride ( 200 mg ) | H |  |  | G (05/00) | [7048-04-6] | \$156 |
| 1162002 | Cytarabine ( 250 mg ) | G-2 |  |  | G-1 (07/00) | [147-94-4] | \$156 |
| 1162308 | Dacarbazine ( 125 mg ) | H |  |  | G (01/99) | [4342-03-4] | \$124 |
| 1162320 | Dacarbazine Related Compound A (50 mg) (5-aminoimidazole-4-carboxamide Hydrochloride) | H0C052 |  |  | $\begin{aligned} & \mathrm{G}(03 / 04) \\ & \mathrm{F}(03 / 00) \\ & \hline \end{aligned}$ | [72-40-2] | \$487 |
| 1162330 | Dacarbazine Related Compound B (50 mg) (2azahypoxanthine) | G0C325 |  |  | $\begin{aligned} & \hline \text { F-1 (03/05) } \\ & \text { F (12/01) } \\ & \hline \end{aligned}$ | [63907-29-9] | \$600 |
| 1162400 | Dactinomycin (50 mg) | 1 |  |  |  | [50-76-0] | \$427 |
| 1162501 | Danazol ( 200 mg ) | H |  |  | G (10/00) | [17230-88-5] | \$156 |
| 1164008 | Dapsone (125 mg) | G-3 |  |  | G-2 (08/99) | [80-08-0] | \$124 |
| 1164700 | Daunorubicin Hydrochloride (200 mg) | LOB307 |  |  | $\begin{array}{\|l\|l\|} \hline \mathrm{K}(11 / 03) \\ \mathrm{J}(08 / 00) \\ \hline \end{array}$ | [23541-50-6] | \$479 |
| 1165000 | Decamethonium Bromide ( 250 mg ) | F |  |  |  | [541-22-0] | \$156 |
| 1166003 | Deferoxamine Mesylate ( 500 mg ) | 1 |  |  |  | [138-14-7] | \$156 |
| 1166309 | Dehydroacetic Acid (200 mg) | F |  |  |  | [520-45-6] | \$156 |
| 1166400 | Dehydrocarteolol Hydrochloride ( 100 mg ) | F |  |  |  | n/f | \$487 |
| 1166502 | Dehydrocholic Acid (200 mg) | F-1 |  |  | F (03/04) | [81-23-2] | \$156 |
| 1169001 | Demecarium Bromide ( $250 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [56-94-0] | \$156 |
| 1170000 | Demeclocycline Hydrochloride (200 mg) | H1C036 |  |  | $\begin{aligned} & \text { H (08/04)G-1 } \\ & (08 / 01) \end{aligned}$ | [64-73-3] | \$156 |
| 1171003 | Denatonium Benzoate ( 200 mg ) | IOB129 |  |  | H (09/02) | [86398-53-0] | \$156 |
| 1171706 | Desacetyl Diltiazem Hydrochloride ( 50 mg ) | 1 |  |  | H (08/00) | [23515-45-9] | \$487 |
| 1171900 | Desflurane ( 0.5 mL ) | F0C187 |  |  |  | [57041-67-5] | \$156 |
| 1171910 | Desflurane Related Compound A ( 0.1 mL ) (bis-(1,2,2,2-tetrafluoroethyl) ether) | F0C031 |  |  |  | n/f | \$487 |
| 1172006 | Desipramine Hydrochloride ( 125 mg ) | H-1 |  |  | H (10/99) | [58-28-6] | \$124 |
| 1173009 | Deslanoside ( 100 mg ) | H-1 |  |  |  | [17598-65-1] | \$156 |
| 1173235 | Desogestrel ( 50 mg ) | G0C390 |  |  | FOB282 (11/04) | [54024-22-5] | \$156 |
| 1173246 | Desogestrel Related Compound A ( 15 mg ) (13-Ethyl-11-methylene-18, 19-dinor-5alpha, 17al-pha-preg-3-en-20-yl-17-ol, desogestrel delta-3 isomer) | F0B279 |  |  |  | n/f | \$487 |
| 1173257 | Desogestrel Related Compound B (15 mg) (3-Hydroxy-desogestrel) | F0B284 |  |  |  | n/f | \$487 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1173268 | Desogestrel Related Compound C (25 mg) (3-Keto-desogestrel) | FOB281 |  |  |  | [54048-10-1] | \$487 |
| 1173508 | Desoximetasone ( 200 mg ) | H0B036 |  |  | G (01/04) | [382-67-2] | \$156 |
| 1174001 | Desoxycorticosterone Acetate (200 mg) | J0C014 |  |  | $\begin{aligned} & 1(01 / 04) \\ & H(05 / 00) \end{aligned}$ | [56-47-3] | \$156 |
| 1175004 | Desoxycorticosterone Pivalate ( 125 mg ) | H0C276 |  |  | G (01/04) | [808-48-0] | \$124 |
| 1176007 | Dexamethasone ( 125 mg ) | J |  |  |  | [50-02-2] | \$124 |
| 1176506 | Dexamethasone Acetate ( 200 mg ) | G |  |  | F-1 (06/99) | [55812-90-3] | \$156 |
| 1177000 | Dexamethasone Phosphate ( 200 mg ) | J1B070 |  |  | $\begin{aligned} & \hline J(08 / 03) \\ & I(03 / 00) \\ & \hline \end{aligned}$ | [312-93-6] | \$156 |
| 1178002 | Dexbrompheniramine Maleate (200 mg) | J |  |  | 1 (03/03) | [2391-03-9] | \$156 |
| 1179005 | Dexchlorpheniramine Maleate ( 500 mg ) | G1A025 |  |  | G (12/02) | [2438-32-6] | \$156 |
| 1179504 | Dexpanthenol ( 500 mg ) | J0C293 |  |  | $\begin{aligned} & \text { I (08/04) } \\ & \mathrm{H}(02 / 02) \\ & \hline \end{aligned}$ | [81-13-0] | \$160 |
| 1179708 | Dextran 40 ( 50 mg ) | F0C247 |  |  |  | [9004-54-0] | \$156 |
| 1179741 | Dextran 70 ( 50 mg ) | F0C260 |  |  |  | [9004-54-0] | \$156 |
| 1179854 | Dextran 4 Calibration (100 mg) | FOC002 |  |  |  | [9004-54-0] | \$156 |
| 1179865 | Dextran 10 Calibration ( 100 mg ) | F0C010 |  |  |  | [9004-54-0] | \$156 |
| 1179876 | Dextran 40 Calibration ( 100 mg ) | F0C011 |  |  |  | [9004-54-0] | \$156 |
| 1179720 | Dextran 40 System Suitability ( 200 mg ) | FOB181 |  |  |  | [9004-54-0] | \$156 |
| 1179887 | Dextran 70 Calibration ( 100 mg ) | F0C013 |  |  |  | [9004-54-0] | \$156 |
| 1179763 | Dextran 70 System Suitability ( 200 mg ) | FOB182 |  |  |  | [9004-54-0] | \$156 |
| 1179898 | Dextran 250 Calibration ( 100 mg ) | F0C039 |  |  |  | [9004-54-0] | \$156 |
| 1179800 | Dextran Vo Marker ( 100 mg ) | FOB242 |  |  |  | [9004-54-0] | \$156 |
| 1180004 | Dextroamphetamine Sulfate CII (500 mg) | I0C311 | $1.000 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{aligned} & \mathrm{H}(05 / 05) \\ & \mathrm{G}(08 / 03) \\ & \mathrm{F}-6(12 / 99) \\ & \hline \end{aligned}$ | [51-63-8] | \$216 |
| 1180503 | Dextromethorphan (2 g) | H |  |  | G (06/00) | [125-71-3] | \$487 |
| 1181007 | Dextromethorphan Hydrobromide ( 500 mg ) | JOB167 |  |  | 1 (07/03) | [6700-34-1] | \$156 |
| 1181302 | Dextrose ( 500 mg ) | J-1 |  |  | $\begin{aligned} & \hline J(11 / 02) \\ & I(08 / 99) \\ & \hline \end{aligned}$ | [50-99-7] | \$124 |
| 1181506 | Diacetylated Monoglycerides ( 200 mg ) | G |  |  |  | [68990-54-5] | \$156 |
| 1182000 | Diacetylfluorescein (200 mg) | H |  |  | G (01/02) | [596-09-8] | \$156 |
| 1183002 | Diacetylmorphine Hydrochloride $\mathbf{C l}(25 \mathrm{mg})$ (AS) (Heroin Hydrochloride) | J |  |  | I-1 (10/99) | [1502-95-0] | \$207 |
| 1184005 | Diatrizoic Acid ( 100 mg ) | G |  |  |  | [50978-11-5] | \$156 |
| 1184027 | Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid) | I |  |  | H (02/00) | [1713-07-1] | \$487 |
| 1185008 | Diazepam CIV (100 mg) | 1 |  |  | H (12/01) | [439-14-5] | \$207 |
| 1185020 | Diazepam Related Compound A ( 25 mg ) (2-Methyl-amino-5-chlorobenzophenone) | 1 |  |  | $\begin{aligned} & \hline \mathrm{H}-1(11 / 02) \\ & \mathrm{H}(04 / 00) \\ & \hline \end{aligned}$ | [1022-13-5] | \$487 |
| 1023403 | Diazepam Related Compound B ( 25 mg ) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril) | 11C102 |  |  | $\begin{aligned} & \text { I (12/04) } \\ & \text { H }(04 / 01) \end{aligned}$ | [5220-02-0] | \$487 |
| 1186000 | Diazoxide (200 mg) | G1C017 |  |  | G (12/03) | [364-98-7] | \$156 |
| 1187003 | Dibucaine Hydrochloride (200 mg) | I |  |  | H-2 (01/03) | [61-12-1] | \$156 |
| 1187207 | Dichloralphenazone CIV (200 mg) | F0B010 |  |  |  | [480-30-8] | \$207 |
| 1188006 | Dichlorphenamide ( 200 mg ) | G-1 |  |  |  | [120-97-8] | \$156 |
| 1188800 | Diclofenac Sodium (200 mg) | H0B150 |  |  | $\begin{aligned} & \text { G-1 (03/04) } \\ & \text { G (05/01) } \\ & \hline \end{aligned}$ | [15307-79-6] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1188811 | Diclofenac Related Compound A (100 mg) (N-(2,6-dichlorophenyl)indolin-2-one) | H |  |  | G (05/02) | [15362-40-0] | \$490 |
| 1189009 | Dicloxacillin Sodium ( 500 mg ) | JOC182 |  |  | $\begin{aligned} & \text { IOB142 (09/04) } \\ & \text { H (05/03) } \end{aligned}$ | [13412-64-1] | \$156 |
| 1190008 | Dicumarol (200 mg) | G |  |  |  | [66-76-2] | \$156 |
| 1191000 | Dicyclomine Hydrochloride ( 125 mg ) | H |  |  | G (03/99) | [67-92-5] | \$124 |
| 1192003 | Dienestrol ( 125 mg ) | 1 |  |  |  | [84-17-3] | \$124 |
| 1193006 | Diethylcarbamazine Citrate ( 200 mg ) | G-1 |  |  |  | [1642-54-2] | \$156 |
| 1193301 | Diethylene Glycol Monoethyl Ether ( $0.5 \mathrm{~mL} /$ ampule) | F0B095 |  |  |  | [111-90-0] | \$156 |
| 1193505 | Diethyl Phthalate (200 mg) | G |  |  | F-1 (03/00) | [84-66-2] | \$156 |
| 1194009 | Diethylpropion Hydrochloride CIV (200 mg) | H |  |  |  | [134-80-5] | \$207 |
| 1195001 | Diethylstilbestrol ( 200 mg ) | K5B291 |  |  | K-4 (05/04) | [56-53-1] | \$156 |
| 1197007 | Diethyltoluamide ( 3 g ) | H |  |  |  | [134-62-3] | \$124 |
| 1197302 | Diflorasone Diacetate (200 mg) | G |  |  | F-1 (03/00) | [33564-31-7] | \$156 |
| 1197506 | Diflunisal ( 200 mg ) | G |  |  |  | [22494-42-4] | \$156 |
| 1198000 | Digitalis (3 g) | F |  |  |  | [8031-42-3] | \$156 |
| 1199002 | Digitoxin (200 mg) | M |  |  |  | [71-63-6] | \$156 |
| 1200000 | Digoxin (250 mg) | O0B096 |  |  | N-1 (04/03) | [20830-75-5] | \$156 |
| 1200600 | Dihydrocapsaicin (25 mg) | G0C071 |  |  | $\begin{array}{\|l} \hline \text { F-1 (12/03) } \\ \text { F (01/00) } \\ \hline \end{array}$ | [19408-84-5] | \$156 |
| 1200804 | Dihydrocodeine Bitartrate CII (200 mg) | H |  |  | G (03/01) | [5965-13-9] | \$207 |
| 1201002 | 17alpha-Dihydroequilin ( 50 mg ) | 10C277 |  |  | H (07/04) | [6639-99-2] | \$208 |
| 1202005 | Dihydroergotamine Mesylate ( 250 mg ) (List Chemical) | JOB085 |  |  | I (03/03) | [6190-39-2] | \$156 |
| 1203008 | Dihydrostreptomycin Sulfate ( 200 mg ) | J |  |  |  | [5490-27-7] | \$156 |
| 1204000 | Dihydrotachysterol ( $30 \mathrm{mg} / \mathrm{ampule}$; 4 ampules) | 1 |  |  |  | [67-96-9] | \$156 |
| 1204102 | Dihydroxyacetone (250 mg) | F |  |  |  | [96-26-4] | \$156 |
| 1204805 | Diloxanide Furoate ( 200 mg ) | F0C026 |  |  |  | [3736-81-0] | \$156 |
| 1205003 | Diltiazem Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  |  |  | [33286-22-5] | \$156 |
| 1206006 | Dimenhydrinate ( 100 mg ) | JOB055 |  |  | I (06/03) | [523-87-5] | \$156 |
| 1208001 | Dimethisoquin Hydrochloride (2 g) | G |  |  |  | [2773-92-4] | \$156 |
| 1210105 | N -(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8germaspiro [4:5]decane-1,3-dione (AS) | F |  |  |  | [41992-23-8] | \$156 |
| 1211006 | Dimethyl Sulfoxide (3 g) | G0C198 |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-3 }(07 / 04) \\ \text { F-2 } & (05 / 02) \\ \hline \end{array}$ | [67-68-5] | \$208 |
| 1213001 | Dinoprost Tromethamine ( 50 mg ) | F |  |  |  | [38562-01-5] | \$1,525 |
| 1213103 | Dinoprostone ( 50 mg ) | F0C030 |  |  |  | [363-24-6] | \$1,525 |
| 1214004 | Dioxybenzone ( 150 mg ) | F1B277 |  |  | F (10/03) | [131-53-3] | \$156 |
| 1216000 | Diphemanil Methylsulfate ( 500 mg ) | H |  |  |  | [62-97-5] | \$156 |
| 1217909 | Diphenhydramine Citrate ( 125 mg ) | H0B128 |  |  | G (04/03) | [88637-37-0] | \$124 |
| 1218005 | Diphenhydramine Hydrochloride ( 200 mg ) | JOB013 |  |  | I (07/03) | [147-24-0] | \$156 |
| 1219008 | Diphenoxylate Hydrochloride CII (200 mg) | 1 |  |  | H (03/02) | [3810-80-8] | \$207 |
| 1220302 | Dipivefrin Hydrochloride (200 mg) | 1 |  |  | H (06/99) | [64019-93-8] | \$156 |
| 1220506 | Dipyridamole (200 mg) | H |  |  | G-1 (01/99) | [58-32-2] | \$156 |
| 1220700 | Dirithromycin (200 mg) | F |  |  |  | [62013-04-1] | \$156 |
| 1221000 | Disodium Guanylate ( 300 mg ) (FCC) | F-1 |  |  |  | [5550-12-9] | \$156 |
| 1222002 | Disodium Inosinate ( 500 mg ) (FCC) | F |  |  |  | [4691-65-0] | \$156 |
| 1222501 | Disopyramide Phosphate ( 200 mg ) | H-1 |  |  | H (03/02) | [22059-60-5] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1223005 | 2,4-Disulfamyl-5-trifluoromethylaniline ( 125 mg ) | G |  |  |  | [654-62-6] | \$487 |
| 1224008 | Disulfiram ( 200 mg ) | F-3 |  |  | F-2 (07/02) | [97-77-8] | \$156 |
| 1224507 | Dobutamine Hydrochloride ( 600 mg ) | H-1 |  |  | H (01/00) | [49745-95-1] | \$156 |
| 1224700 | Docusate Calcium ( 500 mg ) | H0B044 |  |  | G-1 (07/02) | [128-49-4] | \$156 |
| 1224802 | Docusate Sodium ( 500 mg ) | $J$ |  |  | I-1 (05/02) | [577-11-7] | \$156 |
| 1224904 | Docusate Potassium ( 100 mg ) | F-1 |  |  | F (11/99) | [7491-09-0] | \$156 |
| 1224959 | Dolasetron Mesylate (200 mg) | F0C319 |  |  |  | [115956-13-3] | \$156 |
| 1224960 | Dolasetron Mesylate Related Compound A ( 25 mg ) (Hexahydro-8-hydroxy-2,6-methano2 H -quinolizin-3(4H)-one hydrochloride) | F0C321 |  |  |  | n/f | \$487 |
| 1225204 | Dopamine Hydrochloride ( 200 mg ) | G |  |  | F-5 (05/02) | [62-31-7] | \$156 |
| 1225281 | Dorzolamide Hydrochloride ( 500 mg ) | F0C040 |  |  |  | [130693-82-2] | \$156 |
| 1225292 | Dorzolamide Hydrochloride Related Compound A (20 mg) ((4R,6R)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide, monohydrochloride) | F0C068 |  |  |  | n/f | \$487 |
| 1225000 | Doxapram Hydrochloride (200 mg) | F4C053 |  |  | F-3 (07/04) | [7081-53-0] | \$156 |
| 1225419 | Doxazosin Mesylate ( 200 mg ) | F0C079 |  |  |  | [77883-43-3] | \$156 |
| 1225500 | Doxepin Hydrochloride ( 500 mg ) | 1 |  |  |  | [1229-29-4] | \$156 |
| 1225703 | Doxorubicin Hydrochloride ( 50 mg ) | K |  |  | $\mathrm{J}(06 / 02)$ | [25316-40-9] | \$479 |
| 1226003 | Doxycycline Hyclate ( 200 mg ) | 1 |  |  | H (01/00) | [24390-14-5] | \$156 |
| 1227006 | Doxylamine Succinate ( 300 mg ) | IOB266 |  |  | H (01/04) | [562-10-7] | \$156 |
| 1229001 | Droperidol ( 250 mg ) | 10C029 |  |  | $\begin{aligned} & \hline \text { H-1 (01/05) } \\ & \text { H (04/99) } \\ & \hline \end{aligned}$ | [548-73-2] | \$156 |
| 1230000 | Dyclonine Hydrochloride (200 mg) | G |  |  |  | [536-43-6] | \$156 |
| 1231003 | Dydrogesterone (200 mg) | IOB114 |  |  | H (01/04) | [152-62-5] | \$156 |
| 1231502 | Dyphylline ( 200 mg ) | G-2 |  |  | G-1 (11/02) | [479-18-5] | \$156 |
| 1231728 | Powdered Echinacea Purpurea Extract (1 g) | F0D018 |  |  |  | [90028-20-9] | \$520 |
| 1231706 | Powdered Echinacea Angustifolia Extract (1 g) | F0D019 |  |  |  | [84696-11-7] | \$520 |
| 1231808 | Econazole Nitrate ( 200 mg ) | G |  |  |  | [68797-31-9] | \$156 |
| 1232006 | Edetate Calcium Disodium ( 200 mg ) | H0B272 |  |  | $\begin{aligned} & \text { G-3 (11/04) } \\ & \text { G-2 }(11 / 99) \\ & \hline \end{aligned}$ | [23411-34-9] | \$156 |
| 1233009 | Edetate Disodium (200 mg) | H |  |  | G-2 (04/02) | [6381-92-6] | \$156 |
| 1233508 | Edetic Acid ( 200 mg ) | F-1 |  |  |  | [60-00-4] | \$156 |
| 1234001 | Edrophonium Chloride ( 200 mg ) | H |  |  | G (08/99) | [116-38-1] | \$156 |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 |  |  |  | [84696-12-5] | \$520 |
| 1234806 | Emedastine Difumarate ( 100 mg ) | F0C059 |  |  |  | [87233-62-3] | \$156 |
| 1235004 | Emetine Hydrochloride ( 300 mg ) | H0B201 |  |  | G (05/03) | [316-42-7] | \$156 |
| 1235274 | Enalaprilat ( 300 mg ) | J0C268 |  |  | $\begin{array}{\|l\|} \hline \text { I (11/04) } \\ \text { H (03/01) } \\ \text { G (08/99) } \\ \hline \end{array}$ | [84680-54-6] | \$124 |
| 1235300 | Enalapril Maleate ( 200 mg ) | $J$ |  |  | I (06/01) | [76095-16-4] | \$156 |
| 1235503 | Endotoxin (10,000 USP Endotoxin Units) | G2B274 |  |  | $\begin{aligned} & \text { G-1 (12/03) } \\ & \text { G (06/99) } \\ & \hline \end{aligned}$ | n/f | \$156 |
| 1235809 | Enflurane (1 mL) | G-1 |  |  | G (02/01) | [13838-16-9] | \$156 |
| 1236007 | Ephedrine Sulfate (200 mg) (List Chemical) | H-2 |  |  | H-1 (11/02) | [134-72-5] | \$156 |
| 1236506 | 4-Epianhydrotetracycline Hydrochloride ( 50 mg ) | J0C041 |  |  | $\begin{array}{\|l\|} \hline \text { I-1 (12/03) } \\ \text { I (06/00) } \\ \hline \end{array}$ | [4465-65-0] | \$487 |
| 1236801 | Epilactose ( 200 mg ) | G |  |  | F-1 (06/00) | [103302-12-1] | \$487 |
| 1237000 | Epinephrine Bitartrate (200 mg) | 0 |  |  |  | [51-42-3] | \$156 |
| 1237509 | Epitetracycline Hydrochloride (200 mg) | F |  |  |  | [23313-80-6] | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1238002 | Equilin ( 25 mg ) | 11B290 |  |  | $\begin{array}{\|l\|} \hline \text { I (11/04) } \\ \text { H-1 (05/00) } \\ \hline \end{array}$ | [474-86-2] | \$208 |
| 1239005 | Ergocalciferol ( $30 \mathrm{mg} /$ ampule; 5 ampules) (Vitamin D2) | P0B275 |  |  | $\begin{aligned} & \hline \mathrm{O}(02 / 04) \\ & \mathrm{N}(12 / 99) \end{aligned}$ | [50-14-6] | \$168 |
| 1239504 | Ergoloid Mesylates ( 300 mg ) | 1 |  |  | H-1 (01/00) | [8067-24-1] | \$156 |
| 1240004 | Ergonovine Maleate (100 mg) (List Chemical) | N |  |  | M-1 (07/02) | [129-51-1] | \$156 |
| 1241007 | Ergosterol ( 50 mg ) | H |  |  |  | [57-87-4] | \$156 |
| 1241506 | Ergotamine Tartrate (150 mg) (List Chemical) | IOB174 |  |  | H (01/04) | [379-79-3] | \$156 |
| 1241550 | Ergotaminine ( 100 mg ) (List Chemical) | G0B177 |  |  | F-1 (06/04) | [639-81-6] | \$156 |
| 1242000 | Erythromycin ( 250 mg ) | M |  |  | L (08/99) | [114-07-8] | \$156 |
| 1242010 | Erythromycin B (150 mg) | G1C080 |  |  | $\begin{array}{\|l\|l} \hline \text { G (11/04) } \\ \text { F-1 (09/01) } \\ \text { F (05/01) } \\ \hline \end{array}$ | [527-75-3] | \$156 |
| 1242021 | Erythromycin C (50 mg) | F-3 |  |  | $\begin{array}{\|l\|l} \hline \text { F-2 (01/03) } \\ \text { F-1 (02/02) } \\ \text { F (02/99) } \\ \hline \end{array}$ | n/f | \$156 |
| 1242032 | Erythromycin Related Compound $\mathrm{N}(50 \mathrm{mg})(\mathrm{N}-$ Demethylerythromycin A) | F2A023 |  |  | $\begin{array}{\|l} \hline \text { F-1 (06/04) } \\ \text { F (09/99) } \\ \hline \end{array}$ | n/f | \$156 |
| 1243002 | Erythromycin Estolate (200 mg) | H |  |  | G (01/03) | [3521-62-8] | \$156 |
| 1245008 | Erythromycin Ethylsuccinate ( 200 mg ) | H |  |  | G-1 (06/01) | [1264-62-6] | \$156 |
| 1246000 | Erythromycin Gluceptate ( 200 mg ) | H |  |  | G (07/03) | [23067-13-2] | \$156 |
| 1247003 | Erythromycin Lactobionate ( $200 \mathrm{mg} \mathrm{)}$ | H-1 |  |  | H (01/02) | [3847-29-8] | \$156 |
| 1248006 | Erythromycin Stearate ( $200 \mathrm{mg} \mathrm{)}$ | H0B187 |  |  | G-1 (05/03) | [643-22-1] | \$156 |
| 1249009 | Erythrosine Sodium ( 100 mg ) | F |  |  |  | [49746-10-3] | \$156 |
| 1250008 | Estradiol ( 500 mg ) | K1B007 |  |  | K (04/03) | [50-28-2] | \$156 |
| 1251000 | Estradiol Benzoate ( 250 mg ) (AS) | G-1 |  |  |  | [50-50-0] | \$156 |
| 1252003 | Estradiol Cypionate ( 200 mg ) | G-1 |  |  | G (02/00) | [313-06-4] | \$156 |
| 1254009 | Estradiol Valerate ( 100 mg ) | L |  |  | K (05/02) | [979-32-8] | \$156 |
| 1254508 | Estriol ( 100 mg ) | J |  |  | 1-1 (06/01) | [50-27-1] | \$156 |
| 1255001 | Estrone ( 200 mg ) | K1B099 |  |  | $\begin{array}{\|l\|} \hline \mathrm{K}(07 / 03) \\ \mathrm{J}-1(07 / 00) \\ \hline \end{array}$ | [53-16-7] | \$156 |
| 1255500 | Estropipate ( 500 mg ) | J0B262 |  |  | $\begin{array}{\|l\|} \hline I(12 / 03) \\ H(09 / 01) \\ \hline \end{array}$ | [7280-37-7] | \$156 |
| 1256004 | Ethacrynic Acid (200 mg) | F |  |  |  | [58-54-8] | \$156 |
| 1257007 | Ethambutol Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  | G (08/02) | [1070-11-7] | \$156 |
| 1258305 | Ethchlorvynol CIV ( 0.7 ml ) | F0B011 |  |  |  | [113-18-8] | \$207 |
| 1260001 | Ethinyl Estradiol ( 150 mg ) | Q0C162 |  |  | $\begin{array}{\|l\|} \hline \text { P1B193 (11/04) } \\ \text { P0B052 (01/04) } \\ \text { P (03/03) } \\ \text { O (08/99) } \\ \hline \end{array}$ | [57-63-6] | \$156 |
| 1260012 | Ethinyl Estradiol Related Compound A (20 mg) (6-Keto-ethinyl estradiol) | F0B252 |  |  |  | n/f | \$487 |
| 1261004 | Ethionamide ( $200 \mathrm{mg} \mathrm{)}$ | H0B148 |  |  | G (03/03) | [536-33-4] | \$156 |
| 1262801 | Ethopabate ( 125 mg ) | F |  |  |  | [59-06-3] | \$156 |
| 1262823 | Ethopabate Related Compound A ( 25 mg ) (Methyl-4-acetamido-2-hydroxybenzoate) | F |  |  |  | n/f | \$487 |
| 1263000 | Ethopropazine Hydrochloride ( 300 mg ) | G |  |  |  | [1094-08-2] | \$156 |
| 1264002 | Ethosuximide ( 125 mg ) | H |  |  | $\begin{array}{ll} \mathrm{G}-2 & (11 / 01) \\ \mathrm{G}-1 & (05 / 99) \\ \hline \end{array}$ | [77-67-8] | \$124 |
| 1264501 | Ethotoin (200 mg) | F |  |  |  | [86-35-1] | \$156 |
| 1265005 | Ethoxzolamide (200 mg) | F |  |  |  | [452-35-7] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1265504 | Ethylcellulose ( 1 g ) | H-1 |  |  | H (06/99) | [9004-57-3] | \$156 |
| 1266008 | Ethyl Maltol (1 g) (FCC) | H |  |  |  | [4940-11-8] | \$156 |
| 1266507 | Ethylnorepinephrine Hydrochloride ( 200 mg ) | F |  |  |  | [3198-07-0] | \$156 |
| 1267000 | Ethylparaben ( 200 mg ) | IOA016 |  |  | H (01/04) | [120-47-8] | \$156 |
| 1267500 | Ethyl Vanillin (200 mg) | F2B134 |  |  | F-1 (04/04) | [121-32-4] | \$156 |
| 1268003 | Ethynodiol Diacetate ( 200 mg ) | 10A033 |  |  | $\begin{aligned} & \mathrm{H}-1(01 / 03) \\ & \mathrm{H}(04 / 01) \end{aligned}$ | [297-76-7] | \$156 |
| 1268502 | Etidronate Disodium ( 200 mg ) | G |  |  | F-2 (02/03) | [7414-83-7] | \$156 |
| 1268604 | Etidronic Acid Monohydrate (1 g) | G |  |  | F-1 (05/99) | [2809-21-4] | \$156 |
| 1268706 | Etodolac ( 400 mg ) | G |  |  | F (10/01) | [41340-25-4] | \$156 |
| 1268728 | Etodolac Related Compound A (25 mg) ((+/-)-8-ethyl-1-methyl-1,3,4,9-tetrahydropyrano [3,4-b]-indole-1-acetic acid) | F-1 |  |  | F (05/02) | [109518-50-5] | \$208 |
| 1268808 | Etoposide ( $300 \mathrm{mg} \mathrm{)}$ | H0C315 |  |  | G (11/04) | [33419-42-0] | \$124 |
| 1268852 | Etoposide Resolution Mixture ( 30 mg ) | F0B209 |  |  |  | [33419-42-0] | \$208 |
| 1269200 | Famotidine ( 125 mg ) | H-1 |  |  | $\begin{aligned} & \mathrm{H}(11 / 02) \\ & \mathrm{G}(03 / 99) \end{aligned}$ | [76824-35-6] | \$124 |
| 1269389 | Felodipine (200 mg) | G0D065 | $0.999 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | $\begin{aligned} & \text { F-1 (04/05) } \\ & F(09 / 02) \\ & \hline \end{aligned}$ | [72509-76-3] | \$156 |
| 1269390 | Felodipine Related Compound A ( 100 mg ) (ethyl methyl 4-(2,3-dichlorophenyl)-2,6-di-methylpyridine-3,5-dicarboxylate) | F0B207 |  |  |  | [96302-71-7] | \$487 |
| 1269403 | Fenbendazole ( 100 mg ) | F |  |  |  | [43210-67-9] | \$487 |
| 1269414 | Fenbendazole Related Compound A ( 30 mg ) (Methyl (1H-benzimidazole-2-yl)carbamate) | F0D009 | $0.99 \mathrm{mg} / \mathrm{mg}$ (ai) | 1 |  | [10605-21-7] | \$487 |
| 1269425 | Fenbendazole Related Compound B ( 30 mg ) (Methyl [5(6)-chlorobenzimidazole-2-yl]carbamate) | F0D008 | $0.99 \mathrm{mg} / \mathrm{mg}$ (ai) | 1 |  | n/f | \$487 |
| 1269458 | Fenoldopam Mesylate ( 200 mg ) | F0C125 |  |  |  | [67227-57-0] | \$156 |
| 1269469 | Fenoldopam Related Compound A (20 mg) (1-Methyl-3-benzazapine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate) | FOC124 |  |  |  | n/f | \$487 |
| 1269470 | Fenoldopam Related Compound B ( 20 mg ) (1H-3-Benzazapine-7,8-diol, 2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate) | F0C126 |  |  |  | n/f | \$487 |
| 1269505 | Fenoprofen Calcium ( 500 mg ) | G-1 |  |  |  | [53746-45-5] | \$156 |
| 1269550 | Fenoprofen Sodium ( 500 mg ) | G |  |  | F-1 (05/02) | [66424-46-2] | \$156 |
| 1270005 | Fentanyl Citrate CII (100 mg) | K0C264 |  |  | $\begin{aligned} & \hline \text { J2B227 (11/04) } \\ & \mathrm{J}-1(09 / 03) \\ & \mathrm{J}(05 / 02) \\ & \mathrm{I}(06 / 00) \end{aligned}$ | [990-73-8] | \$207 |
| 1270402 | Finasteride (200 mg) | F |  |  |  | [98319-26-7] | \$156 |
| 1270800 | Flecainide Acetate (200 mg) | F2A022 |  |  | $\begin{aligned} & \text { F-1 (02/05) } \\ & \text { F (06/03) } \\ & \hline \end{aligned}$ | [54143-56-5] | \$156 |
| 1270821 | Flecainide Related Compound A (75 mg) (3-[2,5-bis(2,2,2-trifluoroethoxy)phenyl]-1,5,6,7,8,8a-hexahydroimidazo-[1,5a]pyridine Hydrochloride) | F |  |  |  | n/f | \$487 |
| 1271008 | Floxuridine ( 250 mg ) | F-2 |  |  | F-1 (08/01) | [50-91-9] | \$156 |
| 1272000 | Flucytosine ( 200 mg ) | F |  |  |  | [2022-85-7] | \$156 |
| 1272204 | Fludarabine Phosphate ( $300 \mathrm{mg} \mathrm{)}$ | F0C374 |  |  |  | [75607-67-9] | \$156 |
| 1273003 | Fludrocortisone Acetate ( $250 \mathrm{mg} \mathrm{)}$ | H |  |  | G (08/01) | [514-36-3] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1273808 | Flumazenil ( $200 \mathrm{mg} \mathrm{)}$ | F0C305 |  |  |  | [78755-81-4] | \$780 |
| 1274006 | Flumethasone Pivalate ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  |  | H (01/02) | [2002-29-1] | \$156 |
| 1274505 | Flunisolide ( 200 mg ) | 1 |  |  | H (01/01) | [77326-96-6] | \$156 |
| 1274607 | Flunixin Meglumine ( 300 mg ) | G |  |  | $\begin{aligned} & \hline \text { F-1 (04/02) } \\ & \text { F (09/99) } \\ & \hline \end{aligned}$ | [42461-84-7] | \$156 |
| 1275009 | Fluocinolone Acetonide ( 100 mg ) | J |  |  | I (11/99) | [67-73-2] | \$156 |
| 1276001 | Fluocinonide ( 100 mg ) | 1 |  |  |  | [356-12-7] | \$156 |
| 1277004 | Fluorescein (200 mg) | G0B171 |  |  | F-1 (02/03) | [2321-07-5] | \$156 |
| 1277252 | Fluoride Dentifrice: Sodium Fluoride/Silica (4.5 oz) | J0C294 |  |  | $\begin{aligned} & \mathrm{I}(08 / 04) \\ & \mathrm{H}(04 / 99) \\ & \hline \end{aligned}$ | n/f | \$458 |
| 1277274 | Fluoride Dentifrice: Sodium Fluoride/Sodium Bicarbonate Powder (4 oz) | F |  |  |  | n/f | \$487 |
| 1277300 | Fluoride Dentifrice: Sodium Monofluoropho-sphate-Calcium Carbonate (4.6 oz) | G |  |  |  | n/f | \$487 |
| 1277354 | Fluoride Dentifrice: Sodium Monofluorophosphate/Dicalcium Phosphate (4.6 oz) | G |  |  |  | n/f | \$487 |
| 1277401 | Fluoride Dentifrice: Sodium Monofluorophosphate ( 1000 ppm )/Silica ( 5.25 oz ) | G-1 |  |  | G (08/99) | n/f | \$487 |
| 1277423 | Fluoride Dentifrice: Sodium Monofluorophosphate ( 1500 ppm )/Silica ( 5.25 oz ) | F-1 |  |  | F (07/99) | n/f | \$487 |
| 1277456 | Fluoride Dentifrice: Stannous Fluoride-Silica (4 oz) | H0B105 |  |  | G (11/02) | n/f | \$487 |
| 1278007 | Fluorometholone ( 200 mg ) | IOB184 |  |  | H-1 (11/02) | [426-13-1] | \$156 |
| 1278109 | Fluorometholone Acetate ( 200 mg ) | F |  |  |  | [3801-06-7] | \$156 |
| 1278302 | Fluoroquinolonic Acid (50 mg) | H0C140 |  |  | $\begin{array}{\|l\|} \hline G(01 / 05) \\ \text { F-1 }(12 / 99) \\ \hline \end{array}$ | [86393-33-1] | \$487 |
| 1279000 | Fluorouracil (250 mg) | H-1 |  |  | H (01/02) | [51-21-8] | \$156 |
| 1279804 | Fluoxetine Hydrochloride ( 200 mg ) | F2C132 |  |  | $\begin{array}{\|l\|l} \hline \text { F-1 (02/05) } \\ \text { F (11/99) } \\ \hline \end{array}$ | [59333-67-4] | \$156 |
| 1279815 | Fluoxetine Related Compound A ( 15 mg ) ( N -methyl-3-phenyl-3-[(alpha,alpha,alpha-(trifluoro-m-tolyl)oxy]propylamine Hydrochloride) | H0C131 |  |  | $\begin{array}{\|l\|} \hline \text { G (06/04) } \\ \text { F-1 (05/01) } \\ F(06 / 00) \\ \hline \end{array}$ | n/f | \$487 |
| 1279826 | Fluoxetine Related Compound B ( 5 mL of a 0.01 N HCl solution, approx. $2 \mathrm{mg} / \mathrm{mL}$ ) ( N -methyl-3-phenylpropylamine) | F3C085 |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 (06/04) } \\ \text { F-1 (09/02) } \\ \text { F (09/00) } \\ \hline \end{array}$ | [23580-89-4] | \$156 |
| 1279837 | Fluoxetine Related Compound C ( 15 mg ) ( N -Methyl-N-[3-phenyl-3-(4-trifluoromethyl-phe-noxy)-propyl]-succinamic acid) | F0C352 |  |  |  | n/f | \$487 |
| 1280009 | Fluoxymesterone CIII (200 mg) | G-2 |  |  | G-1 (04/00) | [76-43-7] | \$207 |
| 1280803 | Fluphenazine Decanoate Dihydrochloride ( 500 mg ) | G |  |  | F-1 (10/01) | n/f | \$159 |
| 1281001 | Fluphenazine Enanthate Dihydrochloride ( 125 mg ) | H |  |  | G (02/99) | [3105-68-8] | \$124 |
| 1282004 | Fluphenazine Hydrochloride ( 125 mg ) | H |  |  |  | [146-56-5] | \$124 |
| 1284000 | Flurandrenolide ( 100 mg ) | IOB245 |  |  | H (09/03) | [1524-88-5] | \$156 |
| 1285002 | Flurazepam Hydrochloride CIV ( 200 mg ) | J0C365 | $0.996 \mathrm{mg} / \mathrm{mg}$ (ai) |  | I (09/03) | [1172-18-5] | \$207 |
| 1285308 | Flurazepam Related Compound C ( 50 mg ) (5-chloro-2-(2-diethylaminoethyl(amino)-2'-fluorobenzophenone Hydrochloride) | H-1 |  |  |  | n/f | \$487 |
| 1285603 | Flurazepam Related Compound F (50 mg) (7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one) | 10 C 092 |  |  | H (01/04) | [2886-65-9] | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1285750 | Flurbiprofen (200 mg) | G |  |  |  | [5104-49-4] | \$156 |
| 1285760 | Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid) | H |  |  | G (03/01) | n/f | \$487 |
| 1285807 | Flurbiprofen Sodium ( 200 mg ) | F |  |  |  | [56767-76-1] | \$156 |
| 1285851 | Flutamide (200 mg) | H0B278 |  |  | $\begin{aligned} & \hline \text { G (11/04) } \\ & \text { F-1 (06/00) } \\ & \hline \end{aligned}$ | [13311-84-7] | \$156 |
| 1285862 | o-Flutamide ( 50 mg ) | F-1 |  |  | F (01/00) | n/f | \$156 |
| 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) | P |  |  | O (07/00) | [59-30-3] | \$156 |
| 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) | 10B176 |  |  | $\begin{aligned} & \text { H-1 (04/04) } \\ & \text { H (01/00) } \\ & \hline \end{aligned}$ | [1492-18-8] | \$156 |
| 1286060 | Formononetin ( 50 mg ) | FOC196 |  |  |  | [485-72-3] | \$520 |
| 1286209 | 4-Formylbenzenesulfonamide ( 50 mg ) | F |  |  |  | n/f | \$487 |
| 1286300 | 10-Formylfolic Acid (25 mg) | F2B226 |  |  | F-1 (01/04) | [134-05-4] | \$156 |
| 1286366 | Fosphenytoin Sodium ( 250 mg ) | F0C156 |  |  |  | [92134-98-0] | \$156 |
| 1286504 | Fructose (125 mg) | I-2 |  |  | $\begin{array}{\|l\|} \hline \text { I-1 (11/02) } \\ \text { I (08/99) } \\ \hline \end{array}$ | [57-48-7] | \$124 |
| 1286708 | Fumaric Acid (200 mg) | G-1 |  |  | G (04/02) | [110-17-8] | \$156 |
| 1286800 | Furazolidone (200 mg) | G-2 |  |  | G-1 (01/01) | [67-45-8] | \$156 |
| 1287008 | Furosemide ( 125 mg ) | J1B131 |  |  | $J(10 / 03)$ | [54-31-9] | \$124 |
| 1287020 | Furosemide Related Compound A ( 50 mg ) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid) | J |  |  | I (08/02) | n/f | \$487 |
| 1287030 | Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid) | 10C248 |  |  | $\begin{aligned} & \text { H (08/04) } \\ & \text { G-3 }(03 / 01) \\ & \hline \end{aligned}$ | [3086-91-7] | \$487 |
| 1287303 | Gabapentin ( 250 mg ) | F |  |  |  | [60142-96-3] | \$156 |
| 1287325 | Gabapentin Related Compound A ( 100 mg ) (3,3-pentamethylene-5-butyrolactam) | F |  |  |  | [64744-50-9] | \$487 |
| 1287507 | Gadodiamide ( 500 mg ) | F |  |  |  | [131410-48-5] | \$156 |
| 1287518 | Gadodiamide Related Compound A ( 50 mg ) (gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide) | F |  |  |  | n/f | \$487 |
| 1287529 | Gadodiamide Related Compound B ( 50 mg ) (gadolinium disodium diethylenetriamine pentaacetic acid) | F |  |  |  | n/f | \$487 |
| 1287609 | Gadopentetate Monomeglumine ( 500 mg ) | F |  |  |  | [92923-57-4] | \$156 |
| 1287631 | Gadoteridol ( 500 mg ) | F |  |  |  | [120066-54-8] | \$156 |
| 1287642 | Gadoteridol Related Compound A (50 mg) (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclodode-cane-1,4,7-triacetic acid) | F0A002 |  |  |  | [120041-08-9] | \$487 |
| 1287653 | Gadoteridol Related Compound B ( 50 mg ) (1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, monogadolinium salt) | F0B198 |  |  |  | [112188-16-6] | \$487 |
| 1287664 | Gadoteridol Related Compound C (50 mg) (1,4,7,10-Tetraaza-11-oxo-bicyclo[8.2.2]tetrade-cane-4,7-diacetic acid) | FOB199 |  |  |  | [220182-19-4] | \$487 |
| 1287675 | Gadoversetamide ( 200 mg ) | F0C172 |  |  |  | [131069-91-5] | \$156 |
| 1287686 | Gadoversetamide Related Compound A (200 mg) (Hydrogen[8,11,14-tris(carboxy-methyl)-6-oxo-2-oxa-5,8,11,14-tetraazahexade-can-16-oato(4-)]gadolinium) | F0C173 |  |  |  | n/f | \$487 |
| 1287700 | Galactose (200 mg) | F-4 |  |  | F-3 (05/01) | [59-23-4] | \$487 |
| 1288000 | Gallamine Triethiodide ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [65-29-2] | \$156 |
| 1288306 | Ganciclovir (200 mg) | F0C287 |  |  |  | [82410-32-0] | \$364 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1288317 | Ganciclovir Related Compound A ( 15 mg ) ((RS)-2-Amino-9-(2,3-dihydroxy-propoxy-methyl)-1,9-dihydro-purin-6-one) | F0C288 |  |  |  | n/f | \$624 |
| 1288500 | Gemfibrozil ( 200 mg ) | H |  |  |  | [25812-30-0] | \$156 |
| 1288510 | Gemfibrozil Related Compound A (20 mg) (2,2-dimethyl-5-[2,5-dimethyl-4-propene-1-yl)phenoxy]valeric acid) | F0C101 |  |  |  | n/f | \$487 |
| 1289003 | Gentamicin Sulfate (200 mg) | L0C279 | 667 ug/mg (dr) |  | $\begin{aligned} & \hline \mathrm{K}(12 / 04) \\ & \mathrm{J}-1(04 / 00) \end{aligned}$ | [1405-41-0] | \$156 |
| 1290002 | Gentian Violet (650 mg) | F |  |  |  | [548-62-9] | \$156 |
| 1291005 | Gibberellic Acid ( 200 mg ) (FCC) | G |  |  | F (04/01) | [77-06-5] | \$156 |
| 1291504 | Powdered Ginger ( 500 mg ) | F |  |  |  | n/f | \$156 |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | FOB289 |  |  |  | [50647-08-0] | \$520 |
| 1292008 | Gitoxin ( 50 mg ) | G |  |  | F-3 (07/00) | [4562-36-1] | \$487 |
| 1292507 | Glipizide ( 125 mg ) | G1C174 |  |  | G (07/04) | [29094-61-9] | \$124 |
| 1292609 | Glipizide Related Compound A ( 25 mg ) ( $\mathrm{N}-\{2-$ [(4-aminosulfonyl)phenyl]ethyl\}-5-methyl-pyrazinecarboxamide) | G-1 |  |  | G (04/99) | n/f | \$487 |
| 1294003 | Glucagon ( $25 \mathrm{mg}, 0.95 \mathrm{U} / \mathrm{mg}$ ) |  |  |  | H (01/05) | [16941-32-5] | \$156 |
| 1294207 | Glucosamine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F0C363 |  |  |  | [66-84-2] | \$156 |
| 1294976 | Glutamic Acid (200 mg) | FOC069 |  |  |  | [56-86-0] | \$156 |
| 1294808 | Glutamine ( 100 mg ) | FOB244 |  |  |  | [56-85-9] | \$156 |
| 1294848 | gamma-Glutamyl-S-allyl-L-cysteine ( 25 mg ) | F |  |  |  | n/f | \$675 |
| 1295006 | Glutethimide CII ( 500 mg ) | F |  |  |  | [77-21-4] | \$207 |
| 1295505 | Glyburide ( 200 mg ) | G |  |  | F-2 (11/02) | [10238-21-8] | \$156 |
| 1295607 | Glycerin (2 mL) | H0C073 |  |  | $\begin{array}{\|l\|} \hline \text { G1A001 (04/04) } \\ \text { G (12/02) } \\ \hline \text { F (04/99) } \\ \hline \end{array}$ | [56-81-5] | \$156 |
| 1295709 | Glyceryl Behenate (200 mg) | F3B113 |  |  | F-2 (03/03) | [18641-57-1] | \$156 |
| 1295800 | Glycine (200 mg) | F-3 |  |  | F-2 (02/00) | [56-40-6] | \$156 |
| 1296009 | Glycopyrrolate ( 200 mg ) | H0B304 |  |  | G (05/04) | [596-51-0] | \$156 |
| 1295888 | Glycyrrhizic Acid (25 mg) | F0C006 |  |  |  | [1405-86-3] | \$487 |
| 1297001 | Human Chorionic Gonadotropin (1 vial, 5,760 USP Units per package) | H |  |  | G (07/00) | [9002-61-3] | \$156 |
| 1298004 | Gramicidin ( 200 mg ) | 1 |  |  | H-1 (07/02) | [1405-97-6] | \$156 |
| 1299007 | Griseofulvin (200 mg) | 1 |  |  | H-1 (09/02) | [126-07-8] | \$156 |
| 1299200 | Griseofulvin Permeability Diameter (2 g) | J0C380 |  |  | $\begin{aligned} & \text { I0C138 (10/04) } \\ & H(08 / 03) \\ & \hline \end{aligned}$ | [126-07-8] | \$156 |
| 1300004 | Guaiacol ( 1 g ) | K |  |  | J (04/00) | [90-05-1] | \$156 |
| 1301007 | Guaifenesin (200 mg) | 1 |  |  | H (09/02) | [93-14-1] | \$156 |
| 1301404 | Guanabenz Acetate ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | F-1 (06/00) | [23256-50-0] | \$156 |
| 1301608 | Guanadrel Sulfate (200 mg) | F-1 |  |  |  | [22195-34-2] | \$156 |
| 1301801 | Guanethidine Monosulfate ( 200 mg ) | F |  |  |  | [645-43-2] | \$156 |
| 1302000 | Guanethidine Sulfate ( 500 mg ) | G-1 |  |  |  | [60-02-6] | \$156 |
| 1302101 | Guanfacine Hydrochloride ( 125 mg ) | G0B123 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (02/03) } \\ \text { F (11/99) } \\ \hline \end{array}$ | [29110-48-3] | \$124 |
| 1302305 | Halazepam CIV (200 mg) (AS) | F1C224 |  |  | F (12/04) | [23092-17-3] | \$207 |
| 1302509 | Halcinonide ( 300 mg ) | F |  |  |  | [3093-35-4] | \$156 |
| 1303002 | Haloperidol ( 200 mg ) | 1 |  |  | H-1 (05/02) | [52-86-8] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| 1303013 | Haloperidol Related Compound A (15 mg) (4,4-Bis[(4-p-chlorophenyl)-4-hydroxy-piperidino]-butyrophenone) | K0C362 |  |  | J (12/04) | [67987-08-0] | \$487 |
| 1303308 | Haloprogin ( 200 mg ) | F |  |  |  | [777-11-7] | \$156 |
| 1303501 | Halothane ( 1 mL ) |  |  |  | F-1 (03/05) | [151-67-7] | \$156 |
| 1304005 | Heparin Sodium ( $10 \times 1 \mathrm{~mL}$ ) | K-5 |  |  | $\begin{aligned} & \hline \text { K-4 (08/03) } \\ & \text { K-3 (02/99) } \\ & \hline \end{aligned}$ | [9041-08-1] | \$156 |
| 1305008 | Hexachlorophene ( 500 mg ) | 1 |  |  | H-2 (01/01) | [70-30-4] | \$156 |
| 1305507 | 2E, 4E-Hexadienoic Acid Isobutylamide ( 25 mg ) | F0C353 | $1.00 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | [82240-09-3] | \$540 |
| 1307003 | Hexobarbital CIII ( 500 mg ) | F |  |  |  | [56-29-1] | \$207 |
| 1308006 | Hexylcaine Hydrochloride (1 g) | F-1 |  |  |  | [532-76-3] | \$156 |
| 1308200 | Hexylene Glycol (125 mg) | G |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 (04/02) } \\ \text { F-1 (04/99) } \\ \hline \end{array}$ | [107-41-5] | \$156 |
| 1308307 | Hexylresorcinol (200 mg) | F |  |  |  | [136-77-6] | \$156 |
| 1308505 | L-Histidine (200 mg) | G0A018 |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 (01/03) } \\ \text { F-1 (04/00) } \\ \hline \end{array}$ | [71-00-1] | \$156 |
| 1309009 | Histamine Dihydrochloride (250 mg) | M0C280 |  |  | L (07/04) | [56-92-8] | \$156 |
| 1310008 | Homatropine Hydrobromide (200 mg) | H2C049 |  |  | $\begin{array}{\|l\|} \hline \mathrm{H}-1(02 / 05) \\ \mathrm{H}(08 / 02) \\ \hline \end{array}$ | [51-56-9] | \$156 |
| 1311000 | Homatropine Methylbromide (250 mg) | J |  |  | $\begin{array}{\|l\|l} \hline \text { I-1 }(06 / 01) \\ \text { H-1 }(10 / 01) \\ \hline \end{array}$ | [80-49-9] | \$156 |
| 1311306 | Homopolymer Polypropylene (3 Strips) | F0C096 |  | 1 |  | [9003-07-0] | \$156 |
| 1311408 | Homosalate ( $500 \mathrm{mg} / \mathrm{ampule}$ ) |  |  |  | F0B102 (04/05) | [118-56-9] | \$156 |
| 1312003 | Hyaluronidase ( 500 mg ) | H |  |  |  | [9001-54-1] | \$156 |
| 1313006 | Hydralazine Hydrochloride (200 mg) | K |  |  | J-1 (09/02) | [304-20-1] | \$156 |
| 1314009 | Hydrochlorothiazide ( 200 mg ) | I |  |  | H (05/02) | [58-93-5] | \$156 |
| 1315001 | Hydrocodone Bitartrate ClI ( 250 mg ) | K0C217 |  |  | $\begin{array}{\|l\|} \hline \text { JOA026 (01/05) } \\ \text { I-1 (12/02) } \\ \text { I (07/02) } \\ \text { H-2 (11/99) } \\ \hline \end{array}$ | [34195-34-1] | \$207 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl) | F0C214 |  |  |  | [847-86-9] | \$513 |
| 1316004 | Hydrocortisone (200 mg) | M1C110 |  |  | $\begin{array}{\|l\|} \hline M(10 / 04) \\ L \\ \hline \end{array}(09 / 00)$ | [50-23-7] | \$156 |
| 1317007 | Hydrocortisone Acetate (200 mg) | K |  |  | J (10/99) | [50-03-3] | \$156 |
| 1317302 | Hydrocortisone Butyrate ( 200 mg ) | H |  |  |  | [13609-67-1] | \$156 |
| 1318000 | Hydrocortisone Cypionate (200 mg) | F |  |  |  | [508-99-6] | \$156 |
| 1319002 | Hydrocortisone Hemisuccinate ( 200 mg ) | H |  |  | $\begin{aligned} & \text { G-3 (03/02) } \\ & \text { G-2 }(08 / 99) \\ & \hline \end{aligned}$ | [83784-20-7] | \$156 |
| 1320001 | Hydrocortisone Phosphate Triethylamine ( 200 mg ) | F-1 |  |  |  | n/f | \$156 |
| 1321004 | Hydrocortisone Valerate (200 mg) | F-1 |  |  | F (07/02) | [57524-89-7] | \$156 |
| 1322007 | Hydroflumethiazide ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  |  |  | [135-09-1] | \$156 |
| 1323000 | Hydromorphone Hydrochloride CII (50 mg) | J0C372 |  |  | $\begin{aligned} & \hline \text { I (01/05) } \\ & \text { H-2 (03/01) } \\ & \hline \end{aligned}$ | [71-68-1] | \$207 |
| 1324002 | Hydroquinone ( 500 mg ) | H0C249 |  |  | $\begin{array}{\|l} \hline \text { G-1 (10/04) } \\ \text { G (11/01) } \\ \text { F-4 (02/99) } \\ \hline \end{array}$ | [123-31-9] | \$156 |
| 1325005 | Hydroxyamphetamine Hydrobromide ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | F (06/01) | [306-21-8] | \$156 |
| 1327000 | Hydroxychloroquine Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | J0B297 |  |  | I (05/04) | [747-36-4] | \$156 |
| 1329006 | Hydroxyprogesterone Caproate ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  |  | [630-56-8] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1329709 | Hydroxypropyl Betadex (200 mg) | F0B295 |  |  |  | [128446-35-5] | \$156 |
| 1329800 | Hydroxypropyl Cellulose (200 mg) | F-1 |  |  |  | [9004-64-2] | \$156 |
| 1332000 | Hydroxyurea (200 mg) | H |  |  | G (01/00) | [127-07-1] | \$156 |
| 1333003 | Hydroxyzine Hydrochloride ( 500 mg ) | H |  |  |  | [2192-20-3] | \$156 |
| 1333058 | Hydroxyzine Related Compound A ( 25 mg ) (pChlorobenzhydrylpiperazine) | H |  |  |  | [303-26-4] | \$208 |
| 1334006 | Hydroxyzine Pamoate ( 500 mg ) | H0C016 |  |  | G-1 (07/03) | [10246-75-0] | \$156 |
| 1335009 | Hyoscyamine Sulfate (125 mg) | H0C193 |  |  | $\begin{array}{\|l} \hline \text { G2A007 (09/04) } \\ \text { G-1 (08/02) } \\ \text { G (10/99) } \\ \hline \end{array}$ | [6835-16-1] | \$124 |
| 1335202 | Hyperoside ( 50 mg ) | F |  |  |  | [482-36-0] | \$855 |
| 1330005 | Hypromellose ( 250 mg ) (Hydroxypropyl Methylcellulose) | H0C387 |  |  | $\begin{aligned} & \text { G-1 (11/04) } \\ & \text { G (02/02) } \end{aligned}$ | [9004-65-3] | \$156 |
| 1335304 | Hypromellose Phthalate ( 100 mg ) | F-1 |  |  | F (12/00) | [9050-31-1] | \$156 |
| 1335508 | Ibuprofen ( 750 mg ) | J |  |  | I (06/02) | [15687-27-1] | \$156 |
| 1335701 | Idarubicin Hydrochloride ( 50 mg ) | H0C061 |  |  | $\begin{aligned} & \text { G (11/03) } \\ & \text { F (06/00) } \end{aligned}$ | [57852-57-0] | \$479 |
| 1336001 | Idoxuridine ( 250 mg ) | H1B230 |  |  | H (07/04) | [54-42-2] | \$156 |
| 1336205 | Ifosfamide ( 500 mg ) | G |  |  | $\begin{array}{\|l} \hline \text { F-1 (11/00) } \\ \text { F (02/99) } \\ \hline \end{array}$ | [3778-73-2] | \$156 |
| 1336500 | Imidazole (200 mg) | G1B132 |  |  | G (01/04) | [288-32-4] | \$487 |
| 1336806 | Imidurea (200 mg) | H |  |  | G (10/99) | [39236-46-9] | \$156 |
| 1337004 | Iminodibenzyl (25 mg) | I0C253 |  |  | H (11/04) | [494-19-9] | \$487 |
| 1337809 | Imipenem Monohydrate ( 100 mg ) | G1C296 | 930 ug/mg (ai) |  | $\begin{aligned} & \mathrm{G}(01 / 05) \\ & \mathrm{F}(01 / 01) \end{aligned}$ | [74431-23-5] | \$156 |
| 1338007 | Imipramine Hydrochloride (200 mg) | 1 |  |  | H (09/01) | [113-52-0] | \$156 |
| 1338801 | Indapamide ( 250 mg ) | H |  |  | G (07/02) | [26807-65-8] | \$156 |
| 1339000 | Indigotindisulfonate Sodium ( 500 mg ) | H1B153 |  |  | H (06/03) | [860-22-0] | \$156 |
| 1340009 | Indocyanine Green ( 200 mg ) | IOB045 |  |  | H (09/01) | [3599-32-4] | \$156 |
| 1341001 | Indomethacin (200 mg) | JOB165 |  |  | $\begin{aligned} & \text { I (01/04) } \\ & \mathrm{H}(05 / 99) \end{aligned}$ | [53-86-1] | \$156 |
| 1342004 | Insulin (100 mg) | H |  |  |  | [9004-10-8] | \$156 |
| 1342106 | Insulin Human (100 mg) | H1A031 |  |  | $\begin{aligned} & \hline \text { H }(11 / 02) \\ & \text { G }(04 / 00) \\ & \hline \end{aligned}$ | [11061-68-0] | \$156 |
| 1342208 | Insulin (Beef) (100 mg) | F |  |  |  | [11070-73-8] | \$156 |
| 1342300 | Insulin (Pork) ( 100 mg ) | F |  |  |  | [12584-58-6] | \$156 |
| 1342503 | locetamic Acid (200 mg) | F |  |  |  | [16034-77-8] | \$156 |
| 1343007 | lodipamide (200 mg) | G |  |  |  | [606-17-7] | \$156 |
| 1343517 | lodixanol (200 mg) | FOB240 |  |  |  | [92339-11-2] | \$156 |
| 1343540 | lodixanol Related Compound C ( 25 mg ) (5-Acetyl[3-[[3,5-bis[[2,3-dihydroxypropyl)amino]-carbonyl]-2,4,6-triiodophenyl]amino]-2-hydroxy-propyl]amino]-N,N'-bis-(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B236 |  |  |  | n/f | \$487 |
| 1343550 | Iodixanol Related Compound D (50 mg) (5-[Acetyl(2-hydroxy-3-methylpropyl)amino]-N,N'-bis(2,3-dihydroxypropyl)2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B231 |  |  |  | [89797-00-2] | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1343561 | Iodixanol Related Compound E ( 25 mg ) ( $5-[[3-$ [[3-[[(2,3-Dihydoxypropyl)amino]carbonyl]-5-[[amino]carbonyl]-2,4,6-triiodophenyl](acetylimi-no)]-2-hydroxypropyl]-(acetylimino)]-N,N'-bis(2,3-dihydoxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B229 |  |  |  | n/f | \$487 |
| 1344305 | o-lodohippuric Acid (100 mg) | F |  |  |  | [147-58-0] | \$156 |
| 1344509 | lodoquinol ( 100 mg ) | H |  |  | G (07/02) | [83-73-8] | \$156 |
| 1344600 | lohexol ( 100 mg ) | F-1 |  |  | F (01/99) | [66108-95-0] | \$124 |
| 1344622 | Iohexol Related Compound A (100 mg) (5-(acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F-1 |  |  | F (10/01) | n/f | \$487 |
| 1344644 | Iohexol Related Compound B ( 50 mg ) (5-amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triio-do-1,3-benzenedicarboxamide) | F-1 |  |  | F (01/04) | [76801-93-9] | \$487 |
| 1344666 | Iohexol Related Compound C ( 100 mg ) ( $\mathrm{N}, \mathrm{N}$ '-bis(2,3-dihydroxypropyl)-5-nitro-1,3-benzenedicarboxamide) | F-1 |  |  | F (09/03) | n/f | \$156 |
| 1344702 | lopamidol (200 mg) | G |  |  |  | [60166-93-0] | \$156 |
| 1344724 | lopamidol Related Compound A ( 50 mg ) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triio-doiso-phthalamide) | G |  |  |  | [60166-98-5] | \$487 |
| 1344735 | lopamidol Related Compound B (100 mg) (5-Glycolamido-N,N'-bis[2-hydroxy-1-(hydroxy-methyl)ethyl]-2,4,6-triiodoisophthalamide) | F |  |  |  | n/f | \$487 |
| 1344804 | lopromide ( 400 mg ) | F |  |  |  | [73334-07-3] | \$156 |
| 1344826 | lopromide Related Compound A ( 50 mg ) ( 5 -Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triio-do-N-methyl-1,3-benzenedicarboxamide) | F |  |  |  | n/f | \$487 |
| 1344837 | lopromide Related Compound B ( 50 mg ) (5-(Acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide) | F |  |  |  | n/f | \$487 |
| 1345002 | lothalamic Acid (200 mg) | G |  |  |  | [2276-90-6] | \$156 |
| 1345104 | loversol ( 200 mg ) | F |  |  |  | [87771-40-2] | \$156 |
| 1345115 | Ioversol Related Compound A ( 50 mg ) ( $5-$ Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide) | F |  |  |  | [76801-93-9] | \$487 |
| 1345126 | Ioversol Related Compound B ( 50 mg ) ( $\mathrm{N}, \mathrm{N}$ '-bis(2,3-dihydroxypropyl)-5-[(N-(2-hydroxyethyl)-carbonyl)methoxy]-2,4,6-triiodoisophthalamide) | F |  |  |  | n/f | \$487 |
| 1345159 | Ioxaglic Acid (100 mg) | F |  |  |  | [59017-64-0] | \$156 |
| 1345206 | Ioxilan ( 400 mg ) | F |  |  |  | [107793-72-6] | \$156 |
| 1345228 | Ioxilan Related Compound A (100 mg) (5-amino-2,4,6-triiodo-3 N -(2-hydroxyethyl)carbamoyl benzoic acid) | F |  |  |  | [22871-58-5] | \$487 |
| 1346005 | Ipodate Calcium (200 mg) | F |  |  |  | [1151-11-7] | \$156 |
| 1347008 | Ipodate Sodium (200 mg) | F-1 |  |  |  | [1221-56-3] | \$156 |
| 1347755 | Isoamyl Methoxycinnamate ( $750 \mathrm{mg} / \mathrm{ampule}$ ) | F0B017 |  |  |  | [71617-10-2] | \$156 |
| 1348000 | Isocarboxazid (200 mg) | F-1 |  |  |  | [59-63-2] | \$156 |
| 1348500 | Isoetharine Hydrochloride ( 250 mg ) | F-2 |  |  |  | [2576-92-3] | \$156 |
| 1348907 | Isoflupredone Acetate (200 mg) | F0C109 |  |  |  | [338-98-7] | \$156 |
| 1349003 | Isoflurane ( 1 mL ) | H1C199 |  |  | H (12/04) | [26675-46-7] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1349014 | Isoflurane Related Compound A ( 0.1 mL ) (1-Chloro-2,2,2-trifluoroethyl chlorodifluoromethyl ether) | F0C232 |  |  |  | n/f | \$487 |
| 1349025 | Isoflurane Related Compound B ( 0.1 mL ) (2,2,2Trifluoroethyldifluoromethyl ether) | F0C233 |  |  |  | n/f | \$487 |
| 1349502 | L-Isoleucine ( 200 mg ) | F-2 |  |  | F-1 (09/02) | [73-32-5] | \$156 |
| 1349604 | Isomalathion ( 50 mg ) | F1B107 |  |  | F (01/03) | [3344-12-5] | \$487 |
| 1349659 | Isometheptene Mucate (200 mg) | F |  |  |  | [7492-31-1] | \$156 |
| 1349706 | Isoniazid (200 mg) | H |  |  |  | [54-85-3] | \$156 |
| 1350002 | Isopropamide lodide ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  |  |  | [71-81-8] | \$156 |
| 1350400 | Isopropyl Myristate ( 500 mg ) | I1C183 |  |  | I (01/05) | [110-27-0] | \$156 |
| 1350603 | Isopropyl Palmitate ( 500 mg ) | 1 |  |  | H (10/99) | [142-91-6] | \$156 |
| 1351005 | Isoproterenol Hydrochloride ( 125 mg ) | K |  |  |  | [51-30-9] | \$124 |
| 1352008 | Isosorbide ( $75 \%$ solution, 1 g ) | 1 |  |  | H-2 (10/00) | [652-67-5] | \$156 |
| 1353000 | Diluted Isosorbide Dinitrate ( 500 mg of $25 \%$ mixture with mannitol) | I-1 |  |  | I (10/99) | [87-33-2] | \$156 |
| 1353500 | Isotretinoin ( 200 mg ) | 1 |  |  | H (10/00) | [4759-48-2] | \$156 |
| 1354003 | Isoxsuprine Hydrochloride (200 mg) | F-3 |  |  |  | [579-56-6] | \$156 |
| 1354207 | Isradipine (200 mg) | G0B054 |  |  | F (05/03) | [75695-93-1] | \$156 |
| 1354218 | Isradipine Related Compound A ( 25 mg ) (Isopropyl methyl 4-(4-benzofurazanyl)-2,6-di-methyl-3,5-pyridinedicarboxylate) | F |  |  |  | n/f | \$487 |
| 1354309 | Ivermectin ( 200 mg ) | FOB196 |  |  |  | [70288-86-7] | \$156 |
| 1355006 | Kanamycin Sulfate (200 mg) | $J$ |  |  | I (06/99) | [25389-94-0] | \$156 |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 |  |  |  | n/f | \$260 |
| 1355753 | Kawain (200 mg) | FOC160 |  |  |  | [500-64-1] | \$208 |
| 1356009 | Ketamine Hydrochloride CIII ( 250 mg ) | G-2 |  |  | G-1 (07/00) | [1867-66-9] | \$207 |
| 1356020 | Ketamine Related Compound A (50 mg) (1-[(2-Chlorophenyl)(methylimino)methyl]cylcopentanol) | F0C118 |  |  |  | [6740-87-0] | \$487 |
| 1356508 | Ketoconazole (200 mg) | G4B179 |  |  | $\begin{aligned} & \text { G-3 (01/04) } \\ & \text { G-2 (06/01) } \\ & \text { G-1 }(01 / 99) \end{aligned}$ | [65277-42-1] | \$156 |
| 1356632 | Ketoprofen (200 mg) | H0B216 |  |  | $\begin{array}{\|l\|} \hline \text { G (07/04) } \\ \text { F-2 (05/99) } \end{array}$ | [22071-15-4] | \$156 |
| 1356643 | Ketoprofen Related Compound A ( 25 mg ) (al-pha-Methyl-3-(4-methylbenzoyl) benzeneacetic acid) | G |  |  |  | [107257-20-5] | \$487 |
| 1356665 | Ketorolac Tromethamine (200 mg) | G |  |  | F-2 (04/99) | [74103-07-4] | \$156 |
| 1356654 | Labetalol Hydrochloride ( 200 mg ) | G |  |  | $\begin{array}{\|l} \hline \text { F-2 (01/02) } \\ \text { F-1 (03/01) } \\ \hline \end{array}$ | [32780-64-6] | \$156 |
| 1356676 | Anhydrous Lactose (100 mg) | G1C004 |  |  | $\begin{array}{\|l\|l\|} \hline G(12 / 04) \\ F(06 / 01) \\ \hline \end{array}$ | [63-42-3] | \$156 |
| 1356687 | Lactitol ( 500 mg ) | F0B005 |  |  |  | [81025-04-9] | \$156 |
| 1356701 | Lactose Monohydrate ( 500 mg ) | G-1 |  |  | G (08/02) | [5989-81-1] | \$156 |
| 1356803 | Lactulose (1 g) | H |  |  | G-1 (08/00) | [4618-18-2] | \$156 |
| 1356836 | Lamivudine (200 mg) | F0C361 |  |  |  | [134678-17-4] | \$156 |
| 1356847 | Lamivudine Resolution Mixture A (10 mg) | FOD024 |  | 1 |  | [134678-17-4] | \$487 |
| 1356880 | Lanolin (20 g) | F |  |  |  | [8006-54-0] | \$156 |
| 1356905 | Lanolin Alcohols (5 g) | F |  |  |  | [8027-33-6] | \$156 |
| 1356916 | Lansoprazole (200 mg) | F0B310 |  |  |  | [103577-45-3] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1356927 | Lansoprazole Related Compound A ( 25 mg ) (2-[[[3-methyl-4-(2,2,2-triflouroethoxy)-2-pyridyl]methyl]sulfonyl]benzimidazole) | F0B311 |  |  |  | n/f | \$487 |
| 1356971 | Letrozole ( 200 mg ) | FOB170 |  |  |  | [112809-51-5] | \$156 |
| 1356982 | Letrozole Related Compound A ( 15 mg ) (4,4'( $1 \mathrm{H}-1,3,4$-triazol-1-ylmethylene)dibenzonitrile) | F0B168 |  |  |  | n/f | \$487 |
| 1357001 | L-Leucine (200 mg) | H0B237 |  |  | $\begin{aligned} & \text { G-1 (04/04) } \\ & \text { G (08/00) } \end{aligned}$ | [61-90-5] | \$156 |
| 1358004 | Leucovorin Calcium (500 mg) | J2B219 |  |  | $\begin{array}{\|l\|} \hline \mathrm{J}-1(07 / 04) \\ \mathrm{J}(05 / 02) \\ \hline \end{array}$ | [1492-18-8] | \$160 |
| 1358503 | Leuprolide Acetate (200 mg) | F0C430 | $0.907 \mathrm{mg} / \mathrm{mg}$ (an,fb) | 1 |  | [74381-53-6] | \$1,525 |
| 1359007 | Levallorphan Tartrate ( 200 mg ) DISCONTINUED |  |  |  | $\begin{aligned} & \text { G-1 (09/04) } \\ & \text { G (11/02) } \end{aligned}$ | [71-82-9] | \$156 |
| 1359302 | Levamisole Hydrochloride (125 mg) | F2C122 |  |  | F-1 (05/04) | [16595-80-5] | \$124 |
| 1359506 | Levmetamfetamine CII (75 mg) | F |  |  |  | [33817-09-3] | \$207 |
| 1359801 | Levobunolol Hydrochloride (200 mg) | G |  |  |  | [27912-14-7] | \$156 |
| 1359903 | Levocarnitine (400 mg) | G0B197 |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 } & (06 / 03) \\ \text { F-1 } & (12 / 00) \\ \hline \end{array}$ | [541-15-1] | \$156 |
| 1359925 | Levocarnitine Related Compound A ( 100 mg ) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride) | F-1 |  |  | F (08/01) | [6538-82-5] | \$208 |
| 1361009 | Levodopa (200 mg) | 1 |  |  | H (09/00) | [59-92-7] | \$156 |
| 1361010 | Levodopa Related Compound A ( 50 mg ) (3-(3,4,6-Trihydroxyphenyl)-alanine) | K |  |  | $\begin{array}{\|l\|} \hline J(01 / 03) \\ I(06 / 00) \\ \hline \end{array}$ | [27244-64-0] | \$487 |
| 1420006 | Levodopa Related Compound B ( 50 mg ) (3Methoxytyrosine) | $10 C 300$ |  |  | H (07/04) |  | \$487 |
| 1362500 | Levonordefrin ( 200 mg ) | F-1 |  |  |  | [829-74-3] | \$156 |
| 1363004 | Levopropoxyphene Napsylate ( 300 mg ) | G |  |  |  | [55557-30-7] | \$156 |
| 1364007 | Levorphanol Tartrate CII (500 mg) | H |  |  | G (03/01) | [5985-38-6] | \$207 |
| 1365000 | Levothyroxine ( 500 mg ) | K |  |  | $J(10 / 00)$ | [51-48-9] | \$156 |
| 1366002 | Lidocaine ( 250 mg ) | L |  |  |  | [137-58-6] | \$156 |
| 1367005 | Lincomycin Hydrochloride (200 mg) | H2B130 |  |  | H-1 (01/04) | [7179-49-9] | \$156 |
| 1367504 | Lindane ( 200 mg ) | F-2 |  |  |  | [58-89-9] | \$156 |
| 1367708 | Linoleoyl Polyoxylglycerides ( 100 mg ) | F0C283 |  | 1 |  | n/f | \$156 |
| 1368008 | Liothyronine ( 250 mg ) | L1C262 |  |  | $\begin{array}{\|l\|l\|} \hline \mathrm{L}(08 / 04) \\ \mathrm{K}(08 / 01) \\ \hline \end{array}$ | [6893-02-3] | \$156 |
| 1368609 | Lisinopril (300 mg) | I1C045 |  |  | $\begin{aligned} & \hline \text { I (11/04) } \\ & \text { H (09/01) } \\ & \text { G (10/99) } \\ & \hline \end{aligned}$ | [83915-83-7] | \$156 |
| 1369000 | Lithium Carbonate (300 mg) | G0B031 |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 (01/03) } \\ \text { F-1 (01/01) } \\ \hline \end{array}$ | [554-13-2] | \$156 |
| 1370000 | Loperamide Hydrochloride (200 mg) | H0C202 |  |  | $\begin{aligned} & \text { G-2 }(09 / 04) \\ & \text { G-1 } \\ & (02 / 03) \end{aligned}$ | [34552-83-5] | \$156 |
| 1370203 | Loracarbef ( 200 mg ) | F |  |  |  | [121961-22-6] | \$156 |
| 1370225 | Loracarbef L-Isomer ( 25 mg ) | F |  |  |  | n/f | \$156 |
| 1370270 | Loratadine ( 200 mg ) | F0C414 |  |  |  | [79794-75-5] | \$260 |
| 1370305 | Lorazepam CIV (200 mg) | 10C048 |  |  | H0B023 (06/04) | [846-49-1] | \$207 |
| 1370327 | Lorazepam Related Compound A (25 mg) (7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-3-acet-oxy-2H-1,4-benzodiazepin-2-one) | G |  |  | F-1 (06/01) | [2848-96-6] | \$487 |
| 1370338 | Lorazepam Related Compound B ( 25 mg ) (2-Amino-2',5-dichlorobenzophenone) | G |  |  | F-2 (01/04) | [2958-36-3] | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1370349 | Lorazepam Related Compound C ( 25 mg ) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde) | H |  |  | $\begin{aligned} & \hline \mathrm{G}(01 / 03) \\ & \mathrm{F}-3(01 / 02) \end{aligned}$ | n/f | \$487 |
| 1370350 | Lorazepam Related Compound D ( 25 mg ) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid) | G0A014 |  |  | F-2 (01/04) | [54643-79-7] | \$487 |
| 1370360 | Lorazepam Related Compound E ( 25 mg ) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol) | G |  |  | $\begin{aligned} & \text { F-3 (07/02) } \\ & \text { F-2 (04/99) } \end{aligned}$ | n/f | \$487 |
| 1370600 | Lovastatin (125 mg) | H2C012 |  |  | $\begin{aligned} & \text { H1B067 (01/04) } \\ & \text { H (08/03) } \end{aligned}$ | [75330-75-5] | \$124 |
| 1370611 | Lovastatin Related Compound A (20 mg) (Butanoic acid, 2-methyl-,1,2,3,4,4a,7,8,8a-octahy-dro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[alpha(R*), 3alpha,7beta,8beta( $2 \mathrm{~S}^{*}, 4 \mathrm{~S}^{*}$ ), 8alpha beta]]-) | G0C326 |  |  | F0B235 (09/04) | n/f | \$487 |
| 1370702 | Loxapine Succinate (125 mg) | G0B026 |  |  | $\begin{aligned} & \hline \text { F-2 (06/03) } \\ & \text { F-1 (07/01) } \\ & \text { F (03/99) } \\ & \hline \end{aligned}$ | [27833-64-3] | \$124 |
| 1370906 | Lynestrenol (20 mg) | FOB314 |  |  |  | [52-76-6] | \$203 |
| 1371002 | Lysergic Acid Diethylamide Tartrate CI (10 mg) (AS) (LSD) | 1 |  |  |  | [50-37-3] | \$207 |
| 1371501 | L-Lysine Acetate ( 200 mg ) | F1C027 |  |  | F (11/04) | [57282-49-2] | \$156 |
| 1372005 | L-Lysine Hydrochloride (200 mg) | H |  |  | G (07/00) | [657-27-2] | \$156 |
| 1373008 | Mafenide Acetate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [13009-99-9] | \$156 |
| 1374000 | Magaldrate ( 200 mg ) | F-1 |  |  |  | [74978-16-8] | \$156 |
| 1374306 | Magnesium Salicylate ( 200 mg ) | F2B081 |  |  | F-1 (01/04) | [18917-95-8] | \$156 |
| 1374408 | Malathion ( 500 mg ) | F-1 |  |  | F (08/01) | [121-75-5] | \$156 |
| 1374500 | Maleic Acid ( 300 mg ) | G |  |  | F-2 (12/00) | [110-16-7] | \$487 |
| 1374601 | Malic Acid (200 mg) | G0B158 |  |  | F-1 (04/03) | [617-48-1] | \$156 |
| 1374907 | Maltitol (200 mg) | G |  |  | F-1 (12/99) | [585-88-6] | \$156 |
| 1375003 | Maltol (4 g) (FCC) | G |  |  | F-1 (12/99) | [118-71-8] | \$156 |
| 1375058 | Mandelic Acid ( 500 mg ) | F |  |  |  | [90-64-2] | \$156 |
| 1375105 | Mannitol ( 200 mg ) | IOB212 |  |  | H (03/04) | [69-65-8] | \$156 |
| 1375207 | Maprotiline Hydrochloride ( 200 mg ) | H |  |  | G (07/02) | [10347-81-6] | \$156 |
| 1375309 | Mazindol CIV ( 350 mg ) | H |  |  | G (02/03) | [22232-71-9] | \$207 |
| 1375502 | Mebendazole ( 200 mg ) | G1C195 |  |  | G (11/04) | [31431-39-7] | \$156 |
| 1375706 | Mebrofenin ( 100 mg ) | F |  |  |  | [78266-06-5] | \$156 |
| 1376006 | Mecamylamine Hydrochloride ( 200 mg ) | F-2 |  |  |  | [826-39-1] | \$156 |
| 1376505 | Mechlorethamine Hydrochloride ( 100 mg ) (FOR U.S. SALE ONLY) | F-1 |  | 3 | F (09/00) | [55-86-7] | \$156 |
| 1377009 | Meclizine Hydrochloride ( 500 mg ) | I-1 |  |  |  | [31884-77-2] | \$156 |
| 1377508 | Meclocycline Sulfosalicylate ( 300 mg ) | G |  |  |  | [73816-42-9] | \$156 |
| 1377803 | Meclofenamate Sodium ( 500 mg ) | H |  |  |  | [6385-02-0] | \$156 |
| 1378001 | Medroxyprogesterone Acetate (200 mg) | H-2 |  |  | H-1 (04/03) | [71-58-9] | \$156 |
| 1378012 | Medroxyprogesterone Acetate Related Compound A ( 25 mg ) (4,5-beta-Dihydromedroxyprogesterone acetate) | F0C427 | $1.00 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | n/f | \$500 |
| 1379004 | Medrysone ( 500 mg ) | F |  |  |  | [2668-66-8] | \$156 |
| 1379605 | Mefenamic Acid (200 mg) | G0C025 |  |  | $\begin{aligned} & \text { F3A032 (08/04) } \\ & \text { F-2 (01/03) } \end{aligned}$ | [61-68-7] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1379106 | Megestrol Acetate ( 500 mg ) | I |  |  | H (05/00) | [595-33-5] | \$156 |
| 1379300 | Melphalan Hydrochloride ( 100 mg ) (FOR U.S. SALE ONLY) | H0B296 | 0.975 mg/mg (ai) | 3 | G (01/05) | [3223-07-2] | \$156 |
| 1381006 | Menadione (200 mg) (Vitamin K3) | H-3 |  |  | H-2 (02/00) | [58-27-5] | \$156 |
| 1381709 | Menthol (250 mg) | IOB049 |  |  | H (04/03) | [2216-51-5] | \$156 |
| 1381742 | Menthyl Anthranilate ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | F0B103 |  |  |  | [134-09-8] | \$156 |
| 1382009 | Mepenzolate Bromide (200 mg) | F |  |  |  | [76-90-4] | \$156 |
| 1383001 | Meperidine Hydrochloride CII (200 mg) | I |  |  | H-1 (12/99) | [50-13-5] | \$207 |
| 1384004 | Mephentermine Sulfate ( $250 \mathrm{mg} \mathrm{)}$ |  |  |  | F-1 (04/05) | [1212-72-2] | \$156 |
| 1385007 | Mephenytoin ( 250 mg ) | G |  |  |  | [50-12-4] | \$156 |
| 1386000 | Mephobarbital CIV (250 mg) | G |  |  | F (01/01) | [115-38-8] | \$207 |
| 1387002 | Mepivacaine Hydrochloride ( 200 mg ) | H |  |  | G-4 (02/99) | [1722-62-9] | \$156 |
| 1388005 | Meprednisone ( 200 mg ) | G |  |  |  | [1247-42-3] | \$156 |
| 1389008 | Meprobamate CIV (200 mg) | G-1 |  |  | G (03/02) | [57-53-4] | \$207 |
| 1390007 | Meprylcaine Hydrochloride (200 mg) | F |  |  |  | [956-03-6] | \$156 |
| 1391000 | 3-Mercapto-2-methylpropanoic Acid 1,2-Diphenylethylamine Salt ( 75 mg ) | G |  |  |  | n/f | \$487 |
| 1392002 | Mercaptopurine ( 500 mg ) | I2C263 |  |  | $\begin{aligned} & \hline \text { I-1 (10/04) } \\ & \text { I (07/02) } \\ & \text { H (12/99) } \\ & \hline \end{aligned}$ | [6112-76-1] | \$156 |
| 1392454 | Meropenem ( 300 mg ) | F0C201 |  |  |  | [119478-56-7] | \$182 |
| 1392705 | Mesalamine ( 200 mg ) | G1B001 |  |  | $\begin{aligned} & \hline \text { G (01/03) } \\ & \text { F-1 }(03 / 00) \\ & \hline \end{aligned}$ | [89-57-6] | \$156 |
| 1393005 | Mesoridazine Besylate ( 250 mg ) | J0C117 |  |  | I-1 (12/04) | [32672-69-8] | \$156 |
| 1394008 | Mestranol (200 mg) | K0C065 |  |  | $\begin{aligned} & J(07 / 04) \\ & I-1(09 / 99) \\ & \hline \end{aligned}$ | [72-33-3] | \$156 |
| 1395500 | Metaproterenol Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | F-3 |  |  |  | [5874-97-5] | \$156 |
| 1396003 | Metaraminol Bitartrate (200 mg) | F-3 |  |  |  | [33402-03-8] | \$156 |
| 1396309 | Metformin Hydrochloride (200 mg) | F0C209 |  |  |  | [1115-70-4] | \$182 |
| 1396310 | Metformin Related Compound A ( 50 mg ) (1Cyanoguanidine) | F0C210 |  |  |  | [461-58-5] | \$487 |
| 1396400 | Methacrylic Acid Copolymer Type A (200 mg) | G0B140 |  |  | F-2 (04/03) | n/f | \$156 |
| 1396502 | Methacrylic Acid Copolymer Type B (200 mg) | G0B141 |  |  | F-2 (04/03) | n/f | \$156 |
| 1396604 | Methacrylic Acid Copolymer Type C (100 mg) | G1B088 |  |  | G (08/03) | n/f | \$124 |
| 1397006 | Methacycline Hydrochloride (200 mg) | H |  |  | G (04/01) | [3963-95-9] | \$156 |
| 1398009 | Methadone Hydrochloride CII (200 mg) | IOB163 |  |  | H-1 (08/03) | [1095-90-5] | \$207 |
| 1399001 | Methamphetamine Hydrochloride CII (125 mg) | 1 |  |  |  | [51-57-0] | \$207 |
| 1401001 | Methantheline Bromide ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  |  | [53-46-3] | \$156 |
| 1402004 | Methapyrilene Fumarate (200 mg) | F-1 |  |  |  | [33032-12-1] | \$156 |
| 1404000 | Methaqualone Cl ( 500 mg ) | F-1 |  |  |  | [72-44-6] | \$207 |
| 1405002 | Metharbital CIII (200 mg) | F-2 |  |  | F-1 (07/99) | [50-11-3] | \$207 |
| 1406005 | Methazolamide ( 500 mg ) | H0B239 |  |  | G-1 (05/04) | [554-57-4] | \$156 |
| 1407008 | Methdilazine ( 200 mg ) | F-1 |  |  |  | [1982-37-2] | \$156 |
| 1408000 | Methdilazine Hydrochloride ( 200 mg ) | G |  |  |  | [1229-35-2] | \$156 |
| 1409003 | Methenamine ( 500 mg ) | H0C047 |  |  | G (05/04) | [100-97-0] | \$156 |
| 1409502 | Methenamine Hippurate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [5714-73-8] | \$156 |
| 1409604 | Methenamine Mandelate ( $200 \mathrm{mg} \mathrm{)}$ | G0C304 |  |  | $\begin{aligned} & \hline \text { F-2 }(01 / 05) \\ & \text { F-1 }(11 / 00) \\ & \hline \end{aligned}$ | [587-23-5] | \$156 |
| 1410002 | Methicillin Sodium (500 mg) | J0C333 |  |  | $\begin{aligned} & \text { I1B186 (11/04) } \\ & \mathrm{I}(03 / 03) \\ & \mathrm{H}(03 / 00) \\ & \hline \end{aligned}$ | [7246-14-2] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1411005 | Methimazole (200 mg) | G |  |  | F (02/01) | [60-56-0] | \$156 |
| 1411504 | L-Methionine ( 200 mg ) | G |  |  | F-2 (11/99) | [63-68-3] | \$156 |
| 1412008 | Methocarbamol (200 mg) | H2B029 |  |  | H-1 (03/04) | [532-03-6] | \$156 |
| 1413000 | Methohexital CIV ( 500 mg ) | F-2 |  |  |  | [18652-93-2] | \$207 |
| 1414003 | Methotrexate ( 500 mg ) | I |  |  |  | [59-05-2] | \$156 |
| 1415006 | Methotrimeprazine ( 125 mg ) | F-2 |  |  | F-1 (05/99) | [60-99-1] | \$124 |
| 1416009 | Methoxamine Hydrochloride ( 200 mg ) | F |  |  |  | [61-16-5] | \$156 |
| 1417001 | Methoxsalen ( 500 mg ) | H |  |  |  | [298-81-7] | \$156 |
| 1418004 | Methoxyflurane ( 1 mL ) | G |  |  |  | [76-38-0] | \$156 |
| 1419007 | Methoxyphenamine Hydrochloride ( 250 mg ) | F |  |  |  | [5588-10-3] | \$156 |
| 1421009 | Methscopolamine Bromide ( 200 mg ) | G1D004 | $0.999 \mathrm{mg} / \mathrm{mg}$ (dr) |  | G (02/05) | [155-41-9] | \$156 |
| 1422001 | Methsuximide ( 500 mg ) | F-2 |  |  | F-1 (08/99) | [77-41-8] | \$156 |
| 1424007 | Methyclothiazide ( 200 mg ) | G |  |  |  | [135-07-9] | \$156 |
| 1424018 | Methyclothiazide Related Compound A ( 100 mg ) (4-amino-6-chloro-N-3-methyl-m-benzenedisulfonamide) | G |  |  | F-2 (12/00) | n/f | \$487 |
| 1424222 | Methyl Benzylidene Camphor (200 mg) | F0B118 |  |  |  | [36861-47-9] | \$156 |
| 1424233 | Methyl Caprate ( 300 mg ) | F |  |  |  | [110-42-9] | \$156 |
| 1424244 | Methyl Caproate ( 300 mg ) | F |  |  |  | [106-70-7] | \$156 |
| 1424255 | Methyl Caprylate ( 300 mg ) | F |  |  |  | [111-11-5] | \$156 |
| 1424506 | Methylcellulose (1 g) (AS) | G0B222 |  |  | F-2 (05/03) | [9004-67-5] | \$156 |
| 1425000 | 4-Methyl-2,5-dimethoxyamphetamine Hydrochloride $\mathbf{C l}(25 \mathrm{mg})$ (AS) (STP) | F |  |  |  | [15589-00-1] | \$207 |
| 1426002 | Methyldopa ( 500 mg ) | I |  |  |  | [41372-08-1] | \$156 |
| 1427005 | Methyldopate Hydrochloride ( 200 mg ) | G-2 |  |  |  | [2508-79-4] | \$156 |
| 1428008 | Methylene Blue (250 mg) | G |  |  |  | [7220-79-3] | \$156 |
| 1429000 | Methylenedioxy-3,4-amphetamine Hydrochloride $\mathbf{C l}(25 \mathrm{mg})$ (AS) (MDA) | F-1 |  |  |  | [6292-91-7] | \$207 |
| 1430000 | Methylergonovine Maleate ( 50 mg ) (List Chemical) | J |  |  | I (05/02) | [57432-61-8] | \$156 |
| 1430305 | Methyl Laurate ( 500 mg ) | G0C356 | $0.998 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | F (03/05) | [111-82-0] | \$156 |
| 1430327 | Methyl Linoleate ( $5 \times 50 \mathrm{mg}$ ) | F |  |  |  | [112-63-0] | \$156 |
| 1430349 | Methyl Linolenate ( $5 \times 50 \mathrm{mg}$ ) | F |  |  |  | [301-00-8] | \$156 |
| 1430509 | $3-\mathrm{O}-\mathrm{Methylmethyldopa} \mathrm{( } 50 \mathrm{mg}$ ) | G-1 |  |  |  | $\mathrm{n} / \mathrm{f}$ | \$487 |
| 1431002 | Methyl 5-methyl-3-isoxazolecarboxylate ( 25 mg ) | F-1 |  |  | F (01/01) | n/f | \$487 |
| 1431501 | Methyl Myristate ( 300 mg ) | G0C357 | $0.998 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | F (03/05) | [124-10-7] | \$156 |
| 1431556 | Methyl Oleate ( 500 mg ) | G0C148 |  |  | F (04/04) | [112-62-9] | \$156 |
| 1431603 | Methyl Palmitate ( 300 mg ) | F |  |  |  | [112-39-0] | \$156 |
| 1431625 | Methyl Palmitoleate ( $300 \mathrm{mg} \mathrm{)}$ | F |  |  |  | n/f | \$156 |
| 1432005 | Methylparaben (125 mg) | J-1 |  |  | J (03/03)) | [99-76-3] | \$124 |
| 1433008 | Methylphenidate Hydrochloride CII (125 mg) | 11C241 |  | 2 | $\begin{aligned} & \hline \text { I (04/05) } \\ & \text { H (05/01) } \\ & \hline \end{aligned}$ | [298-59-9] | \$165 |
| 1434000 | Methylphenidate Hydrochloride Erythro Isomer CII ( 25 mg ) DISCONTINUED; please order 1434011 |  |  | 9 | $\begin{aligned} & \text { JOB294 (04/05) } \\ & \text { IOA006 (09/03) } \\ & \text { H-1 (01/03) } \\ & \text { H (06/01) } \\ & \hline \end{aligned}$ | [298-59-9] | \$560 |
| 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution CII ( 0.5 mL ) | F0C368 | $0.5 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$560 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1434022 | Methylphenidate Related Compound A ( 50 mg ) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride) | G |  |  | F-2 (10/99) | n/f | \$487 |
| 1435003 | Methylprednisolone ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  |  | [83-43-2] | \$156 |
| 1436006 | Methylprednisolone Acetate ( 200 mg ) | G-2 |  |  | G-1 (02/00) | [53-36-1] | \$156 |
| 1437009 | Methylprednisolone Hemisuccinate (200 mg) | IOC146 |  |  | H (07/04) | [2921-57-5] | \$156 |
| 1437508 | Methyl Stearate ( 300 mg ) | F |  |  |  | [112-61-8] | \$156 |
| 1438001 | Methyltestosterone CIII ( 200 mg ) | J |  |  | I (11/01) | [58-18-4] | \$207 |
| 1440003 | Methysergide Maleate ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  |  | [129-49-7] | \$156 |
| 1440808 | Metoclopramide Hydrochloride ( 500 mg ) | G |  |  | F-2 (06/99) | [54143-57-6] | \$156 |
| 1441006 | Metocurine lodide ( 300 mg ) | G |  |  |  | [7601-55-0] | \$156 |
| 1441200 | Metolazone ( 200 mg ) | G0B246 |  |  | F-1 (05/03) | [17560-51-9] | \$156 |
| 1441287 | Metoprolol Fumarate (200 mg) | F |  |  |  | [119637-66-0] | \$156 |
| 1441232 | Metoprolol Related Compound A (20 mg) ( (+/-)1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol) | F0C343 |  |  |  | n/f | \$520 |
| 1441243 | Metoprolol Related Compound B ( 50 mg ) ( $(+/-$ )1-chloro-2-hydroxy-3-[4-(2-methoxyethyl)phe-noxy]-propane) | F0C377 |  |  |  | n/f | \$520 |
| 1441254 | Metoprolol Related Compound C (20 mg) ( $(+/-$ )4-[2-Hydroxy-3-(1-methylethyl)aminopropoxy]benzaldehyde) | F0C344 |  |  |  | n/f | \$520 |
| 1441265 | Metoprolol Related Compound D (50 mg) ( $(+/-$ )N,N-bis-[2-hydroxy-3-[4-(2-methoxyethyl)phe-noxy]propyl](1-methylethyl)amine) | F0C378 |  |  |  | n/f | \$520 |
| 1441298 | Metoprolol Succinate ( $200 \mathrm{mg} \mathrm{)}$ | F0C415 | $0.998 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | [98418-47-4] | \$156 |
| 1441301 | Metoprolol Tartrate (200 mg) | H1B059 |  |  | $\begin{aligned} & \hline \text { H (01/04) } \\ & \text { G-1 }(11 / 99) \end{aligned}$ | [56392-17-7] | \$156 |
| 1441505 | Metrizamide ( 500 mg ) | F |  |  |  | [31112-62-6] | \$156 |
| 1442009 | Metronidazole ( 100 mg ) | I |  |  |  | [443-48-1] | \$156 |
| 1443001 | Metyrapone ( 200 mg ) | H |  |  | G (06/01) | [54-36-4] | \$156 |
| 1443205 | Metyrosine ( 200 mg ) | F |  |  |  | [672-87-7] | \$156 |
| 1443250 | Mexiletine Hydrochloride (200 mg) | F-2 |  |  | F-1 (09/02) | [5370-01-4] | \$156 |
| 1443307 | Mezlocillin Sodium ( 350 mg ) | G |  |  |  | [59798-30-0] | \$156 |
| 1443409 | Miconazole ( 200 mg ) | G-1 |  |  | G (07/02) | [22916-47-8] | \$156 |
| 1443500 | Miconazole Nitrate (200 mg) | I |  |  | H (06/99) | [22832-87-7] | \$156 |
| 1443850 | Powdered Milk Thistle Extract (250 mg) | F0B321 |  |  |  | [84604-20-6] | \$260 |
| 1443908 | Milrinone ( 500 mg ) | F0C050 |  |  |  | [78415-72-2] | \$260 |
| 1443919 | Milrinone Related Compound A ( 50 mg ) ( $1,6-$ Dihydro-2-methyl-6-oxo(3,4'-bipyridine)-5-carboxamide) | F0C051 |  |  |  | [80047-24-1] | \$487 |
| 1444004 | Minocycline Hydrochloride (200 mg) | 10 C 178 |  |  | $\begin{aligned} & \mathrm{H}-3(04 / 04) \\ & \mathrm{H}-2(07 / 02) \\ & \hline \end{aligned}$ | [13614-98-7] | \$156 |
| 1444208 | Minoxidil (125 mg) | H1C168 |  |  | $\begin{array}{\|l\|} \hline \mathrm{H}(03 / 04) \\ \mathrm{G}(05 / 99) \\ \hline \end{array}$ | [38304-91-5] | \$124 |
| 1444707 | Mitomycin (50 mg) | K |  |  | $J(07 / 01)$ | [50-07-7] | \$479 |
| 1445007 | Mitotane ( 500 mg ) | GOC044 |  |  | F (07/04) | [53-19-0] | \$156 |
| 1445200 | Mitoxantrone Hydrochloride ( 400 mg ) | H |  |  | G (03/01) | [70476-82-3] | \$498 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1445222 | Mitoxantrone Related Compound A Hydrochloride ( 30 mg ) ( 8 -amino-1,4-dihydroxy-5[[2-[(2-hy-droxyethyl)amino]ethyl]amino]-9,10-anthracenedione Hydrochloride) DISCONTINUED; Please order 1445211 |  |  |  | $\begin{aligned} & \text { F-1 (07/04) } \\ & \text { F (03/01) } \end{aligned}$ | n/f | \$208 |
| 1445211 | Mitoxantrone System Suitability Mixture ( 0.3 mg ) | F0D010 |  |  |  | n/f | \$500 |
| 1445459 | Molindone Hydrochloride ( 500 mg ) | F |  |  |  | [15622-65-8] | \$156 |
| 1445470 | Mometasone Furoate (200 mg) | G0B073 |  |  | $\begin{array}{\|l} \hline \text { F-1 (04/03) } \\ \text { F (02/01) } \\ \hline \end{array}$ | [83919-23-7] | \$156 |
| 1445481 | Monensin Sodium (200 mg) | F0B293 |  |  |  | [22373-78-0] | \$156 |
| 1445506 | Monobenzone ( 200 mg ) | F |  |  |  | [103-16-2] | \$156 |
| 1445801 | Mono- and Di-acetylated Monoglycerides ( 200 mg ) | F |  |  |  | [68990-54-5] | \$156 |
| 1446000 | Monoglycerides (125 mg) | H |  |  |  | [68990-53-4] | \$124 |
| 1446804 | Monostearyl Maleate ( 100 mg ) | G |  |  | F-2 (04/00) | [2424-62-6] | \$487 |
| 1446950 | Moricizine Hydrochloride ( 100 mg ) |  |  |  | F (03/05) | [29560-58-5] | \$156 |
| 1447002 | Morphine Monohydrate CII (50 mg) (AS) | G |  |  |  | [6009-81-0] | \$207 |
| 1448005 | Morphine Sulfate CII (500 mg) | M0D016 | $0.999 \mathrm{mg} / \mathrm{mg}$ (an) | 2 | $\begin{array}{\|l\|} \hline \text { LOB056 (04/05) } \\ \text { K (06/03) } \\ \mathrm{J}-1(07 / 00) \\ \hline \end{array}$ | [6211-15-0] | \$332 |
| 1448504 | Moxalactam Disodium ( 500 mg ) | F-1 |  |  |  | [64953-12-4] | \$156 |
| 1448901 | Mupirocin (50 mg) | F2C158 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (12/04) } \\ \text { F (03/02) } \\ \hline \end{array}$ | [12650-69-0] | \$156 |
| 1448923 | Mupirocin Lithium ( 100 mg ) | H0C176 | 926 ug/mg (ai) | 2 | $\begin{aligned} & \mathrm{G}(03 / 05) \\ & \mathrm{F}(02 / 01) \\ & \hline \end{aligned}$ | [73346-79-9] | \$156 |
| 1449008 | Myristyl Alcohol (1 g) | G |  |  | F (02/02) | [112-72-1] | \$156 |
| 1449518 | Nabumetone (200 mg) | F0C072 |  |  |  | [42924-53-8] | \$156 |
| 1449700 | Nadolol (200 mg) |  |  |  | $\begin{aligned} & \text { F-3 }(04 / 05) \\ & \text { F-2 (04/02) } \\ & \hline \end{aligned}$ | [42200-33-9] | \$156 |
| 1450007 | Nafcillin Sodium (200 mg) | H |  |  |  | [7177-50-6] | \$156 |
| 1450404 | Naftifine Hydrochloride ( 200 mg ) | F |  |  |  | [65473-14-5] | \$156 |
| 1451000 | Nalidixic Acid (200 mg) | G |  |  |  | [389-08-2] | \$156 |
| 1452002 | Nalorphine Hydrochloride CIII (250 mg) | I |  |  |  | [57-29-4] | \$207 |
| 1453005 | Naloxone (125 mg) | LOB124 |  |  | $\begin{array}{\|l\|} \hline \text { K-1 }(12 / 02) \\ \text { K (07/01) } \\ \hline \end{array}$ | [465-65-6] | \$124 |
| 1453504 | Naltrexone (200 mg) | H0C150 |  |  | $\begin{aligned} & \text { G1B039 (03/04) } \\ & \text { G (02/03) } \end{aligned}$ | [16590-41-3] | \$156 |
| 1453526 | Naltrexone Related Compound A CII (30 mg) ( N -(3-butenyl)-noroxymorphone Hydrochloride) | F |  |  |  | n/f | \$207 |
| 1454008 | Nandrolone CIII ( 50 mg ) |  |  |  | F-3 (04/05) | [434-22-0] | \$560 |
| 1455000 | Nandrolone Decanoate CIII ( 250 mg ) | 1 |  |  |  | [360-70-3] | \$207 |
| 1456003 | Nandrolone Phenpropionate CIII (250 mg) | H |  |  |  | [62-90-8] | \$207 |
| 1457006 | Naphazoline Hydrochloride (200 mg) | K |  |  |  | [550-99-2] | \$156 |
| 1457301 | Naproxen ( 200 mg ) | I-1 |  |  | $\begin{array}{\|l\|} \hline \text { I (03/03) } \\ \text { H-1 }(01 / 01) \end{array}$ | [22204-53-1] | \$156 |
| 1457403 | Naproxen Sodium (200 mg) | 1 |  |  |  | [26159-34-2] | \$156 |
| 1457469 | Naratriptan Hydrochloride ( 125 mg ) | F0C360 | $0.998 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | [143388-64-1] | \$208 |
| 1457505 | Natamycin (200 mg) | 1 |  |  | H (11/99) | [7681-93-8] | \$156 |
| 1458009 | Neomycin Sulfate (200 mg) | L-2 |  |  | $\begin{array}{\|l} \hline \text { L-1 (09/01) } \\ \text { L (02/99) } \\ \hline \end{array}$ | [1405-10-3] | \$156 |
| 1459001 | Neostigmine Bromide (200 mg) | G |  |  |  | [114-80-7] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1460000 | Neostigmine Methylsulfate (200 mg) | 1 |  |  | H (07/00) | [51-60-5] | \$156 |
| 1460500 | Netilmicin Sulfate ( 500 mg ) | 10 C 388 | $653 \mathrm{ug} / \mathrm{mg}$ (dr) |  | $\begin{aligned} & \text { H (01/05) } \\ & \text { G }(05 / 02) \end{aligned}$ | [56391-57-2] | \$156 |
| 1460714 | Nevirapine Hemihydrate (100 mg) | F0D034 |  | 1 |  | [129618-40-2] | \$156 |
| 1460725 | Nevirapine Related Compound A ( 15 mg ) ( 5,11 -Dihydro-6H-11-ethyl-4-methyl-dipyrido[3,2b2', 3'-e][1,4]diazepin-6-one) | F0D035 |  | 1 |  | n/f | \$487 |
| 1460736 | Nevirapine Related Compound B ( 15 mg ) $(5,11-$ Dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one) | F0D033 |  | 1 |  | n/f | \$487 |
| 1461003 | Niacin (200 mg) | H2C121 |  |  | H-1 (01/05) | [59-67-6] | \$156 |
| 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) | M-1 |  |  | M (02/01) | [98-92-0] | \$156 |
| 1463304 | Nicotine Bitartrate Dihydrate ( 500 mg ) | G |  |  | F (05/99) | [6019-06-3] | \$156 |
| 1463508 | Nifedipine ( 125 mg ) | J0B243 |  |  | I-1 (04/04) | [21829-25-4] | \$124 |
| 1463600 | Nifedipine Nitrophenylpyridine Analog ( 25 mg ) | K |  |  | J (04/01) | n/f | \$487 |
| 1463701 | Nifedipine Nitrosophenylpyridine Analog ( 25 mg ) | K |  |  | J (07/02) | n/f | \$487 |
| 1464001 | Nitrofurantoin ( 500 mg ) | J |  |  | I-1 (11/02) | [67-20-9] | \$156 |
| 1465004 | Nitrofurazone ( 200 mg ) | H-1 |  |  | H (09/01) | [59-87-0] | \$156 |
| 1465503 | Nitrofurfural Diacetate ( 100 mg ) | G0D066 | $0.99 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | F-1 (12/04) | [92-55-7] | \$487 |
| 1466007 | Nitrofurazone Related Compound A ( 500 mg ) (5-Nitro-2-furfuraldazine) | H0B100 |  |  | G (07/03) | n/f | \$487 |
| 1466506 | Diluted Nitroglycerin (5 ampules, approx. 200 mg of a $0.948 \%$ solution in propylene glycol each) | G |  |  |  | [55-63-0] | \$156 |
| 1467804 | Nizatidine (200 mg) | G |  |  | F-1 (06/00) | [76963-41-2] | \$156 |
| 1467950 | Nonoxynol 9 ( 0.5 mL ) | H-1 |  |  | H (03/02) | [26027-38-3] | \$156 |
| 1468002 | Nonoxynol 10 (200 mg) | F |  |  |  | [26027-38-3] | \$156 |
| 1468400 | Nordazepam CIV ( 50 mg ) (7-Chloro-1,3-dihy-dro-5-phenyl-2H-1,4-benzodiazepin-2-one) | H1B035 |  |  | $\begin{aligned} & \hline \mathrm{H}(03 / 03) \\ & \mathrm{G}(03 / 00) \\ & \hline \end{aligned}$ | [1088-11-5] | \$560 |
| 1468501 | Norepinephrine Bitartrate ( 125 mg ) | I0C381 |  | 2 | H (04/05) | [69815-49-2] | \$124 |
| 1469005 | Norethindrone ( 200 mg ) | J1B065 |  |  | $\begin{aligned} & \hline J-1(05 / 03) \\ & J(07 / 02) \\ & 1-1(03 / 01) \\ & \hline \end{aligned}$ | [68-22-4] | \$156 |
| 1470004 | Norethindrone Acetate (100 mg) | J0B072 |  |  | $\begin{aligned} & \hline \text { I (04/03) } \\ & \text { H (06/99) } \end{aligned}$ | [51-98-9] | \$156 |
| 1471007 | Norethynodrel ( 200 mg ) | G |  |  |  | [68-23-5] | \$156 |
| 1471506 | Norfloxacin (200 mg) | H |  |  | G (04/01) | [70458-96-7] | \$156 |
| 1471914 | Norgestimate (200 mg) | F0C086 |  |  |  | [35189-28-7] | \$156 |
| 1472000 | Norgestrel ( 125 mg ) | J0C269 |  |  | $\begin{array}{\|l\|l\|} \hline I(07 / 04) \\ H(05 / 99) \\ \hline \end{array}$ | [6533-00-2] | \$124 |
| 1473002 | Noroxymorphone Hydrochloride CII (50 mg) | H1C177 |  |  | H (11/04) | n/f | \$560 |
| 1474005 | Nortriptyline Hydrochloride ( 200 mg ) | 1 |  |  | H (04/00) | [894-71-3] | \$156 |
| 1474504 | Noscapine ( 500 mg ) | G |  |  |  | [128-62-1] | \$156 |
| 1475008 | Novobiocin ( 200 mg ) |  |  |  | G-2 (05/05) | [303-81-1] | \$156 |
| 1476000 | Nylidrin Hydrochloride (200 mg) | F-2 |  |  |  | [849-55-8] | \$156 |
| 1477003 | Nystatin (200 mg) | N1B004 |  |  | N (01/03) | [1400-61-9] | \$156 |
| 1477900 | Octinoxate ( 500 mg ) (Octyl Methoxycinnamate) | G0C024 |  |  | F0B032 (12/03) | [5466-77-3] | \$156 |
| 1477411 | Octocrylene ( 500 mg ) | G0C211 |  |  | FOB104 (05/04) | [6197-30-4] | \$156 |
| 1477502 | Octoxynol 9 ( 200 mg ) | G |  |  | F-2 (07/00) | [9002-93-1] | \$156 |
| 1477808 | Octyldodecanol (200 mg) | G |  |  | F-1 (07/99) | [5333-42-6] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1477943 | Octyl Salicylate (400 mg) | F0B091 |  |  |  | [118-60-5] | \$156 |
| 1478108 | Ofloxacin (200 mg) | F-2 |  |  | F-1 (08/02) | [82419-36-1] | \$156 |
| 1478152 | Oleoyl Polyoxylglycerides ( 100 mg ) | F0C313 |  | 1 |  | n/f | \$156 |
| 1478505 | Omeprazole (200 mg) | H1B211 |  |  | $\begin{aligned} & \text { H (05/04) } \\ & \text { G-1 (04/02) } \\ & \text { G (09/01) } \\ & \hline \end{aligned}$ | [73590-58-6] | \$156 |
| 1478582 | Ondansetron Hydrochloride ( 300 mg ) | F0C222 |  |  |  | [103639-04-9] | \$208 |
| 1478593 | Ondansetron Related Compound A (50 mg) (3[(Dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride) | FOC191 |  |  |  | [119812-29-2] | \$487 |
| 1478618 | Ondansetron Related Compound C ( 50 mg ) (1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4one) | F0C251 |  |  |  | [27397-31-1] | \$487 |
| 1478629 | Ondansetron Related Compound D ( 50 mg ) (1,2,3,9-Tetrahydro-9-methyl-3-methylene-4H-carbazol-4-one) | F0C226 |  |  |  | n/f | \$487 |
| 1479009 | Orphenadrine Citrate (200 mg) | G |  |  | F-4 (05/02) | [4682-36-4] | \$156 |
| 1481000 | Oxacillin Sodium ( 200 mg ) | $J$ |  |  | 1 (03/02) | [7240-38-2] | \$156 |
| 1481500 | Oxamniquine ( 200 mg ) | F |  |  |  | [21738-42-1] | \$156 |
| 1481703 | Oxamniquine Related Compound A ( 25 mg ) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolinemethyl methanesulfonate) | F |  |  |  | n/f | \$487 |
| 1481805 | Oxamniquine Related Compound B ( 25 mg ) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-5-nitro-6-quinolinemethanol) | F |  |  |  | n/f | \$487 |
| 1482003 | Oxandrolone CIII ( 50 mg ) | G0B220 |  |  | F-4 (07/03) | [53-39-4] | \$207 |
| 1482207 | Oxaprozin (200 mg) | F0C115 |  |  |  | [21256-18-8] | \$156 |
| 1483006 | Oxazepam CIV (200 mg) | G-1 |  |  | G (12/00) | [604-75-1] | \$207 |
| 1483301 | Oxfendazole (200 mg) | FOC128 |  |  |  | [53716-50-0] | \$156 |
| 1483505 | Oxprenolol Hydrochloride ( 200 mg ) | IOC344 |  |  | H (02/05) | [6452-73-9] | \$156 |
| 1484009 | Oxtriphylline ( 500 mg ) | G |  |  |  | [4499-40-5] | \$156 |
| 1485001 | Oxybenzone ( 150 mg ) | H0B263 |  |  | $\begin{array}{\|l\|} \hline \text { G (11/03) } \\ \text { F-2 (12/99) } \\ \hline \end{array}$ | [131-57-7] | \$156 |
| 1485103 | Oxybutynin Chloride (200 mg) | G-1 |  |  | G (11/02) | [1508-65-2] | \$156 |
| 1485114 | Oxybutynin Related Compound A ( 100 mg ) (Phenylcyclohexylglycolic Acid) | G |  |  | F-2 (01/00) | [4335-77-7] | \$487 |
| 1485125 | Oxybutynin Related Compound B ( 20 mg ) (Cyclohexyl mandelic acid methyl ester) | F0D061 |  | 1 |  | [10399-13-0] | \$487 |
| 1485136 | Oxybutynin Related Compound C (20 mg) (4(Ethylmethyamino) but-2-ynyl (+/-)-2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride) | F0D062 |  | 1 |  | n/f | \$487 |
| 1485191 | Oxycodone CII (200 mg) | 10B046 |  |  | $\begin{aligned} & \hline \mathrm{H}(01 / 03) \\ & \mathrm{G}-1(01 / 01) \\ & \hline \end{aligned}$ | [76-42-6] | \$207 |
| 1486004 | Oxymetazoline Hydrochloride ( 200 mg ) | J0C206 |  |  | 1 (03/05) | [2315-02-8] | \$156 |
| 1487007 | Oxymetholone CIII (200 mg) | G1B247 |  |  | G (10/03) | [434-07-1] | \$207 |
| 1488000 | Oxymorphone CII ( 500 mg ) | H0B214 |  |  | G (03/03) | [76-41-5] | \$207 |
| 1489002 | Oxyphenbutazone (1 g) | H |  |  |  | [7081-38-1] | \$156 |
| 1490103 | Oxyquinoline Sulfate (200 mg) | F-1 |  |  | F (07/02) | [134-31-6] | \$156 |
| 1491004 | Oxytetracycline (200 mg) | J0C084 | $913 \mathrm{ug} / \mathrm{mg}$ (ai) |  | I-1 (10/04) | [6153-64-6] | \$156 |
| 1491300 | Oxytocin (5 vials, 46 USP units per vial) | F |  |  |  | [50-56-6] | \$156 |
| 1491332 | Paclitaxel ( 200 mg ) | FOC180 |  |  |  | [33069-62-4] | \$1,508 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1491343 | Paclitaxel Related Compound A (20 mg) (Cephalomannine) | F0C179 |  |  |  | [71610-00-9] | \$754 |
| 1491354 | Paclitaxel Related Compound B (20 mg) (10-Deacetyl-7-epipaclitaxel) | F0C181 |  |  |  | nf | \$754 |
| 1491503 | Padimate O ( 300 mg ) | H0B154 |  |  | G (04/03) | [21245-02-3] | \$156 |
| 1492007 | Palmitic Acid ( 500 mg ) | I |  |  |  | [57-10-3] | \$156 |
| 1493000 | Pamoic Acid (250 mg) | G-4 |  |  | G-3 (01/03) | [130-85-8] | \$156 |
| 1494057 | Pancreatin Amylase and Protease (2 g) | 1 |  |  | H (10/00) | [8049-47-6] | \$156 |
| 1494079 | Pancreatin Lipase (2 g) | 1 |  |  | $\mathrm{H}-1$ (03/01) | [8049-47-6] | \$156 |
| 1494501 | Panthenol, Racemic ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | F-1 (02/00) | [16485-10-2] | \$156 |
| 1494807 | Pantolactone ( 500 mg ) | F |  |  |  | [599-04-2] | \$487 |
| 1495005 | Papain (1 g) | H |  |  | G (12/01) | [9001-73-4] | \$156 |
| 1496008 | Papaverine Hydrochloride ( 200 mg ) | H |  |  |  | [61-25-6] | \$156 |
| 1497000 | Paramethadione ( 500 mg ) | G |  |  |  | [115-67-3] | \$156 |
| 1498003 | Paramethasone Acetate (200 mg) | G |  |  | F-1 (05/01) | [1597-82-6] | \$156 |
| 1498706 | Parbendazole ( 200 mg ) | F |  |  |  | [14255-87-9] | \$156 |
| 1499006 | Pargyline Hydrochloride (200 mg) | F-1 |  |  |  | [306-07-0] | \$156 |
| 1500003 | Paromomycin Sulfate ( 125 mg ) | G |  |  | F-3 (01/01) | [1263-89-4] | \$156 |
| 1500218 | Paroxetine Hydrochloride ( 350 mg ) | G0D003 | $0.972 \mathrm{mg} / \mathrm{mg}$ (ai) |  | F0B288 (09/04) | [110429-35-1] | \$156 |
| 1500229 | Paroxetine Related Compound A ( 20 mg ) (trans-4-(p-methoxyphenyl)-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine Hydrochloride) | F0B172 |  |  |  | n/f | \$487 |
| 1500230 | Paroxetine Related Compound B ( 20 mg ) (trans-4-phenyl-3-([(3,4-methylenedioxy)phenoxy]methylpiperidine acetate) | FOB189 |  |  |  | n/f | \$487 |
| 1500240 | Paroxetine Related Compound C (15 mg) ((+)-trans-Paroxetine hydrochloride) | G0D053 | $0.96 \mathrm{mg} / \mathrm{mg}$ (ai) | 2,3 | F0B192 (05/05) | [130855-30-0] | \$487 |
| 1500251 | Paroxetine Related Compound D ( 15 mg ) ((-)-cis-Paroxetine hydrochloride) | FOC228 |  |  |  | n/f | \$487 |
| 1500400 | Parthenolide ( 25 mg ) | F |  |  |  | [20554-84-1] | \$156 |
| 1500502 | Particle Count Set (2 blanks and 2 suspensions) | I |  |  | H (09/02) | n/f | \$487 |
| 1500808 | Penbutolol Sulfate (200 mg) | F |  |  |  | [38363-32-5] | \$156 |
| 1501006 | Penicillamine (200 mg) | H1B164 |  |  | H (01/04) | [52-67-5] | \$156 |
| 1501108 | Penicillamine Disulfide ( 100 mg ) | H |  |  | G (07/00) | [20902-45-8] | \$487 |
| 1502009 | Penicillin G Benzathine (200 mg) | J |  |  |  | [41372-02-5] | \$156 |
| 1502508 | Penicillin G Potassium ( $200 \mathrm{mg} \mathrm{)}$ | I |  |  | H (02/99) | [113-98-4] | \$156 |
| 1502552 | Penicillin G Procaine ( 200 mg ) | G0C271 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (08/04) } \\ \text { F (03/99) } \\ \hline \end{array}$ | [6130-64-9] | \$156 |
| 1502701 | Penicillin G Sodium ( 200 mg ) | L-3 |  |  | L-2 (09/01) | [69-57-8] | \$156 |
| 1504489 | Penicillin V ( 200 mg ) | F |  |  |  | [87-08-1] | \$156 |
| 1504503 | Penicillin V Potassium ( 200 mg ) | H0C213 |  |  | $\begin{aligned} & \text { G-1 (06/04) } \\ & \text { G (06/00) } \\ & \hline \end{aligned}$ | [132-98-9] | \$156 |
| 1505007 | Pentazocine CIV (500 mg) | 10 C 418 | $0.998 \mathrm{mg} / \mathrm{mg}$ (dr) |  | $\begin{aligned} & \hline \text { H }(01 / 05) \\ & \text { G-1 }(11 / 00) \\ & \hline \end{aligned}$ | [359-83-1] | \$207 |
| 1505506 | Pentetic Acid (100 mg) | F-1 |  |  | F (09/01) | [67-43-6] | \$156 |
| 1507002 | Pentobarbital CII (200 mg) | H3C144 |  |  | $\begin{array}{\|l\|l} \hline \mathrm{H}-2(07 / 04) \\ \mathrm{H}-1 & (08 / 02) \\ \hline \end{array}$ | [76-74-4] | \$207 |
| 1508901 | Pentoxifylline (200 mg) | F0B202 |  |  |  | [6493-05-6] | \$156 |
| 1510007 | Pepsin (5 g) | F-2 |  |  |  | [9001-75-6] | \$156 |
| 1510801 | Perflubron ( 0.5 mL ) | G0C103 |  |  | F (04/04) | [423-55-2] | \$156 |
| 1510845 | Pergolide Mesylate ( 200 mg ) | F1C225 |  |  | F (07/04) | [66104-23-2] | \$194 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1510867 | Pergolide Sulfoxide ( 50 mg ) | FOB014 |  |  |  | [72822-01-6] | \$194 |
| 1511000 | Perphenazine ( 200 mg ) | J0B249 |  |  | I (10/03) | [58-39-9] | \$156 |
| 1511203 | Perphenazine Sulfoxide (100 mg) | G-1 |  |  | G (07/02) | [10078-25-8] | \$487 |
| 1512002 | Phenacemide ( 250 mg ) | F |  |  |  | [63-98-9] | \$156 |
| 1513005 | Phenacetin ( 500 mg ) | H-1 |  |  | H (09/00) | [62-44-2] | \$156 |
| 1514008 | Phenacetin Melting Point Standard ( 500 mg ) (Approximately 135 degrees) | H3A009 |  |  | $\begin{aligned} & \mathrm{H}-2(02 / 03) \\ & \mathrm{H}-1(06 / 01) \\ & \hline \end{aligned}$ | [62-44-2] | \$92 |
| 1515000 | Phenazopyridine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H0C426 | $0.998 \mathrm{mg} / \mathrm{mg}$ (dr) |  | G-4 (12/04) | [136-40-3] | \$156 |
| 1516003 | Phencyclidine Hydrochloride CII ( 25 mg ) (AS) | G1B025 |  |  | G (12/02) | [956-90-1] | \$207 |
| 1516502 | Phendimetrazine Tartrate CIII ( 350 mg ) | G |  |  | F (01/01) | [50-58-8] | \$207 |
| 1517006 | Phenelzine Sulfate (200 mg) | G |  |  | F-1 (04/02) | [156-51-4] | \$156 |
| 1517301 | D-Phenethicillin Potassium (200 mg) | F |  |  |  | n/f | \$487 |
| 1517607 | L-Phenethicillin Potassium (200 mg) | F |  |  |  | n/f | \$156 |
| 1520000 | Phenformin Hydrochloride (200 mg) | G |  |  |  | [834-28-6] | \$156 |
| 1522006 | Phenindione (250 mg) | F |  |  |  | [83-12-5] | \$156 |
| 1522301 | Pheniramine Maleate ( 100 mg ) | F1C342 |  |  | F (08/04) | [132-20-7] | \$156 |
| 1523009 | Phenmetrazine Hydrochloride CII (200 mg) | F-2 |  |  |  | [1707-14-8] | \$207 |
| 1524001 | Phenobarbital CIV (200 mg) | $J$ |  |  |  | [50-06-6] | \$207 |
| 1524908 | Phenolphthalein ( 250 mg ) | F-3 |  |  |  | [77-09-8] | \$156 |
| 1525004 | Phenolsulfonphthalein ( 100 mg ) | F-2 |  |  |  | [143-74-8] | \$156 |
| 1526007 | Phenoxybenzamine Hydrochloride ( $250 \mathrm{mg} \mathrm{)}$ | G |  |  |  | [63-92-3] | \$156 |
| 1528002 | Phensuximide ( 500 mg ) | G |  |  | F-1 (03/01) | [86-34-0] | \$156 |
| 1528501 | Phentermine Hydrochloride CIV (200 mg) | H0B309 |  |  | G (08/03) | [1197-21-3] | \$207 |
| 1529005 | Phentolamine Hydrochloride ( 300 mg ) | F |  |  |  | [73-05-2] | \$156 |
| 1530004 | Phentolamine Mesylate (200 mg) | 1 |  |  |  | [65-28-1] | \$156 |
| 1530503 | L-Phenylalanine (200 mg) | H |  |  | G (02/02) | [63-91-2] | \$156 |
| 1530809 | Phenylbenzimidazole Sulfonic Acid (200 mg) | F |  |  |  | [27503-81-7] | \$156 |
| 1531007 | Phenylbutazone (250 mg) | J0A008 |  |  | 1-1 (02/03) | [50-33-9] | \$156 |
| 1533002 | Phenylephrine Hydrochloride (125 mg) | K1C290 |  | 2 | $\begin{array}{\|l\|} \hline \mathrm{K}(03 / 05) \\ \mathrm{J}(02 / 99) \end{array}$ | [61-76-7] | \$124 |
| 1533308 | 5-Phenylhydantoin (100 mg) | F |  |  |  | [89-24-7] | \$487 |
| 1533851 | Phenylpropanediol ( 100 mg ) | F |  |  |  | n/f | \$487 |
| 1533909 | Phenylpropanolamine Bitartrate ( 100 mg ) (List Chemical) | F |  |  |  | [67244-90-0] | \$156 |
| 1534005 | Phenylpropanolamine Hydrochloride ( 250 mg ) (List Chemical) | J |  |  | I (02/02) | [154-41-6] | \$156 |
| 1535008 | Phenytoin (200 mg) | I2B233 |  |  | $\begin{array}{\|l\|} \hline \text { I-1 (03/04) } \\ \text { I (04/01) } \\ \hline \end{array}$ | [57-41-0] | \$156 |
| 1535507 | Phenytoin Sodium (200 mg) | H |  |  | G (05/99) | [630-93-3] | \$156 |
| 1535019 | Phenytoin Related Compound A ( 50 mg ) (2,2Diphenylglycine) | F0C155 |  |  |  | [3060-50-2] | \$487 |
| 1535020 | Phenytoin Related Compound B ( 50 mg ) (al-pha-((aminocarbonyl)amino)-alpha-phenyl benzeneacetic acid) | F0C157 |  |  |  | [6802-95-5] | \$487 |
| 1535700 | Phosphated Riboflavin ( 100 mg ) | G1B286 |  |  | G (07/04) | [6184-17-4] | \$124 |
| 1537003 | Physostigmine Salicylate ( 200 mg ) | H-1 |  |  | H (06/00) | [57-64-7] | \$156 |
| 1538006 | Phytonadione (500 mg) (Vitamin K1) | N0B303 |  |  | $\begin{aligned} & \mathrm{M}-1(07 / 04) \\ & \mathrm{M}(09 / 01) \\ & \hline \end{aligned}$ | [84-80-0] | \$156 |
| 1538505 | Pilocarpine ( 300 mg ) | F |  |  |  | [92-13-7] | \$156 |
| 1538902 | Pilocarpine Hydrochloride ( 200 mg ) | H |  |  |  | [54-71-7] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1539009 | Pilocarpine Nitrate (200 mg) | 1 |  |  |  | [148-72-1] | \$156 |
| 1539508 | Pimozide ( 200 mg ) | G |  |  |  | [2062-78-4] | \$156 |
| 1539701 | Pindolol ( 200 mg ) | IOB210 |  |  | H-1 (12/04) | [13523-86-9] | \$156 |
| 1541000 | Piperacetazine ( 250 mg ) | F |  |  |  | [3819-00-9] | \$156 |
| 1541500 | Piperacillin ( 500 mg ) | H |  |  |  | [66258-76-2] | \$156 |
| 1541703 | Piperazine Adipate ( 200 mg ) | F |  |  |  | [142-88-1] | \$156 |
| 1541805 | Piperazine Citrate (200 mg) | F |  |  |  | [144-29-6] | \$156 |
| 1541907 | Piperazine Dihydrochloride (200 mg) | F |  |  |  | [142-64-3] | \$156 |
| 1542003 | Piperazine Phosphate ( 200 mg ) | F |  |  |  | [14538-56-8] | \$156 |
| 1543006 | Piperidolate Hydrochloride ( 200 mg ) | F |  |  |  | [129-77-1] | \$156 |
| 1544508 | Piroxicam (200 mg) | H |  |  | G (01/99) | [36322-90-4] | \$156 |
| 1545205 | Plicamycin ( 50 mg ) | H |  |  | G (04/00) | [18378-89-7] | \$479 |
| 1545409 | Polacrilex Resin (100 mg) | F |  |  |  | n/f | \$156 |
| 1545500 | Polacrilin Potassium (200 mg) | F-2 |  |  | F-1 (09/00) | n/f | \$156 |
| 1546106 | Poloxalene ( 500 mg ) | F0C009 |  |  |  | [9003-11-6] | \$156 |
| 1546300 | Polydimethylsiloxane ( 500 mg ) | H0C020 |  |  | $\begin{array}{ll} \text { G-5 (05/04) } \\ \text { G-4 }(06 / 01) \end{array}$ | [9016-00-6] | \$156 |
| 1546707 | Polyethylene, High Density (3 strips) | G |  |  | F-1 (04/01) | [9002-88-4] | \$156 |
| 1546809 | Polyethylene, Low Density (3 strips) | G1B166 |  |  | $\begin{array}{\|l\|} \hline \text { G (06/04) } \\ \text { F-2 (12/99) } \\ \hline \end{array}$ | [9002-88-4] | \$156 |
| 1546853 | Polyethylene Oxide ( 100 mg ) | F-1 |  |  |  | [25322-68-3] | \$156 |
| 1546900 | Polyethylene Terephthalate (PET) (3 Strips) | F |  |  |  | [25038-59-9] | \$156 |
| 1546922 | Polyethylene Terephthalate G (PETG) (3 Strips) | F |  |  |  | [25640-14-6] | \$156 |
| 1547007 | Polymyxin B Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | K |  |  | J-1 (09/99) | [1405-20-5] | \$156 |
| 1547404 | Polyoxyl 50 Stearate (200 mg) | F |  |  |  | [9004-99-3] | \$156 |
| 1547903 | Polyoxyl 40 Stearate (200 mg) | F-2 |  |  | F-1 (05/00) | [9004-99-3] | \$156 |
| 1548000 | Polythiazide ( 200 mg ) | F-1 |  |  |  | [346-18-9] | \$156 |
| 1548134 | Potassium Bicarbonate (1 g) (AS) | FOD074 | 99.9\% (dr) | 1 |  | [298-14-6] | \$156 |
| 1550001 | Potassium Gluconate (200 mg) | H0C064 |  |  | G (06/04) | [299-27-4] | \$156 |
| 1551004 | Potassium Guaiacolsulfonate ( 500 mg ) | J0B292 |  |  | $\begin{array}{\|l\|} \hline \text { I-1 (07/03) } \\ \text { I (11/00) } \\ \hline \end{array}$ | [78247-49-1] | \$156 |
| 1551150 | Potassium Sucrose Octasulfate ( $300 \mathrm{mg} \mathrm{)}$ | 10B283 |  |  | $\begin{array}{\|l} \hline \text { H0B119 (04/04) } \\ \text { G-1 (04/03) } \\ \text { G (02/01) } \\ \hline \end{array}$ | [76578-81-9] | \$156 |
| 1551300 | Potassium Trichloroammineplatinate (20 mg) | 10D022 | $0.84 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{aligned} & \hline \text { H0B149 (12/04) } \\ & \text { G-1 (01/03) } \\ & \text { G (07/99) } \\ & \hline \end{aligned}$ | [13820-91-2] | \$487 |
| 1551503 | Povidone (100 mg) | F-1 |  |  | F (11/01) | [9003-39-8] | \$156 |
| 1553000 | Pralidoxime Chloride ( $200 \mathrm{mg} \mathrm{)}$ | G-2 |  |  | $\begin{aligned} & \text { G-1 (03/01) } \\ & \text { G (08/99) } \end{aligned}$ | [51-15-0] | \$156 |
| 1554002 | Pramoxine Hydrochloride ( 500 mg ) | 1 |  |  | H (11/02) | [637-58-1] | \$156 |
| 1554501 | Prazepam CIV ( 500 mg ) | G0C066 |  |  | F-1 (11/02) | [2955-38-6] | \$207 |
| 1554603 | Praziquantel ( 200 mg ) | G |  |  | $\begin{array}{\|l\|l\|l\|l\|l\|} \hline \text { F-3 } \\ \text { F-2 }(09 / 00) \\ \hline \end{array}$ | [55268-74-1] | \$156 |
| 1554658 | Praziquantel Related Compound A (50 mg) (2-benzoyl-1,2,3,6,7,11b-hexahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one) | F-1 |  |  |  | n/f | \$487 |
| 1554669 | Praziquantel Related Compound B (50 mg) (2-(cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one) | F-2 |  |  | F-1 (06/00) | n/f | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1554670 | Praziquantel Related Compound C $(50 \mathrm{mg})(2-$ (N-formylhexahydrohippuroyl-1,2,3,4-tetrahy-droisoquinolin-1-one) | F-2 |  |  | F-1 (06/00) | n/f | \$487 |
| 1554705 | Prazosin Hydrochloride ( 500 mg ) | H0B254 |  |  | $\begin{aligned} & \text { G-1 (02/05) } \\ & \text { G }(02 / 01) \end{aligned}$ | [19237-84-4] | \$156 |
| 1555005 | Prednisolone (200 mg) | M |  |  | L-1 (04/02) | [50-24-8] | \$156 |
| 1556008 | Prednisolone Acetate ( 200 mg ) | $J$ |  |  | I-1 (02/02) | [52-21-1] | \$156 |
| 1556507 | Prednisolone Hemisuccinate ( 125 mg ) | H-1 |  |  | H (02/99) | [2920-86-7] | \$124 |
| 1558003 | Prednisolone Tebutate ( 200 mg ) | F |  |  |  | [7681-14-3] | \$156 |
| 1559006 | Prednisone ( 250 mg ) | L1B251 |  |  | $\begin{aligned} & \hline \text { L (11/04) } \\ & \text { K-1 (01/02) } \\ & \text { K (02/00) } \\ & \hline \end{aligned}$ | [53-03-2] | \$156 |
| 1559505 | Prednisone Tablets (Dissolution Calibrator, Disintegrating) (30 tablets) | O0C056 |  |  | $\begin{aligned} & \text { N (06/04) } \\ & \text { M (09/02) } \\ & \text { L (11/00) } \end{aligned}$ | [53-03-2] | \$180 |
| 1561008 | Prilocaine Hydrochloride (200 mg) | F3B215 |  |  | F-2 (03/04) | [1786-81-8] | \$156 |
| 1561507 | Primaquine Phosphate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  |  | [63-45-6] | \$156 |
| 1562000 | Primidone ( 200 mg ) | G |  |  | F-6 (04/99) | [125-33-7] | \$156 |
| 1563003 | Probenecid ( 200 mg ) | IOA011 |  |  | H-1 (03/03) | [57-66-9] | \$156 |
| 1563309 | Probucol ( 200 mg ) | G |  |  | F-1 (01/02) | [23288-49-5] | \$156 |
| 1563320 | Probucol Related Compound A ( 25 mg ) (2,2',6,6'-tetra-tert-butyldiphenoquinone) | F-2 |  |  | F-1 (11/04) | n/f | \$487 |
| 1563331 | Probucol Related Compound B ( 25 mg ) (4,4'-dithio-bis(2,6-di-tert-butylphenol)) | F-2 |  |  | F-1 (08/03) | n/f | \$487 |
| 1563342 | Probucol Related Compound C ( 25 mg ) ( $4-$ [(3,5-di-tert-butyl-2-hydroxyphenylthio)isopropy-lidenethio]-2,6-di-tert-butylphenol) | F-2 |  |  | F-1 (05/00) | n/f | \$487 |
| 1563502 | Procainamide Hydrochloride ( 200 mg ) | H1B117 |  |  | H (04/03) | [614-39-1] | \$156 |
| 1564006 | Procaine Hydrochloride (200 mg) | H |  |  |  | [51-05-8] | \$156 |
| 1565009 | Procarbazine Hydrochloride (200 mg) | F |  |  |  | [366-70-1] | \$156 |
| 1566001 | Prochlorperazine Maleate ( 200 mg ) | H-1 |  |  |  | [84-02-6] | \$156 |
| 1567004 | Procyclidine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  |  | [1508-76-5] | \$156 |
| 1568007 | Progesterone (200 mg) | H6C088 |  |  | $\begin{aligned} & \hline \mathrm{H}-5(11 / 04) \\ & \mathrm{H}-4(07 / 02) \\ & \hline \end{aligned}$ | [57-83-0] | \$124 |
| 1568506 | L-Proline (200 mg) | F-2 |  |  | F-1 (01/02) | [147-85-3] | \$156 |
| 1569000 | Promazine Hydrochloride ( 200 mg ) | H0B261 |  |  | G (10/03) | [53-60-1] | \$156 |
| 1570009 | Promethazine Hydrochloride ( 500 mg ) | K |  |  | J-1 (10/00) | [58-33-3] | \$156 |
| 1570304 | Propafenone Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G1C184 |  |  | $\begin{aligned} & \mathrm{G}(12 / 04) \\ & \mathrm{F}-1(01 / 01) \\ & \hline \end{aligned}$ | [34183-22-7] | \$156 |
| 1570508 | Propantheline Bromide ( $200 \mathrm{mg} \mathrm{)}$ | IOA019 |  |  | H (11/02) | [50-34-0] | \$156 |
| 1329505 | Propantheline Bromide Related Compound A ( 50 mg ) (9-Hydroxypropantheline bromide) | G0B258 |  |  | F-1 (12/03) | n/f | \$487 |
| 1571001 | Proparacaine Hydrochloride ( 200 mg ) | G |  |  |  | [5875-06-9] | \$156 |
| 1573007 | Propoxycaine Hydrochloride ( 200 mg ) | F |  |  |  | [550-83-4] | \$156 |
| 1574000 | Propoxyphene Hydrochloride CII (1 g) | L0C285 |  |  | K (09/04) | [1639-60-7] | \$207 |
| 1575002 | Propoxyphene Napsylate CII (1 g) | H |  |  |  | [26570-10-5] | \$207 |
| 1575206 | Propoxyphene Related Compound A ( 50 mg ) (alpha-d-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride) | G-5 |  |  |  | n/f | \$487 |
| 1576005 | Propranolol Hydrochloride (200 mg) | 10C170 |  |  | $\begin{aligned} & \hline \text { H-1 (12/04) } \\ & \text { H (09/01) } \\ & \hline \end{aligned}$ | [318-98-9] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1576504 | Propylene Carbonate (200 mg) | F |  |  |  | [108-32-7] | \$156 |
| 1576708 | Propylene Glycol (1 mL) | $10 \mathrm{C022}$ |  |  | $\begin{aligned} & \hline \text { H }(03 / 04) \\ & \text { G }(02 / 99) \end{aligned}$ | [57-55-6] | \$156 |
| 1576720 | Propylene Glycol Diacetate ( 250 mg ) | F |  |  |  | [623-84-7] | \$156 |
| 1576800 | Propyl Gallate ( 200 mg ) | G-1 |  |  | G (01/03) | [121-79-9] | \$156 |
| 1577008 | Propylparaben (200 mg) | 1 |  |  | H (02/00) | [94-13-3] | \$156 |
| 1578000 | Propylthiouracil (200 mg) | G |  |  | F-1 (01/00) | [51-52-5] | \$156 |
| 1578500 | Prostaglandin A1 (25 mg) | H0B108 |  |  | G (04/03) | [14152-28-4] | \$529 |
| 1580002 | Protriptyline Hydrochloride ( 200 mg ) | F-1 |  |  |  | [1225-55-4] | \$156 |
| 1581005 | Pseudoephedrine Hydrochloride (125 mg) (List Chemical) | J1B203 |  |  | $\begin{array}{\|l\|l\|} \hline J(01 / 04) \\ I \\ \hline \end{array}$ | [345-78-8] | \$124 |
| 1581504 | Pseudoephedrine Sulfate ( 200 mg ) (List Chemical) | G1C135 |  |  | $\begin{aligned} & \hline \mathrm{G}(06 / 04) \\ & \mathrm{F}-2(05 / 02) \end{aligned}$ | [7460-12-0] | \$156 |
| 1584003 | Pyrantel Pamoate (1 g) | 1 |  |  | H-1 (04/00) | [22204-24-6] | \$156 |
| 1585006 | Pyrazinamide (200 mg) | G |  |  | F-2 (02/00) | [98-96-4] | \$156 |
| 1586009 | Pyridostigmine Bromide ( $200 \mathrm{mg} \mathrm{)}$ | IOC324 | $0.999 \mathrm{mg} / \mathrm{mg}$ (dr) |  | H (01/05) | [101-26-8] | \$156 |
| 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) | P |  |  | O-1 (04/00) | [58-56-0] | \$156 |
| 1588004 | Pyrilamine Maleate ( $200 \mathrm{mg} \mathrm{)}$ | IOB276 |  |  | H (12/03) | [59-33-6] | \$156 |
| 1589007 | Pyrimethamine (200 mg) | H |  |  | G (07/02) | [58-14-0] | \$156 |
| 1592001 | Pyrvinium Pamoate ( 500 mg ) | G |  |  |  | [3546-41-6] | \$156 |
| 1592205 | Quazepam CIV (200 mg) | F |  |  |  | [36735-22-5] | \$207 |
| 1592227 | Quazepam Related Compound A ( 30 mg ) (7-Chloro-1-(2,2,2-trifluoroethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one) | F |  |  |  | n/f | \$487 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 |  |  |  | [6151-25-3] | \$156 |
| 1593004 | Quinacrine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  |  | [6151-30-0] | \$156 |
| 1593412 | Quinapril Related Compound A ( 50 mg ) (Ethyl[3S-[2(R*),3a,11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-pheny-lethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate) | F0C114 |  |  |  | [103733-49-9] | \$487 |
| 1593423 | Quinapril Related Compound B ( 50 mg ) (3Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetra-hydro-,[3S-[2[R*( $\left.\left.\left.\left.\mathrm{R}^{\star}\right)\right], 3 \mathrm{R}^{\star}\right]\right]$-) | F0C116 |  |  |  | [85441-60-7] | \$487 |
| 1594007 | Quinethazone (1.5 g) | G |  |  |  | [73-49-4] | \$156 |
| 1594506 | Quinic Acid ( 200 mg ) | F |  |  |  | [77-95-2] | \$156 |
| 1595000 | Quinidine Gluconate (200 mg) | H1A028 |  |  | H (04/03) | [7054-25-3] | \$156 |
| 1595509 | Quinidine Sulfate ( 500 mg ) | H-1 |  |  | H (12/99) | [6591-63-5] | \$156 |
| 1596807 | Quinine Hydrochloride Dihydrate (1 g) | F0C108 |  |  |  | [6119-47-7] | \$156 |
| 1597005 | Quinine Sulfate (200 mg) | H |  |  |  | [6119-70-6] | \$156 |
| 1597504 | Quininone ( 50 mg ) | H0B034 |  |  | G-1 (03/04) | [84-31-1] | \$487 |
| 1598008 | 3-Quinuclidinyl Benzilate ( 25 mg ) (FOR U.S. SALE ONLY) | H |  |  | G (11/01) | [6581-06-2] | \$515 |
| 1598303 | Ramipril ( 200 mg ) | F0C099 |  |  |  | [87333-19-5] | \$156 |
| 1598314 | Ramipril Related Compound A ( 20 mg ) ((2S,3aS,6aS)-1-[(S)2-[[(S)1-(methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydro-cyclopenta[b]pyrrole-2-carboxylic acid) | FOC100 |  |  |  | [91224-69-0] | \$487 |
| 1598405 | Ranitidine Hydrochloride ( 200 mg ) | H0B268 |  |  | G (01/04) | [66357-59-3] | \$156 |
| 1598507 | Ranitidine Related Compound A (50 mg) (5-[[(2-aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine hemifumarate) | H1B137 |  |  | $\begin{aligned} & \mathrm{H}(01 / 04) \\ & \mathrm{G}(01 / 01) \end{aligned}$ | [91224-69-0] | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1598609 | Ranitidine Related Compound B $(50 \mathrm{mg})(\mathrm{N}, \mathrm{N}$ '-bis[2-[[[5-[(dimethylamino)methyl]-2-furanyl]-methyl]thio]ethyl]-2-nitro-1,1-ethenediamine) | G |  |  | F-4 (04/02) | [72126-78-4] | \$487 |
| 1598700 | Ranitidine Related Compound C $(50 \mathrm{mg})(\mathrm{N}-[2-$ [[[5-[(dimethylamino)methyl]-2-furanyl]methyl]-sulfinyl]ethyl]-N-methyl-2-nitro-1,1-ethenediamine) | 11B136 |  |  | $\begin{aligned} & \text { I (01/04) } \\ & \text { H (05/01) } \end{aligned}$ | [73851-70-4] | \$487 |
| 1599000 | Rauwolfia Serpentina (15 g) | G |  |  |  | [8063-17-0] | \$156 |
| 1599500 | Powdered Red Clover Extract (500 mg) | F0C188 |  |  |  | n/f | \$260 |
| 1600813 | Repaglinide ( 200 mg ) | F0B265 |  |  |  | [135062-02-1] | \$156 |
| 1600824 | Repaglinide Related Compound A (50 mg) ((S)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butylamine, N -acetyl-L-glutamate salt) | F0B267 |  |  |  | n/f | \$487 |
| 1600835 | Repaglinide Related Compound B (50 mg) (3-Ethoxy-4-ethoxycarbonyl-phenylacetic acid) | F0B269 |  |  |  | [99469-99-5] | \$487 |
| 1600846 | Repaglinide Related Compound C (25 mg) ((S)-2-Ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)phe-nyl]ethyl]amino]-2-oxoethyl] benzoic acid) | F0B271 |  |  |  | [107362-12-9] | \$487 |
| 1601000 | Reserpine ( 200 mg ) | O0C106 |  |  | N (06/03) | [50-55-5] | \$156 |
| 1601102 | Residual Solvent Mixture - Class $1(1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C407 |  |  |  | n/f | \$156 |
| 1601146 | Residual Solvent Class 1 - Benzene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C408 | $10.1 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601168 | Residual Solvent Class 1 - Carbon Tetrachloride ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C409 | $19.7 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601180 | Residual Solvent Class 1-1,2-Dichloroethane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C412 | $25.1 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601204 | Residual Solvent Class 1-1,1-Dichloroethene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C411 | $37.9 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601226 | Residual Solvent Class 1-1,1,1-Trichloroethane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C410 | $49.1 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601340 | Residual Solvent Class 2 - Acetonitrile ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | FOD049 | $2.00 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601361 | Residual Solvent Class 2 - Chlorobenzene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D048 | $1.81 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601420 | Residual Solvent Class 2-1,2-Dichloroethene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D040 | $9.2 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601521 | Residual Solvent Class 2 - 1,4-Dioxane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D050 | $1.89 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601623 | Residual Solvent Class 2 - Methanol ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D045 | $14.8 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601441 | Residual Solvent Class 2 - Methylene Chloride ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D046 | $2.90 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601770 | Residual Solvent Class 2 - Tetrahydrofuran ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D043 | $3.49 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601805 | Residual Solvent Class 2 - Toluene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D042 | $4.39 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601849 | Residual Solvent Class 2 - Xylenes ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D041 | $10.7 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1602003 | Resorcinol ( 200 mg ) | H-1 |  |  | H (04/01) | [108-46-3] | \$156 |
| 1602706 | Ribavirin (200 mg) | H1C335 |  | 2 | $\begin{aligned} & \mathrm{H}(03 / 05) \\ & \mathrm{G}(08 / 01) \\ & \hline \end{aligned}$ | [36791-04-5] | \$289 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1603006 | Riboflavin (500 mg) (Vitamin B2) | N0C021 |  |  | $\begin{aligned} & \hline \text { M-1 (09/04) } \\ & M(11 / 00) \\ & \hline \end{aligned}$ | [83-88-5] | \$156 |
| 1603800 | Rifabutin ( 50 mg ) | G0B040 |  |  | F (11/02) | [72559-06-9] | \$156 |
| 1604009 | Rifampin ( 300 mg ) | $J$ |  |  | I (09/00) | [13292-46-1] | \$156 |
| 1604202 | Rifampin Quinone ( 50 mg ) | H |  |  | G (12/01) | [13983-13-6] | \$156 |
| 1604508 | Rimantadine Hydrochloride ( 300 mg ) | F0C266 |  |  |  | [1501-84-4] | \$156 |
| 1604600 | Rimexolone ( 100 mg ) | F |  |  |  | [49697-38-3] | \$156 |
| 1604701 | Ritodrine Hydrochloride (200 mg) | G-1 |  |  |  | [23239-51-2] | \$156 |
| 1606208 | Roxarsone ( 200 mg ) | F |  |  |  | [121-19-7] | \$156 |
| 1606503 | Rutin ( 100 mg ) | F |  |  |  | [153-18-4] | \$156 |
| 1607007 | Saccharin (200 mg) | G-3 |  |  | G-2 (12/01) | [81-07-2] | \$156 |
| 1608000 | Salicylamide (200 mg) | F-4 |  |  | F-3 (05/03) | [65-45-2] | \$156 |
| 1609002 | Salicylic Acid (125 mg) | J2B147 |  |  | $\begin{array}{\|l} \hline J-1(10 / 03) \\ \mathrm{J}(10 / 02) \\ \mathrm{I}(07 / 99) \\ \hline \end{array}$ | [69-72-7] | \$124 |
| 1609501 | Salicylic Acid Tablets (Dissolution Calibrator, Non-disintegrating) (33 tablets) | 0 |  |  | N (02/02) | [69-72-7] | \$156 |
| 1609807 | Salsalate ( 125 mg ) | G |  |  |  | [552-94-3] | \$124 |
| 1609829 | Saquinavir Mesylate (200 mg) | F0B008 |  |  |  | [149845-06-7] | \$156 |
| 1609831 | Saquinavir Related Compound A ( 25 mg ) ( N -tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-D-asparaginyl]ami-no]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide) | F0B009 |  |  |  | n/f | \$487 |
| 1610001 | Scopolamine Hydrobromide ( 250 mg ) | J0B051 |  |  | I-1 (01/03) | [6533-68-2] | \$156 |
| 1610090 | Scopoletin (20 mg) | F0C329 |  |  |  | [92-61-5] | \$156 |
| 1611004 | Secobarbital CII (200 mg) | H |  |  |  | [76-73-3] | \$207 |
| 1611900 | Selegiline Hydrochloride (200 mg) | G |  |  |  | [14611-52-0] | \$156 |
| 1611955 | Selenomethionine (100 mg) | F0B006 |  |  |  | [1464-42-2] | \$156 |
| 1612007 | Sennosides (250 mg) | H1B223 |  |  | H (04/04) | $\begin{aligned} & {[81-27-6] \quad \text { (A) }} \\ & {[128-57-4] \text { (B) }} \end{aligned}$ | \$156 |
| 1612506 | L-Serine ( 200 mg ) | G |  |  | F-3 (11/00) | [56-45-1] | \$156 |
| 1612540 | Sevoflurane ( 1 mL ) | F0C219 |  |  |  | [28523-86-6] | \$156 |
| 1612550 | Sevoflurane Related Compound A ( 0.2 mL ) (1,1,3,3,3-Pentafluoroisopropenyl fluoromethyl ether) | F0C261 |  |  |  | [58109-34-5] | \$487 |
| 1612608 | Silver Sulfadiazine ( 200 mg ) | 1 |  |  | H (04/01) | [22199-08-2] | \$156 |
| 1612630 | Silybin ( 50 mg ) | F |  |  |  | [22888-70-6] | \$156 |
| 1612641 | Silydianin ( 20 mg ) | F |  |  |  | [29782-68-1] | \$156 |
| 1612652 | Simethicone (50 g) |  |  |  | $\begin{aligned} & G(01 / 05) \\ & F(07 / 00) \\ & \hline \end{aligned}$ | [8050-81-5] | \$156 |
| 1612700 | Simvastatin (200 mg) | H1B093 |  |  | H (07/03) G (02/02) F-1 (05/99) | [79902-63-9] | \$156 |
| 1612801 | Sisomicin Sulfate ( 500 mg ) | 10 C 238 |  |  | $\begin{aligned} & \hline H(04 / 04) \\ & G(10 / 00) \\ & \hline \end{aligned}$ | [53179-09-2] | \$156 |
| 1613509 | Sodium Ascorbate (200 mg) | G2C067 |  |  | G-1 (03/05) | [134-03-2] | \$156 |
| 1613600 | Sodium Butyrate ( 25 mg ) | F |  |  |  | [156-54-7] | \$156 |
| 1614002 | Sodium Fluoride ( 1 g ) | H-1 |  |  | H (05/01) | [7681-49-4] | \$156 |
| 1614308 | Sodium Lactate (200 mg) | 10C299 |  | 2 | $\begin{aligned} & \mathrm{H}(04 / 05) \\ & \mathrm{G}(06 / 00) \\ & \hline \end{aligned}$ | [867-56-1] | \$156 |
| 1614501 | Sodium Nitroprusside ( 500 mg ) | H |  |  | G (11/99) | [13755-38-9] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1614603 | Sodium Propionate ( 200 mg ) | F-1 |  |  | F (03/02) | [6700-17-0] | \$156 |
| 1614669 | Sodium Starch Glycolate ( 400 mg ) | F0C087 |  |  |  | [9063-38-1] | \$156 |
| 1614705 | Sodium Stearyl Fumarate ( 200 mg ) | G |  |  | F-2 (05/01) | [4070-80-8] | \$156 |
| 1616008 | 1,4-Sorbitan (200 mg) | 10A003 |  |  | $\begin{aligned} & \mathrm{H}(04 / 03) \\ & \mathrm{G}(02 / 00) \end{aligned}$ | [27299-12-3] | \$156 |
| 1617000 | Sorbitol ( 125 mg ) | H1B139 |  |  | H (01/04) | [50-70-4] | \$124 |
| 1617408 | Sotalol Hydrochloride ( 300 mg ) | F0C234 |  |  |  | [959-24-0] | \$182 |
| 1617419 | Sotalol Related Compound A ( 50 mg ) (N-[4-[[(1-Methylethyl)amino]acetyl]phenyl]methanesulfonamide monohydrochloride) | F0C235 |  |  |  | n/f | \$487 |
| 1617420 | Sotalol Related Compound B ( 50 mg ) (N-(4Formylphenyl)methanesulfonamide) | F0C236 |  |  |  | n/f | \$487 |
| 1617430 | Sotalol Related Compound C ( 50 mg ) ( $\mathrm{N}-[4-[2-$ [(1-Methylethyl)amino]ethyl]phenyl]methanesulfonamide hydrochloride) | F0C237 |  |  |  | n/f | \$487 |
| 1618003 | Spectinomycin Hydrochloride ( 200 mg ) | GOC310 | $650 \mathrm{ug} / \mathrm{mg}$ (ai) |  | F-2 (01/05) | [22189-32-8] | \$156 |
| 1619006 | Spironolactone (125 mg) | J-1 |  |  |  | [52-01-7] | \$124 |
| 1619505 | Squalane ( 500 mg ) | G-1 |  |  |  | [111-01-3] | \$156 |
| 1620005 | Stanozolol CIII (200 mg) | F-3 |  |  | F-2 (02/01) | [10418-03-8] | \$207 |
| 1621008 | Stearic Acid ( 500 mg ) | J |  |  | 1 (10/01) | [57-11-4] | \$156 |
| 1621507 | Stearoyl Polyoxyglycerides (100 mg) | F0C286 |  |  |  | n/f | \$156 |
| 1622000 | Stearyl Alcohol (125 mg) | H2B217 |  |  | $\begin{aligned} & \hline \text { H-1 (12/04) } \\ & \text { H (09/99) } \\ & \hline \end{aligned}$ | [112-92-5] | \$124 |
| 1623003 | Streptomycin Sulfate (200 mg) | JOB195 |  |  | I (04/03) | [3810-74-0] | \$156 |
| 1623502 | Succinylcholine Chloride ( 500 mg ) | H |  |  |  | [71-27-2] | \$156 |
| 1623604 | Succinylmonocholine Chloride ( 150 mg ) | G |  |  | F-1 (02/01) | n/f | \$487 |
| 1623626 | Sucralose ( 400 mg ) | G0B028 |  |  | F (04/03) | [56038-13-2] | \$156 |
| 1623637 | Sucrose ( 100 mg ) | H1C223 |  |  | $\begin{aligned} & \text { HOB002 (11/04) } \\ & \text { G-1 (03/03) } \\ & \text { G (05/99) } \\ & \hline \end{aligned}$ | [57-50-1] | \$156 |
| 1623648 | Sufentanil Citrate ClI (25 mg) | H0B208 |  |  | $\begin{aligned} & \mathrm{G}(05 / 03) \\ & \mathrm{F}-1(04 / 02) \\ & \mathrm{F}(09 / 99) \\ & \hline \end{aligned}$ | [60561-17-3] | \$207 |
| 1623670 | Sulbactam (250 mg) |  |  |  | $\begin{array}{\|l\|} \hline \text { G (05/05) } \\ \text { F-1 }(05 / 00) \\ \hline \end{array}$ | [68373-14-8] | \$156 |
| 1623681 | Sulconazole Nitrate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | F (05/02) | [61318-91-0] | \$156 |
| 1623706 | Sulfabenzamide (200 mg) | G |  |  |  | [127-71-9] | \$156 |
| 1623808 | Sulfacetamide ( 300 mg ) | G-1 |  |  |  | [144-80-9] | \$156 |
| 1624006 | Sulfacetamide Sodium ( 500 mg ) | 11B318 |  |  | $\begin{array}{\|l\|} \hline I(09 / 04) \\ H(08 / 01) \\ \hline \end{array}$ | [6209-17-2] | \$156 |
| 1624505 | Sulfachlorpyridazine ( 200 mg ) | F |  |  |  | [80-32-0] | \$156 |
| 1625009 | Sulfadiazine ( $200 \mathrm{mg} \mathrm{)}$ | J |  |  | 1 (03/04) | [68-35-9] | \$156 |
| 1626001 | Sulfadimethoxine ( 200 mg ) | F4C298 |  |  | $\begin{aligned} & \hline \text { F-3 }(11 / 04) \\ & \text { F-2 (03/99) } \\ & \hline \end{aligned}$ | [122-11-2] | \$156 |
| 1626500 | Sulfadoxine (200 mg) | F-2 |  |  | F-1 (07/02) | [2447-57-6] | \$156 |
| 1628007 | Sulfamerazine ( 500 mg ) | H1C171 |  |  | H (12/04) | [127-79-7] | \$156 |
| 1629000 | Sulfamethazine (1 g) | G-3 |  |  |  | [57-68-1] | \$156 |
| 1630009 | Sulfamethizole (200 mg) | F-3 |  |  | F-2 (01/03) | [144-82-1] | \$156 |
| 1631001 | Sulfamethoxazole ( 200 mg ) | I-1 |  |  | I (04/02) | [723-46-6] | \$156 |
| 1631500 | Sulfamethoxazole N4-glucoside ( 25 mg ) | H |  |  | G (11/01) | n/f | \$487 |
| 1632004 | Sulfanilamide (5 g) | OOB047 |  |  | N (01/04) | [63-74-1] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1633007 | Sulfanilamide Melting Point Standard ( 500 mg ) (Approximately 165 degrees) | K0B133 |  |  | $\begin{aligned} & \hline \mathrm{J}-1(03 / 04) \\ & \mathrm{J}(09 / 99) \\ & \hline \end{aligned}$ | [63-74-1] | \$75 |
| 1633506 | Sulfanilic Acid ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | F-2 (09/00) | [121-57-3] | \$487 |
| 1634000 | Sulfapyridine (200 mg) | IOB298 |  |  | H (07/04) | [144-83-2] | \$156 |
| 1635002 | Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees) | J |  |  | I (07/00) | [144-83-2] | \$92 |
| 1635206 | Sulfaquinoxaline ( 200 mg ) | F0A005 |  |  |  | [59-40-5] | \$156 |
| 1636005 | Sulfasalazine ( 125 mg ) | G-2 |  |  | G-1 (06/99) | [599-79-1] | \$124 |
| 1636504 | Sulfathiazole ( 350 mg ) | H |  |  | G (08/00) | [72-14-0] | \$156 |
| 1637008 | Sulfinpyrazone (200 mg) | H0C416 | $0.992 \mathrm{mg} / \mathrm{mg}$ (ai) |  | G (03/05) | [57-96-5] | \$156 |
| 1638000 | Sulfisoxazole (200 mg) | J |  |  | I-1 (06/99) | [127-69-5] | \$156 |
| 1639003 | Sulfisoxazole Acetyl ( 200 mg ) | H-1 |  |  |  | [80-74-0] | \$156 |
| 1640002 | Sulfisoxazole Diolamine ( 500 mg ) | F |  |  |  | [4299-60-9] | \$156 |
| 1642008 | Sulindac ( 200 mg ) | H |  |  | G-1 (12/01) | [38194-50-2] | \$156 |
| 1642154 | Sumatriptan ( 50 mg ) | F0C220 |  |  |  | [103628-46-2] | \$208 |
| 1642201 | Sumatriptan Succinate ( 200 mg ) | F0C231 |  |  |  | [103628-48-4] | \$208 |
| 1642212 | Sumatriptan Succinate Related Compound A ( 15 mg ) ([33-[2-(dimethylamino)ethyl]-2-[[3-[2-(di-methylamino)ethyl]-1H-indol-5-yl]methyl]-1H-in-dol-5-yl]-N-methylmethansulfonamide, succinate salt) | F0C221 |  |  |  | n/f | \$624 |
| 1642223 | Sumatriptan Succinate Related Compound C ( 50 mg ) ([3-[2-(dimethylamino)ethyl]-1-(hydro-xymethyl)-1H-indol-5-yl]-N-methylmethanesulfonamide succinate salt) | F0C230 |  |  |  | n/f | \$624 |
| 1642507 | Suprofen (200 mg) | F |  |  |  | [40828-46-4] | \$156 |
| 1642700 | Tacrine Hydrochloride ( 500 mg ) | F0C119 |  |  |  | [1684-40-8] | \$156 |
| 1643000 | Talbutal CIII ( 250 mg ) | F |  |  |  | [115-44-6] | \$207 |
| 1643306 | Tamoxifen Citrate (200 mg) | H |  |  | $\begin{aligned} & \text { G-2 }(09 / 01) \\ & \text { G-1 }(05 / 00) \\ & \hline \end{aligned}$ | [54965-24-1] | \$156 |
| 1643361 | Taurine ( 100 mg ) | F0C104 |  |  |  | [107-35-7] | \$156 |
| 1643408 | Temazepam CIV (200 mg) | H0C205 |  |  | $\begin{aligned} & \hline \text { G (06/04) } \\ & \mathrm{F}(12 / 99) \\ & \hline \end{aligned}$ | [846-50-4] | \$207 |
| 1643452 | Terazosin Hydrochloride (200 mg) | F0C244 |  |  |  | [70024-40-7] | \$156 |
| 1643463 | Terazosin Related Compound A (50 mg) (1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)piperazine dihydrochloride) | F0C245 |  |  |  | n/f | \$487 |
| 1643474 | Terazosin Related Compound B (50 mg) (1-(4-hydroxy-6,7-dimethoxy-2-quinazolinyl)-4-[(tetra-hydro-2-furanyl)carbonyl]piperazine) | F0C218 |  |  |  | n/f | \$487 |
| 1643485 | Terazosin Related Compound C (25 mg) (1,4-bis(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine dihydrochloride) | F0C257 |  |  |  | n/f | \$487 |
| 1643500 | Terbutaline Sulfate ( 125 mg ) | H |  |  | G (04/99) | [23031-32-5] | \$124 |
| 1643703 | Terconazole (200 mg) | G-2 |  |  | $\begin{aligned} & \text { G-1(04/01) } \\ & \text { G (03/99) } \end{aligned}$ | [67915-31-5] | \$156 |
| 1643805 | Terfenadine (200 mg) | H |  |  | G (12/99) | [50679-08-8] | \$156 |
| 1643907 | Terfenadine Related Compound A (100 mg) (1-[4-(1,1-dimethylethyl)phenyl]-4-[4-(hydroxydi-phenylmethyl)-1-piperidinyl]-1-butanone) | G |  |  |  | n/f | \$487 |
| 1643929 | Terfenadine Related Compound B ( 50 mg ) (Terfenadine-N-oxide) | F |  |  |  | n/f | \$487 |
| 1644003 | Terpin Hydrate ( 750 mg ) | G |  |  |  | [2451-01-6] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1645006 | Testolactone CIII (125 mg) | F-1 |  |  |  | [968-93-4] | \$165 |
| 1646009 | Testosterone CIII ( 125 mg ) | 11B253 |  |  | I (08/04) | [58-22-0] | \$165 |
| 1647001 | Testosterone Cypionate CIII ( 200 mg ) |  |  |  | $\begin{aligned} & \text { G-1 (03/05) } \\ & \text { G }(08 / 01) \\ & \hline \end{aligned}$ | [58-20-8] | \$207 |
| 1648004 | Testosterone Enanthate CIII ( 200 mg ) | J |  |  |  | [315-37-7] | \$207 |
| 1649007 | Testosterone Propionate CIII ( $200 \mathrm{mg} \mathrm{)}$ | L1C005 |  |  | $\begin{aligned} & \hline \text { L (08/04) } \\ & \text { K-1 }(11 / 01) \\ & \hline \end{aligned}$ | [57-85-2] | \$207 |
| 1650006 | Tetracaine Hydrochloride ( 200 mg ) | J |  |  |  | [136-47-0] | \$156 |
| 1651009 | Tetracycline Hydrochloride ( 200 mg ) | L0C216 | 976 ug/mg (ai) |  | K (12/04) | [64-75-5] | \$156 |
| 1652001 | Tetrahydrozoline Hydrochloride ( 200 mg ) | G1A015 |  |  | G (03/03) | [522-48-5] | \$156 |
| 1652500 | Thalidomide ( 200 mg ) | F0C107 |  |  |  | [50-35-1] | \$182 |
| 1653004 | Theophylline ( 200 mg ) | J0B180 |  |  | I (01/04) | [58-55-9] | \$156 |
| 1653106 | Theophylline Extended-Release Beads (Drug Release Calibrator, Multiple Unit) (20 g) |  |  |  | F-1 (11/04) | [58-55-9] | \$156 |
| 1655000 | Thiabendazole ( 100 mg ) | G0A027 |  |  | $\begin{aligned} & \hline \text { F-1 (04/03) } \\ & \text { F (04/01) } \\ & \hline \end{aligned}$ | [148-79-8] | \$156 |
| 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) | 0 |  |  | $\begin{aligned} & \hline \mathrm{N}(11 / 02) \\ & \mathrm{M}-1(04 / 99) \end{aligned}$ | [67-03-8] | \$156 |
| 1656308 | Thiamylal CIII ( 200 mg ) | F |  |  |  | [77-27-0] | \$207 |
| 1657005 | Thiethylperazine Malate ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | F-1 (09/00) | [52239-63-1] | \$156 |
| 1658008 | Thiethylperazine Maleate ( 200 mg ) | F-1 |  |  |  | [1179-69-7] | \$156 |
| 1659000 | Thimerosal ( 500 mg ) | H1B205 |  |  | $\begin{aligned} & \hline \mathrm{H}(09 / 04) \\ & \mathrm{G}(12 / 99) \\ & \hline \end{aligned}$ | [54-64-8] | \$156 |
| 1660000 | Thioguanine (200 mg) | F-1 |  |  |  | [154-42-7] | \$156 |
| 1661002 | Thiopental CIII ( 250 mg ) | 1 |  |  |  | [76-75-5] | \$207 |
| 1662504 | Thioridazine (200 mg) | H |  |  |  | [50-52-2] | \$156 |
| 1663008 | Thioridazine Hydrochloride ( 200 mg ) | H |  |  |  | [130-61-0] | \$156 |
| 1663700 | Thiostrepton ( 200 mg ) | F1B022 |  |  | F (11/02) | [1393-48-2] | \$156 |
| 1664000 | Thiotepa ( 500 mg ) | 1 |  |  | H (01/99) | [52-24-4] | \$156 |
| 1665003 | Thiothixene ( 250 mg ) | G |  |  |  | [3313-26-6] | \$156 |
| 1666006 | (E)-Thiothixene ( 100 mg ) | H |  |  | G-1 (05/00) | [3313-27-7] | \$487 |
| 1667100 | Thonzonium Bromide ( 200 mg ) | F |  |  |  | [553-08-2] | \$156 |
| 1667202 | L-Threonine (200 mg) | G |  |  | F-3 (12/00) | [72-19-5] | \$156 |
| 1667279 | Thromboplastin, Human Recombinant (set) (1 vial Thromboplastin and 1 vial Diluent) DISCONTINUED |  |  |  | F (10/04) | [9002-05-5] | \$156 |
| 1667290 | Tiamulin Fumarate ( 250 mg ) | F0C327 |  |  |  | [55297-96-6] | \$156 |
| 1667337 | Tiamulin Related Compound A ( 50 mg ) (Tosyl pleuromutilin) | F0C328 |  |  |  | n/f | \$494 |
| 1667304 | Ticarcillin Monosodium Monohydrate ( 200 mg ) | H |  |  | G-1 (03/99) | [74682-62-5] | \$156 |
| 1667359 | Tiletamine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F0C019 |  |  |  | [14176-50-2] | \$156 |
| 1667406 | Timolol Maleate (200 mg) | G-1 |  |  |  | [26921-17-5] | \$156 |
| 1667520 | Tinidazole (200 mg) | F0C093 |  |  |  | [19387-91-8] | \$156 |
| 1667530 | Tinidazole Related Compound A (100 mg) (2-methyl-5-nitroimidazole) | F0C091 |  |  |  | [696-23-1] | \$487 |
| 1667439 | Tioconazole ( 200 mg ) | H |  |  | G (04/02) | [65899-73-2] | \$156 |
| 1667450 | Tioconazole Related Compound A ( 25 mg ) (1-[2,4-Dichloro-beta-[(3-thenyl)-oxy]phenethyl]imidazole Hydrochloride) | G |  |  |  | n/f | \$487 |

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| Cat. <br> No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1667461 | Tioconazole Related Compound B ( 25 mg ) (1-[2,4-Dichloro-beta-[(2,5-dichloro-3-thenyl)oxy]phenethyl]jimidazole Hydrochloride) | G |  |  |  | n/f | \$487 |
| 1667472 | Tioconazole Related Compound C ( 25 mg ) (1-[2,4-Dichloro-beta-[(5-bromo-2-chloro-3-thenyl)-oxy]-phenethyl]imidazole Hydrochloride) | G |  |  |  | n/f | \$487 |
| 1667508 | Tobramycin (250 mg) | K0B248 |  |  | $J$ (08/03) | [32986-56-4] | \$156 |
| 1667552 | Tocainide Hydrochloride ( 125 mg ) | F-1 |  |  | F (04/99) | [35891-93-1] | \$124 |
| 1667600 | Alpha Tocopherol (250 mg) (Vitamin E Alcohol) | M |  |  | L-1 (01/00) | [10191-41-0] | \$156 |
| 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) | K |  |  | J (06/99) | [7695-91-2] | \$156 |
| 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) | F-5 |  |  | F-4 (01/02) | [4345-03-3] | \$156 |
| 1668001 | Tolazamide ( 200 mg ) | G-2 |  |  | G-1 (06/00) | [1156-19-0] | \$156 |
| 1669004 | Tolazoline Hydrochloride ( 300 mg ) | F |  |  |  | [59-97-2] | \$156 |
| 1670003 | Tolbutamide ( 200 mg ) | 1 |  |  | H (06/00) | [64-77-7] | \$156 |
| 1670502 | Tolmetin Sodium ( 500 mg ) | IOB064 |  |  | H (09/03) | [64490-92-2] | \$156 |
| 1671006 | Tolnaftate (200 mg) | J0C405 | $1.000 \mathrm{mg} / \mathrm{mg}$ (dr) |  | I (02/05) | [2398-96-1] | \$156 |
| 1672009 | Toluenesulfonamides, ortho and para ( 200 mg of each supplied in a set) | F-4 |  |  | F-3 (11/99) | $\begin{array}{\|l} \hline[88-19-7](0) \\ {[70-55-3](\mathrm{p})} \\ \hline \end{array}$ | \$487 |
| 1672304 | Torsemide ( 200 mg ) | F0B090 |  |  |  | [56211-40-6] | \$156 |
| 1672315 | Torsemide Related Compound A (75 mg) (4-[(3-methylphenyl)amino]-3-pyridinesulfonamide) | F0B071 |  |  |  | n/f | \$487 |
| 1672326 | Torsemide Related Compound B ( 75 mg ) ( N -[(n-butylamino)carbonyl]-4-[(3-methylphenyl)a-mino]-3-pyridinesulfonamide) | F0B083 |  |  |  | n/f | \$487 |
| 1672337 | Torsemide Related Compound C ( 75 mg ) ( N -[(ethylamino)carbonyl]-4-[(3-methylphenyl)ami-no]-3-pyridinesulfonamide) | F0B078 |  |  |  | n/f | \$487 |
| 1672803 | Transplatin ( 25 mg ) | H0B287 |  |  | G (03/04) | [14913-33-8] | \$487 |
| 1673500 | Trazodone Hydrochloride ( 200 mg ) | F-2 |  |  |  | [25332-39-2] | \$156 |
| 1674004 | Tretinoin ( $30 \mathrm{mg} / \mathrm{ampule}$; 5 ampules) | I2B185 |  |  | $\begin{array}{\|l\|} \hline \text { I-1 (01/04) } \\ \text { I (01/02) } \\ H(06 / 01) \\ \hline \end{array}$ | [302-79-4] | \$156 |
| 1675007 | Triacetin (1 g) | H0C413 |  |  | $\begin{aligned} & \text { G-1 (02/05) } \\ & \text { G }(06 / 01) \\ & \hline \end{aligned}$ | [102-76-1] | \$156 |
| 1676000 | Triamcinolone (250 mg) | H-1 |  |  |  | [124-94-7] | \$156 |
| 1677002 | Triamcinolone Acetonide ( 500 mg ) | K |  |  | J (03/99) | [76-25-5] | \$156 |
| 1678005 | Triamcinolone Diacetate ( 200 mg ) | G |  |  |  | [67-78-7] | \$156 |
| 1679008 | Triamcinolone Hexacetonide ( 125 mg ) | G |  |  |  | [5611-51-8] | \$124 |
| 1680007 | Triamterene ( 200 mg ) | 1 |  |  |  | [396-01-0] | \$156 |
| 1680506 | Triazolam CIV (200 mg) | H0B041 |  |  | G-1 (03/03) | [28911-01-5] | \$207 |
| 1680608 | Tributyl Citrate ( 500 mg ) | G0C227 |  |  | F (01/05) | [77-94-1] | \$156 |
| 1680801 | Trichlorfon (200 mg) | F |  |  |  | [52-68-6] | \$156 |
| 1681000 | Trichlormethiazide ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  |  | [133-67-5] | \$156 |
| 1682206 | Triclosan (200 mg) | F0B135 |  |  |  | [3380-34-5] | \$156 |
| 1683005 | Tridihexethyl Chloride ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  |  | [4310-35-4] | \$156 |
| 1683504 | Trientine Hydrochloride (125 mg) | F2B257 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (09/03) } \\ \text { F (08/96) } \\ \hline \end{array}$ | [38260-01-4] | \$124 |
| 1683606 | Triethyl Citrate ( 500 mg ) | F-1 |  |  | F (03/02) | [77-93-0] | \$156 |
| 1685000 | Trifluoperazine Hydrochloride (200 mg) | H0A010 |  |  | G (03/03) | [440-17-5] | \$156 |

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| Cat. <br> No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1685500 | 2-[N-(2,2,2-Trifluoro-ethyl)amino-5]-chlorobenzophenone ( 25 mg ) | F |  |  |  | n/f | \$487 |
| 1686003 | Triflupromazine Hydrochloride (200 mg) | F-2 |  |  | F-1 (03/04) | [1098-60-8] | \$156 |
| 1686309 | Trifluridine ( 200 mg ) | F |  |  |  | [70-00-8] | \$156 |
| 1686310 | Trifluridine Related Compound A (20 mg) (5-Carboxy-2'-deoxyuridine) | F |  |  |  | [14599-46-3] | \$487 |
| 1687006 | Trihexyphenidyl Hydrochloride ( 200 mg ) | J |  |  | $1(07 / 01)$ | [52-49-3] | \$156 |
| 1689001 | Trimeprazine Tartrate (200 mg) | F-3 |  |  | F-2 (08/01) | [4330-99-8] | \$156 |
| 1690000 | Trimethadione (200 mg) | G |  |  |  | [127-48-0] | \$156 |
| 1692006 | Trimethobenzamide Hydrochloride ( 500 mg ) | H-2 |  |  | H-1 (06/02) | [554-92-7] | \$156 |
| 1692505 | Trimethoprim ( 300 mg ) | JOB228 |  |  | I (01/04) | [738-70-5] | \$156 |
| 1693009 | Trioxsalen (200 mg) | H0C278 |  |  | G (04/04) | [3902-71-4] | \$156 |
| 1694001 | Tripelennamine Citrate ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | F (02/03) | [6138-56-3] | \$156 |
| 1695004 | Tripelennamine Hydrochloride (200 mg) | J |  |  |  | [154-69-8] | \$156 |
| 1696007 | Triprolidine Hydrochloride ( 500 mg ) | 1 |  |  | H-1 (02/02) | [6138-79-0] | \$156 |
| 1696109 | Triprolidine Hydrochloride Z-Isomer (100 mg) | G |  |  | F-1 (02/02) | n/f | \$487 |
| 1696200 | Trisalicylic Acid (100 mg) | G |  |  | F-1 (10/99) | n/f | \$487 |
| 1697000 | Troleandomycin (250 mg) | F-1 |  |  |  | [2751-09-9] | \$156 |
| 1698002 | Tromethamine ( 125 mg ) | G |  |  | F-3 (07/99) | [77-86-1] | \$124 |
| 1699005 | Tropicamide ( 125 mg ) | G-1 |  |  | G (02/99) | [1508-75-4] | \$124 |
| 1700002 | Trypsin Crystallized ( 300 mg ) | H |  |  | G (12/99) | [9002-07-7] | \$156 |
| 1700501 | L-Tryptophan (200 mg) | G-1 |  |  | G (09/00) | [73-22-3] | \$156 |
| 1702008 | Tubocurarine Chloride ( 250 mg ) | K-1 |  |  |  | [6989-98-6] | \$156 |
| 1703805 | Tylosin (250 mg) | F0C008 |  |  |  | [1401-69-0] | \$156 |
| 1704003 | Tyloxapol (600 mg) | H |  |  | G (02/00) | [25301-02-4] | \$156 |
| 1704502 | Tyropanoate Sodium (500 mg) | F |  |  |  | [7246-21-1] | \$156 |
| 1705006 | L-Tyrosine ( 500 mg ) | $J$ |  |  |  | [60-18-4] | \$156 |
| 1705301 | Ubidecarenone (200 mg) | FOB191 |  |  |  | [303-98-0] | \$156 |
| 1705312 | Ubidecarenone for System Suitability ( 25 mg ) | FOB194 |  |  |  | [303-98-0] | \$156 |
| 1705505 | Undecylenic Acid (200 mg) | G2C018 |  |  | $\begin{aligned} & \text { G-1 (11/04) } \\ & \text { G (01/02) } \\ & \hline \end{aligned}$ | [112-38-9] | \$156 |
| 1705800 | Uracil Arabinoside ( 50 mg ) | G |  |  | F-1 (06/99) | [3083-77-0] | \$156 |
| 1706009 | Uracil Mustard ( 500 mg ) | F |  |  |  | [66-75-1] | \$156 |
| 1706701 | Urea C 13 (100 mg) | F0C078 |  |  |  | [57-13-6] | \$182 |
| 1707806 | Ursodiol ( 125 mg ) | G |  |  | $\begin{aligned} & \hline F-1(11 / 01) \\ & F(09 / 99) \\ & \hline \end{aligned}$ | [128-13-2] | \$124 |
| 1707908 | Valerenic Acid (25 mg) | G0B146 |  |  | F (01/04) | [3569-10-6] | \$696 |
| 1708503 | L-Valine (200 mg) | F-2 |  |  | F-1 (05/02) | [72-18-4] | \$156 |
| 1708707 | Valproic Acid (500 mg) | J1B127 |  |  | $\begin{array}{\|l\|} \hline J(01 / 04) \\ \text { I-1 }(11 / 00) \\ \hline \end{array}$ | [99-66-1] | \$156 |
| 1708729 | Valproic Acid Related Compound A ( 0.25 mL ) (diallylacetic acid) | F1B156 |  |  | F (01/03) | [99-67-2] | \$208 |
| 1708762 | Valsartan (350 mg) | F0C147 | $0.995 \mathrm{mg} / \mathrm{mg}$ (an) |  |  | [137862-53-4] | \$156 |
| 1708773 | Valsartan Related Compound A $(20 \mathrm{mg})((\mathrm{R})-\mathrm{N}-$ Valeryl-N-([2'-(1-H-tetrazole)-5-yl)-biphenyl-4-yl]-methyl)-valine) | F0C215 |  |  |  | n/f | \$624 |
| 1708795 | Valsartan Related Compound C (10 mg) ((S)-N-Valeryl-N-([2'-(1-H-tetrazole)-5-yl)biphenyl-4-yl]methyl)valine benzyl ester) | F0C208 |  |  |  | n/f | \$624 |

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| Cat. <br> No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \text { CAS } \\ \text { No. } \\ \hline \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1709007 | Vancomycin Hydrochloride (4 vials, each vial contains $100,500 \mathrm{mcg}$ of vancomycin activity) | L |  |  | K (08/01) | [1404-93-9] | \$156 |
| 1710006 | Vanillin (200 mg) | J0A021 |  |  | $\begin{aligned} & \text { I (03/05) } \\ & \mathrm{H}(04 / 99) \\ & \hline \end{aligned}$ | [121-33-5] | \$156 |
| 1711009 | Vanillin Melting Point Standard (1 g) (Approximately 82 degrees) | J |  |  | $\begin{array}{\|l\|} \hline \text { I-1 (03/03) } \\ \text { I (11/00) } \\ \hline \end{array}$ | [121-33-5] | \$92 |
| 1711155 | Vecuronium Bromide ( 50 mg ) | F0C367 |  |  |  | [50700-72-6] | \$156 |
| 1711166 | Vecuronium Bromide Related Compound A ( 25 mg ) (3alpha, 17beta-diacetyl-oxy-2beta, 16beta-bispiperidinyl-5alpha-androstan) | FOB178 |  |  |  | n/f | \$487 |
| 1711202 | Verapamil Hydrochloride ( 200 mg ) | G |  |  | F-4 (06/00) | [152-11-4] | \$156 |
| 1711304 | Verapamil Related Compound A ( 50 mg ) (3,4-Dimethoxy-alpha-[3-(methylamino)propyl]-al-pha-(1-methylethyl)-benzeneacetonitrile monoHydrochloride) | H |  |  | G (01/01) | n/f | \$487 |
| 1711406 | Verapamil Related Compound B ( 50 mg ) (al-pha-[2-[[2-(3,4-dimethoxyphenyl)-ethyl]methyla-mino]ethyl]-3,4-dimethoxy-alpha-(1-methy-lethyl)-benzeneacetonitrile monoHydrochloride) | G |  |  |  | [1794-55-4] | \$487 |
| 1711461 | Verteporfin ( 200 mg ) | F0C166 |  |  |  | [129497-78-5] | \$156 |
| 1711472 | Verteporfin Related Compound A ( 50 mg ) ( $(+/-$ )18-Ethenyl-4,4a-dihydro-3,4-bis(methoxycarbo-nyl)-4a, 8, 14,19-tetramethyl-23H,25H-benzo[b]-prophine-9,13-dipropanoic acid) | FOC167 |  |  |  | n/f | \$487 |
| 1711508 | Vidarabine ( 200 mg ) | G-1 |  |  |  | [24356-66-9] | \$156 |
| 1713004 | Vinblastine Sulfate ( 50 mg ) | M0B308 |  |  | $\begin{aligned} & \mathrm{L}(12 / 04) \\ & \mathrm{K}(05 / 99) \\ & \hline \end{aligned}$ | [143-67-9] | \$354 |
| 1714007 | Vincristine Sulfate ( $50 \mathrm{mg} / \mathrm{ampule}$ ) | O0B062 |  |  | $\begin{aligned} & \mathrm{N}(01 / 03) \\ & \mathrm{M}(04 / 99) \\ & \hline \end{aligned}$ | [2068-78-2] | \$479 |
| 1714506 | Vinorelbine Tartrate (200 mg) | F0C243 |  |  |  | [125317-39-7] | \$156 |
| 1714528 | Vinorelbine Related Compound A ( 25 mg ) (4-ODeacetylvinorelbine tartrate) | FOC242 |  |  |  | n/f | \$487 |
| 1715000 | Viomycin Sulfate (200 mg) | F |  |  |  | [37883-00-4] | \$156 |
| 1716002 | Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil) | V0C258 |  |  | U (04/04) | [127-47-9] | \$156 |
| 1717504 | Vitamin D Assay System Suitability (1.5 g) | F |  |  |  | [67-97-0] | \$156 |
| 1717708 | Vitexin ( 30 mg ) | FOC142 |  |  |  | [3681-93-4] | \$520 |
| 1719000 | Warfarin ( 200 mg ) | 10B305 |  |  | $\begin{array}{\|l\|l} \hline \mathrm{H}-2(08 / 04) \\ \mathrm{H}-1(11 / 01) \\ \hline \end{array}$ | [81-81-2] | \$156 |
| 1719102 | Warfarin Related Compound A (50 mg) (3-(o-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one) | G1B111 |  |  | G (01/04) | [37209-23-7] | \$156 |
| 1720000 | Xanthanoic Acid ( 100 mg ) | G-1 |  |  | G (12/00) | [82-07-5] | \$487 |
| 1720203 | Xanthone ( 100 mg ) | F-1 |  |  |  | [90-47-1] | \$487 |
| 1720407 | Xylazine ( 200 mg ) | F1C001 |  |  | F (02/05) | [7361-61-7] | \$156 |
| 1720429 | Xylazine Hydrochloride (200 mg) | F |  |  |  | [23076-35-9] | \$156 |
| 1720600 | Xylitol (1 g) | G0B037 |  |  | $\begin{aligned} & \hline \text { F-3 }(11 / 02) \\ & \text { F-2 }(05 / 00) \\ & \hline \end{aligned}$ | [87-99-0] | \$156 |
| 1721002 | Xylometazoline Hydrochloride (125 mg) | IOB101 |  |  | H-1 (05/03) | [1218-35-5] | \$124 |
| 1722005 | Xylose (1 g) | F |  |  |  | [58-86-6] | \$156 |
| 1724000 | Yohimbine Hydrochloride ( 200 mg ) | F |  |  |  | [65-19-0] | \$156 |
| 1724306 | Zalcitabine ( 200 mg ) | F |  |  |  | [7481-89-2] | \$156 |
| 1724317 | Zalcitabine Related Compound A (50 mg) (2', $3^{\prime}$ -Didehydro-2',3'-dideoxycytidine) | F0B234 |  |  |  | [7481-88-1] | \$487 |

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| Cat. No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1724500 | Zidovudine ( 400 mg ) | G |  |  | F (09/01) | [30516-87-1] | \$156 |
| 1724521 | Zidovudine Related Compound B ( 25 mg ) ( 3 '-chloro-3'-deoxythymidine) | G0B116 |  |  | $\begin{array}{\|l} \hline \text { F-1 (03/03) } \\ \text { F (06/01) } \\ \hline \end{array}$ | [25526-94-7] | \$487 |
| 1724532 | Zidovudine Related Compound C (100 mg) (thymine) | F-1 |  |  | F (09/01) | [65-71-4] | \$487 |
| 1724656 | Zileuton ( 150 mg ) | F0C062 |  |  |  | [111406-87-2] | \$156 |
| 1724667 | Zileuton Related Compound A (50 mg) ( N -(1-Benzo[b]thien-2-ylethyl) urea) | FOB316 |  |  |  | n/f | \$487 |
| 1724678 | Zileuton Related Compound B ( 50 mg ) (2-(Benzo[b]thien-2-oyl)benzo[b]thiophene) | F0B313 |  |  |  | n/f | \$487 |
| 1724689 | Zileuton Related Compound C ( 50 mg ) (1-Benzo[b]thien-2-ylethanone) | F0B299 |  |  |  | n/f | \$487 |
| 1724805 | Zolazepam Hydrochloride ( 500 mg ) | G0C023 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (03/04) } \\ \text { F (05/02) } \\ \hline \end{array}$ | [33754-49-3] | \$156 |

## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. <br> No. | New Description |
| :---: | :---: | :---: | :---: |
| 00200-6 | 5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid ( 50 mg ) (Limit Test) | 1184027 | Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid) |
| 02200-3 | 3-Amino-4-carboxamidopyrazole Hemisulfate ( 50 mg ) (Limit Test) | 1013024 | Allopurinol Related Compound A ( 50 mg ) (3-Amino-4-carboxamidopyrazole Hemisulfate) |
| 02250-2 | 4-Amino-6-chloro-1,3-benzenedisulfonamide ( 100 mg ) (Lim- it Test) | 1057507 | Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide) |
| 1023403 | 3-Amino-6-chloro-1-methyl-4-phenylcarbostyril (25 mg) | 1023403 | Diazepam Related Compound B ( 25 mg ) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril) |
| 02380-0 | 2-Amino-2'-chloro-5-nitrobenzophenone ( 25 mg ) (Limit Test) | 1140338 | Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5-nitrobenzophenone) |
| 02420-2 | 4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide $(100 \mathrm{mg})$ (Limit Test) | 1424018 | Methyclothiazide Related Compound A (100 mg) (4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide) |
| 02240-6 | 2-Amino-4-chlorophenol (50 mg) (Limit Test) | 1130527 | Chlorzoxazone Related Compound A ( 25 mg ) ( 2-Amino-4chlorophenol) |
| 02460-0 | 3-Amino-4-(2-chloro-phenyl)-6-nitrocarbostyril ( 25 mg ) (Lim- it Test) | 1140327 | Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril) |
| 02490-5 | 2-Amino-2',5-dichlorobenzophenone (25 mg) (Limit Test) | 1370338 | Lorazepam Related Compound B ( 25 mg ) (2-Amino-2',5dichlorobenzophenone) |
| 02610-6 | 3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid (25 mg) (Limit Test) | 1078325 | Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid) |
| 02620-8 | alpha-Aminopropiophenone Hydrochloride ( 50 mg ) (Limit Test) | 1096804 | Cathinone Hydrochloride CI (50 mg) (alpha-Aminopropiophenone Hydrochloride) |
| 06300-0 | 5-Benzyl-3,6-dioxo-2-piperazineacetic Acid ( 250 mg ) (Limit Test) | 1043728 | Aspartame Related Compound A ( 75 mg ) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid) |
| 07350-3 | 2-(4-Biphenylyl)propionic Acid (100 mg) (Limit Test) | 1285760 | Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid) |
| 07480-1 | N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide ( 50 mg ) (Limit Test) | 1344724 | lopamidol Related Compound A ( 50 mg ) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide) |
| 07500-4 | 4,4'-Bis[4-(p-chlorophenyl)-4-hydroxypiperidino]-butyrophenone ( 25 mg ) (Limit Test) | 1303013 | Haloperidol Related Compound A ( 25 mg ) ( $4,4-\mathrm{Bis}[4-\mathrm{p}-$ chlorophenyl)-4-hydroxypiperidino]-butyrophenone |
| 08650-5 | Calcium Formyltetrahydrofolate ( 50 mg ) (AS) (For Qualitiative Use Only) | 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) |
| 11230-0 | p -Chlorobenzhydrylpiperazine ( 25 mg ) | 1333058 | Hydroxyzine Related Compound A ( 25 mg ) (p-Chlorobenzhydrylpiperazine) |
| 11310-9 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxaldehyde ( 25 mg ) (Limit Test) | 1370349 | Lorazepam Related Compound C (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde) |
| 11320-0 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxylic Acid ( 25 mg ) (Limit Test) | 1370350 | Lorazepam Related Compound D ( 25 mg ) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid) |
| 11330-2 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazoline Methanol ( 25 mg ) (Limit Test) | 1370360 | Lorazepam Related Compound E (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol) |
| 11400-0 | 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one ( 50 mg ) (Limit Test) | 1468400 | Nordazepam CIV ( 50 mg ) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) |
| 11500-2 | 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4 -oxide ( 25 mg ) (Limit Test) | 1110020 | Chlordiazepoxide Related Compound A ( 25 mg ) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide) |
| 11510-4 | 2-Chloro-4-N-furfuryl-amino-5-sulfamolybenzoic acid ( 50 mg ) (Limit Test) | 1287020 | Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid) |
| 11550-1 | 2-Chloro-3,5-dimethyl-phenol (50 mg) (Limit Test) | 1122722 | Chloroxylenol Related Compound A (50 mg) (2-Chloro-3,5-dimethyl-phenol) |
| 11650-4 | (o-Chlorophenyl)diphenyl-methanol (25 mg) (Limit Test) | 1141024 | Clotrimazole Related Compound A ( 25 mg ) ((0-Chlorophe-nyl)diphenyl-methanol ) |
| 11670-8 | 4-(4-Chlorophenyl)-2-pyrrolidinone (75 mg) (Limit Test) | 1048222 | Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone) |
| 11900-3 | 4-Chloro-5-sulfamoylanthranilic Acid (100 mg) (Limit Test) | 1287030 | Furosemide Related Compound B (100 mg) (4-Chloro-5sulfamoylanthranilic Acid) |

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## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. <br> No. | New Description |
| :---: | :---: | :---: | :---: |
| 1119309 | 4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid ( 100 mg ) | 1119309 | Chlorthalidone Related Compound A ( 25 mg ) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid) |
| 1153001 | Cyclizine ( 1 g ) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F (04/04) |
| 15870-8 | Cyclosporine U (25 mg) DISCONTINUED | 1158650 | Cyclosporine Resolution Mixture ( 25 mg ) (Replaces Cat. No. 15870-8 Cyclosporine U ( 25 mg )) |
| 21000-3 | alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride (125 mg) (Limit Test) | 1575206 | Propoxyphene Related Compound A ( 50 mg ) (alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride) |
| 1268820 | Etoposide Related Compound A ( 25 mg ) (4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-alpha-D-glucopyranoside) DISCONTINUED | 1268852 | Etoposide Resolution Mixture ( 30 mg ) |
| 1269006 | Evans Blue ( 200 mg ) | N/A | DISCONTINUED, Last Lot/Valid Use Date: G (04/04) |
| 1277208 | Fluoride Dentifrice: Sodium Fluoride-Calcium Pyrophosphate (high beta-phase) ( 180 g ) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F (01/04) |
| 32720-4 | 3-Hydroxy-1-methylquinuclidinium Bromide ( 250 mg ) (Limit Test) | 1135021 | Clidinium Bromide Related Compound A ( 250 mg ) (3-Hydroxy -1-methylquinuclindinium Bromide) |
| 1329505 | 9-Hydroxypropantheline Bromide ( 50 mg ) | 1329505 | Propantheline Bromide Related Compound A ( 50 mg ) (9Hydroxypropantheline bromide) |
| 1330005 | Hydroxypropyl Methylcellulose ( $250 \mathrm{mg} \mathrm{)}$ | 1330005 | Hypromellose (250 mg) (Hydroxypropyl Methylcellulose) |
| 33010-7 | Hydroxypropyl Methylcellulose Phthalate ( 100 mg ) | 1335304 | Hypromellose Phthalate ( 100 mg ) |
| 1362001 | Levo-alpha-acetylmethadol Hydrochloride CII ( 25 mg ) (AS) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F-1 (08/03) |
|  | Melting Point Standard - Acetanilide ( 500 mg ; approximately 114 degrees) | 1004001 | Acetanilide Melting Point Standard ( 500 mg ) (Approximately 114 degrees) |
|  | Melting Point Standard - Caffeine (1 g; approximately 236 degrees) | 1086006 | Caffeine Melting Point Standard (1 g) (Approximately 236 degrees) |
|  | Melting Point Standard - Phenacetin ( 500 mg ; approximately 135 degrees) | 1514008 | Phenacetin Melting Point Standard (500 mg) (Approximately 135 degrees) |
|  | Melting Point Standard - Sulfanilamide ( 1 g ; approximately 165 degrees) | 1633007 | Sulfanilamide Melting Point Standard ( 500 mg ) (Approximately 165 degrees) |
|  | Melting Point Standard - Sulfapyridine (2 g; approximately 191 degrees) | 1635002 | Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees) |
|  | Melting Point Standard - Vanillin (1 g; approximately 82 degrees) | 1711009 | Vanillin Melting Point Standard (1 g) (Approximately 82 degrees) |
| 1420006 | 3 -Methoxytyrosine ( 50 mg ) | 1420006 | Levodopa Related Compound B (50 mg) (3-Methoxytyrosine) |
| 42420-0 | 2-Methylamino-5-chlorobenzophenone (25 mg) (Limit Test) | 1185020 | Diazepam Related Compound A ( 25 mg ) (2-Methylamino-5chlorobenzophenone) |
| 42430-2 | 3-O-Methylcarbidopa ( 50 mg ) | 1095517 | Carbidopa Related Compound A ( 50 mg ) (3-O-Methylcarbidopa) |
| 1434000 | Methylphenidate Hydrochloride Erythro Isomer CII (25 mg) DISCONTINUED; please order 1434011 | 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution CII ( 0.5 mL ) |
| 1445222 | Mitoxantrone Related Compound A Hydrochloride ( 30 mg ) (8-amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]a-mino]-9,10-anthracenedione Hydrochloride) DISCONTINUED; Please order 1445211 | 1445211 | Mitoxantrone System Suitability Mixture ( 0.3 mg ) |
| 46600-7 | 5-Nitro-2-furfuraldazine ( 500 mg ) | 1466007 | Nitrofurazone Related Compound A (500mg) (5-Nitro-2furfuraldazine) |
| 46660-8 | 3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid (25 mg) (Limit Test) | 1078336 | Bumetanide Related Compound B ( 25 mg ) (3-Nitro-4-phe-noxy-5-sulfamoylbenzoic Acid) |
| 1477900 | Octyl Methoxycinnamate ( 500 mg ) | 1477900 | Octinoxate ( 500 mg ) (Octyl Methoxycinnamate) |
| 49400-2 | Pancreatin (2 g) | $\begin{array}{\|l} \hline 1494057 \\ \text { and/or } \\ 1494079 \\ \hline \end{array}$ | Pancreatin Amylase and Protease (2 g) and/or Pancreatin Lipase (2 g) |
| 1527000 | Phenprocoumon (200 mg) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F-1 (02/04) |

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## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. <br> No. | New Description |
| :---: | :---: | :---: | :---: |
| 53180-1 | Phenylcyclohexylglycolic Acid (100 mg) (Limit Test) | 1485114 | Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid) |
| 53350-1 | alpha-Phenyl-2-piperidineacetic Acid Hydrochloride ( 50 mg ) (Limit Test) | 1434022 | Methylphenidate Related Compound A ( 50 mg ) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride) |
| 54500-1 | Plastic, Negative Control | 1546707 | Polyethylene, High Density (3 strips) |
| 61500-5 | Sodium Taurocholate (20 g) | 1071304 | Bile Salts (10 g) (Sodium Taurocholate) |
| 68800-9 | 3 -(3,4,6-Trihydroxyphenyl)-alanine (50 mg) (Limit Test) | 1361010 | Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydrox-yphenyl)-alanine) |
|  | Vitamin B1 Hydrochloride | 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) |
|  | Vitamin B2 | 1603006 | Riboflavin ( 500 mg ) (Vitamin B2) |
|  | Vitamin B3 | 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) |
|  | Vitamin B5 | 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) |
|  | Vitamin B6 | 1587001 | Pyridoxine Hydrochloride ( 200 mg ) (Vitamin B6) |
|  | Vitamin B12 | 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) |
|  | Vitamim Bc | 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) |
|  | Vitamin C | 1043003 | Ascorbic Acid (1 g) (Vitamin C) |
|  | Vitamin D2 | 1239005 | Ergocalciferol ( $150 \mathrm{mg} ; 30 \mathrm{mg} / \mathrm{ampule} ; 5$ ampules) (Vitamin D2) |
|  | Vitamin D3 | 1131009 | Cholecalciferol (30 mg/ampul; 5 ampuls) (Vitamin D3) |
|  | Vitamin E Alcohol | 1667600 | Alpha Tocopherol ( 250 mg ) (Vitamin E Alcohol) |
|  | Vitamin E Acetate | 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) |
|  | Vitamin E Acid Succinate | 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) |
|  | Vitamin K1 | 1538006 | Phytonadione ( 500 mg ) (Vitamin K1) |
|  | Vitamin K3 | 1381006 | Menadione (200 mg) (Vitamin K3) |
|  | Vitamin M | 1286005 | Folic Acid (500 mg) (Vitamin M or Vitamin Bc) |

## Dietary Supplement Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| AMINO ACIDS |  |  |  |
| 1012509 | L-Alanine (200 mg) | F-2 | \$156 |
| 1021000 | Aminocaproic Acid (200 mg) | F-4 | \$156 |
| 1042500 | L-Arginine (200 mg) | G-1 | \$156 |
| 1042601 | Arginine Hydrochloride ( 125 mg ) | G0B060 | \$124 |
| 1161509 | L-Cysteine Hydrochloride ( 200 mg ) | H | \$156 |
| 1294976 | Glutamic Acid ( 200 mg ) | F0C069 | \$156 |
| 1294808 | Glutamine ( 100 mg ) | FOB244 | \$156 |
| 1295800 | Glycine ( 200 mg ) | F-3 | \$156 |
| 1308505 | L-Histidine ( 200 mg ) | G0A018 | \$156 |
| 1349502 | L-Isoleucine ( 200 mg ) | F-2 | \$156 |
| 1357001 | L-Leucine (200 mg) | H0B237 | \$156 |
| 1359903 | Levocarnitine ( 400 mg ) | G0B197 | \$156 |
| 1359925 | Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride) | F-1 | \$208 |
| 1371501 | L-Lysine Acetate ( 200 mg ) | F1C027 | \$156 |
| 1372005 | L-Lysine Hydrochloride (200 mg) | H | \$156 |
| 1411504 | L-Methionine ( 200 mg ) | G | \$156 |
| 1530503 | L-Phenylalanine ( 200 mg ) | H | \$156 |
| 1568506 | L-Proline (200 mg) | F-2 | \$156 |
| 1612506 | L-Serine (200 mg) | G | \$156 |
| 1667202 | L-Threonine ( 200 mg ) | G | \$156 |
| 1700501 | L-Tryptophan (200 mg) | G-1 | \$156 |
| 1705006 | L-Tyrosine ( 500 mg ) | $J$ | \$156 |
| 1708503 | L-Valine ( 200 mg ) | F-2 | \$156 |
| BOTANICALS |  |  |  |
| CAPSAICIN/CAPSICUM |  |  |  |
| 1091108 | Capsaicin (100 mg) | G-1 | \$156 |
| 1200600 | Dihydrocapsaicin (25 mg) | G0C071 | \$156 |
| CHAMOMILE |  |  |  |
| 1040708 | Apigenin-7-Glucoside ( 30 mg ) | F | \$487 |
| CHASTE TREE |  |  |  |
| 1105009 | Powdered Chaste Tree Extract (1.5 g) | F0C406 | \$520 |
| CRANBERRY LIQUID |  |  |  |
| 1134368 | Citric Acid (200 mg) | F1B092 | \$156 |
| 1181302 | Dextrose ( 500 mg ) | J-1 | \$124 |
| 1286504 | Fructose ( 125 mg ) | I-2 | \$124 |
| 1374601 | Malic Acid (200 mg) | G0B158 | \$156 |
| 1594506 | Quinic Acid ( 200 mg ) | F | \$156 |
| 1617000 | Sorbitol ( 125 mg ) | H1B139 | \$124 |
| 1623637 | Sucrose (100 mg) | H1C223 | \$156 |
| ELEUTHERO |  |  |  |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | \$520 |
| ECHINACEA |  |  |  |
| 1115545 | Chlorogenic Acid ( 50 mg ) | FOC420 | \$156 |
| 1231728 | Powdered Echinacea Purpurea Extract (1 g) | F0D018 | \$520 |
| 1231706 | Powdered Echinacea Angustifolia Extract (1 g) | F0D019 | \$520 |
| 1305507 | 2E, 4E-Hexadienoic Acid Isobutylamide ( 25 mg ) | F0C353 | \$540 |
| FEVERFEW |  |  |  |
| 1500400 | Parthenolide (25 mg) | F | \$156 |

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## Dietary Supplement Reference Standards Available from USP

| Cat. No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| GARLIC |  |  |  |
| 1012145 | Agigenin (25 mg) | F | \$156 |
| 1012950 | Alliin ( 25 mg ) | F | \$1,525 |
| 1115556 | beta-Chlorogenin ( 20 mg ) | F | \$156 |
| 1294848 | gamma-Glutamyl-S-allyl-L-cysteine ( 25 mg ) | F | \$675 |
| 1411504 | L-Methionine (200 mg) | G | \$156 |
| GARLIC FLUID EXTRACT |  |  |  |
| 1013057 | S-Allyl-L-Cysteine (25 mg) | F | \$487 |
| GINGER |  |  |  |
| 1091108 | Capsaicin (100 mg) | G-1 | \$156 |
| 1291504 | Powdered Ginger ( 500 mg ) | F | \$156 |
| GINKGO |  |  |  |
| 1115545 | Chlorogenic Acid (50 mg) | FOC420 | \$156 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| AMERICAN GINSENG |  |  |  |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | F0B289 | \$520 |
| ASIAN GINSENG |  |  |  |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | F0B289 | \$520 |
| HAWTHORN LEAF WITH FLOWER |  |  |  |
| 1115545 | Chlorogenic Acid ( 50 mg ) | FOC420 | \$156 |
| 1335202 | Hyperoside ( 50 mg ) | F | \$855 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| 1717708 | Vitexin ( 30 mg ) | F0C142 | \$520 |
| KAVA |  |  |  |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 | \$260 |
| KAWAIN |  |  |  |
| 1355753 | Kawain (200 mg) | F0C160 | \$208 |
| LICORICE |  |  |  |
| 1295888 | Glycyrrhizic Acid (25 mg) | F0C006 | \$487 |
| MILK THISTLE |  |  |  |
| 1443850 | Powdered Milk Thistle Extract (250 mg) | F0B321 | \$260 |
| 1612630 | Silybin ( 50 mg ) | F | \$156 |
| 1612641 | Silydianin (20 mg) | F | \$156 |
| RED CLOVER |  |  |  |
| 1286060 | Formononetin ( 50 mg ) | F0C196 | \$520 |
| 1599500 | Powdered Red Clover Extract (500 mg) | F0C188 | \$260 |
| SAW PALMETTO |  |  |  |
| 1424233 | Methyl Caprate ( 300 mg ) | F | \$156 |
| 1424244 | Methyl Caproate ( $300 \mathrm{mg} \mathrm{)}$ | F | \$156 |
| 1424255 | Methyl Caprylate ( 300 mg ) | F | \$156 |
| 1430305 | Methyl Laurate ( 500 mg ) | G0C356 | \$156 |
| 1430327 | Methyl Linoleate ( $5 \times 50 \mathrm{mg}$ ) | F | \$156 |
| 1430349 | Methyl Linolenate ( $5 \times 50 \mathrm{mg}$ ) | F | \$156 |
| 1431501 | Methyl Myristate ( $300 \mathrm{mg} \mathrm{)}$ | G0C357 | \$156 |
| 1431556 | Methyl Oleate ( 500 mg ) | G0C148 | \$156 |
| 1431603 | Methyl Palmitate ( 300 mg ) | F | \$156 |

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## Dietary Supplement Reference Standards Available from USP

| Cat. No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1431625 | Methyl Palmitoleate ( $300 \mathrm{mg} \mathrm{)}$ | F | \$156 |
| 1437508 | Methyl Stearate ( 300 mg ) | F | \$156 |
| ST. JOHN S WORT |  |  |  |
| 1115545 | Chlorogenic Acid ( 50 mg ) | FOC420 | \$156 |
| 1335202 | Hyperoside ( 50 mg ) | F | \$855 |
| 1485001 | Oxybenzone ( 150 mg ) | H0B263 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| VALERIAN |  |  |  |
| 1707908 | Valerenic Acid (25 mg) | G0B146 | \$696 |
| MISCELLANEOUS DIETARY SUPPLEMENTS |  |  |  |
| 1133570 | Chondroitin Sulfate Sodium ( 300 mg ) | FOB256 | \$156 |
| 1133638 | Chromium Picolinate ( 100 mg ) | F | \$156 |
| 1150353 | Creatinine ( 100 mg ) | F | \$156 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 | \$156 |
| 1611955 | Selenomethionine ( 100 mg ) | FOB006 | \$156 |
| VITAMINS-MINERALS |  |  |  |
| 1043003 | Ascorbic Acid (1 g) (Vitamin C) | Q0B012 | \$156 |
| 1071508 | Biotin (200 mg) | H1B019 | \$156 |
| 1086356 | Calcium Ascorbate ( 200 mg ) | F-1 | \$156 |
| 1087009 | Calcium Pantothenate ( 200 mg ) (Vitamin B5) | N-1 | \$156 |
| 1131009 | Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3) | M0B157 | \$159 |
| 1131803 | Delta-4,6-cholestadienol ( 30 mg ) | F | \$156 |
| 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) | N | \$156 |
| 1179504 | Dexpanthenol ( 500 mg ) | J0C293 | \$160 |
| 1239005 | Ergocalciferol ( $30 \mathrm{mg} / \mathrm{ampule}$; 5 ampules) (Vitamin D2) | P0B275 | \$168 |
| 1241007 | Ergosterol ( 50 mg ) | H | \$156 |
| 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) | P | \$156 |
| 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) | IOB176 | \$156 |
| 1381006 | Menadione ( 200 mg ) (Vitamin K3) | H-3 | \$156 |
| 1461003 | Niacin (200 mg) | H2C121 | \$156 |
| 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) | M-1 | \$156 |
| 1494501 | Panthenol, Racemic ( 200 mg ) | G | \$156 |
| 1494807 | Pantolactone ( 500 mg ) | F | \$487 |
| 1538006 | Phytonadione ( 500 mg ) (Vitamin K1) | N0B303 | \$156 |
| 1550001 | Potassium Gluconate (200 mg) | H0C064 | \$156 |
| 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) | P | \$156 |
| 1603006 | Riboflavin ( 500 mg ) (Vitamin B2) | N0C021 | \$156 |
| 1613509 | Sodium Ascorbate (200 mg) | G2C067 | \$156 |
| 1614002 | Sodium Fluoride ( 1 g ) | H-1 | \$156 |
| 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) | 0 | \$156 |
| 1667600 | Alpha Tocopherol ( 250 mg ) (Vitamin E Alcohol) | M | \$156 |
| 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) | K | \$156 |
| 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) | F-5 | \$156 |
| 1716002 | Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil) | V0C258 | \$156 |
| 1717504 | Vitamin D Assay System Suitability (1.5 g) | F | \$156 |

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## Controlled Substances Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1012906 | Alfentanil Hydrochloride CII (500 mg) | F0B016 | \$207 |
| 1014005 | Alphaprodine Hydrochloride CII (250 mg) | F | \$207 |
| 1015008 | Alprazolam CIV (200 mg) | H | \$207 |
| 1030001 | Amobarbital CII (200 mg) | F-2 | \$207 |
| 1036008 | Anileridine Hydrochloride CII ( 250 mg ) | F | \$207 |
| 1042000 | Aprobarbital CIII ( 200 mg ) (AS) | F-1 | \$207 |
| 1059003 | Benzphetamine Hydrochloride CIII (200 mg) (AS) | F-1 | \$207 |
| 1078700 | Buprenorphine Hydrochloride CIII ( 50 mg ) | F-1 | \$207 |
| 1079000 | Butabarbital CIII ( 200 mg ) | H0C007 | \$207 |
| 1081002 | Butalbital CIII ( 200 mg ) | H0C054 | \$207 |
| 1082504 | Butorphanol Tartrate CIV (500 mg) | J | \$207 |
| 1089004 | Cannabidiol CI (25 mg) (AS) | F-2 | \$207 |
| 1090003 | Cannabinol CI (25 mg) (AS) |  | \$207 |
| 1096804 | Cathinone Hydrochloride CI (50 mg) (alpha-Aminopropiophenone Hydrochloride) | 1 | \$560 |
| 1109000 | Chlordiazepoxide CIV ( 200 mg ) | IOB063 | \$207 |
| 1110009 | Chlordiazepoxide Hydrochloride CIV (200 mg) | G-4 | \$207 |
| 1140305 | Clonazepam CIV (200 mg) | G1B175 | \$207 |
| 1140509 | Clorazepate Dipotassium CIV (125 mg) | G0B027 | \$207 |
| 1143008 | Cocaine Hydrochloride CII (250 mg) | IOB074 | \$207 |
| 1143802 | Codeine N-Oxide CI (50 mg) | G0A034 | \$207 |
| 1144000 | Codeine Phosphate CII (100 mg) | J0C200 | \$207 |
| 1145003 | Codeine Sulfate CII ( 250 mg ) | H-2 | \$207 |
| 1180004 | Dextroamphetamine Sulfate CII (500 mg) | IOC311 | \$216 |
| 1183002 | Diacetylmorphine Hydrochloride (Heroin Hydrochloride) CI (25 mg) (AS) | J | \$207 |
| 1185008 | Diazepam CIV (100 mg) | 1 | \$207 |
| 1187207 | Dichloralphenazone CIV (200 mg) | F0B010 | \$207 |
| 1194009 | Diethylpropion Hydrochloride CIV (200 mg) | H | \$207 |
| 1200804 | Dihydrocodeine Bitartrate CII (200 mg) | H | \$207 |
| 1219008 | Diphenoxylate Hydrochloride CII (200 mg) | 1 | \$207 |
| 1258305 | Ethchlorvynol CIV ( 0.7 ml ) | F0B011 | \$207 |
| 1270005 | Fentanyl Citrate CII (100 mg) | K0C264 | \$207 |
| 1280009 | Fluoxymesterone CIII ( 200 mg ) | G-2 | \$207 |
| 1285002 | Flurazepam Hydrochloride CIV ( $200 \mathrm{mg} \mathrm{)}$ | J0C365 | \$207 |
| 1295006 | Glutethimide CII ( 500 mg ) | F | \$207 |
| 1302305 | Halazepam CIV (200 mg) (AS) | F1C224 | \$207 |
| 1307003 | Hexobarbital CIII ( 500 mg ) | F | \$207 |
| 1315001 | Hydrocodone Bitartrate ClI (250 mg) | K0C217 | \$207 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl) | F0C214 | \$513 |
| 1323000 | Hydromorphone Hydrochloride CII (50 mg) | J0C372 | \$207 |
| 1356009 | Ketamine Hydrochloride CIII ( $250 \mathrm{mg} \mathrm{)}$ | G-2 | \$207 |
| 1359506 | Levmetamfetamine CII ( 75 mg ) | F | \$207 |
| 1364007 | Levorphanol Tartrate CII ( 500 mg ) | H | \$207 |
| 1370305 | Lorazepam CIV (200 mg) | $10 \mathrm{CO48}$ | \$207 |
| 1371002 | Lysergic Acid Diethylamide Tartrate (LSD) CI (10 mg) (AS) | 1 | \$207 |
| 1375309 | Mazindol CIV ( 350 mg ) | H | \$207 |
| 1383001 | Meperidine Hydrochloride CII (200 mg) | 1 | \$207 |
| 1386000 | Mephobarbital CIV (250 mg) | G | \$207 |
| 1389008 | Meprobamate CIV (200 mg) | G-1 | \$207 |
| 1398009 | Methadone Hydrochloride CII (200 mg) | IOB163 | \$207 |

[^232]
## Controlled Substances Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1399001 | Methamphetamine Hydrochloride CII (125 mg) | I | \$207 |
| 1404000 | Methaqualone $\mathbf{C l}(500 \mathrm{mg}$ ) | F-1 | \$207 |
| 1405002 | Metharbital CIII ( 200 mg ) | F-2 | \$207 |
| 1413000 | Methohexital CIV ( 500 mg ) | F-2 | \$207 |
| 1425000 | 4-Methyl-2,5-dimethoxyamphetamine Hydrochloride (STP) CI (25 mg) (AS) | F | \$207 |
| 1429000 | Methylenedioxy-3,4-amphetamine Hydrochloride (MDA) CI (25 mg) (AS) | F-1 | \$207 |
| 1433008 | Methylphenidate Hydrochloride CII (125 mg) | 11-241 | \$165 |
| 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution CII ( 0.5 mL ) | F0C368 | \$560 |
| 1438001 | Methyltestosterone CIII ( 200 mg ) | $J$ | \$207 |
| 1447002 | Morphine Monohydrate CII (50 mg) (AS) | G | \$207 |
| 1448005 | Morphine Sulfate CII ( 500 mg ) | M0D016 | \$332 |
| 1452002 | Nalorphine Hydrochloride CIII (250 mg) | 1 | \$207 |
| 1453526 | Naltrexone Related Compound A CII (30 mg) ( N -(3-butenyl)-noroxymorphone hydrochloride) | F | \$207 |
| 1454008 | Nandrolone CIII ( 50 mg ) |  | \$560 |
| 1455000 | Nandrolone Decanoate CIII (250 mg) | 1 | \$207 |
| 1456003 | Nandrolone Phenpropionate CIII (250 mg) | H | \$207 |
| 1468400 | Nordazepam CIV (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) | H1B035 | \$560 |
| 1473002 | Noroxymorphone Hydrochloride CII ( 50 mg ) | H1C177 | \$560 |
| 1482003 | Oxandrolone CIII ( 50 mg ) | G0B220 | \$207 |
| 1483006 | Oxazepam CIV (200 mg) | G-1 | \$207 |
| 1485191 | Oxycodone CII (200 mg) | IOB046 | \$207 |
| 1487007 | Oxymetholone CIII (200 mg) | G1B247 | \$207 |
| 1488000 | Oxymorphone CII ( 500 mg ) | H0B214 | \$207 |
| 1505007 | Pentazocine CIV ( 500 mg ) | 10 C 418 | \$207 |
| 1507002 | Pentobarbital CII ( 200 mg ) | H3C144 | \$207 |
| 1516003 | Phencyclidine Hydrochloride CII (25 mg) (AS) | G1B025 | \$207 |
| 1516502 | Phendimetrazine Tartrate CIII ( 350 mg ) | G | \$207 |
| 1523009 | Phenmetrazine Hydrochloride CII (200 mg) | F-2 | \$207 |
| 1524001 | Phenobarbital CIV (200 mg) | J | \$207 |
| 1528501 | Phentermine Hydrochloride CIV (200 mg) | H0B309 | \$207 |
| 1554501 | Prazepam CIV (500 mg) | G0C066 | \$207 |
| 1574000 | Propoxyphene Hydrochloride CII (1 g) | LOC285 | \$207 |
| 1575002 | Propoxyphene Napsylate CII (1 g) | H | \$207 |
| 1592205 | Quazepam CIV (200 mg) | F | \$207 |
| 1611004 | Secobarbital CII (200 mg) | H | \$207 |
| 1620005 | Stanozolol CIII ( 200 mg ) | F-3 | \$207 |
| 1623648 | Sufentanil Citrate Cll ( 25 mg ) | H0B208 | \$207 |
| 1643000 | Talbutal CIII ( 250 mg ) | F | \$207 |
| 1643408 | Temazepam CIV ( 200 mg ) | H0C205 | \$207 |
| 1645006 | Testolactone CIII ( 125 mg ) | F-1 | \$165 |
| 1646009 | Testosterone CIII ( 125 mg ) | 11B253 | \$165 |
| 1647001 | Testosterone Cypionate CIII ( 200 mg ) | G-1 | \$207 |
| 1648004 | Testosterone Enanthate CIII ( 200 mg ) | $J$ | \$207 |
| 1649007 | Testosterone Propionate CIII ( $200 \mathrm{mg} \mathrm{)}$ | L1C005 | \$207 |
| 1656308 | Thiamylal CIII ( 200 mg ) | F | \$207 |
| 1661002 | Thiopental CIII ( 250 mg ) | 1 | \$207 |
| 1680506 | Triazolam CIV (200 mg) | H0B041 | \$207 |

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Vol. 30(4) July-Aug. 2004]

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# CHROMATOGRAPHIC REAGENTS USED IN $\boldsymbol{U S P} \boldsymbol{- N F}$ AND PHARMACOPEIAL FORUM 

This is an update based on the proposals published in this issue of $P F$.

## CHROMATOGRAPHIC REAGENTS

## Chromatographic Reagents Used in USP-NF and Pharmacopeial Forum

July-August 2004

| <571> VITAMIN A ASSAY |  |  |  | DSD Mgh \#99330 |
| :---: | :---: | :---: | :---: | :---: |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(4) | L8 | Zorbax NH2 | Assay | $4.6 \mathrm{~mm} \times 15 \mathrm{~cm}, 5 \mu \mathrm{~m}$, manufacturer Agilent Technologies. |
| FLUMAZENIL |  |  |  | DSD Mgh \#33370 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(4) | L1 | Inertsil ODS-2 | Assay and Related Compounds | $25 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer GL Science. |
| FLUVASTATIN CAPSULES |  |  |  | DSD Mgh \#34228 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(4) | L1 | Hypersil-ODS | Dissolution | $10 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5: \mathrm{m}$, manufacturer Thermo |
| 30(4) | L1 | Hypersil-ODS | Assay \& Chrom. purity | $5 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5: \mathrm{m}$;, manufacturer Thermo |

FLUVASTATIN SODIUM DSD Mgh \#34227
$\frac{\mathrm{PF}}{30(4)}$
$\frac{\text { LGS\# }}{\text { L1 }} \frac{\text { Reagent Brand }}{\text { Hypersil-ODS }}$

LORATADINE ORAL SOLUTION

$\frac{\text { LGS\# }}{\text { L11 }} \frac{\text { Reagent Brand }}{\text { MicroBondapak Phenyl }}$
$\frac{\text { Type of Test }}{\text { Assay }}$

$\frac{\text { Comments }}{30 \mathrm{~cm} \times 4 \mathrm{~mm}, 10:$|  m, manufacturer Waters  |
| :--- |
|  Corp.  |}

PACLITAXEL

| $\frac{P F}{30(4)}$ |
| :---: |
| $30(4)$ |


| $\frac{\text { LGS\# }}{\text { L1 }}$ |  |
| :---: | :---: |
|  |  |
|  | YMC-Pack ODS-A |
| YMC-Pack ODS-A |  |


|  | POVID |  |  | DSD Mgh \#68070 |
| :---: | :---: | :---: | :---: | :---: |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(4) | L7 | Symmetry Shield RP8 | Content of . . . | Vinyilpyrrolidone. $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}, 5$ : m, manufacturer Waters Corp. Guard column, L7 Nucleosil 120-5-C8 $4.0 \mathrm{~mm} \times 30 \mathrm{~mm}$, manufacturer Macharey-Nagel. Alternative guard column Zorbax Ace C-8, $4.6 \mathrm{~mm} \times 30 \mathrm{~mm}, 5 \mathrm{~m}$, manufacturer Agilent Tech. |

DSD Mgh \#60190

| Related compounds |
| :---: |
| Related compounds |

Related compound test $2,4.6 \mathrm{~mm} \times 15 \mathrm{~cm}, 3$
$: \mathrm{m}$, manuf. YMC Co., Ltd.
Related compound test $3,4.6 \mathrm{~mm} \times 15 \mathrm{~cm}, 3$
$: \mathrm{m}$, manuf. YMC Co., Ltd.

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## The Journal of Standards Development and Official Compendia Revision

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The United States Pharmacopeial Convention comprises representatives from colleges and national and state organizations of medicine and pharmacy. It publishes the U.S. Pharmacopeia and National Formulary, the legally recognized compendia of standards for drugs and products of other health care technologies. The USP and NF include assays and tests for the determination of strength, quality, and purity and requirements for packaging and labeling.

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[^235]
## STANDARDS DEVELOPMENT

This section presents an overview of the public review and comment process, conducted through Pharmacopeial Forum $(P F)$, for the development of official pharmaceutical standards.

USP publishes Pharmacopeial Forum ( $P F$ ) bimonthly as the working vehicle of the USP Council of Experts. PF provides interested parties an opportunity to review and comment as the Council of Experts develops or revises standards for the United States Pharmacopeia and the National Formulary (USP-NF).
$P F$ includes the following:

1. Potential revisions-entirely new standards, revision ideas, and drafts not yet targeted for official adoption (Pharmacopeial Previews)
2. Proposed revisions - new or revised standards targeted for official adoption (In-Process Revision)
3. Adopted revisions-new or revised standards that become official and binding before the publication of the next $U S P$ NF or Supplement (Interim Revision Announcement)
USP welcomes comments and data on potential, proposed, or official standards. ${ }^{*}$ Comments, along with USP's responses, will be published either in PF Briefings, the Commentary section of $P F$, the Commentary section of Supplements to USP-NF, or the Commentary section of $U S P-N F$.
[^236]The chart below shows the public review and comment process and its relationship to standards development.

# Public Review and Comment Process for Standards Development 



Questions on the process should be addressed to John W. Gasper, M.A., J.D., Director, Office of the Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: jg@usp.org).

## HOW TO USE PF

This section provides descriptions of the various parts of $P F$. It also includes Committee Designations and the Staff Directory.

The contents of the different sections of $P F$ are briefly described below. Readers will get an idea of how each section is relevant to their job functions. They may contact USP scientific staff liaisons or staff members of the Executive Secretariat (listed in the Staff Directory) if they have any questions. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a Request for Revision is available on the USP website (www.usp.org/standards/revisionguideline/).

Proposed and Adopted Revisions

| Section | Content | How Readers Can Respond |
| :---: | :---: | :---: |
| Pharmacopeial <br> Previews <br> Early ideas for revisions | -Briefing: Scientific rationale for potential inclusion or change. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -Potential revisions not yet targeted for official adoption that require a longer public review and comment process because of issues such as: <br> - the controversial nature of an item; <br> - the application of new technologies that require further study; and <br> - articles produced by multiple sources. | Review drafts and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview. |
| In-Process Revision Revisions targeted for adoption | -BriEfing: Scientific rationale for proposed changes. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -New and revised standards that have been approved for publication by the appropriate USP Committee when it is considering whether to advance standards to official status (see Standards Development). New or revised text is marked with symbols ( ${ }^{\square}$ or ) to specify the tentative earliest date on which the revision would be officially adopted. | Review material and send comments promptly to USP staff liaison (see the Staff Directory). Guidelines on how to comment are found at the end of the Po licies and Announcements section. |
| Harmonization <br> Items the Pharmacopeial Discussion Group (PDG) is trying to harmonize internationally | -Briefing: Scientific rationale for the potential inclusion or change or for the proposed change. The designated stage of harmonization. The stage determines whether an item appears under Pharmacopeial Previews or under In-Process Revision, both separate sections of Harmonization. <br> -For In-Process Revision, new or revised text is marked with symbols (■) to specify the tentative, earliest date on which the revision would be officially adopted. | Review material and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview or In-Process Revision. |
| Interim Revision <br> Announcement <br> Adopted standards | Standards that have been adopted and will become officially binding on the specified date. Effective date is specified in the section's introductory page or within parentheses following a particular item. New or revised text is set off by the symbols ${ }^{\circ}$. | Review to see if affected by any of the changes. Note effective date when standards become official and ensure compliance. |

## Other Sections

## Committee Designations

Names of the committees (composed of volunteer scientific experts) that USP staff work with on the development of standards.

## Staff Directory

Names of all USP scientific staff liaisons with contact information.

## Policies and Announcements

- General scientific and policy issues affecting $U S P-N F$ standards and processes
- Update on standards-related issues being considered by USP
- Summaries of meetings of the Council of Experts
- Guidelines on how to comment
- Publication and comment schedules


## Stimuli to the Revision Process

- Articles on standards development issues authored by the USP Council of Experts, USP staff, or other interested parties
- Discussions of issues on which USP desires public input prior to further development


## Nomenclature

- Latest adopted United States Adopted Names (USAN) and International Nonproprietary Names (INN) for drugs
- Revisions to existing names as a supplement to the USP Dictionary of USAN and International Drug Names
- Suggested, proposed, and recommended USAN and INN
- Information on how nonproprietary drug names are devised
- Articles relevant to compendial nomenclature issues


## Index

Cumulative directory for the content of all issues of $P F$ beginning with $P F 30(1)$.

## Reference Standards Catalog

List of official USP Reference Standards specified in $U S P-N F$, along with availability and ordering information.

## Chromatographic Reagents Used in USP-NF and Pharmacopeial Forum

Update of chromatographic reagents based on the proposals published in this issue of $P F$.

## EXPERT COMMITTEE DESIGNATIONS*

The names of the Committees and their abbreviations are as follows:

| AER | Aerosols |
| :--- | :--- |
| AMB | Analytical Microbiology |
| BBP | Blood and Blood Products |
| BNA | Bioavailability and Nutrient Absorption |
| BNT | Biotechnology and Natural Therapeutics and Diagnostics |
| BPC | Biopharmaceutics |
| BST | Biostatistics |
| CRX | Compounding Pharmacy |
| DSB | Dietary Supplements-Botanicals |
| DSI | Dietary Supplements-Information |
| DSN | Dietary Supplements-Non-Botanicals |
| EMC | Excipient Monograph Content |
| ETM | Excipients-Test Methods |
| GCT | Gene Therapy, Cell Therapy, and Tissue Engineering |
| GTB | General Toxicity and Biocompatibility |
| NL | Nomenclature and Labeling |
| PA1 | Pharmaceutical Analysis 1 |
| PA2 | Pharmaceutical Analysis 2 |
| PA3 | Pharmaceutical Analysis 3 |
| PA4 | Pharmaceutical Analysis 4 |
| PA5 | Pharmaceutical Analysis 5 |
| PA6 | Pharmaceutical Analysis 6 |
| PA7 | Pharmaceutical Analysis 7-Antibiotics |
| PDF | Pharmaceutical Dosage Forms |
| PPC | Parenteral Products-Compounding and Preparation |
| PPI | Parenteral Products-Industrial |
| PSD | Packaging, Storage, and Distribution |
| PW | Pharmaceutical Waters |
| RMI | Radiopharmaceuticals and Medical Imaging |
| SMU | Safe Medication Use |
| VET | Veterinary Drugs |
| VVI | Vaccines, Virology, and Immunology |
|  |  |

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## STAFF DIRECTORY

This is an updated directory that reflects assignment changes based on the reorganization of USP. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Committee is not identified. The Fax number is (301) 816-8373.

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## POLICIES AND ANNOUNCEMENTS

In this section, readers may find statements about general scientific and policy issues that may have an impact on $U S P-N F$ standards and processes, announcements about issues being considered by USP, and summaries of Council of Experts meetings. This section also includes publication and comment schedules.

USP TO HOLD FIRST ANNUAL SCIENTIFIC MEETING. MEETING FOCUSES ON PRODUCT AND PROCESS STANDARDS. The United States Pharmacopeia (USP) is pleased to announce that it will hold its first USP Annual Scientific Meeting at the Sheraton Woodbridge Place in Iselin, N.J. from Sept. 27 to 29,2004 . The new USP Annual Scientific Meeting, which replaces the organization's open conference format, will allow stakeholders the opportunity to learn about and discuss science topics that are the foundation of USP's standards-setting activities.
"We are creating one annual meeting to allow USP to address multiple topics and to allow more people to participate in USP's standards-setting activities," said Roger L. Williams, M.D., USP Executive Vice President and Chief Executive Officer. "This one-stop approach allows stakeholders the opportunity to meet with USP at one time and in one convenient location."

Preliminary USP Annual Scientific Meeting topics to be presented are the following:

- Biologics and Biotechnology Products
- Chromatography
- Dissolution
- Excipients and Pharmaceutical Waters
- Making the $U S P-N F$ Work for You
- Microbiology
- Process Analytical Technology
- Specifications

In addition, USP will offer its Pharmacopeial Education courses on Analytical Method Validation, Basic Statistics and their Practical Applications to USP, Dissolution, Microbiology, and USP 100 and 101. These courses and the USP Annual Scientific Meeting session tracks will be approved for continuing pharmaceutical education units (CEUs). Attendees of the USP Annual Scientific Meeting also can learn about other USP initiatives and how to become involved in USP's processes through the various USP volunteer bodies.

The USP Annual Scientific Meeting is designed for USP$N F$ and USP Reference Standards customers and other USP stakeholders including pharmaceutical scientists focusing on chemistry, microbiology, biologics and biotechnology, Process Analytical Technology, excipients, dissolution, and chromatography.

For further information about the USP Annual Scientific Meeting, please visit www.usp.org/conferences, or call 301-816-8226.

## USAN COUNCIL SECRETARIAT REVISES USAN

 FEE-FOR-SERVICE CHARGES. A revised schedule of fee-for-service charges has been placed in effect as of January 1, 2004. The increased fees appear on the USAN submission forms that are provided under Appendix XI of the 2004 edition of the USP Dictionary of USAN and International Drug Names. This announcement will be important to inform users of the USP Dictionary who are not yet using the revised 2004 edition of the changes.For further information please contact:

United States Adopted Names (USAN) Program<br>American Medical Association<br>515 North State Street<br>Chicago, IL 60610<br>Phone: 312-464-4046<br>Fax: 312-464-4028<br>Web site: http://www.ama-assn.org/go/usan

USP GUIDELINE FOR SUBMITTING REQUESTS FOR REVISION TO THE USP-NF. We are pleased to announce the availability of the USP Guideline for Submitting Requests for Revision to the $U S P-N F$. This document was developed in conjunction with the USP Council of Experts and its Expert Committees, USP Staff, and the Drug Substance, Complex Actives, and Excipients Project Teams of the Prescription/Nonprescription Stakeholders Forum. This document includes information to aid submission of new monographs and revisions to existing monographs for Non-Complex Active Substances and Products, Biological and Biotech Substances and Products, Excipients, and Vaccines. It incorporates many of the concepts and suggestions included in the ICH Q3A, Q3B, Q3C, Q6A, and Q6B guidelines. These include the definition of a specification and incorporate much of the terminology of Q3A for the control of impurities. The guideline clearly defines the information needed for the USP's Council of Experts and its Expert Committees to evaluate a request for revision. The document is approximately 75 pages in length with about 25 pages of addenda and is available in PDF format from the USP website at www.usp.org. Hard copies will be provided upon request.

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education series has been developed to enhance the knowledge, skills, and expertise of pharmaceutical industry personnel.

The following list indicates tentatively scheduled course dates. For further information, contact Laura A. McCurry, Manager, Pharmacopeial Education, lam@usp.org, 301-816-8285; Diana Lenahan, Program Associate, dpl@
usp.org, 301-816-8530; or visit the website at www. usp.org/education to register. Call 301-816-8530 to get information on customized courses offered at USP or at your site.

Calendar of Pharmacopeial Education Courses, 2004

| Date | Name of course | Location |
| :--- | :--- | :--- |
| October 14 | Fundamentals of Microbiological Testing | USP Headquarters, Rockville, MD |
| October 18 and 19 | Fundamentals of Dissolution | USP Headquarters, Rockville, MD |
| November 11 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| November 11 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| November 12 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| November 12 | Fundamentals of Dissolution (Lecture) | USP Headquarters, Rockville, MD |
| December 2 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| December 8 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| December 9 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |

VISIT THE USP WEB SITE AT 〈http://www.usp.org $\rangle$. Various resources related to Pharmacopeial standards are presented, including highlights from $P F$.

## USP-NF AVAILABLE IN THREE ELECTRONIC

FORMATS. The trusted reference for official pharmaceutical standards is available in three convenient electronic formats-CD, intranet, and online. The CD is ideal for single users who prefer to have $U S P-N F$ on their hard drives. The intranet format allows Web browser-based access to multiple users within a company, through their own intranet server. The online format can be accessed by individual registered users through the World Wide Web. All three electronic formats provide fast and easy access to official $U S P-N F$ content. More information can be obtained by visiting www.usp.org/products or by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

## CHROMATOGRAPHIC REAGENTS NOW

 AVAILABLE. Chromatographic Reagents lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic test methods that has been published in Pharmacopeial Forum (PF) since 1980. Chromatographic Reagents also helps to track which column reagents were used to validate methods that have become official and are included in $U S P-N F$. The branded column reagents list is updated bimonthly through Pharmacopeial Forum.Chromatographic Reagents can be ordered by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

INTERNATIONAL CORRESPONDENCE. Individuals who wish to correspond with the European and Japanese Pharmacopoeias concerning monographs in the Official Inquiry and Consensus stages of international harmonization should address their comments to the coordinating pharmacopeia for a given article. The addresses for the European and Japanese Pharmacopoeias are as follows:

Technical Secretariat of the
European Pharmacopoeia Commission
B.P. 907

F 67029 Strasbourg Cedex 1
France

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E-mail: nakashima-nobumasa@mhlw.go.jp

HOW TO SUBMIT COMMENTS. The USP welcomes and encourages interested parties to submit comments and data regarding potential, proposed, or adopted (official) standards. Submissions concerning a particular item that has appeared in a $P F$ should be submitted to the
appropriate USP scientific staff liaison identified at the end of the Briefing accompanying each item. To submit comments and data to a liaison, use the e-mail address and telephone numbers listed in the Staff Directory included in every $P F$.

Please note that $U S P-N F$ is being published in an annual edition with one main book and two Supplements a year. In addition, the following schedule will repeat every year so that users will know what to expect and become familiar with the deadlines.

The publication and comment schedule for USP 27-NF 22 is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2003 | November 2003 | January 2004 |
| Supplement One | October 15, 2003 | February 2004 | April 2004 |
| Supplement Two | February 17, 2004 | June 2004 | August 2004 |

The publication and comment schedule for USP $28-N F 23$ is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2004 | November 2004 | January 2005 |
| Supplement One | October 15, 2004 | February 2005 | April 2005 |
| Supplement Two | February 17, 2005 | June 2005 | August 2005 |

In the future, USP anticipates including the comment submission deadline in each briefing of every revision proposal when it is published for public review and comment.

For general inquiries or in cases where a particular liaison is not identified, use the general USP telephone number 301-881-0666 or FAX number 301-816-8373.

All official revisions are published in Supplements to $U S P-N F$ (twice yearly). Between Supplements, official revisions are published in $P F$ in the Interim Revision Announcement; these revisions are also incorporated in the upcoming Supplement. The electronic version of $U S P-N F$ is updated as each Supplement becomes available and, therefore, contains all official text up to and including the contents of the latest Supplement.

Publication Schedules

| Publication | Publication Date | Official Date |
| :---: | :---: | :---: |
| $1^{\text {st }}$ Supplement | Feb. 2004 | Apr. 1, 2004 |
| $P F 30(2)[$ Mar.-Apr. 2004] | Mar. 2004 | Not Applicable |
| $2^{\text {nd }} I R A$ [published in $\left.P F 30(2)\right]$ | Mar. 2004 | Apr. 1, 2004 |
| $P F 30(3)[$ May-June 2004] | May 2004 | Not Applicable |
| $3^{\text {rd }} I R A$ [published in $\left.P F 30(3)\right]$ | May 2004 | June 1, 2004 |
| $2^{\text {nd }}$ Supplement | June 2004 | Aug. 1, 2004 |
| $P F 30(4)[$ July-Aug. 2004] | July 2004 | Not Applicable |
| $4^{\text {th }} I R A$ [published in $\left.P F 30(4)\right]$ | July 2004 | Aug. 1, 2004 |
| $P F 30(5)[$ Sept.-Oct. 2004] | Sept. 2004 | Not Applicable |
| $5^{\text {th }} I R A$ [published in $\left.P F 30(5)\right]$ | Sept. 2004 | Oct. 1, 2004 |
| $P F 30(6)[$ Nov.-Dec. 2004] | Nov. 2004 | Not Applicable |
| $6^{\text {th }} I R A[$ published in $P F 30(6)]$ | Nov. 2004 | Dec. 1, 2004* |

[^238]
## INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

- The list of new USP Reference Standards that have become available
- The list of assays or tests that are adopted but held in abeyance pending availability of required USP Reference Standards
- New adopted (official) revisions to the $U S P-N F$ that become effective before the effective date of the next Supplement or that were not ready for adoption by the closing date for the upcoming Supplement. (The effective date for these revisions is stated on the next page.)

Readers should review this section to determine if they are affected by any of the changes.
Symbols-Interim revisions are shown with new text (if any) enclosed in circles, ${ }^{\bullet}$ new text $\boldsymbol{m}_{\bullet}$. Text enclosed in squares, $\boldsymbol{\square}_{\text {new }}$ text $_{\boldsymbol{\bullet}}$, has already been adopted in a Supplement. Where the symbols appear together with no enclosed text, such as ${ }^{\bullet}$ • or $\boldsymbol{m}^{\boldsymbol{\bullet}} \boldsymbol{\square}$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the $I R A$ or Supplement in which the revision first appeared. For example, $\bullet 2$ indicates that the revision was officially adopted in the Second Interim Revision Announcement, and $\boldsymbol{m}_{2 \mathrm{~S}(\text { USP27) }}$ indicates that the revision was officially adopted in the Second Supplement to USP 27.

Errata-At the end of the Interim Revision Announcement section is a list of errata and corrections to USP 27-NF 22. The page number indicates where the item is found in $U S P-N F$. If necessary, this list will be updated with every issue of $P F$. This information will also be cumulative in the next available Supplement, and will appear in its corrected form in the next annual edition of $U S P-N F$. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.
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# FIFTH INTERIM REVISION ANNOUNCEMENT <br> to USP 27 and to NF 22 

By authority of the United States Pharmacopeial Convention, Inc. Prepared by the Council of Experts and published by the Board of Trustees

Larry L. Braden, Chair
USP Board of Trustees
Roger L. Williams, Executive Vice President and Chairman, USP Council of Experts

John W. Gasper, Director, Executive Secretariat

Official October 1, 2004.
Released September 1, 2004.

[^239]
## New USP Reference Standards

The following USP Reference Standards, which were indicated in past Supplements to $U S P-N F$ as being not yet available, have since become available. Thus, the official date of each USP 27 or NF 22 standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list. (AS) indicates Authentic Substances, which are materials that have no specified use in monographs or General Chapters and are offered for the convenience of USF-NF users

USP Alcohol Determination-Acetonitrile RS (March 1, 2005)
USP Alcohol Determination-Alcohol RS (March 1, 2005)
USP Benazepril Related Compound C RS (January 1, 2005)
USP Positive Bioreaction RS (November 1, 2004)
USP Powdered Black Cohosh Extract RS (March 1, 2005)
USP Boric Acid (AS) RS
USP Butylated Hydroxytoluene RS (March 1, 2005)
USP Calcium Choride (AS) RS
USP Candelilla Wax RS (March 1, 2005)
USP Caprylocaproyl Polyoxylglycerides RS (March 1, 2005)
USP Cefpiramide RS (September 1, 2004)
USP Cefpodoxime Proxetil RS (January 1, 2005)
USP Powdered Chaste Tree Extract RS (November 1, 2004)
USP Chlorhexidine Related Compounds RS (November 1, 2004)
USP Chlorogenic Acid RS (November 1, 2004)
USP Clonidine RS (September 1, 2004)
USP Clonidine Related Compound A RS (September 1, 2004)
USP Clonidine Related Compound B RS (November 1, 2004)
USP Cyclandelate RS (September 1, 2004)
USP Dibutyl Phthalate RS (March 1, 2005)
USP Powdered Echinacea purpurea Extract RS (November 1, 2004)

USP Fenbendazole Related Compound A RS (January 1, 2005)
USP Fenbendazole Related Compound B RS (January 1, 2005)
USP Fludarabine RS (September 1, 2004)
USP Gemcitabine Hydrochloride RS (March 1, 2005)
USP Glacial Acetic Acid (AS) RS
USP $2 E, 4 E$-Hexadienoic Acid Isobutylamide RS (November 1, 2004)

USP Homopolymer Polypropylene RS (January 1, 2005)
USP Isoflurane Related Compound A RS (September 1, 2004)
USP Isoflurane Related Compound B RS (September 1, 2004)
USP Lamivudine Resolution Mixture A RS (November 1, 2004)
USP Lauroyl Polyoxylglycerides (AS) RS
USP Leuprolide Acetate RS (January 1, 2005)
USP Linoleoyl Polyoxylglycerides RS (January 1, 2005)
USP Loratadine RS (September 1, 2004)
USP Magnesium Hydroxide (AS) RS
USP Manganese Chloride (AS) RS
USP Medroxyprogesterone Acetate Related Compound A RS (November 1, 2004)
USP Methylphenidate Hydrochloride Erythro Isomer Solution CII RS (November 1, 2004)
USP Metoprolol Related Compound B RS (September 1, 2004)
USP Metoprolol Related Compound C RS (September 1, 2004)
USP Metoprolol Related Compound D RS (September 1, 2004)
USP Metoprolol Succinate RS (November 1, 2004)
USP Mirtazapine RS (March 1, 2005)
USP Mitoxantrone System Suitability Mixture RS (November 1, 2004)

USP Naratriptan Hydrochloride RS (November 1, 2004)
USP Nevirapine Anhydrous RS (March 1, 2005)
USP Nevirapine Hemihydrate RS (January 1, 2005)
USP Nevirapine Related Compound A RS (January 1, 2005)
USP Nevirapine Related Compound B RS (January 1, 2005)

USP Oxybutynin Related Compound B RS (January 1, 2005)
USP Oxybutynin Related Compound C RS (January 1, 2005)
USP Oleoyl Polyoxylglycerides RS (January 1, 2005)
USP Potassium Bicarbonate RS (January 1, 2005)
USP Potassium Carbonate (AS) RS
USP Potassium Chloride (AS) RS
USP Potassium Iodide (AS) RS
USP Propionic Acid (AS) RS
USP Residual Solvent Class 1-Benzene RS (November 1, 2004)
USP Residual Solvent Class 1-1,2 Dichloroethane RS (November 1, 2004)
USP Residual Solvent Class 1-1,2 Dichloroethene RS (November 1, 2004)
USP Residual Solvent Class 1-Carbon Tetrachloride RS (November 1, 2004)
USP Residual Solvent Class 1—1,1,1-Trichloroethane RS (November 1, 2004)
USP Residual Solvent Class 2-Chlorobenzene RS (January 1, 2005)

USP Residual Solvent Class 2-1,2-Dichoroethene RS (March 1, 2005)

USP Residual Solvent Class 2-1,4-Dioxane RS (January 1, 2005)
USP Residual Solvent Class 2-Methanol RS (January 1, 2005)
USP Residual Solvent Class 2-Methylcyclohexane RS (March 1, 2005)

USP Residual Solvent Class 2-Methylene Chloride RS (January 1, 2005)
USP Residual Solvent Class 2-Tetrahydrofuran RS (January 1, 2005)

USP Residual Solvent Class 2-Toluene RS (January 1, 2005)
USP Residual Solvent Class 2-Xylenes RS (January 1, 2005)
USP Residual Solvent Mixture-Class 1 RS (November 1, 2004)
USP Rimantidine Hydrochloride RS
USP Sodium Acetate (AS) RS
USP Sodium Carbonate Anhydrous (AS) RS
USP Sodium Metabisulfite (AS) RS
USP Sodium Nitrite (AS) RS
USP Sodium Sulfate Anhydrous (AS) RS
USP Titanium Dioxide (AS) RS
USP Valsartan RS (November 1, 2004)
USP Vecuronium Bromide RS (September 1, 2004)
USP Zinc Sulfate (AS) RS

The official dates of any $U S P 27$ or $N F 22$ standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards.

[^240]USP Narasin RS
USP Ondansetron Related Compound B RS
USP Potassium Perchlorate RS
USP Pyrethrum Extract RS
USP Sargramostim RS
USP Sulisobenzone RS
USP Terbutaline Related Compound A RS
USP $\Delta^{8}$-tetrahydrocannabinol RS
USP $\Delta^{9}$-tetrahydrocannabinol RS

USP Thiacetarsamide RS
USP Tilmicosin RS
USP Tinidazole Related Compound B RS
USP Trenbolone RS
USP Trenbolone Acetate RS
USP Powdered Valerian RS
USP Vasopressin RS

## MONOGRAPHS (USP)

## Bupropion Hydrochloride ExtendedRelease Tablets

## Add the following:

${ }^{\circ}$ Labeling-When more than one Drug release test is given, the labeling states the Drug release test used only if Test 1 is not used.es

## Change to read:

Drug release $\langle 724\rangle$ -
$\bullet$ TEST 1-•
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Times: 1, 4, and 8 hours.
Procedure-Determine the amount of $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{ClNO} \cdot \mathrm{HCl}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 298 nm , using a $1.0-\mathrm{cm}$ cell, on filtered portions of the solution under test, suitably diluted with Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same Medium.
Tolerances-The percentages of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{ClNO} \cdot \mathrm{HCl}$ dissolved at the times specified conform to $A c$ ceptance Table $1\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $25 \%$ and $45 \%$ |
| 4 | between $60 \%$ and $85 \%$ |
| 8 | not less than $80 \%$ |

- TEST 2-If the product complies with this test, the labeling indicates that it meets USP Drug release Test 2.

Medium: $\quad 0.1 \mathrm{~N}$ hydrochloric acid, $\mathrm{pH} 1.5 ; 900 \mathrm{~mL}$.
Apparatus 1: 50 rpm .
Times: 1, 2, 4, and 6 hours.
Determine the percentages of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{ClNO} \cdot \mathrm{HCl}$ dissolved by employing the following method. Buffer solution-Dissolve 3.45 g of sodium phosphate monobasic monohydrate in 996 mL of water, add 4.0 mL of triethylamine, and mix. Adjust with phosphoric acid to a pH of $2.80 \pm 0.05$.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and methanol $(65: 35)$. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Bupropion Hydrochloride RS in Medium, and dilute quantitatively, and stepwise if necessary, with Medium to obtain a solution having a known concentration similar to the one expected in the Test solution.

Test solution-Use portions of the solution under test, and pass through a $0.45-\mu \mathrm{m}$ nylon filter.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a 298 -nm detector and a 4.6 $\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of bupropion hydrochloride dissolved at each time point.

Tolerances-The percentages of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{ClNO} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Ac ceptance Table $1\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $25 \%$ and $50 \%$ |
| 2 | between $40 \%$ and $65 \%$ |
| 4 | between $65 \%$ and $90 \%$ |
| 6 | not less than $80 \%$ |

TEST 3-If the product complies with this test, the labeling indicates that it meets USP Drug release Test 3.

Medium, Apparatus, and Procedure-Proceed as directed for Test 1, except using the wavelength of about 250 nm .

Times: 1, 2, 4, and 6 hours.
Tolerances: The percentages of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{ClNO} \cdot \mathrm{HCl}$ dissolved at the times specified conform to Ac ceptance Table $1\langle 724\rangle$.

| Time (hours) | Amount dissolved |
| :---: | :--- |
| 1 | between $30 \%$ and $55 \%$ |
| 2 | between $50 \%$ and $75 \%$ |
| 4 | between $70 \%$ and $90 \%$ |
| 6 | not less than $80 \%$ |

## Ephedrine

## Change to read:

Ordinary impurities $\langle 466\rangle$ Test solution: methanol. Standard solution: methanol.
Eluant: a mixture of isopropyl alcohol, ${ }^{\bullet}$ ammonium hydroxide, and chloroform ( $80: 15: 5$ ).

Visualization: 1, followed by 4.

## Ephedrine Hydrochloride

## Change to read:

Ordinary impurities $\langle 466\rangle$ -
Test solution: alcohol.
Standard solution: alcohol.
Eluant: a mixture of isopropyl alcohol, $\bullet$ ammonium hydroxide, and chloroform ( $80: 15: 5$ ).

Visualization: 1, followed by 4.

## Ephedrine Sulfate

## Change to read:

Ordinary impurities $\langle 466\rangle$ -
Test solution: alcohol.
Standard solution: alcohol.
Eluant: a mixture of isopropyl alcohol, ©s ammonium hydroxide, and chloroform (80:15:5).

Visualization: 1 , followed by 4.

## Sorbitol Solution <br> Change to read: <br> Packaging and storage-■ Preserve in well-closed containers.■1S (USP27) ${ }^{\circ}$ No storage requirements specified.es

## MONOGRAPHS (NF)

## Ammonium Sulfate

## Change to read:

Packaging and storage-Preserve in well-closed containers. ${ }^{\bullet}$ No storage requirements specified.

## Candelilla Wax

## Change to read:

Packaging and storage-Preserve in well-closed containers. ${ }^{\bullet}$ No storage requirements specified.

## Low-Substituted <br> Carboxymethylcellulose Sodium

## Add the following:

${ }^{\bullet}$ Packaging and storage-Preserve in tight containers. No storage requirements specified. $\bullet$

## Certrimonium Bromide

## Change to read:

Packaging and storage-Preserve in well-closed containers. ${ }^{\bullet}$ No storage requirements specified. $\bullet$ s

## Hydrogenated Cottonseed Oil

Change to read:
Packaging and storage-Preserve in tight, light-resistant containers. ${ }^{\circ}$ No storage requirements specified. $\bullet$

## Dibutyl Phthalate

Change to read:
Packaging and storage-Preserve in tight containers. ${ }^{\bullet}$ No storage requirements specified.es

## Diethylene Glycol Stearates

## Change to read:

Packaging and storage-Preserve in tight containers. ${ }^{\bullet}$ No storage requirements specified.os

## Ethylene Glycol Stearates

Change to read:
Packaging and storage—Preserve in tight containers. ${ }^{\bullet}$ No storage requirements specified. $\bullet$

## Glyceryl Distearate

Change to read:
Packaging and storage-Preserve in tight containers. ${ }^{\circ}$ No storage requirements specified.os

## Glyceryl Monolinoleate

Change to read:

| Packaging and storage—Preserve in tight containers. |
| :--- |
| requirements specified. | requirements specified. $\bullet$

## Glyceryl Monooleate

Change to read:
Packaging and storage—Preserve in tight containers. ${ }^{\bullet}$ No storage
requirements specified.

## Hymetellose

## Add the following:

${ }^{\bullet}$ Packaging and storage-Preserve in well-closed containers. No storage requirements specified. $\bullet$ s

## Maltitol Solution

Change to read:
Packaging and storage-mereserve in well-closed contain-
ers.■1S (NF22) No storage requirements specified.

## Polyisobutylene

## Change to read:

Packaging and storage-Store in well-closed containers. ${ }^{\circ}$ No storage requirements specified. $\bullet$

## Sodium Cetostearyl Sulfate

## Add the following:

${ }^{\bullet}$ Packaging and storage - Preserve in well-closed containers. No storage requirements specified. $\bullet$

## Tribasic Sodium Phosphate

## Change to read:

Packaging and storage-Preserve in tight containers. ${ }^{\circ}$ No storage requirements specified.es

## Sorbitol

## Change to read:

Packaging and storage-mereserve in well-closed containers.■1S (NF22) ${ }^{\bullet}$ No storage requirements specified. $\bullet$

## Noncrystallizing Sorbitol Solution

## Change to read:

Packaging and storage- Preserve in well-closed containers.■1S (NF22) ${ }^{\bullet}$ No storage requirements specified. $\bullet$

## Hydrogenated Soybean Oil

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers. ${ }^{\bullet}$ No storage requirements specified. $\bullet$ s

## GENERAL CHAPTERS

## General Tests and Assays

## General Requirements for Tests and Assays

## 〈11〉 USP REFERENCE STANDARDS

## Add the following:

-USP Candelilla Wax RS——Do not dry. Keep container tightly closed. $\bullet$

## Change to read:

USP Dibutyl Phthalate RS-- Do not dry. After opening ampul, store the materials in a tightly closed container.es

## Change to read:

USP Econazole Nitrate RS- ${ }^{\bullet}$ Do not dry.es Keep container tightly closed. Protect from light.

## Change to read:

USP Gemcitabine Hydrochloride RS-- Do not dry. Keep container tightly closed. Store in a refrigerator.es

## Change to read:

USP Halothane RS-Do not dry. ${ }^{\circ}$ Material is highly volatile. After opening ampul, store in a tightly closed, light-resistant container. Store in a refrigerator. $\bullet$

## Change to read:

USP Methylprednisolone Acetate RS- ${ }^{\bullet}$ Do not dry. ${ }_{\bullet 5}$ Keep container tightly closed. Protect from light. ${ }^{\bullet}$ Store in a freezer. $\bullet$

## Change to read:

USP Moricizine Hydrochloride RS- ${ }^{\bullet}$ Do not dry. For quantitative applications, determine the water content titrimetrically. Keep container tightly closed.

## Change to read:

USP Nabumetone Related Compound A RS [1-(6-methoxy-2-naphthyl)-but-1-en-3-one] ${ }^{\bullet}\left(\mathrm{C}_{15} \mathrm{H}_{14} \mathrm{O}_{2} \diamond 226.27\right)_{\bullet}-$ Do not dry. ${ }^{\bullet}$ Keep container tightly closed. Protect from light. Store in a refrigerator.es

## Change to read:

USP Nadolol RS-•Do not dry.es Keep container tightly closed.

## Change to read:

USP Ondansetron Hydrochloride RS-- ${ }^{\bullet}$ This is the dihydrate form. Do not dry. For quantitative applications, determine the water content titrimetrically. ${ }_{\bullet}$ Keep container tightly closed. Protect from light. $\quad$ 1S (USP27)

## Change to read:

USP Simethicone RS—Mix well before using. Keep container tightly closed. ${ }^{\bullet}$ After opening, store under inert gas.॰5

## Change to read:

USP Testosterone Cypionate RS-- Do not dry.es Keep container tightly closed. Protect from light.

## ERRATA

Following is a list of errata and corrections to USP 27-NF 22. The page number indicates where the item is found in USP 27-NF 22. If necessary, this list will be updated with every issue of $P F$. This information will also be available as a cumulative table in the next available Supplement and will appear in its corrected form in the next annual edition of $U S P-N F$. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff are available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

| Page | Title | Section | Description |
| :--- | :--- | :--- | :--- |
| 691 | Multiple Electrolytes and <br> Dextrose Injection Type 2 | Assay for dextrose | Line 2: Change "Multiple Electrolytes Injection Type <br> l." to: Multiple Electrolytes and Dextrose Injection |
| 776 | Famotidine | Chromatographic purity |  | | Line 11 under Procedure: Change "Test solution corre- |
| :--- |
| sponds to not more than 1.0\% of Standard solution 1." |
| to: Test solution corresponds to not more than $1.0 \%$ |
| (Standard solution 1). |



## IN-PROCESS REVISION

This section contains proposals for adoption as official $U S P$ or $N F$ standards (either proposed new standards or proposed revisions of current $U S P$ or $N F$ standards). These may be any of the following: (1) items that previously appeared under Pharmacopeial Previews and are now formally proposed as revisions; (2) proposed revisions placed directly under In-Process Revision; or (3) modifications of revisions previously proposed under In-Process Revision. Readers should review material in this section and provide comments to the staff liaison (use the Staff Directory to find the contact information). Information on how to comment is found in the Policies and Announcements section. It is important to send comments promptly so that the Committee members can consider readers' input as they are deciding whether to advance standards to official status.

Briefings Each Proposal is preceded by a Briefing in the following format:

## BRIEFING

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being proposed, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see How to Use PF), the name of the scientific staff liaison who handled the particular issue, and the USP tracking correspondence number, as shown in the example below:
(PA5: K. Russo) RTS-55678-1

Symbols Proposed revisions are shown with language proposed for deletion or replacement crossed off. New text (if any) follows, and is enclosed in symbols and set off from the current official text by a paragraph break and by larger type, as shown in the examples below:
${ }^{\bullet}$ new text
if slated for an Interim Revision Announcement to USP 27-NF 22 (IRA);
$\Delta_{\text {new text }}{ }_{\mathbf{\Delta S P 2 8}}$
if slated for $U S P 28-N F 23$; and
${ }^{-}$new text.
if slated for a Supplement to $U S P-N F$. The same symbols not set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as ${ }^{\bullet}$ 。 or $\quad$ or ${ }_{\wedge}$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular IRA or Supplement or indicates the USP or NF as the publication where the revision will appear if approved. For example, $\bullet_{2}$ indicates that the revision is proposed for the Second Interim Revision Announcement, and ${ }^{2 S}$ (USP 27) indicates that the proposed revision is slated for the Second Supplement to USP 27, and $\Delta_{\triangle S P 28}$ and $\Delta_{\triangle F 23}$ indicate that the revisions are proposed for USP 28 and $N F 23$, respectively.

Official Title Changes Where the specification "Monograph title change" is found, it indicates that the official title stated after that specification will be substituted for the former title in the appropriate places throughout that monograph once this revision becomes official.
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Briefing

General Notices and Requirements，USP 27 page 1，page 3238 of the Second Supplement，and page 794 of PF 30（3） ［May－June 2004］．On the basis of information received from the Consumer Product Safety Commission（CPSC）at the PSD Open Conference on October 12－15，2003，an Expert Committee meet－ ing，and through subsequent correspondence，members of the PSD Expert Committee decided that information about the Poison Pre－ vention Packaging Act（PPPA）should be included in the USP．An appropriate statement was solicited from the CPSC，which was ini－ tially included in the draft of the new chapter Packaging－Unit of Use $\langle 1136\rangle$ ．However，it was pointed out during a teleconference that this information is not only applicable to this chapter but also to other chapters concerned with packaging．Therefore，the sugges－ tion was made that the general concepts of the PPPA as stated in the CPSC document be included in the General Notices under Preser－ vation，Packaging，Storage，and Labeling．Then，in other chapters such as Environmentally－Sensitive Preparations $\langle 386\rangle$ ，Containers〈661〉，Pharmaceutical Compounding－Nonsterile Preparations 495），Pharmaceutical Compounding－Sterile Preparations〈797〉，Good Storage and Shipping Practices 〈1079〉，Packag－ ing－Unit of Use $\langle 1136\rangle$ ，and Packaging Practice－Repackaging a Single Solid Oral Drug Product into a Unit Dose Container $\langle 1146\rangle$ ，a short statement with references to the General Notices would be included．This approach would save needless repetition of the same material．
（PSD：C．Okeke）RTS－41271－2

## Change to read：

## TESTS AND ASSAYS

Apparatus－A specification for a definite size or type of con－ tainer or apparatus in a test or assay is given solely as a recom－ mendation．Where volumetric flasks or other exact measuring， weighing，or sorting devices are specified，this or other equipment of at least equivalent accuracy shall be employed．（See also Ther－ mometers $\langle 21\rangle$ ，Volumetric Apparatus $\langle 31\rangle$ ，and Weights and Bal－ ances $\langle 41\rangle$ ．）Where low－actinic or light－resistant containers are specified，clear containers that have been rendered opaque by ap－ plication of a suitable coating or wrapping may be used．

Where an instrument for physical measurement，such as a spec－ trophotometer，is specified in a test or assay by its distinctive name， another instrument of equivalent or greater sensitivity and accuracy may be used．In order to obtain solutions having concentrations that are adaptable to the working range of the instrument being used，solutions of proportionately higher or lower concentrations may be prepared according to the solvents and proportions thereof that are specified for the procedure．

Where a particular brand or source of a material，instrument，or piece of equipment，or the name and address of a manufacturer or distributor，is mentioned（ordinarily in a footnote），this identifica－ tion is furnished solely for informational purposes as a matter of
convenience，without implication of approval，endorsement，or cer－ tification．Items capable of equal or better performance may be used if these characteristics have been validated．

Where the use of a centrifuge is indicated，unless otherwise specified，the directions are predicated upon the use of apparatus having an effective radius of about 20 cm （ 8 inches）and driven at a speed sufficient to clarify the supernatant layer within 15 min － utes．

Unless otherwise specified，for chromatographic tubes and col－ umns the diameter specified refers to internal diameter（ID）；for other types of tubes and tubing the diameter specified refers to out－ side diameter（OD）．

Steam Bath－Where the use of a steam bath is directed，exposure to actively flowing steam or to another form of regulated heat，cor－ responding in temperature to that of flowing steam，may be used．

Water Bath－Where the use of a water bath is directed without qualification with respect to temperature，a bath of vigorously boil－ ing water is intended．

Foreign Substances and Impurities－Tests for the presence of foreign substances and impurities are provided to limit such sub－ stances to amounts that are unobjectionable under conditions in which the article is customarily employed（see also Impurities in Official Articles 〈1086〉）．

While one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity，strength，quality， and purity，it is manifestly impossible to include in each mono－ graph a test for every impurity，contaminant，or adulterant that might be present，including microbial contamination．These may arise from a change in the source of material or from a change in the processing，or may be introduced from extraneous sources． Tests suitable for detecting such occurrences，the presence of which is inconsistent with applicable good manufacturing practice or good pharmaceutical practice，should be employed in addition to the tests provided in the individual monograph．

Other Impurities－Official substances may be obtained from more than one process，and thus may contain impurities not con－ sidered during preparation of monograph assays or tests．Wherever a monograph includes a chromatographic assay or purity test based on chromatography，other than a test for erganic volatile impuri－ ties，
$\mathbf{m}_{\text {residual solvents }}^{\mathbf{m}_{1 S} \text {（USP28）}}$
and that monograph does not detect such an impurity，solvents ex－ cepted，the impurity shall have its amount and identity，where both are known，stated under the heading Other Impurity（ies）by the la－ beling（certificate of analysis）of the official substance．

The presence of any unlabeled impurity in an official substance is a variance from the standard if the content is $0.1 \%$ or greater． Tests suitable for detection and quantitating unlabeled impurities， when present as the result of process change or other identifiable， consistent occurrence，shall be submitted to the USP for inclusion in the individual monograph．Otherwise，the impurity shall be identified，preferably by name，and the amount listed under the heading Other Impurity（ies）in the labeling（certificate of analysis） of the official substance．The sum of all Other Impurities combined with the monograph－detected impurities does not exceed $2.0 \%$（see Ordinary Impurities $\langle 466\rangle$ ），unless otherwise stated in the mono－ graph．

Categories of drug substances excluded from Other Impurities requirements are fermentation products and semi－synthetics de－ rived therefrom，radiopharmaceuticals，biologics，biotechnology－ derived products，peptides，herbals，and crude products of animal or plant origin．Any substance known to be toxic must not be listed under Other Impurities．

■Residual Solvents－The requirements are stated in Or－ ganic Volatile Impurities $\langle 467\rangle$ together with information in Impurities in Official Articles $\langle 1086\rangle$ ．Thus all drug sub－
stances, excipients, and products are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. The requirements have been aligned with the ICH guideline on this topic. If solvents are used during production, they are of suitable quality. In addition, the toxicity and residual level of each solvent are taken into consideration, and the solvents are limited according to the principles defined and the requirements specified in Organic
Volatile Impurities $\langle 467\rangle$, using the general methods presented therein or other suitable methods. $\quad 1 \mathrm{~S}$ (USP28)

Procedures-Assay and test procedures are provided for determining compliance with the Pharmacopeial standards of identity, strength, quality, and purity.

In performing the assay or test procedures in this Pharmacopeia, it is expected that safe laboratory practices will be followed. This includes the utilization of precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures utilized. Prior to undertaking any assay or procedure described in this Pharmacopeia, the individual should be aware of the hazards associated with the chemicals and the procedures and means of protecting against them. This Pharmacopeia is not designed to describe such hazards or protective measures.

Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing process validation studies and from in-process controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards.

Automated procedures employing the same basic chemistry as those assay and test procedures given in the monograph are recognized as being equivalent in their suitability for determining compliance. Conversely, where an automated procedure is given in the monograph, manual procedures employing the same basic chemistry are recognized as being equivalent in their suitability for determining compliance. Compliance may be determined also by the use of alternative methods, chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances. Such alternative or automated procedures or methods shall be validated. However, Pharmacopeial standards and procedures are interrelated; therefore, where a difference appears or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

In the performance of assay or test procedures, not fewer than the specified number of dosage units should be taken for analysis. Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards may be taken, provided the measurement is made with at least equivalent accuracy and provided that any subsequent steps, such as dilutions, are adjusted accordingly to yield concentrations equivalent to those specified and are made in such manner as to provide at least equivalent accuracy. To minimize environ-
mental impact or contact with hazardous materials, apparatus and chemicals specified in Pharmacopeial procedures also may be proportionally changed.

Where it is directed in an assay or a test that a certain quantity of substance or a counted number of dosage units is to be examined, the specified quantity or number is a minimal figure (the singlet determination) chosen only for convenience of analytical manipulation; it is not intended to restrict the total quantity of substance or number of units that may be subjected to the assay or test or that should be tested in accordance with good manufacturing practices.

Where it is directed in the assay of Tablets to "weigh and finely powder not fewer than" a given number, usually 20, of the Tablets, it is intended that a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered tablets taken for assay is representative of the whole Tablets and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Tablet by multiplying this result by the average Tablet weight and dividing by the weight of the portion taken for the assay.

Similarly, where it is directed in the assay of Capsules to remove, as completely as possible, the contents of not fewer than a given number, usually 20, of the Capsules, it is intended that a counted number of Capsules should be carefully opened and the contents quantitatively removed, combined, mixed, and weighed accurately. The portion of mixed Capsules contents taken for the assay is representative of the contents of the Capsules and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Capsule by multiplying this result by the average weight of Capsule content and dividing by the weight of the portion taken for the assay.
Where the definition in a monograph states the tolerances as being "calculated on the dried (or anhydrous or ignited) basis," the directions for drying or igniting the sample prior to assaying are generally omitted from the Assay procedure. Assay and test procedures may be performed on the undried or unignited substance and the results calculated on the dried, anhydrous, or ignited basis, provided a test for Loss on drying, or Water, or Loss on ignition, respectively, is given in the monograph.
-Results are calculated on an "as-is" basis unless otherwise
specified in the monograph. 1 IS (USP28)
Where the presence of moisture or other volatile material may interfere with the procedure, previous drying of the substance is specified in the individual monograph and is obligatory.

Throughout a monograph that includes a test for Loss on drying or Water, the expression "previously dried" without qualification signifies that the substance is to be dried as directed under Loss on drying or Water (gravimetric determination).

Unless otherwise directed in the test or assay in the individual monograph or in a general chapter, USP Reference Standards are to be dried before use, or used without prior drying, specifically in accordance with the instructions given in the chapter USP Reference Standards $\langle 11\rangle$, and on the label of the Reference Standard. Where the label instructions differ in detail from those in the chapter, the label text is determinative.

In stating the appropriate quantities to be taken for assays and tests, the use of the word "about" indicates a quantity within $10 \%$ of the specified weight or volume. However, the weight or volume taken is accurately determined and the calculated result is based upon the exact amount taken. The same tolerance applies to specified dimensions.
Where the use of a pipet is directed for measuring a specimen or an aliquot in conducting a test or an assay, the pipet conforms to the standards set forth under Volumetric Apparatus $\langle 31\rangle$, and is to be used in such manner that the error does not exceed the limit stated for a pipet of its size. Where a pipet is specified, a suitable buret, conforming to the standards set forth under Volumetric Apparatus $\langle 31\rangle$, may be substituted. Where a "to contain" pipet is specified, a suitable volumetric flask may be substituted.

Expressions such as " 25.0 mL " and " 25.0 mg ," used with respect to volumetric or gravimetric measurements, indicate that the quantity is to be "accurately measured" or "accurately weighed" within the limits stated under Volumetric Apparatus $\langle 31\rangle$ or under Weights and Balances $\langle 41\rangle$.

The term "transfer" is used generally to specify a quantitative manipulation.

The term "concomitantly," used in such expressions as "concomitantly determine" or "concomitantly measured," in directions for assays and tests, is intended to denote that the determinations or measurements are to be performed in immediate succession. See also Use of Reference Standards under Spectrophotometry and Light-Scattering $\langle 851\rangle$.

Blank Determination-Where it is directed that "any necessary correction" be made by a blank determination, the determination is to be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test, but with the substance itself omitted.
Desiccator-The expression "in a desiccator" specifies the use of a tightly closed container of suitable size and design that maintains an atmosphere of low moisture content by means of silica gel or other suitable desiccant.

A "vacuum desiccator" is one that maintains the low-moisture atmosphere at a reduced pressure of not more than 20 mm of mercury or at the pressure designated in the individual monograph.

Dilution-Where it is directed that a solution be diluted "quantitatively and stepwise," an accurately measured portion is to be diluted by adding water or other solvent, in the proportion indicated, in one or more steps. The choice of apparatus to be used should take into account the relatively larger errors generally associated with using small-volume volumetric apparatus (see Volumetric Apparatus $\langle 31\rangle$ ).

Drying to Constant Weight-The specification "dried to constant weight" means that the drying shall be continued until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional hour of drying.

Filtration-Where it is directed to "filter," without further qualification, the intent is that the liquid be filtered through suitable filter paper or equivalent device until the filtrate is clear.

Identification Tests-The Pharmacopeial tests headed Identification are provided as an aid in verifying the identity of articles as they are purported to be, such as those taken from labeled containers. Such tests, however specific, are not necessarily sufficient to establish proof of identity; but failure of an article taken from a labeled container to meet the requirements of a prescribed identification test indicates that the article may be mislabeled. Other tests and specifications in the monograph often contribute to establishing or confirming the identity of the article under examination.

Ignition to Constant Weight-The specification "ignite to constant weight" means that the ignition shall be continued, at $800 \pm 25^{\circ}$ unless otherwise indicated, until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional 15 -minute ignition period.

Indicators-Where the use of a test solution ("TS") as an indicator is specified in a test or an assay, approximately 0.2 mL , or 3 drops, of the solution shall be added, unless otherwise directed.

Logarithms-Logarithms used in the assays are to the base 10.
Microbial Strains-Where a microbial strain is cited and identified by its ATCC catalog number, the specified strain shall be used directly or, if subcultured, shall be used not more than five passages removed from the original strain.

Negligible-This term indicates a quantity not exceeding 0.50 mg.

Odor-Terms such as "odorless," "practically odorless," "a faint characteristic odor," or variations thereof, apply to examination, after exposure to the air for 15 minutes, of either a freshly opened package of the article (for packages containing not more than 25 g ) or (for larger packages) of a portion of about 25 g of the article that has been removed from its package to an open evaporating dish of about $100-\mathrm{mL}$ capacity. An odor designation is descriptive only and is not to be regarded as a standard of purity for a particular lot of an article.

Pressure Measurements-The term "mm of mercury" used with respect to measurements of blood pressure, pressure within an apparatus, or atmospheric pressure refers to the use of a suitable manometer or barometer calibrated in terms of the pressure exerted by a column of mercury of the stated height.

Solutions-Unless otherwise specified in the individual monograph, all solutions called for in tests and assays are prepared with Purified Water.

An expression such as "(1 in 10)" means that 1 part by volume of a liquid is to be diluted with, or 1 part by weight of a solid is to be dissolved in, sufficient of the diluent or solvent to make the volume of the finished solution 10 parts by volume.

An expression such as " $(20: 5: 2)$ " means that the respective numbers of parts, by volume, of the designated liquids are to be mixed, unless otherwise indicated.

The notation "VS" after a specified volumetric solution indicates that such solution is standardized in accordance with directions given in the individual monograph or under Volumetric Solutions in the section Reagents, Indicators, and Solutions, and is thus differentiated from solutions of approximate normality or molarity.

Where a standardized solution of a specific concentration is called for in a test or an assay, a solution of other normality or molarity may be used, provided allowance is made for the difference in concentration and provided the error of measurement is not increased thereby.

Specific Gravity-Unless otherwise stated, the specific gravity basis is $25^{\circ} / 25^{\circ}$, i.e., the ratio of the weight of a substance in air at $25^{\circ}$ to the weight of an equal volume of water at the same temperature.

Temperatures-Unless otherwise specified, all temperatures in this Pharmacopeia are expressed in centigrade (Celsius) degrees, and all measurements are made at $25^{\circ}$. Where moderate heat is specified, any temperature not higher than $45^{\circ}\left(113^{\circ} \mathrm{F}\right)$ is indicated. See Storage Temperature under Preservation, Packaging, Storage, and Labeling for other definitions.

Time Limit-In the conduct of tests and assays, 5 minutes shall be allowed for the reaction to take place unless otherwise specified.

Vacuum-The term "in vacuum" denotes exposure to a pressure of less than 20 mm of mercury unless otherwise indicated.
Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used.

Water-Where water is called for in tests and assays, Purified Water is to be used unless otherwise specified. For special kinds of water such as "carbon dioxide-free water," see the introduction to the section Reagents, Indicators, and Solutions. For High-purity Water see Containers $\langle 661\rangle$.

Water and Loss on Drying-Where the water of hydration or adsorbed water of a Pharmacopeial article is determined by the titrimetric method, the test is generally given under the heading Water. Monograph limits expressed as a percentage are figured on a weight/weight basis unless otherwise specified. Where the determination is made by drying under specified conditions, the test is generally given under the heading Loss on drying. However, Loss on drying is most often given as the heading where the loss in weight is known to represent residual volatile constituents including organic solvents as well as water.

Test Results, Statistics, and Standards-Interpretation of results from official tests and assays requires an understanding of the nature and style of compendial standards, in addition to an understanding of the scientific and mathematical aspects of laboratory analysis and quality assurance for analytical laboratories.

Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs. Compendial standards define what is an acceptable article and give test procedures that demonstrate that the article is in compliance. These standards apply at any time in the life of the article from production to consumption. The manufacturer's release specifications, and compliance with good manufacturing practices generally, are developed and followed to assure that the article will indeed comply with compendial standards until its expiration date, when stored as directed. Thus, when tested from the viewpoint of commercial or regulatory compliance, any specimen tested as directed in the monograph for that article shall comply.

Tests and assays in this Pharmacopeia prescribe operation on a single specimen, that is, the singlet determination, which is the minimum sample on which the attributes of a compendial article should be measured. Some tests, such as those for Dissolution and Uniformity of dosage units, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen. These procedures should not be confused with statistical sampling plans. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations are neither specified nor proscribed by the compendia; such decisions are dependent on the objectives of the testing. Commercial or regulatory compliance testing, or manufacturer's release testing, may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies. Treatments of data handling are available from organizations such as ISO, IUPAC, and AOAC.
$\square$ Where the Content Uniformity determinations have been made using the same procedure specified in the Assay, the average of all of the individual Content Uniformity determinations may be used as the Assay value. 1 1S (USP27)

Description-Information on the "description" pertaining to an article, which is relatively general in nature, is provided in the reference table Description and Relative Solubility of USP and NF Articles in this Pharmacopeia for those who use, prepare, and dispense drugs and/or related articles, solely to indicate properties of an article complying with monograph standards. The properties are not in themselves standards or tests for purity even though they may indirectly assist in the preliminary evaluation of an article.

Solubility-The statements concerning solubilities given in the reference table Description and Relative Solubility of USP and NF Articles for Pharmacopeial articles are not standards or tests for purity but are provided primarily as information for those who use, prepare, and dispense drugs and/or related articles. Only where a quantitative solubility test is given, and is designated as such, is it a test for purity.

The approximate solubilities of Pharmacopeial substances are indicated by the descriptive terms in the accompanying table. Soluble Pharmacopeial articles, when brought into solution, may show traces of physical impurities, such as minute fragments of filter paper, fibers, and other particulate matter, unless limited or excluded by definite tests or other specifications in the individual monographs.

|  | Parts of Solvent <br> Required for <br> Descriptive <br> Term |
| :--- | :--- |
| Very soluble | Less than 1 |
| Freely soluble | From 1 to 10 |
| Soluble | From 10 to 30 |
| Sparingly soluble | From 30 to 100 |
| Slightly soluble | From 100 to 1000 |


|  | Parts of Solvent <br> Required for <br> Descriptive <br> Term |
| :--- | :--- |
| Very slightly soluble | From 1000 to 10,000 |
| Practically insoluble, <br> or Insoluble | Greater than or equal to 10,000 |

Interchangeable Methods-Certain general chapters contain a statement that the text in question is harmonized with the corresponding text of the European Pharmacopoeia and/or the Japanese Pharmacopoeia and that these texts are interchangeable. Therefore, if a substance or preparation is found to comply with a requirement using an interchangeable method from one of these pharmacopeias, it should comply with the requirements of the United States Pharmacopeia. However, where a difference appears, or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

## Change to read:

## PRESERVATION, PACKAGING, STORAGE, AND LABELING

Containers-The container is that which holds the article and is or may be in direct contact with the article. The immediate contain$e r$ is that which is in direct contact with the article at all times. The closure is a part of the container.

Prior to its being filled, the container should be clean. Special precautions and cleaning procedures may be necessary to ensure that each container is clean and that extraneous matter is not introduced into or onto the article.

The container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements.

The Pharmacopeial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph.

Tamper-Evident Packaging - The container or individual carton of a sterile article intended for ophthalmic or otic use, except where extemporaneously compounded for immediate dispensing on prescription, shall be so sealed that the contents cannot be used without obvious destruction of the seal.

Articles intended for sale without prescription are also required to comply with the tamper-evident packaging and labeling requirements of the FDA where applicable.

Preferably, the immediate container and/or the outer container or protective packaging utilized by a manufacturer or distributor for all dosage forms that are not specifically exempt is designed so as to show evidence of any tampering with the contents.

Light-Resistant Container (see Light Transmission under Containers $\langle 661\rangle$ )-A light-resistant container protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. Alternatively, a clear and colorless or a translucent container may be made light-resistant by means of an opaque covering, in which case the label of the container bears a statement that the opaque covering is needed until the contents are to be used or administered. Where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended.

Where an article is required to be packaged in a light-resistant container, and if the container is made light-resistant by means of an opaque covering, a single-use, unit-dose container or mnemonic pack for dispensing may not be removed from the outer opaque covering prior to dispensing.

Well-Closed Container-A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Tight Container-A tight container protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight re-closure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article.

A gas cylinder is a metallic container designed to hold a gas under pressure. As a safety measure, for carbon dioxide, cyclopropane, helium, nitrous oxide, and oxygen, the Pin-index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

NOTE-Where packaging and storage in a tight container or a well-closed container is specified in the individual monograph, the container utilized for an article when dispensed on prescription meets the requirements under Containers-Permeation $\langle 671\rangle$.

Hermetic Container-A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Single-Unit Container-A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

Single-Dose Container (see also Containers for Injections under Injections $\langle 1\rangle$ )—A single-dose container is a single-unit container for articles intended for parenteral administration only. A singledose container is labeled as such. Examples of single-dose containers include pre-filled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

Unit-Dose Container-A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container.

Unit-of-Use Container-A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. A unit-of-use container is labeled as such.

Multiple-Unit Container-A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

Multiple-Dose Container (see also Containers for Injections under Injections $\langle 1\rangle$ )-A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only.
-Poison Prevention Packaging Act-This act (see the
Website, www.cpsc.gov/businfo/pppa.html) requires special packaging of most human oral prescription drugs, oral controlled drugs, certain nonoral prescription drugs, certain dietary supplements, and many over-the-counter (OTC) drug preparations in order to protect the public from personal injury or illness from misuse of these preparations (16 CFR § 1700.14).

The immediate packaging of substances regulated under the PPPA must comply with the special packaging standards (16 CFR § 1700.15 and 16 CFR § 1700.20). The PPPA regulations for special packaging apply to all packaging types including reclosable, nonclosable, and unit-dose types.

Special packaging is not required for drugs dispensed within a hospital setting for inpatient administration. Manufacturers and packagers of bulk-packaged prescription drugs do not have to use special packaging if the drug will be repackaged by the pharmacist. PPPA-regulated prescription drugs may be dispensed in nonchild-resistant packaging upon the request of the purchaser or when directed in a legitimate prescription (15 U.S.C. § 1473).

Manufacturers or packagers of PPPA-regulated OTC preparations are allowed to package one size in nonchild-resistant packaging as long as popular-size, special packages are also supplied. The nonchild-resistant package requires special labeling (18 CFR § 1700.5).

Various types of child-resistant packages are covered in ASTM International Standard D-3475, Standard Classification of Child-Resistant Packaging. Examples are included as an aid in the understanding and comprehension of each type of classification.■2S (USP28)

Storage Temperature and Humidity-Specific directions are stated in some monographs with respect to the temperatures and humidity at which Pharmacopeial articles shall be stored and distributed (including the shipment of articles to the consumer) when stability data indicate that storage and distribution at a lower or a higher temperature and a higher humidity produce undesirable results. Such directions apply except where the label on an article states a different storage temperature on the basis of stability studies of that particular formulation. Where no specific storage directions or limitations are provided in the individual monograph, but the label of an article states a storage temperature that is based on stability studies of that particular formulation, such labeled storage directions apply (see also Stability under Pharmaceutical Dosage Forms $\langle 1151\rangle$ ). The conditions are defined by the following terms.

Freezer-A place in which the temperature is maintained ther-mostat-ically between $-25^{\circ}$ and $-10^{\circ}\left(-13^{\circ}\right.$ and $\left.14^{\circ} \mathrm{F}\right)$.

Cold-Any temperature not exceeding $8^{\circ}\left(46^{\circ} \mathrm{F}\right)$. A refrigerator is a cold place in which the temperature is maintained thermostatically between $2^{\circ}$ and $8^{\circ}\left(36^{\circ}\right.$ and $\left.46^{\circ} \mathrm{F}\right)$.

Cool-Any temperature between $8^{\circ}$ and $15^{\circ}\left(46^{\circ}\right.$ and $\left.59^{\circ} \mathrm{F}\right)$. An article for which storage in a cool place is directed may, alternatively, be stored and distributed in a refrigerator, unless otherwise specified by the individual monograph.

Room Temperature-The temperature prevailing in a working area.

Controlled Room Temperature-A temperature maintained thermostatically that encompasses the usual and customary working environment of $20^{\circ}$ to $25^{\circ}\left(68^{\circ}\right.$ to $77^{\circ} \mathrm{F}$ ); that results in a mean kinetic temperature calculated to be not more than $25^{\circ}$; and that allows for excursions between $15^{\circ}$ and $30^{\circ}\left(59^{\circ}\right.$ and $86^{\circ} \mathrm{F}$ ) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to $40^{\circ}$ are permitted as long as they do not exceed 24 hours. Spikes above $40^{\circ}$ may be permitted if the manufacturer so instructs. Articles may be labeled for storage at "controlled room temperature" or at "up to $25^{\circ}$ ", or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations. (See also Stability under Pharmaceutical Dosage Forms $\langle 1151\rangle$. )

An article for which storage at Controlled room temperature is directed may, alternatively, be stored and distributed in a cool place, unless otherwise specified in the individual monograph or on the label.
Warm-Any temperature between $30^{\circ}$ and $40^{\circ}\left(86^{\circ}\right.$ and $104^{\circ} \mathrm{F}$ ).
Excessive Heat-Any temperature above $40^{\circ}\left(104^{\circ} \mathrm{F}\right)$.
Protection from Freezing-Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.
Dry Place-The term "dry place" denotes a place that does not exceed $40 \%$ average relative humidity at Controlled Room Temperature or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place or may be based on reported climatic conditions. Determination is based on not less than 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to $45 \%$ relative humidity provided that the average value is $40 \%$ relative humidity.
Storage in a container validated to protect the article from moisture vapor, including storage in bulk, is considered a dry place.
${ }^{\Delta}$ Storage under Nonspecific Conditions-Where no specific directions or limitations are provided in the packaging and storage section of individual monographs or in the article's labeling, the conditions of storage shall include storage at controlled room temperature, protection from moisture, and, where necessary, protection from light. Articles shall be protected from moisture, freezing, and excessive heat, and, where necessary, from light during shipping and distribution. Active pharmaceutical ingredients are exempt from this requirement. $\triangle$ USP27
-Repackaging Instructions-Except where a drug prod-
uct is packaged in a container intended to be dispensed directly to the patient, such as a unit-of-use or unit-dose container, the labeling shall contain directions specifying the types of containers suitable for repackaging the drug product so as to maintain its identity, strength, quality, and purity. Such directions shall be sufficient to allow a repackager or dispenser to select an adequate container and shall include a description of the composition of the container(s),
e.g., glass, polyethylene, polyvinyl chloride, and any moisture vapor transmission rate characteristics required. The labeling shall also indicate whether or not the container is to afford light protection, and shall include any storage or shipping temperature restrictions to which the drug as repackaged shall be limited (see 21 CFR 201.100).■1S (USP28)
Labeling-The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

A shipping container containing a single article, unless such container is also essentially the immediate container or the outside of the consumer package, is labeled with a minimum of product identification (except for controlled articles), lot number, expiration date, and conditions for storage and distribution.
Articles in this Pharmacopeia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the Pharmacopeial requirements set forth for the articles.
Amount of Ingredient per Dosage Unit-The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.
Pharmacopeial articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each such unit; except that, in the case of unit-dose oral solutions or suspensions, whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon addition of a designated volume of a specific diluent, the label shall express the quantity of each active ingredient or recognized nutrient delivered under the conditions prescribed in Deliverable Volume $\langle 698\rangle$. Pharmacopeial drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient (see Percentage Measurements), except that oral liquids or solids intended to be constituted to yield oral liquids may, alternatively, be labeled in terms of each $5-\mathrm{mL}$ portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, such declarations of strength or quantity shall be stated only in metric units (see also Units of Potency in these General Notices).
Use of Leading and Terminal Zeros-In order to help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg$]$ ). The quantity of active ingredient when expressed as a decimal number smaller than one shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg$]$ ).

Labeling of Salts of Drugs-It is an established principle that Pharmacopeial articles shall have only one official name. For purposes of saving space on labels, and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners as synonymous with the written forms, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids; but these symbols are not used where the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not to be written).

Labeling Vitamin-Containing Products-The vitamin content of an official drug product shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.

## ${ }^{4}$ Labeling Botanical-Containing Products-The label

of an herb or other botanical intended for use as a dietary supplement bears the statement, "If you are pregnant or nursing a baby, seek the advice of a health professional before using this product." $\mathbf{\Delta U S P 2 8}$

Labeling Parenteral and Topical Preparations-The label of a preparation intended for parenteral or topical use states the names of all added substances (see Added Substances in these General Notices and Requirements, and see Labeling under Injections $\langle 1\rangle$ ), and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

Labeling Electrolytes-The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents ( mEq ). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

Labeling Alcohol-The content of alcohol in a liquid preparation shall be stated on the label as a percentage ( $\mathrm{v} / \mathrm{v}$ ) of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Special Capsules and Tablets-The label of any form of Capsule or Tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it is to be used.

Expiration Date and Beyond-Use Date-The label of an official drug product, nutritional or dietary supplement product shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., "EXP 6/89," "Exp. June 89," or "Expires 6/89"). [NOTE-For additional information and guidance, refer to the Nonprescription Drug Manufacturers Association's Voluntary Codes and Guidelines of the OTC Medicines Industry.]

The monographs for some preparations state how the expiration date that shall appear on the label is to be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the article, with the following exception: the label need not show an expiration date in the case of a drug product or nutritional supplement packaged in a container that is intended for sale without prescription and the labeling of which states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions.

Where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article may be expected to meet the requirements of the Pharmacopeial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. Where an expiration date is stated only in terms of the month and the year, it is a representation that the intended expiration date is the last day of the stated month. The beyond-use
date is the date after which an article must not be used. The dispenser shall place on the label of the prescription container a suitable beyond-use date to limit the patient's use of the article based on any information supplied by the manufacturer and the General Notices and Requirements of this Pharmacopeia. The beyond-use date placed on the label shall not be later than the expiration date on the manufacturer's container.

For articles requiring constitution prior to use, a suitable be-yond-use date for the constituted product shall be identified in the labeling.

For all other dosage forms, in determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; any unusual storage conditions to which the article may be exposed; and the expected length of time of the course of therapy. The dispenser shall, on taking into account the foregoing, place on the label of a multipleunit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, or in the absence of stability data to the contrary, such be-yond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) one year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be one year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturer's container, whichever is earlier, unless stability data or the manufacturer's labeling indicates otherwise.

The dispenser must maintain the facility where the dosage forms are packaged and stored, at a temperature such that the mean kinetic temperature is not greater than $25^{\circ}$. The plastic material used in packaging the dosage forms must afford better protection than polyvinyl chloride, which does not provide adequate protection against moisture permeation. Records must be kept of the temperature of the facility where the dosage forms are stored, and of the plastic materials used in packaging.

Pharmaceutical Compounding-The label on the container or package of an official compounded preparation shall bear a be-yond-use date. The beyond-use date is the date after which a compounded preparation is not to be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

The monograph for an official compounded preparation typically includes a beyond-use requirement that states the time period following the date of compounding during which the preparation, properly stored, is to be used. In the absence of stability information that is applicable to a specific drug and preparation, recommendations for maximum beyond-use dates have been devised for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated (see Stability Criteria and Beyond-Use Dating under Stability of Compounded Preparations in the general tests chapter ${ }^{\boldsymbol{\wedge}}$ Pharmaceutical Compounding-Nonsterile Preparations $\mathbf{\Delta U S P 2 7}$ (795〉).
-Guidelines for Packaging and Storage Statements in USP-NF Monographs

In order to provide users of the $U S P-N F$ with proper guidance on how to package and store compendial articles, every monograph in the $U S P-N F$ is required to have a packaging and storage specification.

For those instances where, for some reason, storage information is not yet found in the Packaging and storage specification of a monograph, the section Storage Under NonSpecific Conditions is included in the General Notices as interim guidance. The Storage Under Nonspecific Conditions statement is not meant to substitute for the inclusion of proper, specific storage information in the Packaging and storage statement of any monograph.

For the packaging portion of the statement, the choice of containers is given in the General Notices and includes Light-Resistant Container, Well-Closed Container, Tight Container, Hermetic Container, Single-Unit Container, Sin-gle-Dose Container, Unit-Dose Container, and Unit-of-Use Container. For most preparations, the choice is determined by the container in which it is to be dispensed (e.g., tight, well-closed, hermetic, unit-of-use, etc). For active pharmaceutical ingredients (APIs), the choice would appear to be tight, well-closed, or, where needed, a light-resistant container. For excipients, given their typical nature as large-volume commodity items, with containers ranging from drums to tank cars, a well-closed container is an appropriate default. Therefore, in the absence of data indicating a need for a more protective class of container, the phrase "Preserve in well-closed containers" should be used as a default for excipients.

For the storage portion of the statement, the choice of stor age temperatures presented in the General Notices includes Freezer, Cold, Cool, Room Temperature, Controlled Room Temperature, Warm, Excessive Heat, and Protection from Freezing. The definition of a dry place is provided if protection from humidity is important.

For most preparations, the choice is determined by the experimentally determined stability of the preparation and may include any of the previously stated storage conditions as determined by the manufacturer. For APIs that are expected to be retested before incorporation into a preparation, a more general and nonrestrictive condition may be desired. In this case, the specification "room temperature" (the temperature prevailing in a working area) should suffice. The use of the permissive room temperature condition reflects the stability of an article over a wide temperature range. For excipients, the phrase "No storage requirements specified" in the Packaging and storage statement of the monograph would be appropriate.
Because most APIs in the $U S P-N F$ have associated Reference Standards, special efforts should be considered to ensure that the Reference Standards' storage conditions correspond to the conditions indicated in the $U S P-N F$ monographs.

The Packaging, Storage, and Distribution Expert Committee may review questionable Packaging and storage statements on a case-by-case basis. In cases where the Packaging and storage statements are incomplete, the monographs would move forward to publication while the Packaging and storage statements are temporarily deferred. 1 (USP28)

## MONOGRAPHS (USP)

## BRIEFING

> Acetaminophen Oral Suspension, USP 27 page 18, page 3037 of the First Supplement, and page 40 of PF $30(1)$ [Jan.-Feb. 2004$]$. On the basis of comments received, it is proposed to add a limit test for 4-aminophenol.
(PA2: C. Anthony) RTS-41505-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Acetaminophen $R S$.

- USP 4-Aminophenol RS.■2S (USP28)


## Add the following:

${ }^{\Delta}$ Uniformity of dosage units $\langle 905\rangle-$
FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CON-
TAINERS: meets the requirements. $\triangle$ USP 28

## Add the following:

${ }^{\Delta}$ Deliverable volume $\langle 698\rangle$ -
FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CON-
TAINERS: meets the requirements. $\Delta$ USP28

## Add the following:

## -Limit of 4-aminophenol-

Diluent-Prepare a mixture of water, methanol, and formic acid ( $425: 75: 2$ ).

Mobile phase-Prepare a filtered and degassed mixture of 0.01 M sodium butanesulfonate in Diluent. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP 4-Aminophenol RS, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $24 \mu \mathrm{~g}$ per mL .
Test solution-Transfer an accurately measured portion of Oral Suspension, equivalent to about 120 mg of acetaminophen, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $272-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 20-\mathrm{cm}$ column that contains $10-\mu \mathrm{m}$ packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the Standard solution and Test solution, and record the peak areas as directed for Procedure.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks: the peak area of 4-aminophenol obtained from the Test solution is not greater than the corresponding peak area obtained from the Standard solution. nS $^{\text {S (USP28) }}$

## Briefing

Acetohydroxamic Acid, USP 27 page 43. It is proposed to clarify the calculations in the test for Limit of hydroxylamine.
(PA4: E. Gonikberg) RTS-41555-1

## Change to read:

## Limit of hydroxylamine-

Phosphate buffer-Dissolve 1.36 g of monobasic potassium phosphate in about 950 mL of water, adjust with 1 M potassium hydroxide to a pH of 7.4 , dilute with water to 1000 mL , and mix.

Pyridoxal 5-phosphate solution-Dissolve 50 mg of pyridoxal 5-phosphate monohydrate in 50 mL of Phosphate buffer in a low-actinic flask. Prepare fresh before use.
Standard solutions-Dissolve an accurately weighed quantity of hydroxylamine hydrochloride in water to obtain a final concentration of 2.0 mg per mL . To separate $100-\mathrm{mL}$ volumetric flasks, transfer $5.0,10.0$, and 15.0 mL of the hydroxylamine stock solution, respectively, dilute each flask with water to volume, and mix.

Test solution-Transfer an accurately weighed quantity of about 1500 mg of Acetohydroxamic Acid, previously dried, to a $100-\mathrm{mL}$ beaker, and dissolve in a sufficient amount of water to cover the electrode of a calibrated pH meter (about 60 mL ). While stirring, adjust with 0.05 M potassium hydroxide to a pH of 7.4. Quantitatively transfer the contents of the beaker, with the aid of small portions of water, to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Procedure-Transfer 2.0 mL of each Standard solution and the Test solution into separate $100-\mathrm{mL}$ volumetric flasks. Pipet 2.0 mL of water into a $100-\mathrm{mL}$ volumetric flask for the reagent blank. To each flask, add 4.0 mL of Pyridoxal 5-phosphate solution, and mix. After 8 minutes, accurately timed, dilute the contents of each flask with Phosphate buffer to volume. Immediately determine the fluorescence intensities of the solutions from the Standard solutions and the Test solution in a fluorometer at an excitation wavelength of 350 nm and an emission wavelength of 450 nm , setting the instrument to zero with the reagent blank. Determine the best-fit straight line from the fluorescence intensities of the three Standard solutions versus the hydroxylamine hydrochloride concentrations, in $\mu \mathrm{g}$ per mL . From the best-fit straight line, determine the concentration, in $\mu \mathrm{g}$ per mL , of hydroxylamine hydrochloride
$■_{\text {in }}$ the Test solution. Calculate the percentage of hydroxyl-
amine $_{\text {п2S }}$ (USP28)
in the portion of Acetohydroxamic Acid taken by the formula:

$$
(33.03 / 69.50)(10 C / W)
$$

in which 33.03 and 69.50 are the molecular weights of hydroxylamine and hydroxylamine hydrochloride, respectively; $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of hydroxylamine hydrochloride in the Test solution; and $W$ is the weight, in mg , of Acetohydroxamic Acid taken. Not more than $0.5 \%$ is found.

Acyclovir, USP 27 page 47, page 3039 of the First Supplement, and page 1143 of $P F 30$ (4) [July-Aug. 2004]. On the basis of comments received, it is proposed to revise the column dimensions for the Chromatographic system in the Assay and limit for guanine.
(PA7b: B. Davani) RTS-41388-1

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■1S (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle-U S P$ Acyclovir $R S$.

- USP Endotoxin RS. ■ 1 S (USP28) $^{\text {( }}$


## Add the following:

-Other requirements-Where the label states that Acyclovir is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Acyclovir for Injection. Where the label states that Acyclovir must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Acyclovir for Injection.■1S (USP28)

## Change to read:

## Assay and limit for guanine-

Mobile phase-Prepare a filtered and degassed solution of glacial acetic acid in water ( 1 in 1000). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
-System suitability solution 1-Dissolve accurately weighed quantities of USP Acyclovir RS and guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having known concentrations of about 0.1 mg of each per mL .

System suitability solution 2-Dissolve an accurately weighed quantity of guanine in 0.1 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about $0.7 \mu \mathrm{~g}$ per $\mathrm{mL} . \bullet 4$

Guanine standard preparation-Transfer about 8.75 mg of guanine, accurately weighed, to a $500-\mathrm{mL}$ volumetric flask. Dissolve in 50 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. ${ }^{\bullet}$ Transfer 2.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix to obtain a solution having a known concentration of about $0.7 \mu \mathrm{~g}$ per $\mathrm{mL} . \bullet 4$

Standard preparation-Dissolve about 25 mg of USP Acyclovir RS, accurately weighed, in 5 mL of 0.1 N sodium hydroxide in a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution ${ }^{\circ}$ to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix to obtain a solution having ${ }^{\bullet}$ a known concentration of about 0.1 mg of USP Acyclovir RS per mL.

Assay preparation-Dissolve about 100 mg of Acyclovir, accurately weighed, in 20 mL of 0.1 N sodium hydroxide in a 200mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with 0.01 N sodium hydroxide to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.2 \mathrm{~mm} \times 30 \mathrm{~cm}$
-4.6-mm $\times 25-\mathrm{cm}_{\square 2 \mathrm{~S}}$ (USP28)
column that contains packing L1. The flow rate is about 3 mL per minute. Chromatograph ${ }^{\bullet}$ System suitability solution $1, \bullet 4$ and record the peak responses as directed for Procedure: the resolution, $R$, between acyclovir and guanine is not less than 2.0 ; the tailing factor for the analyte peak is not more than 2 ; and the relative standard deviation for replicate injections ${ }^{\bullet}$ for the acyclovir peak ${ }_{\bullet 4}$ is not more than $2.0 \%$. Chromatograph System suitability solution 2, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than 2.0\%. $\quad 4$

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation, ${ }^{\bullet}$ Guanine standard preparation, $\bullet_{4}$ and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in $\mu \mathrm{g}$, of guanine in the portion of Acyclovir taken by the formula:

$$
1000 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of guanine in the ${ }^{\bullet}$ Guanine standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses due to guanine in the Assay preparation and the ${ }^{\bullet}$ Guanine standard preparation, $\bullet 4$ respectively: not more than $0.7 \%$ of guanine is found. Calculate the quantity, in mg, of $\mathrm{C}_{8} \mathrm{H}_{11} \mathrm{~N}_{5} \mathrm{O}_{3}$ in the portion of Acyclovir taken by the formula:

$$
1000 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Acyclovir RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses due to acyclovir in the Assay preparation and the Standard preparation, respectively.

## BriEfing

Alcohol in Dextrose Injection, USP 27 page 61 and page 3041 of the First Supplement; Anticoagulant Citrate Dextrose Solution, USP 27 page 157; Bretylium Tosylate in Dextrose Injection, $U S P 27$ page 264; Bupivacaine Hydrochloride in Dextrose Injection, USP 27 page 277; Ciprofloxacin Injection, USP 27 page 456 and page 813 of $P F 30(3)$ [May-June 2004]; Dextrose Injection, USP 27 page 582; Dextrose and Sodium Chloride Injection, USP 27 page 582; Dobutamine in Dextrose Injection, USP 27 page 652; Dopamine Hydrochloride and Dextrose Injection, $U S P 27$ page 661; Multiple Electrolytes and Dextrose Injection Type 1, USP 27 page 690 and page 838 of PF 30(3) [May-June 2004]; Lidocaine Hydrochloride and Dextrose Injection, USP 27 page 1089; Potassium Chloride in Dex-
trose Injection, USP 27 page 1516; Potassium Chloride in Dextrose and Sodium Chloride Injection, USP 27 page 1517; Oral Rehydration Salts, USP 27 page 1630; Ringer's and Dextrose Injection, USP 27 page 1657 and page 1293 of $P F$ 30(4) [July-Aug. 2004]; Sodium Chloride and Dextrose Tablets, USP 27 page 1702; Tetracaine Hydrochloride in Dextrose Injection, $U S P 27$ page 1799; Theophylline in Dextrose Injection, USP 27 page 1815. It is proposed to revise the Assay for dextrose procedure by updating the formula to directly calculate the percentage (g per 100 mL ) of dextrose. Formulas are provided to accommodate the use of either anhydrous dextrose or dextrose monohydrate, as specified in each monograph. The proposed formula uses a value of $52.9^{\circ}$, the midpoint of the current specific rotation range for anhydrous dextrose, as indicated in the Dextrose monograph. This replaces the current factor of 1.0425 percent per degree, which was based on a superseded value of $52.75^{\circ}$ for the specific rotation for anhydrous dextrose. Because the procedure contains a reference to Optical Rotation $\langle 781\rangle$, which specifies performing the test at $25^{\circ}$ unless otherwise specified in the individual monograph, all monograph references to $25^{\circ}$ are proposed for deletion.
(PA1: K. Russo; PA2: C. Anthony) RTS-41401-14

## Change to read:

Assay for dextrose-Transfer an accurately measured volume of Injection, containing from 2 to 5 g of dextrose, to a $100-\mathrm{mL}$ volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. Determine the angular rotation in a 200 man tube at $25^{\circ}$ (see Optical Rotation- 784 ) ). The observed rota tion in degrees, multiplied by 1.0425 , represents the weight, in $\frac{g}{5}$, of $\mathrm{C}_{6} \mathrm{H}_{42} \mathrm{\theta}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ - in the volume of Injection taken.
 Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:
$(100 / 52.9)(198.17 / 180.16) A R$,
in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees. $\quad$ 2S (USP28)

## Briefing

Alprazolam Tablets, $U S P 27$ page 65 and page 51 of $P F 30(1)$ [Jan.-Feb. 2004]. It is proposed to delete the wavelengths in which it has been demonstrated that excipients could present signals that interfere in the Identification test.
(PA3: S. Salado) RTS-41359-1

## Change to read:

Identification-Dissolve an amount of finely powdered Tablets, equivalent to about 15 mg of alprazolam, in 10 mL of sodium carbonate solution ( 1 in 100 ). Add 15 mL of chloroform, and shake vigorously for 30 minutes. Centrifuge, withdraw the aqueous layer, and transfer the chloroform to a clean container. Add about 200 mg of potassium bromide. Evaporate the chloroform from this mixture to dryness, and dry the dispersion in vacuum at $60^{\circ}$ for 24 hours. Grind this dispersion into a fine powder. Prepare a suitable pellet for testing by placing about 100 mg of dried potassium bromide into a die. Sprinkle about 20 mg of the finely ground, alprazo-lam-potassium bromide dispersion onto the dried potassium bromide layer, and cover with another specimen of about 100 mg of dried potassium bromide: the IR absorption spectrum of the potassium bromide dispersion so obtained exhibits maxima characteristic of alprazolam, as compared to that of a similar preparation of USP Alprazolam RS, at the following wavenumbers: at 1609 , 1578, 1566, 1539, 1530,

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■_2S (USP28)
1487,4.445, 1428,
■■2S(USP28)
and 1379,4337, and 1320
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■ $\mathbf{m}_{2 S}$ (USP28)
wavenumbers in the region of 1650 to $1300 \mathrm{~cm}^{-1}$; at 970,
■ $\mathbf{m}_{2 S}$ (USP28)
932, 891, 826, 797,
■ $\mathbf{n}_{2 S}$ (USP28)
$779,746,696$, and 669,

Buffer solution-Prepare a 1 in 10 dilution of Stock buffer solution in water to obtain a Working buffer solution having a pH of $6.0 \pm 0.1$.

Medium: Buffer solution; 500 mL .
Apparatus 1: 100 rpm .
Time: 30 minutes.
Procedure-
Stock standard solution-Prepare a solution in methanol of USP Alprazolam RS having a known concentration of about 0.05 mg per mL.
Standard solution-Add 50 mL of Stock buffer solution and 250 mL of water to a $500-\mathrm{mL}$ volumetric flask. Add to the flask 5.0 mL of Stock standard solution for every 0.25 mg of alprazolam contained in the Tablet being assayed. Dilute with water to volume, and mix.

Mobile phase-Prepare a degassed and filtered solution of Buffer solution, acetonitrile, and tetrahydrofuran ( $60: 35: 5$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ analytical column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency is not less than 500 theoretical plates, and the relative standard deviation for replicate injections is not more than $3.0 \%$.

Procedure-
-Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled
sample as the test solution.■1S (USP28)
Separately inject equal volumes of a filtered pertion of the solution under test
$\mathbf{m}_{\text {of the pooled sample }}{ }_{\text {Q1S (USP28) }}$
and the Standard solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity of $\mathrm{C}_{17} \mathrm{H}_{13} \mathrm{ClN}_{4}$ dissolved based on the peak responses obtained from the solution under test and the Standard solution.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{17} \mathrm{H}_{13} \mathrm{ClN}_{4}$ is dissolved in 30 minutes:
-the requirements are met if the quantities of active ingredients dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity, $Q$, is the amount of dissolved active ingredient of interest expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample
Number
Stage Tested Acceptance Criteria
$\mathrm{S}_{1} \quad 6 \quad$ Average amount dissolved is not less than $Q+10 \%$.
$\mathrm{S}_{2} \quad 6 \quad$ Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$.
$\mathrm{S}_{3} \quad 12$ Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ $\mathrm{S}_{3}$ ) is equal to or greater than $Q$.

Amoxicillin Capsules, USP 27 page 139. It is proposed to revise the Apparatus in the test for Dissolution to include the Capsules strength in accordance with the approved test for this product.

$$
\text { (BPC: M. Marques) } \quad \text { RTS—39897-1 }
$$

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: water; 900 mL .
Apparatus 1: 100 rpm ,

- for Capsules containing 250 mg .

Apparatus 2: 75 rpm , for Capsules containing 500
mg. ■2S $_{\text {(USP28) }}$
Time: 60 minutes.
Procedure-Determine the amount of $\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{5} \mathrm{~S}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 272 nm on filtered portions of the solution under test, suitably diluted with water, if necessary, in comparison with a Standard solution having a known concentration of USP Amoxicillin RS in the same Medium.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{5} \mathrm{~S}$ is dissolved in 60 minutes.

Briefing

Anticoagulant Citrate Dextrose Solution, USP 27 page 157See briefing under Alcohol in Dextrose Injection.
(BBP: R. Tirumalai) RTS-41401-15

## Change to read:

Assay for dextrose-Determine the angular rotation of Solution in a 200 -mm tube, using sodium light at $25^{\circ}$. The observed rotation in degrees, multiplied by 1.0425 , represents the weight of $\mathrm{E}_{6} \mathrm{H}_{12} \Theta_{6} \cdot \mathrm{H}_{2} \mathrm{Q}$ in 100 mL of the solution.

■suitable polarimeter tube (see Optical Rotation $\langle 781\rangle$ ). Where the Solution is labeled to contain anhydrous dextrose, calculate the percentage (g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6}$ in the portion of Solution taken by the formula:

$$
(100 / 52.9) A R
$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees. Where the Solution is labeled to contain dextrose monohydrate, calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Solution taken by the formula:

$$
(100 / 52.9)(198.17 / 180.16) A R
$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees.■2S (USP28)

## Briefing

Betahistine Hydrochloride, page 1008 of $P F$ 29(4) [July-Aug. 2003]. On the basis of comments received, it is proposed to replace the TLC analysis in the Related compounds section with an HPLC method. An analogous method is also proposed for the Assay. Validation of the method was done using Zorbax Eclipse XDB-C18, $5-\mu \mathrm{m}$, brand of L1 packing. The typical retention time for the betahistine peak is 8 minutes.
(PA5: A. Wilk) RTS-40643-1

## Add the following:

## ■Betahistine Hydrochloride

$\mathrm{C}_{8} \mathrm{H}_{12} \mathrm{~N}_{2} \cdot 2 \mathrm{HCl} \quad 209.12$

2-Pyridineethanamine, $N$-methyl-, dihydrochloride.

2-[2-(Methylamino)ethyl]pyridine dihydrochloride [5579-84-0].
» Betahistine Hydrochloride contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{8} \mathrm{H}_{12} \mathrm{~N}_{2} \cdot 2 \mathrm{HCl}$, calculated on the dried basis. sistant containers.

USP Reference standards $\langle 11\rangle$ —USP Betahistine Hydrochloride RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The $R_{L}$ value and intensity of the prineipal spet in the ehromatogram of Test solution 2 correspend to these in the ehromatogram of Stadeld solution 1, obtained as directed

The Rels. The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.
$\mathbf{p H}\langle 791\rangle$ : between 2.0 and 3.0, in a solution (1 in 10).
Loss on drying $\langle 731\rangle$ - Dry it between $100^{\circ}$ and $105^{\circ}$ to constant weight: it loses not more than $0.5 \% 1.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Related compounds-

gel mixture.
Diltent Prepare a mixture-of aleohel and water (3:1).
Fest solution 1 Dissolve about 250 mg of Betahistime
Hydrechloride, aceurately weighed, in 5.0 mL of Piltumt.
Test selution 2 Dilute 1.0 mL of Test solution 1 with Dil tent $40-25.0 \mathrm{~mL}$, and mix.
Resolution solution Pepare a solution of USP Betahis tine Hydrochloride RS and 2 vinylpyridine in Diluent containing 1.0 mg of each per mL .
Standerd solution - Prepare a solution of USP Betahistine Hydrochloride RS in Diltent containing 2.0 mg per mL. Standard solution 2 Dilute 1.0 mL of Standard solution -with Diluent to 20.0 mL . Dilute 1.0 mL of this solution with Diluent to 20.0 mL , and mix.

Standerd solution - 3 Dilute 5.0 mL of Standard solution
2 with Diluent to 5.0 mL , and mix.
Application valtme: $5 \mu \mathrm{H}$.
Beveloping solvent system:-a mixttre of toluene, abso-
tute aleohel, and ammenimm hydroxide ( $10: 5: 1$ ).
Procedure Proceed as directed for Thin Lamer Chroma tography under Chromatography $\langle 624$ ), except to developdrythe plate under actrrent of wam air, in a hood, and then dryfollowed by heating for 10 minter at $110^{\circ}$. Examine the plate under short wavelength UV light using a quantitative seanner. The resolution, $R$, between the peaks due to 2 vi
nylpyridine and betahistine in the sean of the chremategram of the Resolution selution is not less than 3.0. The area obtained for any individual impurity is not greater than that obtained for the major peak in the chromatogram of Stan tatrd solution 2: net more than $0.25 \%$ of any individtal im purity is found. The total ameunt of impurities found is net greater than twice the area of the major peak in the same solution: not more than $0.5 \%$ of total impurities is feumd.

Mobile phase and Chromatographic system-Proceed as directed in the Assay.

Test solution-Transfer about 38 mg of Betahistine Hydrochloride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Procedure-Inject about $10 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Betahistine Hydrochloride taken by the formula:

$$
100 F\left(r_{i} / r_{s}\right)
$$

in which $F$ is the response factor of the respective impurity (see Table 1) and 1.0 for all other peaks; $r_{i}$ is the peak response for each impurity; and $r_{s}$ is the sum of the responses of all of the peaks, adjusted for the relative response factor. In addition to not exceeding the limits for impurities in Ta ble 1 , not more than $0.1 \%$ of any other individual impurity is found, and not more than $0.5 \%$ of total impurities is found.

Table 1

| Impurity Name | Relative <br> Retention <br> Time | Response <br> Factor (F) | Limit <br> $(\%)$ |
| :---: | :---: | :---: | :---: |
| 2-(2-Hydroxyethyl) <br> pyridine | 0.3 | 0.5 | 0.2 |
| 2-Vinylpyridine | 0.4 | 0.4 | 0.2 |
| $N$-Methyl- $N, N$-bis(2- <br> pyridin-2-yl-ethyl)- <br> amine | 2.4 | 1.4 | 0.2 |

Assay- Dissolve about 80 mg of Betahistine Hydrechleride, acemrately weighed, in 60 mL of a mixtare of glaciat acetic acid and acetic anhydride ( $5: 1$ ). Titrate with 0.1 N perehloric acid VS, determining the endpoint potentiometrieally, using suitable electrodes (see Titrimetry $\langle 544\rangle$ ). Perform a blank determination, and make any necessary eorrection. Each mL of 0.1 N perchloric acid is equivalent 5 10.455 mg of $\mathrm{G}_{8} \mathrm{H}_{42} \mathrm{~N}_{2}-2 \mathrm{HCl}$.

Ammonium acetate buffer-Dissolve about 0.69 g of ammonium acetate in 1000 mL of water. Adjust with glacial acetic acid to a pH of 4.7 .

Mobile phase-Prepare a filtered and degassed mixture of 350 mL of acetonitrile and 650 mL of Ammonium acetate buffer, containing 2.88 g of sodium lauryl sulfate. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Betahistine Hydrochloride RS in Mobile phase to obtain a solution having a known concentration of about 0.38 mg per mL .

Assay preparation-Transfer about 38 mg of Betahistine Hydrochloride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a 254 -nm detector and $3.0-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The column temperature is maintained at $40^{\circ}$. The flow rate is about 0.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 5000 theoretical plates; the tailing factor for the betahistine peak is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{8} \mathrm{H}_{12} \mathrm{~N}_{2} \cdot 2 \mathrm{HCl}$ in the portion of Betahistine Hydrochloride taken by the formula:

$$
100 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Betahistine Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. ${ }^{2 S}$ (USP28)

## BRIEFING

Bethanechol Chloride, USP 27 page 242 and page 1848 of $P F$ 29(6) [Nov.-Dec. 2003]. It is proposed to revise the test for Related compounds and the Assay to modify the resolution between 2-hydroxypropyltrimethyl ammonium chloride and bethanechol according to the typical resolution values found for the System
suitability solution. In addition, it is proposed to revise the Buffer solution in the Assay to indicate the use of edetic acid instead of edetate disodium.
(PA3: S. Salado) RTS-41191-1; 41627-1

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■1S (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Bethanechol Chloride RS.

- USP Endotoxin RS. ${ }^{\text {|S (USP28) }}$


## Change to read:

## ${ }^{\Delta}$ Related compounds-

Buffer solution-Transfer about 0.48 g of methanesulfonic acid to a $1000-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with water to volume.
Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $95: 5$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Bethanechol Chloride RS in Mobile phase and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $1 \mu \mathrm{~g}$ of USP Bethanechol Chloride RS per mL.

Test solution-Transfer about 25 mg of Bethanechol Chloride, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Mobile phase to volume, and mix.

System suitability solution-Transfer about 25 mg of Bethanechol Chloride, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask. Add 10 mL of 0.1 N sodium hydroxide, and allow to stand for about 15 minutes. Add 10 mL of 0.1 N hydrochloric acid. Dissolve in and dilute with Mobile phase to volume, and mix.

Chromatography system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a conductivity detector and a $3.9-\times 150-\mathrm{mm}$ column containing packing L55. The flow rate is about 1.0 mL per minute. The detector and column temperatures are maintained at $35^{\circ}$ and $30^{\circ}$, respectively. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention time is about 0.9 for 2-hydroxypropyltrimethyl ammonium chloride and 1.0 for bethanechol; the resolution, $R$, between 2-hydroxypropyltrimethyl ammonium chloride and bethanechol is not less than 4.5
-0.8.■2S (USP28)
Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $10.0 \%$ for bethanechol chloride.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Mobile phase, the Standard solution, and the Test solution into the chromatograph, record the chromatograms, and measure the
peak responses for all the peaks. Calculate the percentage of each impurity in the portion of Bethanechol Chloride taken by the formula:

$$
25,000 C(F / W)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Bethanechol Chloride RS in the Standard solution; $F$ is the relative response factor and is equal to 0.79 for 2-hydroxypropyltrimethyl ammonium and 1.0 for any other impurity; $W$ is the weight, in mg , of Bethanechol Chloride taken to prepare the Test solution; $r_{i}$ is the peak response for any impurity in the Test solution; and $r_{S}$ is the peak response of USP Bethanechol Chloride RS in the Standard solution. Not more than $1.0 \%$ of 2-hydroxypropyltrimethyl ammonium is found; not more than $0.1 \%$ of any other impurity is found; and the sum of all the impurities is not more than $1.5 \%$. $\mathbf{U}$ USP27

## Add the following:

-Other requirements-Where the label states that Bethanechol Chloride is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Bethanechol Chloride Injection. Where the label states that Bethanechol Chloride must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Bethanechol Chloride Injec-

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tion.■1S (USP28)
```


## Change to read:

## Assay-

${ }^{\Delta}$ Buffer solution-Transfer about 29 mg of
■edetic acid $_{\mathbf{m}^{2 S}}$ (USP28)
to a $1000-\mathrm{mL}$ volumetric flask, and dissolve in 500 mL of water. Add $300 \mu \mathrm{~L}$ of nitric acid to the volumetric flask, and dilute with water to volume. Pass through a $0.45-\mu \mathrm{m}$ nylon membrane filter.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $95: 5$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Transfer about 25 mg of Bethanechol Chloride, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask. Add 10 mL of 0.1 N sodium hydroxide, and allow to stand for about 15 minutes. Add 10 mL of 0.1 N hydrochloric acid. Dissolve in and dilute with Mobile phase to volume, and mix.

Standard preparation-Dissolve an accurately weighed quantity of USP Bethanechol Chloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.1 mg of USP Bethanechol Chloride RS per mL.

Assay preparation-Transfer about 25 mg of Bethanechol Chloride, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a conductivity detector and a 3.9- $\times 150-\mathrm{mm}$ column containing packing L55. The flow rate is about 1.0 mL per minute. The detector and column temperatures are maintained at $35^{\circ}$ and $30^{\circ}$, respectively. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9
for 2-hydroxypropyltrimethyl ammonium chloride and 1.0 for bethanechol; and the resolution, $R$, between 2 -hydroxypropyltrimethyl ammonium chloride and bethanechol is not less than 1.5
-0.8.m2S (USP28)
Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 3.5; and the relative standard deviation for replicate injections is not more than $3.0 \%$.
Procedure-Separately inject equal volumes (about $25 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg , of $\mathrm{C}_{7} \mathrm{H}_{17} \mathrm{ClN}_{2} \mathrm{O}_{2}$ in the portion of Bethanechol Chloride taken by the formula:

$$
250 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Bethanechol Chloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the bethanechol chloride peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{U}$ USP27

## BRIEFING

Bethanechol Chloride Tablets, USP 27 page 244—See briefing under Bethanechol Chloride. Editorial style changes have also been made.
(PA3: S. Salado) RTS-41627-2

## Change to read:

## ${ }^{4}$ Related compounds-

Buffer solution-Transfer about 0.48 g of methanesulfonic acid to a $1000-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with water to volume.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $95: 5$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve an accurately weighed quantity of USP Bethanechol Chloride RS in Mobile phase, and dilute quantitatively and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $1 \mu \mathrm{~g}$ of USP Bethanechol Chloride RS per mL.

Test solution-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to 1 Tablet, to a suitable volumetric flask so that the final solution yields a concentration of about 0.1 mg per mL of bethanechol chloride. Add an amount of Mobile phase, about $60 \%$ to $70 \%$ of the total volume of the flask. Sonicate for 20 minutes. Shake by mechanical means for about 15 minutes. Dilute with Mobile phase to volume, and mix. Allow to stand for 10 minutes, and pass the solution through a $1-\mu \mathrm{m}$ glass filter, discarding the first 3 mL of the filtrate.

System suitability solution-Transfer about 25 mg of bethanechol chloride, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask. Add 10 mL of 0.1 N sodium hydroxide, and allow to stand for about 15 minutes. Add 10 mL of 0.1 N hydrochloric acid. Dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a conductivity detector and a $3.9-\times 150-\mathrm{mm}$ column containing packing L55. The flow rate is about 1.0 mL per minute. The detector and column temperatures are maintained at $35^{\circ}$ and $30^{\circ}$, respectively. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for 2-hydroxypropyltrimethyl ammonium chloride and 1.0 for bethanechol; and the resolution, $R$, between 2 -hydroxypropyltrimethyl ammonium chloride and bethanechol is not less than 4.5

## -0.8.n2S (USP28)

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $10.0 \%$ for bethanechol chloride.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the responses for all of the peaks. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$
100 V(F / W) C\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Bethanechol Chloride RS in the Standard solution; $F$ is the relative response factor and is equal to 0.79 for 2-hydroxypropyltrimethyl ammonium chloride and 1.0 for any other impurity; $r_{i}$ is the peak response for any impurity in the Test solution; $r_{S}$ is the peak response of USP Bethanechol Chloride RS in the Standard solution; and $W$ is the amount, in mg , of bethanechol chloride based on the average weight, labeled dose, and amount taken to prepare the Test solution. Not more than 1.0\% of 2-hydroxypropyltrimethyl ammonium chloride is found; not more than $0.2 \%$ of any other impurity is found; and the sum of all the impurities is not more than $1.5 \%$. $\Delta U S P 27$

## Change to read:

## Assay-

${ }^{\boldsymbol{\Delta}}$ Buffer solution-Transfer about 29 mg of

- $^{\text {edetic acid }}{ }_{\text {2S }}$ (USP28)
to a $1000-\mathrm{mL}$ volumetric flask, and dissolve in 500 mL of water. Add $300 \mu \mathrm{~L}$ of nitric acid to the volumetric flask, and dilute with water to volume. Pass through a $0.45-\mu \mathrm{m}$ nylon membrane filter.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $95: 5$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Bethanechol Chloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.1 mg of USP Bethanechol Chloride RS per mL.

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to 1 Tablet, to a suitable volumetric flask so that the final solution yields a concentration of about 0.1 mg per mL of bethanechol chloride. Add an amount of Mobile phase, about $60 \%$ to $70 \%$ of the total volume of the flask. Sonicate for 20 minutes. Shake by mechanical means for about 15 minutes. Dilute with Mobile phase to volume, and mix. Allow to stand for 10 minutes, and pass the solution through a $1-\mu \mathrm{m}$ glass filter, discarding the first 3 mL of the filtrate.

System suitability solution-Transfer about 25 mg of bethanechol chloride, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask. Add 10 mL of 0.1 N sodium hydroxide, and allow to stand for about 15 minutes. Add 10 mL of 0.1 N hydrochloric acid. Dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )——The liquid chromatograph is equipped with a conductivity detector and a $3.9-\times 150-\mathrm{mm}$ column containing packing L55. The flow rate is about 1.0 mL per minute. The detector and column temperatures are maintained at $35^{\circ}$ and $30^{\circ}$, respectively. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention time is about 0.9 for 2-hydroxypropyltrimethyl ammonium chloride and 1.0 for bethanechol; and the resolution, $R$, between 2-hydroxypropyltrimethyl ammonium chloride and bethanechol is not less than 4.5

## -0.8. $\mathbf{m}_{2 S}$ (USP28)

Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 3.5 ; and the relative standard deviation for replicate injections is not more than $3.0 \%$.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg , of bethanechol chloride $\left(\mathrm{C}_{7} \mathrm{H}_{17} \mathrm{ClN}_{2} \mathrm{O}_{2}\right)$ in the portion of Tablets taken by the formula:

$$
V C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Bethanechol Chloride RS in the Standard preparation; $V$ is the volume, in mL , of the flask used to prepare the Assay preparation; and $r_{U}$ and $r_{S}$ are the bethanechol chloride peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{U}$ USP27

## Briefing

Bisoprolol Fumarate Tablets, page 3045 of the First Supplement. On the basis of comments received, it is proposed to delete the Water section. In addition, an editorial style change has been made in the Assay.
(PA5: A. Wilk) RTS-41394-1

## Delete the following:

Water, Methed $I\langle 924\rangle$ : net mere than $3.0 \%$.

## Change to read:

```
Assay-
    Diluent-Prepare a mixture of water and acetonitrile (65:35).
    Mobile phase-Prepare mixure of waterande
(65:35). Add
\(\bullet\) To a 1-L portion of Diluent add \(_{\bullet}\)
```

5 mL of heptafluorobutyric acid, 5 mL of diethylamine, and 2.5 mL of formic acid. Mix, filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Prepare a solution in Diluent having a concentration of 0.5 mg of propranolol hydrochloride per mL and 1.0 mg of bisoprolol fumarate per mL .

Standard preparation-Quantitatively dissolve an accurately weighed quantity of USP Bisoprolol Fumarate RS in Diluent to obtain a solution having a known concentration of about 1 mg per mL .

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 25 mg of bisoprolol fumarate, to a $25-\mathrm{mL}$ volumetric flask. Add 10 mL of Diluent, and sonicate for $10 \mathrm{~min}-$ utes. Cool, dilute with Diluent to volume, and mix. Centrifuge for 20 minutes, and use the clear supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $273-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 12.5-\mathrm{cm}$ column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the peak areas as directed for Procedure: the resolution, $R$, between bisoprolol and propranolol is not less than 7.0. Chromatograph the Standard preparation, and record the peak areas as directed for Procedure: the tailing factor for the analyte peak is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg , of bisoprolol fumarate $\left[\left(\mathrm{C}_{18} \mathrm{H}_{31} \mathrm{NO}_{4}\right)_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right]$ in the portion of Tablets taken by the formula:

$$
25 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Bisoprolol Fumarate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Bretylium Tosylate in Dextrose Injection, USP 27 page 264See briefing under Alcohol in Dextrose Injection.
(PA5: A. Wilk) RTS-41401-16

## Change to read:

Assay for dextrose-Transfer an accurately measured volume of Injection, containing 2 to 5 g of dextrose, to a $100-\mathrm{mL}$ volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. Determine the angular rotation in a suitable polarimeter tube at $25^{\circ}$ (see-Optical Rotation $\langle 784$ )). The observed fotation, in degrees, multiplied by 1.0425 , in which 4 is the ratio

200 divided by the length, in mm, of the polarimeter employed, represents the weight, in $\frac{8}{\delta}$, of dextrose $\left(\mathrm{C}_{6} \mathrm{H}_{42} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}\right)$ in the vol ume of Injection taken.
-(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:

$$
(100 / 52.9)(198.17 / 180.16) A R
$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees. $\quad$ 2S (USP28)

## BRIEFING

Bupivacaine Hydrochloride, USP 27 page 276 and page 1432 of PF 29(5) [Sept.-Oct. 2004]. It is proposed to revise the Chromatographic system in the test for Limit of residual solvents to indicate the use of a $4-\mathrm{mm} \times 2-\mathrm{m}$ column.
(PA1: K. Russo) RTS-41601-1

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■1S (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle —$ USP Bupivacaine Hydrochloride $R S$.

- USP Endotoxin RS.■1S (USP28)


## Change to read:

## Limit of residual solvents-

Alcohol standard solution-Pipet 2 mL of dehydrated alcohol into a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. The resulting solution contains $0.08 \%$ of alcohol.

Isopropyl alcohol standard solution-Pipet 2 mL of isopropyl alcohol into a $1000-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. The resulting solution contains $0.004 \%$ of isopropyl alcohol.

Test solution-Transfer 1.0 g of Bupivacaine Hydrochloride, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Chromatographic system-Under typical conditions, the instrument is equipped with a flame-ionization detector and a $2 \rightarrow-6$ mm
-4-mm $\times 2-\mathrm{m}_{\text {nes (USP28) }}$
column that contains packing S3. The carrier gas is nitrogen, flowing at a rate of about 40 mL per minute. The column temperature is maintained at about $175^{\circ}$, the injection port temperature is maintained at about $200^{\circ}$, and the detector temperature is maintained at about $280^{\circ}$.

Procedure-Inject equal volumes (about $5 \mu \mathrm{~L}$ ) of the Test solution, the Alcohol standard solution, and the Isopropyl alcohol standard solution successively into the gas chromatograph. Measure the responses of the alcohol peak and the isopropyl alcohol peak in each chromatogram. Determine the percentage of alcohol taken by the formula:

$$
2\left(r_{U} / r_{S}\right)
$$

and determine the percentage of isopropyl alcohol taken by the formula:

$$
0.1\left(r_{U} / r_{S}\right)
$$

in which $r_{U}$ and $r_{S}$ are the responses of the respective analytes in the Test solution and of the corresponding analytes in the Alcohol standard solution and the Isopropyl alcohol standard solution, respectively. The sum of the content of alcohol and the content of isopropyl alcohol does not exceed $2 \%$.

## Add the following:

-Other requirements-Where the label states that Bupivacaine Hydrochloride is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Bupivacaine Hydrochloride Injection. Where the label states that Bupivacaine Hydrochloride must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Bupivacaine Hydrochloride Injection.■1S (USP28)

## Briefing

Bupivacaine Hydrochloride in Dextrose Injection, USP 27 page 277-See briefing under Alcohol in Dextrose Injection.
(PA1: K. Russo) RTS-41401-1

## Change to read:

Assay for dextrose-Determine the angular rotation of Injection in a suitable polarimeter tube (see Optical Rotation $\langle 781\rangle$ ). The ebserved rotation, in degrees, multiplied by $9.452 A$, in whieh $A$ is the ratio of 200 divided by the length, in mm, of the pelarimeter tube mployed, represents the weight, in mg, of dextrese $\left(\mathrm{C}_{6} \mathrm{H}_{42} \Theta_{6}\right)$ in each mL of the Injection.
-Calculate the percentage (g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6}$ in the portion of Injection taken by the formula:
(100/52.9)AR,
in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees.■2S (USP28)

## Briefing

Caffeine Citrate Injection, page 462 of $P F$ 30(2) [Mar-Apr. 2004]; Caffeine Citrate Oral Solution, page 464 of $P F 30(2)$ [Mar-Apr. 2004]. It is proposed to modify the monographs to express the results in terms of caffeine citrate, the moiety indicated in the title.
(PA3: S. Salado) RTS-41398-1

## Add the following:

## © Caffeine Citrate Injection

## Change to read:

» Caffeine Citrate Injection is a sterile solution containing Gitric Acid and an amount of Caffeine equivalento Caffeine and citric acid in Water for Injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of caffeine $\left(\mathrm{C}_{8} \mathrm{H}_{4} \mathrm{~N}_{4} \mathrm{O}_{z}\right) \cdot \mathbf{c}$ citrate
 or other preservative.

Packaging and storage-Preserve in single-dose, tight containers of Type I glass, and store at a temperature between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Caffeine RS. USP Endotoxin RS.

## Identification-

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

B: It meets the requirements of the test for Citrate $\langle 191\rangle$.

C: Transfer about 4 g of potassium iodide to a $100-\mathrm{mL}$ volumetric flask. Add 10 mL of water, and shake until the potassium iodide is dissolved. Transfer 2 g of iodine to the volumetric flask, and shake until dissolved. Dilute with water to volume, and mix. Transfer 5 drops of the solution so obtained to a $25-\mathrm{mL}$ centrifuge tube containing 5.0 mL of the Injection, and mix. Add 0.5 mL of 2.0 M hydrochloric
acid solution, and mix: a brown precipitate is produced that dissolves on neutralization with 0.5 mL of sodium hydroxide TS.

Color and clarity—Transfer a suitable portion of the Injection to a clear glass test tube, and visually examine the solution in a well-lighted area: the solution is colorless and free of haze, obvious turbidity, and precipitate.

Bacterial endotoxins $\langle 85\rangle$ : not more than 0.25 USP Endotoxin Unit per mg of caffeine.

Sterility $\langle 71\rangle$-It meets the requirements when tested as directed for Membrane Filtration in Test for Sterility of the Product To Be Examined.
$\mathbf{p H}\langle 791\rangle$ : between 4.2 and 5.2.
Particulate matter $\langle 788\rangle$ : not more than 150 particles are equal to or greater than $10 \mu \mathrm{~m}$, and not more than 25 particles are equal to or greater than $25 \mu \mathrm{~m}$.

## Change to read:

## Related compounds-

Mobile phase and Theophylline solution-Proceed as directed in the Assay.
Standard solution-Use the Standard preparation, prepared as directed in the Assay.

System sensitivity solution-Transfer 2.5 mL of the Standard solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay. Chromatograph the System sensitivity solution, and record the peak responses as directed for Procedure: the theophylline peak produces a discernible peak response at its retention time.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of any related compound in the portion of Injection taken by the formula:

$$
100 F\left(G_{s}+G_{\mu}\right)\left(r_{i}+F_{s}\right)
$$

- $100 F(386.31 / 194.19)\left(C_{S} / C_{W}\right)\left(r_{i} / r_{S}\right)$, ■ $^{\text {2S (USP28) }}$
in which $F$ is the relative response factor and is equal to 0.878 for theobromine at a relative retention time of about 0.4 , equal to 1.10 for paraxanthine at a relative retention time of about 0.6 , equal to 0.905 for theophylline at a relative retention time of about 0.7 , and equal to 1.0 for any other related compound; $\mathbf{~} 386.31$ and 194.19 are the molecular weights of caffeine citrate and caffeine, respective$1 \mathrm{y} ; \boldsymbol{m}_{2 S}(U S P 28) C_{S}$ is the concentration, in mg per mL, of USP Caffeine RS in the Standard solution; $C_{W}$ is the caffeine $\mathbf{- c i t r a t e}^{\mathbf{\omega 2 S}}{ }_{(U S P 28)}$ concentration, in mg per mL, in the Test solution, as obtained in the Assay; $r_{i}$ is the individual peak response for each related compound obtained from the Test solution; and $r_{S}$ is the caffeine peak response obtained from the Standard solution: not more than $0.10 \%$ of any individual related compound is found; and not more than $0.1 \%$ of total impurities is found.

Other requirements-It meets the requirements under Injections $\langle 1\rangle$.

## Change to read:

## Assay-

Mobile phase-Prepare a mixture of 0.01 M sodium acetate, acetonitrile, and tetrahydrofuran (191:5:4). Adjust with glacial acetic acid to a pH of 4.5 , filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Theophylline solution-Dissolve an accurately weighed quantity of theophylline in water, and dilute quantitatively, and stepwise if necessary, with water, to obtain a solution having a concentration of about 0.02 mg per mL .

Standard preparation-Transfer about 5 mg of USP Caffeine RS, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask. Add 5 mL of Theophylline solution, dissolve in and dilute with water to volume, and mix.

Assay preparation-Transfer an accurately measured volume of Injection, equivalent to about 50 mg of caffeine, to a $250-\mathrm{mL}$ volumetric flask. Dilute with water to volume, mix, and pass through a polyvinylidene difluoride or equivalent membrane having a porosity of $0.45 \mu \mathrm{~m}$.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $275-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 150-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for theophylline and 1.0 for caffeine; the resolution, $R$, between theophylline and caffeine is not less than 6.0 ; the tailing factor, determined from the theophylline and caffeine peaks, is not more than 2.0 ; and the relative standard deviation for replicate injections, determined from the caffeine peaks, is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and
measure the caffeine peak responses. Calculate the quantity, in mg, of caffeine $\left(\mathrm{C}_{8} \mathrm{H}_{48} \mathrm{~N}_{4} \mathrm{O}_{2}\right)$ - citrate $\left(\mathrm{C}_{14} \mathrm{H}_{18} \mathrm{~N}_{4}\right.$ $\left.\mathrm{O}_{9}\right)_{■ 2 \text { (USP28) }}$ in the volume of Injection taken by the formula:

$$
250 C\left(r_{4}++_{s}\right)
$$


in which $\quad 386.31$ and 194.19 are the molecular weights of caffeine citrate and caffeine respectively; ${ }^{2 S}$ (USP28) $C$ is the concentration, in mg per mL , of USP Caffeine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.aUSP28

BRIEFING

Caffeine Citrate Oral Solution, page 464 of $P F$ 30(2) [Mar.Apr. 2004]-See briefing under Caffeine Citrate Injection.
(PA3: S Salado) RTS-41398-1

## Add the following:

## $\triangle$ Caffeine Citrate Oral Solution

## Change to read:

» Caffeine Citrate Oral Solution is a sterile aqueous solution containing Citric Acid and an amount of Caffeine to Caffeine and citric acid. It contains not less than 90.0 percent and not more
than 110.0 percent of the labeled amount of caffeine $\left(\mathrm{G}_{8} \mathrm{H}_{19} \mathrm{~N}_{4} \Theta_{z}\right) \cdot \mathbf{- c i t r a t e}\left(\mathrm{C}_{14} \mathrm{H}_{18} \mathrm{~N}_{4} \mathrm{O}_{9}\right)$. $\mathbf{n}^{25}$ (USP28) It contains no bacteriostat or other preservative.

Packaging and storage-Preserve in single-dose, tight containers of Туpe I glass, and store at a temperature between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Caffeine RS.

## Identification-

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.
B: It meets the requirements of the test for Citrate $\langle 191\rangle$.
C: Transfer about 4 g of potassium iodide to a $100-\mathrm{mL}$ volumetric flask. Add 10 mL of water, and shake until the potassium iodide is dissolved. Transfer 2 g of iodine to the volumetric flask, and shake until dissolved. Dilute with water to volume, and mix. Transfer 5 drops of the solution so obtained to a $25-\mathrm{mL}$ centrifuge tube containing 5.0 mL of the Oral Solution, and mix. Add 0.5 mL of 2.0 M hydrochloric acid solution, and mix: a brown precipitate is produced that dissolves on neutralization with 0.5 mL of sodium hydroxide TS.

Sterility $\langle 71\rangle$-It meets the requirements when tested as directed for Membrane Filtration in Test for Sterility of the Product To Be Examined.
$\mathbf{p H}\langle 791\rangle$ : between 4.2 and 5.2.
Change to read:

## Related compounds-

Mobile phase and Theophylline solution-Proceed as directed in the Assay.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

System sensitivity solution-Transfer 2.5 mL of the Standard solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay. Chromatograph the System sensitivity solution, and record the peak responses as directed for Procedure: the theophylline peak produces a discernible peak response at its retention time.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of any related compound in the portion of Oral Solution taken by the formula:

$$
\begin{gathered}
100 F\left(\epsilon_{s}+\epsilon_{\mu}\right)\left(x_{i}+\Psi_{s}\right)^{\prime}, \\
-100 F(386.31 / 194.19)\left(C_{S} / C_{W}\right)\left(r_{i} / r_{s}\right), \boldsymbol{\omega}^{2 S}(U S P 28)
\end{gathered}
$$

in which $F$ is the relative response factor and is equal to 0.878 for theobromine at a relative retention time of about 0.4 , equal to 1.10 for paraxanthine at a relative retention time of about 0.6 , equal to 0.905 for theophylline at a relative retention time of about 0.7 , and equal to 1.0 for any other related compound; $\mathbf{- 3 8 6 . 3 1}$ and 194.19 are the molecular weights of caffeine citrate and caffeine respective$\mathrm{ly} ;{ }^{2 S}(U S P 28) C_{S}$ is the concentration, in mg per mL , of USP Caffeine RS in the Standard solution; $C_{W}$ is the caffeine - $_{\text {citrate }}{ }_{\text {■ } 2 \text { (USP28) }}$ concentration, in mg per mL , in the Test solution, as obtained in the Assay; $r_{i}$ is the individual peak response for each related compound obtained from the Test
solution; and $r_{s}$ is the caffeine peak response obtained from the Standard solution: not more than $0.10 \%$ of any individual related compound is found; and not more than $0.1 \%$ of total impurities is found.

## Change to read:

## Assay-

Mobile phase-Prepare a mixture of 0.01 M sodium acetate, acetonitrile, and tetrahydrofuran (191:5:4). Adjust with glacial acetic acid to a pH of 4.5 , filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Theophylline solution-Dissolve an accurately weighed quantity of theophylline in water, and dilute quantitatively, and stepwise if necessary, with water, to obtain a solution having a concentration of about 0.02 mg per mL .

Standard preparation-Transfer about 5 mg of USP Caffeine RS, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask. Add 5 mL of the Theophylline solution, dissolve in and dilute with water to volume, and mix.

Assay preparation-Transfer an accurately measured volume of Oral Solution, equivalent to about 50 mg of caffeine, to a $250-\mathrm{mL}$ volumetric flask. Dilute with water to volume, mix, and pass through a polyvinylidene difluoride or equivalent membrane having a porosity of $0.45 \mu \mathrm{~m}$.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $275-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 150-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.7 for theophylline and 1.0 for caffeine; the resolution, $R$, between theophylline and caffeine is not less than 6.0 ; the tailing factor, determined from the theoph-
ylline and caffeine peaks, is not more than 2.0 ; and the relative standard deviation for replicate injections, determined from the caffeine peaks, is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the caffeine peak responses. Calculate the quantity, in mg , of caffeine $\left(\mathrm{G}_{2} \mathrm{H}_{4-} \mathrm{N}_{4} \Theta_{2}\right)$ - citrate $\left(\mathrm{C}_{14} \mathrm{H}_{18} \mathrm{~N}_{4} \mathrm{O}_{9}\right)^{2 S}$ (USP28) in the volume of Oral Solution taken by the formula:

$$
250 C\left(+_{5}++_{s}\right)
$$

$$
\text { ■250(386.31/194.19) } C\left(r_{U} / r_{S}\right), \llbracket 2 S(U S P 28)
$$

in which $C$ is the concentration, in mg per mL, of USP Caffeine RS in the Standard preparation; 386.31 and 194.19 are the molecular weights of caffeine citrate and caffeine, respectively; ${ }^{2 S}(U S P 28)$ and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\Delta U S P 28$

## Briefing

Ciclopirox Olamine Cream, USP 27 page 449 and page 3049 of the First Suplement; Ciclopirox Olamine Topical Suspension, USP 27 page 449. It is proposed to add USP Benzyl Alcohol RS to the USP Reference standards section and to revise the test for Content of benzyl alcohol to include the use of USP Benzyl Alcohol RS in the Standard preparation. Editorial style changes have also been made.
(PA7b: B. Davani) RTS-41354-1

## Change to read:

USP Reference standards $\langle 11\rangle$ -
-USP Benzyl Alcohol RS..n2S (USP28) USP Ciclopirox Olamine RS.

## Change to read:

## Content of benzyl alcohol (if present)-

Solvent mixture-Mix chloroform and methanol ( $4: 1$ ).
Internal standard solution-Prepare a solution of 1-nonyl alcohol in Solvent mixture containing about 1.75 mg per mL .
Standard preparation-Dilute an accurately weighed quantity of benzyl aleohel,
-USP Benzyl Alcohol RS, ${ }_{\text {2S }}$ (USP28)
quantitatively and stepwise, with Solvent mixture to obtain a solution having a known concentration of about 2 mg per mL . Transfer 5.0 mL of this solution and 5.0 mL of Internal standard solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Solvent mixture to volume, and mix.
Test preparation-Transfer 1.0 g of Cream to a $50-\mathrm{mL}$ volumetric flask, add about 30 mL of Solvent mixture, and mix. Add 5.0 mL of Internal standard solution, dilute with Solvent mixture to volume, and mix to obtain a clear solution.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—The gas chromatograph is equipped with a flame-ionization detector and contains a $4-\mathrm{mm} \times 2-\mathrm{m}$ glass column packed with $3 \%$ phase G3 on 100 - to $120-$ mesh support S1AB. The column is maintained at a temperature of about $100^{\circ}$, the injection port and detector temperatures are maintained at about $315^{\circ}$, and nitrogen is used as the carrier gas at a flow rate of about 45 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between the peaks is not less than 1.6; the tailing factor for the benzyl alcohol peak and the internal standard peak is not greater than 3.5 ; and the relative standard deviation for replicate injections is not more than $3 \%$.
Procedure-Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of the Standard preparation and the Test preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. [nOTE-After 6 injections, raise the column temperature to about $300^{\circ}$ for about 5 minutes, then cool to $100^{\circ}$.] Calculate the percentage of benzyl alcohol in the Cream taken by the formula:

$$
C\left(R_{U} / R_{S}\right),
$$

in which $C$ is the concentration, in mg per mL , of benzyl alcohol in the Standard preparation; and $R_{U}$ and $R_{S}$ are the peak response ratios of the benzyl alcohol peak to the internal standard peak obtained from the Test preparation and the Standard preparation, respectively: between $90.0 \%$ and $110.0 \%$ of the claimed amount is present.

## Briefing

Ciclopirox Olamine Topical Suspension, USP 27 page 449See briefing under Ciclopirox Olamine Cream.
(PA7b: B. Davani) RTS-41355-1

## Change to read:

USP Reference standards $\langle 11\rangle$ -

- USP Benzyl Alcohol RS.■2S (USP28)

USP Ciclopirox Olamine RS.

## BRIEFING

Ciprofloxacin Injection, USP 27 page 456 and page 813 of $P F$ 30(3) [May-June 2004]-See briefing under Alcohol in Dextrose Injection. Editorial style changes have been made.
(PA7b: B. Davani) RTS-41401-17

## Change to read:

» Ciprofloxacin Injection is a sterile solution of Ciprofloxacin
$\Delta_{\text {or Ciprofloxacin Hydrochloride }}^{\Delta U S P 28}$
in Sterile Water for Injection, in 5 percent Dextrose Injection, or in 0.9 percent Sodium Chloride Injection prepared with the aid of Lactic Acid. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ciprofloxacin $\left(\mathrm{C}_{17} \mathrm{H}_{18} \mathrm{FN}_{3} \mathrm{O}_{3}\right)$.

## Change to read:

Limit of ciprofloxacin ethylenediamine analog-Proceed as directed in the Assay under Ciprofloxacin. Calculate the percentage of ciprofloxacin ethylenediamine analog from the chromatogram obtained from the Assay preparation by the formula:

$$
100\left[0.7 r_{A} /\left(0.7 r_{A}+r_{C}\right)\right],
$$

in which 0.7 is the respense

- $_{\text {correction }}$ ■1S (USP28)
factor for ciprofloxacin ethylenediamine analog; for eiprofloxacim
- 1 (USP28)
and $r_{A}$ and $r_{C}$ are the responses of the ciprofloxacin ethylenediamine analog peak and the ciprofloxacin peak, respectively. It contains not more than $0.5 \%$ of ciprofloxacin ethylenediamine analog.


## Change to read:

Dextrose content (if present)—Using the undiluted Injection, determine the angular rotation in a suitable polarimeter tube at $25^{\circ}$ (see-Optieal Rotation-(784)). The observed rotation, in degrees, multiplied by $1.0425 A$, in which $A$ is the ratio 200 divided by the length, in mm, of the polarimeter tube employed, represents the weight, in $\mathrm{g}, \mathrm{of}_{6} \mathrm{H}_{+2} \Theta_{6} \cdot \mathrm{H}_{2} \Theta$ in each 100 mL of Injection tak en: between 4.75 and 5.25 g of $\mathrm{C}_{6} \mathrm{H}_{4} \Theta_{6}-\mathrm{H}_{2} \Theta$ is found.
-(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:
$(100 / 52.9)(198.17 / 180.16) A R$,
in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees: between 4.75 and 5.25 g of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ is found. $\quad$ 2S (USP28)

## Briefing

Clindamycin Injection, USP 27 page 472. It is proposed to revise the Resolution solution in the Assay to include the use of USP Benzyl Alcohol RS. Editorial style changes have also been made.
(PA7b: B. Davani) RTS-41356-1

## Change to read:

USP Reference standards $\langle 11\rangle$ -
-USP Benzyl Alcohol RS.■2S (USP28)
USP Clindamycin Phosphate RS. USP Endotoxin RS.

## Change to read:

## Assay-

Mobile phase-Dissolve 10.54 g of monobasic potassium phosphate in 775 mL of water, and adjust with phosphoric acid to a pH of 2.5. Add 225 mL of acetonitrile, mix, and filter. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ). [NOTE-Ensure that the concentration of acetonitrile in the Mobile phase is not less than $22 \%$ and not more than $25 \%$ in order to retain the correct elution order.]

Standard preparation-Dissolve an accurately weighed quantity of USP Clindamycin Phosphate RS in Mobile phase to obtain a solution having a known concentration of about 0.24 mg per mL .

Assay preparation-Transfer an accurately measured volume of Injection, equivalent to about 300 mg of clindamycin, to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. Transfer 7.0 mL of the resulting solution to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Resolution solution-Prepare a solution of benzylaleohel
-USP Benzyl Alcohol RS $\mathbf{R}^{\text {ns }}$ (USP28)
in Mobile phase to obtain a solution having a concentration of about 0.1 mg per mL . Add about 25 mL of this solution to a $100-\mathrm{mL}$ volumetric flask containing about 25 mg of USP Clindamycin Phosphate RS, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are 1.0 for clindamycin phosphate and about 1.2 for benzyl alcohol; and the resolution, $R$, between clindamycin phosphate and benzyl alcohol is not less than 2.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.5 \%$.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of clindamycin $\left(\mathrm{C}_{18} \mathrm{H}_{33} \mathrm{ClN}_{2} \mathrm{O}_{5} \mathrm{~S}\right)$ in each mL of the Injection taken by the formula:

$$
(10 / 7)(C P / V)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Clindamycin Phosphate RS in the Standard preparation; $P$ is the potency, in $\mu \mathrm{g}$ of $\mathrm{C}_{18} \mathrm{H}_{33} \mathrm{ClN}_{2} \mathrm{O}_{5} \mathrm{~S}$ per mg, of USP Clindamycin Phosphate RS;
$V$ is the volume, in mL , of Injection taken; and $r_{U}$ and $r_{S}$ are the clindamycin phosphate peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Codeine Phosphate, USP 27 page 505, page 3249 of the Second Supplement, and page 1864 of PF 29(6) [Nov.-Dec. 2003]. On the basis of comments received regarding revisions that appeared in the Second Supplement to USP 27, further revisions to the Packaging and storage section are proposed.
(PA2: C. Anthony) RTS-41188-1

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers. -Store $25^{\circ}$, exeursions permitted between $15^{\circ}$ and $30^{\circ} \cdot \mathbf{~} 2 S$ (USP27)

- up to $40^{\circ}$, as permitted by the manufacturer.■2S (USP28)


## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■1S (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Codeine Phosphate RS.

- USP Endotoxin RS.■1S (USP28)


## Add the following:

-Other requirements-Where the label states that Codeine Phosphate is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Codeine Phosphate Injection. Where the label states that Codeine Phosphate must be subjected to further processing during the preparation
of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Codeine Phosphate Injection.■1S (USP28)

## BRIEFING

Cysteine Hydrochloride, USP 27 page 535. It is proposed to make a correction in the text of the Assay.
(HDQ: M. Marques) RTS-41554-1

## Change to read:

Assay-Accurately weigh about 250 mg of Cysteine Hydrochloride into an iodine flask. Add 20 mL of water and 4 g of potassium iodide, and mix to dissolve. Cool the solution in an ice bath, and add 5 mL of 3 N hydrochloric acid and 25.0 mL of 0.1 N iodine VS. Insert the stopper, and allow to stand in the dark for $20 \mathrm{~min}-$ utes. Titrate the excess iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N line
$\mathbf{■}_{\text {Sodium thiosulfate }}{ }_{\square 2 S}$ (USP28)
is equivalent to 15.76 mg of $\mathrm{C}_{3} \mathrm{H}_{7} \mathrm{NO}_{2} \mathrm{~S} \cdot \mathrm{HCl}$.

## BRIEFING

Dalteparin Sodium. Because there is no existing USP monograph for this article, a new monograph is being proposed. The liquid chromatographic procedure for the determination of Molar ratio of sulfate to carboxylate is based on analyses performed on a Dowex 1X8 ( $1.5 \mathrm{~cm} \times 2.5 \mathrm{~cm}$, 200-400 mesh, Fluka) anion exchange column and a Dowex $50 \mathrm{WX} 2\left(\mathrm{H}^{+}\right)(1.5 \mathrm{~cm} \times 7.5 \mathrm{~cm}, 100-$ 200 mesh, Fluka) cation exchange column, in series.
(BBP: R. Tirumalai) RTS-41501-1

■Dalteparin Sodium

[9041-08-1].
» Dalteparin Sodium is the sodium salt of a low-molecular-weight heparin obtained by nitrous acid depolymerization of heparin from pork intestinal mucosa, followed by a chromatographic purification designed to minimize the presence of $\mathrm{N}-\mathrm{NO}$ groups. The majority of the components have a $2-O$-sulfo- $\alpha$-L-idopyranosuronic acid structure at the nonreducing end and a $6-O$-sul-fo-2,5-anhydro-D-mannitol structure at the reducing end of their chains. The weight-average molecular weight of Dalteparin Sodium is 6,000 Da , the range being between $5,600 \mathrm{Da}$ and $6,400 \mathrm{Da}$. The percentage of chains lower than the molecular weight, 3000 Da , is not more than 13.0 percent and the percentage of the chains higher than the molecular weight, 8000 Da , ranges between 15.0 percent and 25 percent. The degree of sulfation is 2.0 to 2.5 per disaccharide unit. The potency is not less than 110 and not more than 210 Anti-Factor $\mathrm{X}_{a}$ International Units of activity per
mg , calculated with reference to the dried substance. The anti-factor $\mathrm{II}_{a}$ activity is not less than 35 International Units and not more than 100 International Units per mg , calculated with reference to the dried substance. The ratio of antifactor $\mathrm{X}_{a}$ activity to anti-factor $\mathrm{II}_{a}$ activity is between 1.9 and 3.2.

Packaging and storage-Preserve in tight, light-resistant containers, and store below $40^{\circ}$, preferably at room temperature.

Labeling-Label it to state the number of Anti-Factor $\mathrm{X}_{a}$ International Units of activity per mg and the number of An-ti-Factor $\mathrm{II}_{a}$ International Units of activity per mg. Label it to state the weight-average molecular weight and the percentage of molecules within the defined molecular weight ranges.

USP Reference standards $\langle 11\rangle$ —USP Dalteparin Sodium RS. USP Endotoxin RS. USP Low-Molecular-Weight Heparin Molecular Weight $R S$.

## Identification-

A: ${ }^{13}$ C NMR spectrum (see Nuclear Magnetic Resonance $\langle 761\rangle$ ).

Standard solution-Dissolve 200 mg of USP Dalteparin Sodium RS in a mixture of 0.2 mL of deuterium oxide and 0.8 mL of water. Add 1 drop of deuterated methanol to serve as an internal reference.

Test solution-Dissolve 200 mg of Dalteparin Sodium in a mixture of 0.2 mL of deuterium oxide and 0.8 mL of water. Add 1 drop of deuterated methanol.

Procedure-Transfer the Standard solution and the Test solution to NMR tubes of $5-\mathrm{mm}$ diameter. Using a pulsed (Fourier transform) NMR spectrometer operating at not less
than 75 MHz for ${ }^{13} \mathrm{C}$, record the ${ }^{13} \mathrm{C}$ NMR spectra of the Standard solution and the Test solution at $40^{\circ}$. The spectra are similar.

B: Molecular weight distribution and weight-average molecular weight (see Chromatography $\langle 621\rangle$ )-

Mobile phase-Prepare a 0.5 M lithium nitrate solution. Pass through a membrane filter having a porosity of 0.45 $\mu \mathrm{m}$ or less, and degas with helium.

Calibration solutions-Prepare two calibration solutions, $A$ and $B$, by dissolving about 2 mg of each of the USP Low-Molecular-Weight Heparin Molecular Weight RS in 1 mL of the Mobile phase. Distribute the molecular weight reference standards in alternating order of magnitude between solutions $A$ and $B$.

Standard solution-Dissolve about 10 mg of USP Dalteparin Sodium RS, accurately weighed, in 1 mL of Mobile phase.
Test solution-Dissolve about 10 mg of Dalteparin Sodium, accurately weighed, in 1 mL of Mobile phase.

Chromatographic system (see Chromatography $\langle 621\rangle$ )— The high performance size exclusion chromatographic system is equipped with a differential refractive index detector, a $6-\mathrm{mm} \times 40-\mathrm{mm}$ guard column, and a $7.8-\mathrm{mm} \times 300-\mathrm{mm}$ analytical column; both analytical and guard columns are prepacked with L20 packing (see Chromatography $\langle 621\rangle$ ). The flow rate is about 0.6 mL per minute, maintained constant to $\pm 0.1 \%$.

Procedure-Separately inject $20 \mu \mathrm{~L}$ of the Calibration solutions $A$ and $B$, record the chromatograms, and measure the retention times. Inject in duplicate, $20 \mu \mathrm{~L}$ of each of the Standard solution and the Test solution, and record the chromatograms for a length of time to ensure complete elution, including salt and solvent peaks. Calculate the total area under each of the Standard solution and Test solution chromatograms, excluding salt and solvent peaks at the end.

Calibration curve-Plot the retention times on the $y$-axis against the peak molecular weights on the $x$-axis for the peaks in the chromatograms of the Calibration solutions $A$ and $B$, and fit the data to a third-order polynomial, using suitable gel permeation chromatography (GPC) software.

Calculations-Compute the data, using the same GPC software, to determine the weight-average molecular weight, $M_{w}$, for each of the duplicate chromatograms of the Standard solution and the Test solution; and take the average for each solution. Correct the mean value of $M_{W}$ to the nearest 50. The Chromatographic system is suitable if $M_{w}$ of USP Dalteparin Sodium RS is within 150 Da of the labeled $M_{W}$ value. The $M_{W}$ for the Test solution is between 5,600 and 6,400 Da . Using the same software, determine for each of the duplicate Test solution chromatograms, the percentage of dalteparin sodium chains with molecular weights lower than $3000 \mathrm{Da}, M_{3000}$; the percentage of dalteparin sodium chains with molecular weights in the range 3000 and 8000 $\mathrm{Da}, M_{3000-8000}$; and the percentage of dalteparin sodium chains with molecular weights greater than 8000 Da , $M_{8000}$. Average the duplicate values and express to the nearest $0.5 \%: M_{3000}$ is not greater than $13.0 \%$, and $M_{8000}$ is between 15.0 \% and 25.0 \%.

C: The ratio of the numerical value of the anti-factor $\mathrm{X}_{a}$ activity, in Anti-Factor $\mathrm{X}_{a}$ International Units per mg, to the numerical value of the anti-factor $\mathrm{II}_{a}$ activity, in Anti-Factor $\mathrm{II}_{a}$ International Units per mg , as determined by the Assay (anti-factor $X_{a}$ activity) and the Anti-factor $I I_{a}$ activity, respectively, is not less than 1.9 and not more than 3.2.

Bacterial endotoxins $\langle 85\rangle$-It contains less than 0.01 Endotoxin International Unit of activity per International Unit of Anti-Factor $X_{a}$ activity.
$\mathbf{p H}\langle 791\rangle$ : between 5.5 and 8.0 of a $1.0 \%$ solution in water.

Loss on drying $\langle 731\rangle$ —Dry 1 g at $60^{\circ}$ over phosphorus pentoxide under a pressure that is not more than 670 Pa for 3 hours: it loses not more than $5.0 \%$ of its weight.

Heavy metals, Method $I\langle 231\rangle$ : not more than 30 ppm .
Nitrogen, Method $I I\langle 461\rangle$ : between 1.5 \% to 2.5 \%, calculated on the dried basis.

Limit of nitrite (see Liquid Chromatography $\langle 621\rangle$ )-
Mobile phase-Prepare a solution containing 13.6 g of sodium acetate in carbon dioxide-free water, adjust with phosphoric acid to a pH of 4.3, and dilute with the same solvent to 1000 mL .

Standard solution A-Dissolve 60.0 mg of sodium nitrite in carbon dioxide-free water and dilute with the same solvent to 1000.0 mL .

Standard solution B-Dilute 1.00 mL of Standard solution $A$ to 50.0 mL with carbon dioxide-free water using a pipette previously rinsed with Standard solution $A$.

Standard solutions $C, D$, and $E-[$ NOTE-Before preparing Standard solutions $C, D$, and $E$, rinse all pipettes with Standard solution B.] Dilute $1.00 \mathrm{~mL}, 3.00 \mathrm{~mL}$, and 5.00 mL of Standard solution B each to 100 mL with carbon di-oxide-free water ( $1 \mathrm{ppm}, 3 \mathrm{ppm}$, and 5 ppm nitrite, respectively).

Test solution-Dissolve 80.0 mg of Dalteparin Sodium in carbon dioxide-free water, and dilute with the same solvent to 10.0 mL . Allow to stand for at least 30 minutes.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with an electrochemical detector containing a working electrode with the potential of +1.00 V against a silver-silver chloride reference electrode, and a detector sensitivity of $0.1 \mu \mathrm{~A}$ full scale. The chromatograph is also equipped with a $4.3-\mathrm{mm} \times$ $12.5-\mathrm{cm}$ column prepacked with styrene-divinylbenzene an-
ion exchange resin. The flow rate is 1.0 mL per minute. Chromatgraph Standard solution D as directed for Procedure: the number of theoretical plates is at least 7000 per meter of the column for the nitrite peak; the tailing factor is not more than 3.0; and the relative standard deviation of the peak area obtained from six injections is not more than 3.0\%. Chromatograph Standard solutions $C$ and $E$ as directed for Procedure: the signal-to-noise ratio for Standard solution $C$ is not less than 5. A blank injection of carbon dioxide-free water does not give rise to false peaks.

Procedure-Inject $100 \mu \mathrm{~L}$ of the Test solution. [NOTEDalteparin sodium may block the binding sites of the stationary phase and cause shorter retention times and lower separation efficiency; the initial performance of the column may be restored using a 58 g per L solution of sodium chloride at a flow rate of 1.0 mL per minute for 1 hour; after regeneration the column is rinsed with 200 to 400 mL of carbon dioxide-free water.]

Calculation-Plot the areas of the nitrite peaks from the chromatograms of the Standard solutions $C, D$, and $E$ against respective concentrations of nitrite. Draw a best-fit regression line through the points. The correlation coefficient is not less than 0.995 . Calculate the concentration of nitrite from the area of the nitrite peak in the chromatogram of the Test solution: not more than 5 ppm of nitrite is found.

## Limit of boron-

Blank solution-Prepare a $1 \%(\mathrm{v} / \mathrm{v})$ solution of nitric acid in water.

Test solution-Dissolve 0.6250 g of Dalteparin Sodium in about 5 mL of the Blank solution, and dilute with the same solvent to 25 mL .

Spiked solution-Add $10 \mu \mathrm{~L}$ of a 5.7 mg per mL solution of boric acid in the Blank solution to 10.0 mL of Test solution, and mix.

Procedure-Boron is determined by measurement of the emission from inductively coupled plasma (ICP) at 249.733 nm . Use an appropriate apparatus whose settings have been optimized as directed by the manufacturer.

Calculation-Calculate the content of boron, in mg per mL of the solution, using the following formula:

$$
\left(Y_{T}-Y_{B}\right) /\left(Y_{S}-Y_{T}\right) \times C / 1000,
$$

in which $Y_{T}, Y_{B}$, and $Y_{S}$ are the responses of the Test solution, Blank solution, and Spiked solution, respectively, at 249.733 nm ; and $C$ is the concentration of boron, in mg per mL , in the boric acid solution spiked. Not more than 1 ppm is found.

Sodium content (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ )-

Cesium chloride stock solution-Prepare a solution of cesium chloride in 0.1 N hydrochloric acid containing 1.27 mg per mL.

Cesium chloride solutions-Dissolve an accurately weighed quantity of sodium chloride in Cesium chloride stock solution to obtain a solution having a concentration of about $0.2 \%$ of sodium. Dilute accurately measured volumes of this solution with Cesium chloride stock solution to obtain solutions having concentrations of $0.0025 \%$, $0.0050 \%$, and $0.0075 \%$ of sodium.

Test solution-Transfer 50.0 mg of Dalteparin Sodium, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Cesium chloride stock solution to volume.

Procedure-Determine the absorbences of the Test solution and Cesium chloride solutions at 330.3 nm using a sodium hollow-cathode lamp as a source of radiation and an air-acetylene flame. The sodium content is between $9.5 \%$ and $12.5 \%$, calculated on the dried basis.

Molar ratio of sulfate to carboxylate (see Chromatography $\langle 621\rangle$ )-

Mobile phase-Use carbon dioxide-free water.
Test solution-Dissolve about 50 mg of Dalteparin Sodium, accurately weighed, in 10 mL of carbon dioxide-free water.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatographic system consists of two peristaltic pumps, a six-port injection valve, an ion detector, and two columns-one $1.5-\times 2.5-\mathrm{cm}$ column packed with L\#\# (see Chromatography $\langle 621\rangle$ ) anion-exchange resin packing and one $1.5-\times 7.5-\mathrm{cm}$ column packed with $\mathrm{L} \# \#$ (see Chromatography $\langle 621\rangle$ ) cation-exchange resin packing. The outlet of the anion-exchange column is connected to the inlet of the cation-exchange column. The flow rate is about 1 mL per minute.

Procedure-[NOTE-Regenerate the anion-exchange column and the cation-exchange column with 1 N sodium hydroxide and 1 N hydrochloric acid, respectively, and equilibrate each with the Mobile phase, between two injections.] Inject the Test solution into the anion-exchange column and collect the eluate from the cation-exchange column in a beaker at the outlet until the ion detector reading returns to the baseline value. Transfer the eluate quantitatively to a titration vessel containing a magnetic stirring bar, and dilute with carbon dioxide-free water as necessary. Position the titration vessel on a magnetic stirrer and immerse the electrodes. Note the initial conductivity reading and titrate with 0.1 N sodium hydroxide in carbon dioxide-free water added in $100 \mu \mathrm{~L}$ portions. Record the burette reading and the conductivity meter reading after each addition of the sodium hydroxide solution.

Calculation-Plot the conductivity measurements on the $y$-axis against the volumes of sodium hydroxide added on the $x$-axis. The graph will have three linear sections-an ini-
tial downward slope, a middle slight rise, and a final rise. For each of these sections draw the best-fit straight lines using linear regression analysis. At the points where the first and second straight lines intersect and where the second and third line intersect, draw perpendiculars to the x -axis to determine the volumes of sodium hydroxide taken up by the sample at those points. The point where the first and second lines intersect corresponds to the volume of sodium hydroxide taken up by the sulfate groups $\left(V_{s}\right)$. The point where the second and third lines intersect gives the volume of sodium hydroxide consumed by the sulfate and the carboxylate groups together $\left(V_{T}\right)$. Calculate the molar ratio of sulfate to carboxylate by the formula:

$$
V_{S} /\left(V_{T}-V_{S}\right)
$$

## Anti-factor II $_{\mathrm{a}}$ activity-

Acetic acid solution, pH 7.4 Polyethylene glycol 6000 buffer, pH 7.4 Buffer, pH 8.4 Buffer, and Antithrombin III solution-Proceed as directed in the Assay (anti-factor $X_{a}$ activity ), except that the concentration of the Antithrombin III solution is 0.5 Antithrombin III Unit per mL.

Thrombin human solution-Reconstitute thrombin human (see Reagents Specifications in the section Reagents, Indicators, and Solutions) in water, and dilute in pH 7.4 Polyethylene glycol 6000 buffer to obtain a solution having a concentration of 5 thrombin Units per mL .

Chromogenic substrate solution-Dissolve D-phenylala-nyl-L-pipecolyl-L-arginine-4-nitroaniline dihydrochloride in water to yield about a 3.0 mM solution. Dilute in pH 8.4 Buffer to 0.5 mM immediately before use.

Standard solutions-Dissolve USP Dalteparin Sodium RS in and dilute with $p H$ 7.4 Buffer to obtain at least four dilutions in the concentration range between 0.015 and 0.075 Anti-Factor $\mathrm{II}_{a}$ International Units of activity per mL.

Test solutions-Proceed as directed under Standard solutions to obtain concentrations of Dalteparin Sodium similar to those obtained for the Standard solutions.

Procedure—Proceed as directed under Assay (anti-factor $X_{a}$ activity), except to use Thrombin human solution instead of Factor $X_{a}$ solution and use the Antithrombin III solution described above.

Calculation-Plot the absorbance values of the Standard solutions and the Test solutions against log concentrations of the dalteparin in mg. Construct separate straight lines of best fit using least-squares linear regression analyses for the Standard solutions and the Test solutions. Determine the slope for each regression line. Calculate the anti-factor $\mathrm{II}_{a}$ activity of Dalteparin Sodium by the formula:

$$
P^{\prime}\left(S^{\prime}{ }_{T} / S_{S}^{\prime}{ }_{S}\right)
$$

in which $P^{\prime}$ is the anti-factor $\mathrm{II}_{a}$ activity of dalteparin, in mg , of USP Dalteparin Sodium RS; and $S^{\prime}{ }_{T}$ and $S^{\prime}{ }_{S}$ are the slopes of the lines from Test solutions and Standard solutions, respectively. Express the anti-factor $\mathrm{II}_{\mathrm{a}}$ activity of Dalteparin Sodium per mg.

## Assay (anti-factor $\mathbf{X}_{a}$ activity)-

Acetic acid solution-Transfer 42 mL of glacial acetic acid to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.
pH 7.4 Polyethylene glycol 6000 buffer—Dissolve 6.08 g of tris(hydroxymethyl)aminomethane and 8.77 g of sodium chloride in 500 mL water. Add 1.0 g of polyethylene glycol 6000 (see Reagents Specifications in the section Reagents, Indicators, and Solutions), and adjust with hydrochloric acid to a pH of 7.4. Dilute with water to 1000 mL .
pH 7.4 Buffer-Dissolve 6.08 g of tris(hydroxy-methyl)aminomethane and 8.77 g of sodium chloride in 500 mL of water. Adjust with hydrochloric acid to a pH of 7.4. Dilute with water to 1000 mL .
pH 8.4 Buffer-Dissolve 3.03 g of tris(hydroxy-methyl)aminomethane, 5.12 g of sodium chloride, and 1.40 g of edetate sodium in 250 mL of water. Adjust with hydrochloric acid to a pH of 8.4. Dilute with water to 500 mL .

Antithrombin III solution-Reconstitute a vial of antithrombin III (see Reagents Specifications in the section Reagents, Indicators, and Solutions) in water to obtain a 5.0 antithrombin III Units per mL solution. Dilute this solution in pH 7.4 Polyethylene glycol 6000 buffer to obtain a solution having a concentration of 1.0 antithrombin III Unit per mL .

Factor $X_{a}$ solution-Reconstitute an accurately weighed quantity of bovine factor $X_{a}$ (see Reagents Specifications in the section Reagents, Indicators, and Solutions) in pH 7.4 Polyethylene glycol 6000 buffer to obtain a solution that gives an increase in absorbance value at 405 nm of 0.15 to 0.20 absorbance units per minute when assayed as described below, but using as an appropriate volume ( $V$, in $\mu \mathrm{L}$ ) of $p H$ 7.4 Buffer instead of $V \mu \mathrm{~L}$ of the dalteparin solution.

Chromogenic substrate solution-Prepare a solution of a suitable chromogenic substrate for amidolytic test (see Reagents Specifications in the section Reagents, Indicators, and Solutions) specific for factor $X_{a}$ in water to obtain a concentration of about 3.0 mM . Dilute this solution with pH 8.4 Buffer to obtain a solution having a concentration of 0.5 mM .

Standard preparations-Dissolve USP Dalteparin Sodium RS in and dilute with $p H$ 7.4 Buffer to obtain four dilutions in the concentration range between 0.025 and 0.2 AntiFactor $X_{a}$ International Units per mL.

Assay preparations-Proceed as directed for Standard preparations to obtain concentrations of Dalteparin Sodium similar to those obtained for the Standard preparations.

Procedure-Label 18 suitable tubes: B1 and B2 for blanks; T1, T2, T3, and T4 (each in duplicate) for the dilutions of the Assay preparations; and S1, S2, S3, and S4
(each in duplicate) for the dilutions of the Standard preparations. [NOTE-Treat the tubes in the order B1, S1, S2, S3, S4, T1, T2, T3, T4, T1, T2, T3, T4, S1, S2, S3, S4, B2.] To each tube add the same volume $V(20$ to $50 \mu \mathrm{~L})$ of $A n$ tithrombin III solution and an equal volume, $V$, of either the blank, pH 7.4 buffer, or an appropriate dilution of the Assay preparations or the Standard preparations. Mix, but do not allow bubbles to form. Incubate at $37^{\circ}$ for 1.0 minute. Add to each tube volume $2 V(40$ to $100 \mu \mathrm{~L})$ of Factor $X_{a}$ solution and incubate for 1.0 minute. Add $5 V(100$ to $250 \mu \mathrm{~L})$ volume of Chromogenic substrate solution. Stop the reaction after 4.0 minutes with $5 V(100$ to $250 \mu \mathrm{~L})$ volume of Acetic acid solution. Measure the absorbance of each solution at 405 nm using a suitable spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) against the blank B1. The reading of the blank B2 is not more than $\pm 0.01$ absorbance units.

Calculation-Plot the absorbance values of the Standard preparations and the Assay preparations against log concentrations of dalteparin in mg. Construct separate straight lines of best fit using least-squares linear regression analyses for the Standard preparations and the Assay preparations. Determine the slope for each regression line. Calculate the potency of Dalteparin Sodium by the formula:

$$
P\left(S_{U} / S_{S}\right),
$$

in which $P$ is potency of dalteparin, in mg, of USP Dalteparin Sodium RS; and $S_{U}$ and $S_{S}$ are the slopes of the lines from Assay preparations and Standard preparations, respectively. Express the anti-factor $\mathrm{X}_{a}$ potency of Dalteparin Sodium per mg. $\mathbf{m}^{2 S}$ (USP28)

## Briefing

Desogestrel and Ethinyl Estradiol Tablets, page 823 of $P F$ 30(3) [May-June 2004]. A correction to the calculation in the amount dissolved is proposed in Test 1 of the Dissolution test.
(BPC: M. Marques) $\quad$ RTS-41560-1

## Add the following:

## Desogestrel and Ethinyl Estradiol Tablets

» Desogestrel and Ethinyl Estradiol Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}\right)$ and ethinyl estradiol $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}\right)$.

Packaging and storage-Preserve in well-closed containers.

Labeling-When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.

USP Reference standards $\langle 11\rangle — U S P$ Desogestrel $R S$. USP Desogestrel Related Compernd B RS. USP Desoges Rel Coll CS. USP Ethinyl Estradiol RS. USP Ethinyl Estradiol Related Compound A RS.

Thin-layer chromatographic identification test $\langle 201\rangle$ -
Adsorbent: octadecylsilanized chromatographic siliea gel mixture.

Fest solution Transfer a quantity of finely ground Tab-
lets, equivalent to about 2.4 mg of desegestrel, to a stop-
pered 10 mL centrifuge tube, add 4.8 mL of acetone, and
shake vigorously for 1 mintute. Centrifuge for 5 minutes, and transfer 2.7 mL of the clear supernatant into a suitable
eentainer, pretected from light. Evaporate to dryness in a hood using nitregen at reom temperature, and dissolve the residue so obtained in 0.45 mL of methylene chloride. 0.25 mL of a mixture of hexanes, methanel, and isepropyl aleehal(90:15:5).

Standard solttions- Prepare-separate-solutions in methy lene chloride, a mixture of hexanes, methanol, and isopropyl alcehol ( $90: 15: 5$ ) to contain about 23 mg of USP Dese gestrel RS per mL and $0.5-0.6 \mathrm{mg}$ of USP Ethinyl Estradiol RS per mL.

Application velume: $110 \mu \mathrm{\mu}$.
Developing solvent system: a mixture of toluene and ethyl acetate (80: 20).

Procedure Proceed as directed in the chapter. Spray the plate with a solution of sulfuric acid in alcohel(1 in -50), and dry at $110^{\circ}$ for 5 to 10 mintutes. Visualize the-spets under long wavelength UV light: ethinyl estradiol and desegestrel exhibit $R_{\perp}$ values of about 0.30 and 0.58 , respectively.

Test solution-Transfer 25 Tablets to a suitable container, add 50 mL of water, and sonicate until the Tablets disintegrate (if necessary, remove any coating with water before sonication). Place the sample in a separatory funnel, add 25 mL of ether, and shake well to extract the actives. Using a glass pipet, transfer the ether layer to a clean beaker, and evaporate to about 10 mL .

Standard solution-Dissolve a quantity of USP Desogestrel RS and USP Ethinyl Estradiol RS in methanol to obtain a solution containing about 0.15 mg per mL and 0.03 mg per mL , respectively.

Application volume: $\quad 30 \mu \mathrm{~L}$.
Developing solvent system: a mixture of chloroform and alcohol (96:4).

Procedure-Proceed as directed in the chapter, and then air-dry. Spray the plate with a mixture of methanol and sulfuric acid (50:50), place in an oven at $105^{\circ}$ for about 5 min utes, and examine the plate: meets the requirements.

## Change to read:

Dissolution $\langle 711\rangle$ —
TEST 1-
Medium: $\quad 0.05 \%$ sodium-latryl-sulfate dodecylsodium sulfate sodium lauryl sulfate with an assay content of not less than $95 \% ; 500 \mathrm{~mL}$.

Apparatus 2: 50 rpm .
Time: 30 minutes.
Determine the amounts of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}\right)$ and ethinyl estradiol $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}\right)$ dissolved by employing the following method.

Piltent, Solution A, Soltion B, and Mobile phase Proceed as directed in the $A$ ssay.

Standard solution- Dissolve aceurately weighed quantities of USP Desogestrel RS and USP Ethinyl Estradiel RS, and dilute quantitatively, and stepwise if necessary, with Pissolution Medium to obtain a solution having knowncen eentrations equivalent to the expected concentrations of the selution under test. [NOTE-A volume of acetonitrile-Diltuent not exceeding $6 \%$ of the final total volume of the Standard solution may be used to dissolve USP Desogestrel RS, and a veltume of a mixture of methanel and water (90:10) Piltent net exceeding $4 \%$ of the fand total volume of the Standard solution may be used to dissolve USP Ethinyl Estradiol RS.] Chrematographic system- Proceed as directed in the $A s$ say. To evaluate the system suitability requirements, use the Standard preparation prepared as directed in the Assaty.

Procedure Separately inject equal volumes (about 200 $\mu \mathrm{L})$ of the Standed solution and a filtered centriftged per tion of the selution under test into the chrematograph, record the chromatograms, and measure the responses for
the major peaks. Caleulate the quantities of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{30} \Theta\right)$ and ethinyl estradiol $\left(\mathrm{C}_{20} \mathrm{H}_{24} \Theta_{2}\right)$ dissolved by eomparisen with the correspending peak respenses obtained
from the Standard solution and the solution under test.
Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 ( $50: 50$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Desogestrel standard stock solution-Dissolve an accurately weighed quantity of USP Desogestrel RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.25 mg per mL .

Ethinyl estradiol standard stock solution-Dissolve an accurately weighed quantity of USP Ethinyl Estradiol RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.25 mg per mL .

Desogestrel diluted standard solution-Transfer 1.0 mL of Desogestrel standard stock solution to a $50-\mathrm{mL}$ volumetric flask. Dilute with Dissolution Medium to volume, and mix. This solution contains about 0.005 mg per mL of USP Desogestrel RS.
Ethinyl estradiol diluted standard solution-Transfer 1.0 mL of Ethinyl estradiol standard stock solution to a $50-\mathrm{mL}$ volumetric flask. Dilute with Dissolution Medium to volume, and mix. This solution contains about 0.005 mg per mL of USP Ethinyl Estradiol RS.

Standard solution-Dilute quantitative portions of Desogestrel diluted standard solution and Ethinyl estradiol diluted standard solution with Dissolution Medium to obtain a solution containing about $0.3 \mu \mathrm{~g}$ per mL and $0.06 \mu \mathrm{~g}$ per mL of USP Desogestrel RS and USP Ethinyl Estradiol RS, respectively.

Test solution-Centrifuge a portion of the dissolution sample, and use the clear supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector (for desogestrel analysis), a spectrofluorometric detector (for ethinyl estradiol analysis) with an excitation wavelength of 285 nm and an emission wavelength of 310 nm ; a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L 11 ; and a $4.6-\mathrm{mm} \times 12.5-\mathrm{mm}$ guard column that also contains packing L11. The flow rate is about 2 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.2 for ethinyl estradiol and 1.0 for desogestrel, and the relative standard deviation is not more than $3.0 \%$.

Procedure-Separately inject equal volumes (about 200 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}$ and $\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}$ dissolved by the formula:

## $(0.05 C)(100 / K)\left(r_{4} \nmid+s\right)$,

$$
\mathbf{\bullet}(0.5 C)(100 / K)\left(r_{U} / r_{S}\right), \mathbf{■}^{2 S}(U S P 28)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Desogestrel RS or USP Ethinyl Estradiol RS in the Standard solution; $K$ is the labeled amount, in mg per Tablet, of $\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}$ or $\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}$; and $r_{U}$ and $r_{s}$ are the peak responses for desogestrel or ethinyl estradiol obtained from the Test solution and the Standard solution, respectively.

Tolerances-Not less than $80 \%(Q)$ of each of the labeled amounts of $\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}$ and $\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}$ is dissolved in 30 minutes.

TEST 2-If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium: $\quad 0.3 \%$ sodium lauryl sulfate; 500 mL .
Apparatus 2: 100 rpm .
Time: 30 minutes.
Determine the amounts of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}\right)$ and ethinyl estradiol $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}\right)$ dissolved by the chromatographic method used in Test 1.

Tolerances-Not less than $80 \%(Q)$ of each of the labeled amounts of $\left(\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}\right)$ and $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}\right)$ is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements for Content Uniformity with respect to desogestrel and to ethinyl estradiol.

Loss on drying $\langle 731\rangle$ —Powder z0-40 40 Tablets, and dry the portion at $105^{\circ}$ for 3 hours: it loses not more than $4.0 \%$ of its weight.

Water, Method Ic $\langle 921\rangle$ : mere than 5.4\%, using 35 me of Tablets her $170^{\circ}$ not more than $5.4 \%$ using a portion of the Tablet containing about 35 mg and a suitable evaporation technique that releases the water by heating the specimen in a stream of dry inert gas, this gas then being passed into the cell.

## Related compounds-

Diluent, Solution A, Solution B, Mobile phase, Desoges trel standard stock solution, and Ethinyl estradiol standard stock solution Prepare as directed in the Assat.

Related compounds standard stock solution-Separately dissolve aceurately weighed quantities of USP Ethinyl Es madiol Related Compound A RS, USP Desogestrel Related Compound B RS, and USP Desogestrel Related Compound GRS in Dildent, and dilute quantitatively, and-stepwise if necessary, with Diluent to obtain a solution having a known eoneentrations of about 0.006 mg per mL, 0.00375 mg per
mL , and 0.00375 mg per mL , respectively. concentration of about $50 \%$ relative to the expected concentration of ethinyl estradiol and desogestrel in the Test solution.

Standatd solution Transfer 5.0 mL of Ethinyl estradiel standurd stock solution and 2.0 mL of Related compeunds standerd stock solution to a $100-\mathrm{ml}$ veltmetric flack, add an accurately measured volume of Desogestrel standard stock solution to obtain a final solution having a concentra tion, in my per mL, correspending to the expected concentration of desogestrel in the Test solution. Dilute with Diltent to volume, and mix. Transfer 2.0 mL of Related eompounds standard stock solution and an accurately measured volume each of Ethimyl estradiol standard stock solthtion and Desogestrel standard stock solution to a 100 mb velumetric flask to obtain a final selution having an ac eurately known concentration in mg per mL , correspending approximately to the expected concentration of desogestrel and ethinyl estradiol in the Test solution. Dilute with Diluent to volume, and mix.

Fest solution Use the Assay preparation.
Chromatographic system- Prepare as directed in the As say. [NOTE The related compernds $A$ and C Ethinyl estradiol related compound $A$ and desogestrel related compennd C are menitored using a wavelength of $230-250 \mathrm{~nm}$, and alt ether compounds are menitered at 210 205 nm.] Chromat egraph the Standard solution, and record the peak respenses as directed for Precedtre: the coltumnefficieney determined from the ethinyl estradiol peak is not less than 2500 theoret ieal plates; the tailing factor for the ethinyl estradiol peak is between 0.9 and 1.5; and the relative standard deviation for replicate injections determined from the desogestrel andethinyl estradiol peaks is net mere than $2.0 \%$, and net mere than $5.0 \%$ determined from the peaks for each related com peund.

Procedtre Separately inject equal volumes (about 25 $200-\mu \mathrm{L})$ of the Standard solution and the Test solution inte the chrematograph, record the chrematograms, and measure the peak heights areas responses for ethinyl estradiol related compeund $A$, desegestrel related compound $B$, and desogestrel related compeund $C$. disfegarding the peak, if any, with a retention time of about 12 minntes. Caleutate the pereentage of ethinyl estradiol related compound $A$ in the per tion of Tablets taken by the formmat:-

$$
4166.6 \mathrm{C}\left(r_{i}, r_{s}\right),
$$

$$
200(C L L)\left(r_{i}++_{s}\right)
$$

in whieh $C$ is the concentration, in mg per mL, Of USP Ethinyl Estradiol Related Compennd $A$ RS in the Standerd sotution; $L$ is the labeled ameunt, in mg, of ethinyl estradiolim each Tablet; andriandrs are the peak heights areas respenses for ethinyl estradiol related compound A obtained from the Test solution and the Standard solution, respectively: net mere than $0.5 \% 2.0 \%$ of ethinylestradiol related compenad $A$ is found. Caleulate the percentages of desogestrel related eompound B and desogestrel related compound $C$ in the pertion of Tablets taken by the formula:

$$
-666.6 \mathrm{C}\left(r_{i}+x_{s}\right)
$$

$$
200(C L)\left(r_{i}+r_{s}\right)
$$

in whieh $C$ is the concentration, in mg per mL, of USP Desegestrel Related Compound B-RS-or USP Desogestrel Re tated Compeund C RS in the-Standard solution; $L$ is the tabeled amount, in mg, of desogestrel in each Tablet; and

Frand s $_{\text {s are the peak heights areas respenses for desegestrel }}$ related compeund $B$ or desogestrel related compound $C$, as appropriate, obtained frem the Test solution and the Standard solution, respectively: not more than $0.5 \%$ each 2.0\% of desegestrel related compennd B is fennd; not more than 3.0\% of desogestrel related compound C is found; and not more than $2.0 \% 5.0 \%$ of total related compounds is found.

Solution A-Prepare a mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 ( $50: 50$ ).

Solution B—Prepare a mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 ( $80: 20$ ).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare a mixture of acetonitrile and water (50:50).

Desogestrel standard stock solution-Dissolve an accurately weighed quantity of USP Desogestrel RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL .
Ethinyl estradiol standard stock solution-Dissolve an accurately weighed quantity of USP Ethinyl Estradiol RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL .

Standard solution-Dilute quantitative portions of Desogestrel standard stock solution and Ethinyl estradiol standard stock solution with Diluent to obtain a solution containing about $0.6 \mu \mathrm{~g}$ per mL and $0.12 \mu \mathrm{~g}$ per mL of USP Desogestrel RS and USP Ethinyl Estradiol RS, respectively.

Test solution 1-Transfer 20 Tablets to a $200-\mathrm{mL}$ volumetric flask. Add about 120 mL of Diluent, and shake for about 30 minutes. Dilute with Diluent to volume, and mix. Centrifuge a portion of the dissolution sample, and use the clear supernatant.

Test solution 2-Dilute a portion of Test solution 1 with Diluent to obtain a solution containing about $0.6 \mu \mathrm{~g}$ per mL of ethinyl estradiol.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a programmable variable wavelength UV detector and a spectrofluorometric detector with an excitation wavelength of 285 nm and an emission wavelength of 310 nm ; a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L11; and a $4.6-\mathrm{mm} \times 12.5$ mm guard column that also contains packing L11. The chromatograph is programmed as follows.

| Time (minutes) | Solution A (\%) | Solution B <br> (\%) | Elution | $\begin{aligned} & \text { UV Detector } \\ & (\mathrm{nm}) \\ & \hline \end{aligned}$ | Flow Rate (mL/min.) |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 0 | 100 | 0 | equilibration | 210 | 2 |
| 0-4 | 100 | 0 | isocratic | 210 | 2 |
| 4-10 | 100 | 0 | isocratic | 244 | 2 |
| 10-20 | 100 | 0 | isocratic | 210 | 2 |
| 20-25 | 0 | 100 | linear gradient | 210 | 2.5 |
| 25-30 | 0 | 100 | isocratic | 210 | 3 |
| 30-32 | 100 | 0 | linear gradient | 210 | 2 |
| 32-35 | 100 | 0 | re-equilibration | 210 | 2 |

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are 0.18 for ethinyl estradiol and 1.0 for desogestrel; the resolution, $R$, between ethinyl estradiol and desogestrel is not less than 2.0; the tailing factor is not more than 2.0 for ethinyl estradiol and desogestrel; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Inject a volume (about $200 \mu \mathrm{~L}$ ) of Test solution 2 into the chromatograph, record the chromatograms, and measure the peak heights for the major peaks obtained within 20 minutes. Calculate the percentage of $17 \beta$-ethinyl estradiol in the portion of Tablets taken by the formula:

$$
100\left(r_{U} / r_{S}\right)
$$

in which $r_{U}$ is the height of any peak at a relative retention time of 0.20 ; and $r_{s}$ is the peak height of ethinyl estradiol obtained with the spectrofluorometric detector. Inject a volume (about $200 \mu \mathrm{~L}$ ) of Test solution 1 into the chromatograph, record the chromatograms, and measure the peak heights for the major peaks obtained within 20 minutes. Calculate the percentage of estrone in the portion of Tablets taken by the formula:

$$
100\left(r_{U} / r_{s}\right)-E
$$

in which $r_{U}$ is the height of any peak at a relative retention time of 0.20 ; $r_{s}$ is the peak height of ethinyl estradiol obtained with the UV detector at 210 nm ; and $E$ is the percent-
age of $17 \beta$-ethinyl estradiol obtained in the Tablets. Calculate the percentage of 3-ketodesogestrel in the portion of Tablets taken by the formula:

$$
100(1 / F)\left(r_{U} / r_{s}\right)
$$

in which $r_{U}$ is the height of any peak at a relative retention time of 0.32 obtained with the UV detector at $244 \mathrm{~nm} ; r_{s}$ is the peak height of desogestrel obtained with the UV detector at 210 nm ; and $F$ is the relative response factor, equal to 4.1. Calculate the percentage of any other impurity taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the height of any peak other than those mentioned above; and $r_{s}$ is the peak height of ethinyl estradiol obtained with the UV detector. Any peak below $0.1 \%$ is not considered. Not more than $0.5 \%$ of ethinyl estradiol impurities is found; not more than $0.5 \%$ of desogestrel impurities is found; and not more than $2.0 \%$ of total impurities is found.

Assay-
Biltent Prepare a mixttre of acetonitrile methanol and Water ( $4: 1$ ). ( $60: 40$ ).

## Solution A Use acenitrile.

Solution $B$ - Prepare a filtered and degassed mixture of acetonitrile and water ( $1: 1$ ).
Mobile phase Use variable mixtures of Solution 4 and Solution B as directed for Chromatographic system. Make adjustments if neeessary (see System Suitability under Chromatography (624)).

Desogestrel standert stock solution-Dissolve an ac etrately weighed quantity of USP Desogestrel RS in Dilt ent methanol to obtain a solution having a known eoncentran of 0.250 .35 mg per mL .

Ethinyl estradiol standard stock solution-Dissolve an accurately weighed quantity of USP Ethinyl Estradial RS in Diltent methanel to obtain a selution having a known eoncentration of about 0.250 .21 mg per mL .

Standard preparation Transfer 5.0 mL of Ethinyl estrat diol standed stock solution to a 100 mL volumetric flask, and add an aceurately measured volume of Desogestrel standerd stock solution to obtain a solution having a known eencentration, in mg per mL , correspending to the expected evneentration of desogestrel in the Assay preparation. Ditete with Diltent to voltme, and mix. Transfer an aceurately measured volume each of Ethinyl estradiol standard stock solution and Desogestrel standerd stoek solution to a 100 ml voltmetric flask to obtain a final solution having an acetrately known concentration in mg per mL , correspending approximately to the expected concentration of desogestrel and ethinyl estradiol in the Assay preparation. Dilute with Biltent to voltume, and mix.

Assay preparation Transfer 101410 Tabletstoa $30-\mathrm{mL}$ 50 mL stoppered centrifuge tube, add $20.0-30 \mathrm{~mL}$ of Dilt ent, and sonicate for 25 mintutes with intermittent mixing on a vortex mixer, until all Tablets have broken apart. Extract for 30 minutes on a benchtop shaker. Centrifuge, and use the elear supernatant. [NOTE-Retain a pertion of this solutionto use as the Test solution in the test for Related eompeatats.]

Chrematographic system (see-Chrematography $\langle 621\rangle$ The liquid-chromatograph-is equipped with either a programmable variable wavelength detector or two separate detectors capable of menitering at $210-205$ nm and at 230250 230 mm and a $4.6 \mathrm{~mm} \times 15-\mathrm{cm} 25-\mathrm{cm}$ coltumn that contains stable bonded $5 \mu \mathrm{~m}$ packing L 1 . The flow rate is about 21.5 mL per mintte, and the eoltmm temperature is maintained at 40. The ehremategraph is programmed as follows.

| Time (minutes) | Solution-4 $(\%)$ | Solution $B$ $(\%)$ | Elution |
| :---: | :---: | :---: | :---: |
| 0-4.5 | $\theta$ | 100 | isecratic |
| $\theta-12.0$ |  |  |  |
| 4.5-4.6 | $\theta \rightarrow 10 \theta$ | $\xrightarrow{+0} \rightarrow$ | linear gradient |
| 12.0-12.4 |  |  |  |
| $4.6-10.7$ | 100 | $\theta$ | isperatic |
| 12.125 .0 |  |  |  |
| 10.7-10.8 | $\xrightarrow{100 \rightarrow 0}$ | $\theta \rightarrow 100$ | linear gradient |
| 25.0-25.4 |  |  |  |
| 25.1-30.0 | $\theta$ | 100 | isocratic |

Chromatograph the Standard preparation, and record the peak respenses as directed for Procedure: the columm effe eieney determined from the ethinyl estradiol peak is not less than 2500 theoretical plates; the tailing factor for the ethinyl estradiol peak is between 0.9 and 1.5 ; and the relative stan dard deviation for repliente injections is net more than $2.0 \%$ $1.5 \%$, determined from the desogestrel and ethinyl estradiol peaks.

Proedure Separately inject equal volumes (about 25 $\mu \mathrm{L})$ of the Standard preparation and the - sisay preparation into the chrematograph, record the chrematograms, and measure the peak areas at $210-205 \mathrm{~nm}$. Separately caleulate the amounts, in $\mu \mathrm{g}$, of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{39} \Theta\right)$ and ethinylesmadiel $\left(\mathrm{C}_{20} H_{24} \Theta_{2}\right)$ in the pertion of Tablets taken by the for mula:-

$$
\left( \pm G_{s}+G_{\downarrow}\right)\left(F_{L}++_{s}\right),
$$

in whieh $L$ is the labeled quantity, in $\mu \mathrm{g}$, of the relevant ant Hyte in each Tablet; $G_{s}$ is the concentration, in $\mu \mathrm{g}$ per mL , of the apprepriate-USP Reference-Standard in the-Standard preparation; $G_{\&}$-is the concentration, in $\mu \mathrm{g}$ per mL , of the eerrespending analyte in the Assay preparation, based on
the labeled quantity per Tablet and the extent of dilution; and $r_{5}$-and $\Psi_{s}$ are the peak responses areas obtained from the Assay preparation and the Standard preparation, respectively.

Mobile phase_Prepare a filtered and degassed mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 (50:50). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare a mixture of acetonitrile and water (50:50).

Desogestrel standard stock solution-Dissolve an accurately weighed quantity of USP Desogestrel RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL .

Ethinyl estradiol standard stock solution-Dissolve an accurately weighed quantity of USP Ethinyl Estradiol RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL .

Standard preparation-Dilute appropriate aliquots of Desogestrel standard stock solution and Ethinyl estradiol standard stock solution with Diluent to obtain a solution having a known concentration of about $0.6 \mu \mathrm{~g}$ per mL and $0.12 \mu \mathrm{~g}$ per mL of USP Desogestrel RS and USP Ethinyl Estradiol RS, respectively.

Assay preparation-Transfer 20 Tablets into a 200-mL volumetric flask. Add about 120 mL of Diluent, and shake for about 30 minutes. Dilute with Diluent to volume, and mix. Centrifuge a portion of the sample, and transfer an accurately measured volume to a $50-\mathrm{mL}$ volumetric flask to obtain a final concentration of about $0.6 \mu \mathrm{~g}$ per mL of desogestrel. Dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector (for desogestrel analysis), a spectrofluorometric detector (for ethinyl estradiol analysis) with an excitation wavelength of 285 nm and an emission wavelength of 310 nm ; a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L11; and a $4.6-\mathrm{mm} \times 12.5-\mathrm{mm}$ guard column that also contains packing L11. The flow rate is about 2 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.2 for ethinyl estradiol and 1.0 for desogestrel; the tailing factor for both analytes is not more than 2.0 ; and the relative standard deviation is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 200
$\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of desogestrel $\left(\mathrm{C}_{22} \mathrm{H}_{30} \mathrm{O}\right)$ and ethinyl estradiol $\left(\mathrm{C}_{20} \mathrm{H}_{24} \mathrm{O}_{2}\right)$ in the portion of Tablets taken by the formula:

$$
(500 C / V)\left(r_{U} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Desogestrel RS or USP Ethinyl Estradiol RS in the Standard preparation; $V$ is the volume of the aliquot of solution taken ses for desogestrel or ethinyl estradiol obtained from the $A s$ say preparation and the Standard preparation, respectively.■1S (USP28)

## Briefing

Dextroamphetamine Sulfate Elixir, USP 27 page 577. It is proposed to delete this monograph from the $U S P$ because there is no marketed product for this dosage form.
(PA3: S. Salado) RTS-41478-1

## Delete the following:

## Dextroamphetamine-Stlfate-Elixir

## (Current title-not to change untildume 1, 2005)

Alonograph title-change-to-become-officialdume-1, 2005 See-Dextroamphetamine-Sulfate-Oral-Solution
\#-Dextroamphetamine Sulfate Elixir contains, in each 100 mL , net less tham 90.0 mg and net mere than 110.0 me of $\left(\mathrm{C}_{2} \mathrm{H}_{13} \mathrm{~N}\right)_{2} \cdot \cdot \mathrm{H}_{2} \mathrm{SO}_{4}$ -

Packaging and-storage Preserve in tight, light resistant containers.
USP Reference standards- $\langle 14\rangle$ _ USP Dextroamphetamine Sul fate RS.
Identifieation Transfer 25 mL of Elixir to a 250 mL separator, ade 25 mL of water and 5 mL of 2.5 N sodium hydroxide, mix, and extract with 60 mL of ether. Wash the ether extract with ww 5 mL pertions of 0.25 N sedium hydroxide, and diseard the washings. Filter the ether extract threugh a pledget of entton, previously saturated with ether, into a $100-\mathrm{mL}$ beaker, and evaporate-on a steam bath in a current of air to about 1 mL . Dissolve the residue in 3 mL of aleohol, and transfer to a gilass-stoppered, 125 mL coniealflask containimg 25 mL of water. Rinse the beaker with 3 mL of aleohel, and transfer to the flask. Cool to about $15^{\circ}$, add 3 mL of 1 Nsoditam hydroxide, then add 1 mL of a mixtureof 1 volume of benzoyl ehtoride and 2 volumes of anhydreus ethyl ether, and shake for 2 minutes. Filter the precipitate, wash with about 15 mL of cold water, and reerystallize twiee from diluted alcohol: the benzoylderivative of dextroamphetamine so obtained, after be ing dried at $105^{\circ}$ for 1 heur, melts between $154^{\circ}$ and $160^{\circ}$.
Aleohelcontent $\langle 614\rangle$ : between $9.0 \%$ and $11.0 \%$ of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.
Isomeric purity Transfer 150 mL of Elixir to a 500 mL separa tor, add 15 mL Of 2.5 N sodium hydroxide, andextract with 0 ne 60 mL and -40 mL pertiens ofether. Wash the cembined etherex tracts with 010 mL pertions of 0.25 N sodium hydrexide. Wash the aqueeus alkaline extracts with 20 mL of ether, adding the ether washing to the combined ether extracts. Filter the ether extracts through a pledget of cotton, previously saturated with ether, inte a 250 mL beaker, rinse the cotton with a small amount of ether, and evaperate on a steam bath im a current of air to about 2 mL . Dissolve the residue-in 20 mL of chloroform, and transfer to a separator containing 35 mL of 0.1 N sulfuric acid. Complete the transfer with two additienal 20 mL pertiens of chloroferm. Shake the-separater vigereusly for 1 minute, allow the layers to separate, and discard the ehloroform. Adeto the liquid in the separator 2.5 s of sodium bicarbenate, preventing it frem coming in contact with the mouth of the separater, and swirl until mest of the bicarbenate has dissolved. By means of a 1 mL syringe, rapidly inject 1.0 mL
of acetic anhydride directly into the contents of the separator. Immediately insert the stopper in the separator, and shake vigorously until the evolution of earben dioxide has ceased, releasing the pressure as neeessary through the stopeock. Allow to stand for 5 min utes, and extract the solution with 50 mL of chleroform, shaking vigoreusly for 1 minute. Filter the chloroform extact through a pledget of flter cotten into a 100 mL beaker, rimse the cotton with a small amount of ehloreform, and evaporate on a steam bath in a eurrent of air or nitrogen to dryness. Heat and triturate the residue until the oder of chloreform is no longer pereeptible. Allow the residut to cool, induring it to erystallize. Reduce the erystats to a fine powder, heat at $80^{\circ}$ for 30 minttes, and cool: the specific retation of the ace lamphetamine so obtained, determined in a so lation in chloreform containing 20 mg per mL, a 200 mm semimi ero polarimeter tube being used, is between- $37.5^{\circ}$ and $44.0^{\circ}$.

## Assay -

Chromatographic edumn Proeed as direeted for Coltman Partition Chromatography under Chromatography $\langle 621$ ), packing achromatographic tube with a mix ture of 2 gof Solid Support and 1 mL of 0.06 N hydrochleric acid.

Standardpreparation Dissolve an aecurately weighed quantity of USP Dextrommphetamine-Sulfate $R$ S in 1.8 N sulfuric acid (previously saturated with chloreform), and dilute quantitatively and stepwise with the same solvent to obtain a solution having a known encentration of about 0.5 mg per mL .

Assay preparation Pipet 5 mL of Elixir into a 100 mL beaker, add 1 drop of 3 N hydrechloric acid, and swinl to mix. Add 6 g of puriffed siliceous anth, and mix with a glass rod until a fluffy mix fare is obtained.

Procedtre- Transfer the Assay preparation to the-Chromato graphic oluma, and complete the preparation of the columa. Wash the prepared column with 100 mL of chloreform that previeusly has been saturated with water, and diseard the washing. Arrange to collect the eluate in a separator containing 10.0 mL of 1.8 N sul furie acid that previously has been saturated with chloroform. Pass through the coltmmn 60 mL of a freshly prepared ammeniacal chlo reform solution, made by shaking 50 velumes of chloreform with 4 volume of ammenium hylroxide for 1 to 2 minutes and discarding the queeus phase. Complete the elution with 60 mL of chloroform (previously saturated with water). Shake the separator vigoreusly for 1 minute, allow the layers to separate, and diseard the chloroform. Coneomitantly determine the abserbances of the Standard preparation and the Assay preparation in 1 cm cells at 280 nm and at the maximum at about 257 nm , with a suitable-spectrophetometer, using 1.8 N sulftric acid (previously saturated with chloroform) as the blank. Caleulate the quantity, in me, of $\left(\mathrm{G}_{2} \mathrm{H}_{4} \mathrm{~N}_{2}\right)_{2} \cdot \mathrm{H}_{3} \mathrm{SO}_{4}$ in the pertion of Elixir taken by the formula:

$$
10 C\left(A_{2 s 7}-A_{200}\right)_{l}+\left(A_{2 s 7}-A_{200}\right)_{s}
$$

in which $C$ is the ene phetamine-Sulfate RS in the-Standard preparation; and the paren thetic expressions are the differences in the absorbanees of the two solutions at the wavelengths indicated by the subseripts, for the $A s$ say preptration (U) and the Stand preparaion (S), respective-サ-W2S (USP28)

## Briefing

Dextroamphetamine Sulfate Oral Solution, USP 27 page 578. See briefing under Dextroamphetamine Sulfate Elixir.
(PA3: S. Salado)
RTS-41478-1

## Delete the following:

## ■Dextroamphetamine Sulfate Oral Solution

(AHonograph under this new-title-to-become-official dume-1, 2005)
(Current monegraph title-is Dextreamphetamine-Sulfate-Elixir)
\#-Dextroamphetamine Sulfate Oral Solution contains, in each 100 mL , not less than- 90.0 mg and not more than 110.0 mg of dextroamphetamine sulfate $\left[\left(\mathrm{G}_{2} \mathrm{H}_{43} \mathrm{~N}\right)_{2}-\mathrm{H}_{2} \mathrm{~S}_{4}\right\}$.

Paekaging and-storage- Preserve in tight, light resistant conminers.
USP Referenee-standards- $\langle 4\rangle$ - USP Dextant fate RS.
Identifiention_Transfer 25 mL of Oral Solution to - 250 mL separator, add 25 mL of water and 5 mL of 2.5 N soditm hydrox ide, mix, and extract with 60 mL of ether. Wash the ether extract with wo- 5 mL pertions of 0.25 N sodium hydroxide, and diseard the washings. Filter the ether extract through a pledget of cetten, previously sattrated with ether, into a 100 ml beaker, andevape rateon a steam bath in acemrent of air to about 1 mL . Dissolve the residue in 3 mL of aleohol, and transfer to a glass stoppered, 125 mL conieal flack eon aining 25 mL of water. Pinse the benker with 3 mL of aleohol, and transfer to the flack. Cool to about $15^{\circ}$, add 3 mL of 1 N sodium hydroxide, then add 1 mL of a mixture of 1 vol ume of benzoyl chloride and 2 volumes of anhydrous ethyl ether, and shake for 2 minutes. Filter the precipitate, wash with about 15 mL of cold water, and recrystallize twiee from diluted aleohel: the benzoyl derivative of dextroamphetmine so obtained, after being dried at $105^{\circ}$ for 1 heur, melts between $154^{\circ}$ and $160^{\circ}$.
Aleohol content $\langle 614\rangle$ :- between $9.0 \%$ and $11.0 \%$ of $\mathrm{C}_{2} \mathrm{H}_{5} \Theta H$.
Isomerie purity Transfer 150 mL of Oral Solution to a 500 mL separater, add 15 mL of 2.5 N soditm hydroxide, andeetract with ene 60 mL and two -40 mL pertions of ether. Wash the combined ether extracts with two 10 mL portions of 0.25 N sodium hydrox ide. Wash the aqueeus alkaline extracts with 20 mL of ether, add ing the ether washing to the combined ether extracts. Filler the ether extracts hrough a pledget of eotton, previously sattrated with ether, into a 250 mL beaker, rinse the cotten with a small a momnt of ether, and evaporate on a steam bath in actirent of air to about 2 mL . Dissolve the residue in 20 mL of chloroform, and transfer to a-separator containing 35 mL of 0.1 N sulfuric acid. Gomplete the transfer with two additional $20-\mathrm{mL}$ portions of ehloreform. Shake the separator vigoreusly for 1 minute, allow the lay ers to separate, and diseard the chloreform. Add to the liquid in the separator 2.5 g of sodium bieabenate, preventing it from coming
in contact with the mouth of the separator, and swirl until most of the biearbenate has dissolved. By means of a 1 mL syringe, rapidly inject 1.0 mL of acetic mhydride directly into the contents of the separator. Immediately insent the stopper in the separator, and shake vigerously until the volution of carben dioxide has eeased, releasing the pressure as neeessary through the stopeock. Allow to stand for 5 minutes, and extract the solution with 50 mL of ehlo reform, shaking vigorously for 1 minute. Pass the chloroformer tract through a pledget of filter cotton into a 100 mL beaker, rinse the cotton with a small amount of chloroform, and evaporate on a steam bath in a current of air or nitrogen to drymess. Heat and trit trate the residue until the odor of chloreform is no lenger pereep tible. Allow the residue to eool, induring it to crystallize. Reduee the erystals to a fine powder, heat at $80^{\circ}$ for 30 mintuter, and cool: the specific rotation of the ace ylamphetamine so obtained, deter mined in a solution in chloroform eontaining 20 mg per mL, a 200 mm semimiere polarimeter tube being used, is between $37.5^{\circ}$ and $-44.0^{\circ}$.

## Assay

Chromatographic olumn Proeed as direeted for Coltman
 achromatographic tube with a mix of 2 g of Solid Suppert and 1 mL of 0.06 N hydrechloric acid.

Standardpreparation Dissolve an aceurately weighedquantity ef USP Dextreamphetamine Sulfate $R S$ in $1.8 N$ sulfuric acid (previously saturated with chloroform), and dilute quantitatively and stepwise with the same solvent obtain a solution having a known eoneentration of about 0.5 mg per mL .

Assay preparation Pipet 5 mL of Oral Solation inte a 100 mL beaker, add 1 drop of 3 N hydrochloric acid, and swirl to mix. Add 6 of purified silieeous enth, andmix with a glass roduntila fluffy mixture is obtained.

Procedure Transfer the Assay preparation to the Chromatographic columa, and complete the preparation of the column. Wash the prepared columa with 100 mL of chloroform that previously has been sattrated with water, and diseard the washing. Arrange to collee the eltate in a separator containing 10.0 mL of 1.8 N sut furie acid that previously has been saturated with ehloreform. Pass through the coltumm 60 mL of a freshly prepared ammeniacal chloroform solution, made by shaking 50 volumes of chloroform with 4 volume of ammonium hydroxide for 1 to 2 minutes and disearding the aqueous phase. Complete the elution with 60 mL of chloreform (previously saturated with water). Shake the separater vigoreusly for 1 minute, allow the layers to separate, and diseard the chloreform. Coneomitantly determine the abserbances of the Standard preparation and the Assay preparation in 1 cm cells at 280 mm and at the maximum at about 257 nm , with a suitable-spectrophetometer, using 1.8 N sulfaric acid (previously saturated with chloroform) as the blank. Calculate the quantity, in me, of dextreamphetamine sulfate $\left[\left(\mathrm{G}_{4} \mathrm{H}_{43} \mathrm{~N}\right)_{2}-\mathrm{H}_{2} \mathrm{~S}_{4}\right.$ \} in the pertion of $\theta$ ral Solution taken by the formula:-

$$
10 C\left(A_{257}-A_{280}\right)_{6}+\left(A_{257}-A_{280}\right)_{5}
$$

in which $C$ is the eoneentration, in mg per mL, of USP Dextroamphetamine Sulfate RS in the Standard preparation; and the paren thetic expressions are the differences in the absorbances of the two solutions at the wavelengths indieated by the subseripts, for the $-4 s$ say preparation (U) and the Standard preparation (S),respectively.
(Official June 1, 2005)
$\square 2$ (USP28)

Dextrose Injection, USP 27 page 582-See briefing under Alcohol in Dextrose Injection.
(PA1: K. Russo) RTS-41401-3

## Change to read:

Assay-Transfer an accurately measured volume of Injection, containing 2 to 5 g of dextrose, to a $100-\mathrm{mL}$ volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. Determine the angular rotation in a suitable polarimeter tube at $25^{\circ}$ (see-9ptical Rotation- 784 )). The observed retation, in degrees, multiplied by 1.0425 , in which $A$ is the ratio 200 divided by the length, in mm, of the polarimeter tube employed, represents the weight, in $\frac{8}{5}$, of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{\theta}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the voltme of Injection taken.
-(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:

$$
(100 / 52.9)(198.17 / 180.16) A R
$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees. $\quad$ 2S (USP28)

BRIEFING

Dextrose and Sodium Chloride Injection, USP 27 page 582See briefing under Alcohol in Dextrose Injection.
(PA1: K. Russo) RTS-41401-2

## Change to read:

Assay for dextrose-Transfer an accurately measured volume of Injection, containing from 2 to 5 g of dextrose, to a $100-\mathrm{mL}$ volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. Determine the angular rotation in a suitable polarimeter tube at $25^{\circ}(\sec -9 p t i c h l$ Rotion $\langle 784\rangle)$. The ob served rotation, in degrees, multiplied by 1.04254 , in which $A$ is the ratio 200 divided by the length, in mm, of the polarimeter tube employed, represents the weight, in of, of $\mathrm{G}_{6} \mathrm{H}_{42} \Theta_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the wh ume of Injection taken.
-(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:

$$
(100 / 52.9)(198.17 / 180.16) A R
$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees. $\quad$ 2S (USP28)

BRIEFING

Dobutamine in Dextrose Injection, USP 27 page 652—See briefing under Alcohol in Dextrose Injection.
(PA5: A. Wilk) RTS-41401-18

## Change to read:

Assay for dextrose-Determine the angular rotation of Injection
 eulate the quantity, in mg, of $\mathrm{C}_{6} \mathrm{H}_{42} \mathrm{O}_{6} \cdot \mathrm{H}_{3} \mathrm{O}$ - in each mL of the In jection taken by the formula:-

$$
1000 a l(47.96)
$$

in which $a$ is the observed retation in degrees; $l$ is the length, indm, of the pelarimeter tube; and 47.96 is the specifie rotation of der trese monohydrate.
-(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:

$$
(100 / 52.9)(198.17 / 180.16) A R,
$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees. $\quad$ 2S (USP28)

## BRIEFING

Dopamine Hydrochloride and Dextrose Injection, USP 27 page 661-See briefing under Alcohol in Dextrose Injection.
(PA5: A. Wilk) RTS-41401-19

## Change to read:

Assay for dextrose-Transfer an accurately measured volume of Injection, containing 2 to 5 g of dextrose, to a $100-\mathrm{mL}$ volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. Determine the angular rotation in a suitable polarimeter tube at $25^{\circ}$ (see-Optical Ron-(784)). Theobserved retation, in degrees, multiplied by 1.04254 , in which $A$ is the ratio 200 divided by the length, in mm, of the pelarimeter tube-em ployed, represents the weight, in si, $\mathrm{of}_{6} \mathrm{H}_{42} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the volume of Injection taken.
-(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:
$(100 / 52.9)(198.17 / 180.16) A R$,
in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm; and $R$ is the observed rotation, in degrees.■2S (USP28)

## Briefing

Multiple Electrolytes and Dextrose Injection Type 1, USP 27 page 690 and page 838 of $P F$ 30(3) [May-June 2004]—See briefing under Alcohol in Dextrose Injection.
(PA1: K. Russo) RTS-41401-5

## Change to read:

» Multiple Electrolytes and Dextrose Injection Type 1 is a sterile solution of Dextrose and suitable salts in Water for Injection to provide sodium, potassium, magnesium, and chloride ions. In addition, the salts may

■1S (USP28)
provide ions of acetate, or acetate and gluconate, or acetate and phosphate, or phosphate and lactate, or phosphate and sulfate. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of sodium $(\mathrm{Na})$, potassium $(\mathrm{K})$, magnesium $(\mathrm{Mg})$, acetate $\left(\mathrm{C}_{2} \mathrm{H}_{3} \mathrm{O}_{2}\right)$, gluconate $\left(\mathrm{C}_{6} \mathrm{H}_{11} \mathrm{O}_{7}\right)$, phosphate $\left(\mathrm{PO}_{4}\right)$, lactate $\left(\mathrm{C}_{3} \mathrm{H}_{5} \mathrm{O}_{3}\right)$, and sulfate $\left(\mathrm{SO}_{4}\right)$, not less than 90.0 percent and not more than 120.0 percent of the labeled amount of chloride ( Cl ), and not less than 90.0 percent and not more than 105.0 percent of the labeled amount of dextrose $\left(\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}\right)$. It may contain Hydrochloric Acid or Sodium Hydroxide used to adjust the pH . It contains no antimicrobial agents.
divided by the length, in mm, of the pelarimeter tube employed, represents the weight, in of, of dextrose monohydrate $\left(\mathrm{C}_{6} \mathrm{H}_{42} \Theta_{6} \cdot \mathrm{H}_{2} \mathrm{O}\right)$ in the volume of Injection taken.
-(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:
(100/52.9)(198.17/180.16)AR,
in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm; and $R$ is the observed rotation, in degrees. $\quad$ 2S (USP28)

## BRIEFING

Etidronate Disodium, USP 27 page 769; Etidronate Disodium Tablets, USP 27 page 770. It is proposed to replace the current titration procedure in the test for Limit of phosphite with a high performance ion chromatography method that provides an upgrade in technology, with an increase in sensitivity, selectivity, and accuracy as compared with the current $U S P$ method. This liquid chromatographic procedure is based on analyses performed with the Dionex IonPac AS11 brand of L46 column and Dionex IonPac AG11 brand of Lxx guard column. The typical retention times for the phosphite and phosphate peaks are about 4 and 6 minutes, respectively.

It is also proposed to replace the current titration Assay with a new high performance ion chromatography method that eliminates the use of radioactive thorium nitrate and provides an upgrade in technology. The liquid chromatographic procedure in the Assay is based on analyses performed with Waters IC-Pak Anion HC brand of L23 column. The typical retention time for etidronate peak is about 3 minutes.
(PA4: E. Gonikberg) RTS-40992-1

## Change to read:

Assay for dextrose-Transfer an accurately measured volume of Injection, containing 2 to 5 g of dextrose, to a $100-\mathrm{mL}$ volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. Determine the angular rotation in a polarimeter tube at $25^{\circ}$ (see-Optical Rotan (784)). The observed reta tion, in degrees, multiplied by 1.0425 , in which $A$ is the ratio 200

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Etidronate Disodium RS.

- USP Etidronate Disodium Related Compound A


## $R S$. nen $_{\text {(USP28) }}$

USP Etidronic Acid Monohydrate RS.

## Change to read:

Limit of phosphite-
Buffer solution- Dissolve 6.9 g of monobasie sodium phosphate in 500 mL of water, add 400 mL of 0.1 N sodimm hydroxide, and mix.

Fest preparation Transfer about 3.5 g of Etidronate Disodium, aceurately weighed, to a glass stoppered, 250 mL conieal flask, and dissolve in 70 mL of water.

Procedure Add 20 mL of Buffer solution to the Test prepara tion, and adjust with sodium hydroxide solution (25 in 100), using a pH meter, to a pH of $7.3 \pm 0.2$. Add 20 mL of iodine TS in di vided portions, with mixing, and insert the stopper securely in the flask. [NOTE If mere tham half of the iodine TS is absorbed (deeolerized) by the pertion of Etidrenate Disodium taken, discard the mixture, and use a Test preparation containing a smaller quantity ef Etidrenate Disodium. Allow to stand for 3 hours protected from light, and adjust with 6 N acetic acid to a pH-of $4.5 \pm 0.2$. Titrate with 0.1 N sodium thiosulfate VS. When the iodine color beeomes pale, add 2 mL of stareh TS, and continue the titration until the blue evlor is diseharged. Perform a blank determination (see Titrimetry $\langle 544\rangle$, and make any neeessary correction. Caleulate the pereent age of phosphite in the pertion of Etidrenate Disodimm taken by the formula:-

$$
0.520 Y / H=
$$

in which $V$ is the volume, in mL, of titrant constmed, and Wis the weight, in g , of Etidronate Disodimm taken: not more than $1.0 \%$ is found.

■Solution $A$-Prepare an aqueous solution containing 0.65 mg per mL of anhydrous sodium carbonate and 0.40 mg per mL of sodium bicarbonate.

Solution B-Prepare an aqueous solution containing 4.68 mg per mL of anhydrous sodium carbonate and 2.89 mg per mL of sodium bicarbonate.

Mobile phase—Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Dissolve suitable quantities of USP Etidronate Disodium Related Compound A RS and dibasic sodium phosphate in Solution $A$ to obtain a solution having a known concentration of 0.027 mg of sodium phosphite di-
basic pentahydrate and 0.015 mg of dibasic sodium phosphate in each mL. [NOTE-Etidronate Disodium Related compound A is sodium phosphite dibasic pentahydrate.]

Suppressor regenerant solution-Use 12.5 mM sulfuric acid.

Test solution-Transfer approximately 50 mg of Etidronate Disodium, accurately weighed, to a suitable flask. Dissolve in 10.0 mL of Solution $A$.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a conductivity detector, a $4-\mathrm{mm} \times 25-\mathrm{cm}$ column and a $4-\mathrm{mm} \times 50-$ mm guard column that contain packing L46 and a $4-\mathrm{mm}$ anion self-regenerating suppressor. The flow rate is about 1.0 mL per minute for the Mobile phase and 3 to 5 mL per minute for the Suppressor regenerant solution. The chromatograph is programmed as follows:

| Time | Solution A | Solution B |  |
| :---: | :---: | :---: | :--- |
| (minutes) | $(\%)$ | $(\%)$ | Elution |
| $0-6.0$ | 100 | 0 | isocratic |
| $6.0-6.1$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| $6.1-8.0$ | 0 | 100 | isocratic |
| $8.0-8.1$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $8.1-15$ | 100 | 0 | isocratic |

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the elution order is phosphite, followed by phosphate; the resolution, $R$, between the peaks due to phosphite and those due to phosphate is not less than 2.5 ; and the relative standard deviation for replicate injections is not more than $10 \%$ for each peak.

Procedure—Separately inject equal volumes (about 20 $\mu \mathrm{L})$ of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the
responses for the phosphite peaks. Calculate the percentage of phosphite, determined as monobasic sodium phosphite, in the portion of Etidronate Disodium taken by the formula:

$$
1000(103.98 / 216.06)(C / W)\left(r_{U} / r_{S}\right)
$$

in which 103.98 and 216.06 are the molecular weights of sodium phosphite monobasic pentahydrate and sodium phosphite dibasic pentahydrate, respectively; $C$ is the concentration, in mg per mL, of USP Etidronate Disodium Related Compound A RS in the Standard solution; $W$ is the weight, in mg , of the Etidronate Disodium taken to prepare the Test solution; and $r_{U}$ and $r_{s}$ are the phosphite peak responses obtained from the Test solution and the Standard solution, respectively: not more than $1.0 \%$ of phosphite, determined as monobasic sodium phosphite, is found. $\mathbf{2 S}$ (USP28)

## Change to read:

## Assay-

Fitrant Transfer 6.9 of therimm nitrate, aceurately weighed, a 1000 mL beaker, and dissolve in 25 mL of 1 N nitric acid. Dis solve 4.7 g of $(1,2$ cycloherylenedinitrilo)tetrancetic acid in 41 mL of 1 N sodium hydroxide, and transfer to the 1000 mL benker. Add about 600 mL of water, and adjust with methenamine to a pH of between 5.0 and 5.5. Transfer to a 1000 mb volumetric flask, dilute with water to volume, and mix. Allow to stand for 1 week be fore use. This solution is about 0.0125 M in thoritum eyclohexylenedinitrilotetrancetic acid complex. Each mL is equiv alent to approximately 1.5 mg of $\mathrm{C}_{3} \mathrm{H}_{6} \mathrm{Na}_{2} \mathrm{O}_{7} \mathrm{P}_{3}$ :

Standedrd preparation-Transfer 180 mg of USP Etidrenic Acid Monohydrate PS to a 100 mL volumetric flask, dissolve in 50 mL of water, add 16 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix.

Assely preparation Transfer about 400 mg of Etidrenate Diso dium, aceurately weighed, to a 200 mL volumetric flask, dissolve in 100 mL of water, dilute with water to volume, and mix.

Procedure Pipet 15 mL each of the Standard preparation and the Assay preparation into separate 100 mL beakers. To each bea ker add 20 mL of water, 1 mL of $a 0.1 \%$ solution of xylenol orange, and 2 mL of methenamine solution ( 20 in 100), and mix. Adjust with 0.1 N nitric acid to apHof $6.50 \pm 0.05$. Coneomitantly titrate the resulting solutions to a reddlish violet endpeint. Caleulate the quantity, in me, of $\mathrm{C}_{3} \mathrm{H}_{6} \mathrm{Na}_{2} \mathrm{O}_{7} \mathrm{P}_{2}$ in the pertion of Etidrenate Dise dium taken by the formma:-

$$
z(249.99 / 224.05) H_{s}\left(V_{s}+V_{s}\right)
$$

in whieh 249.99 and 224.05 are the molecular weights of etidre nate disodium and etidronic acid monohydrate, respectively, $\Pi_{s}$ is the weight, in mg, of USP Etidronic Acid Monohydrate RS tak en, and $Y_{t}$ and $Y_{s}$ sare the volumes, in mb, of Titrant consumed by the Assaly preparation and the Standurd preparation, respectively.

- Mobile phase—Prepare a 35 mM to 40 mM ammonium nitrate solution in water, and adjust with dilute ammonium hydroxide to a pH of 7.0.

Standard preparation-Dissolve an accurately weighed quantity of USP Etidronic Acid Monohydrate RS in a mixture of 1 mL of 1 N sodium hydroxide solution and 150 mL of Mobile phase, to obtain a solution having a known concentration of between 0.73 and 0.75 mg of etidronic acid monohydrate per mL.

Assay preparation-Transfer between 42.0 and 43.0 mg of Etidronate Disodium, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with Mobile phase to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a refractive index detector and a $4.6-\times 150-\mathrm{mm}$ column that contains packing L23. The column and the detector temperature are maintained at $32^{\circ}$. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $\mathrm{C}_{2} \mathrm{H}_{6} \mathrm{Na}_{2} \mathrm{O}_{7} \mathrm{P}_{2}$ in the portion of Etidronate Disodium taken by the formula:

$$
100(250.00 / 224.05)\left(C_{S} / C_{U}\right)\left(r_{U} / r_{S}\right)
$$

in which 250.00 and 224.05 are the molecular weights of etidronate disodium and etidronic acid monohydrate, respectively; $C_{S}$ is the concentration, in mg per mL , of USP Etidronic Acid Monohydrate RS in the Standard preparation; $C_{U}$ is the concentration, in mg per mL , of Etidronate

Disodium in the Assay preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP28)

## BRIEFING

Etidronate Disodium Tablets, USP 27 page 770. See briefing under Etidronate Disodium. The liquid chromatographic procedure in the Dissolution test and in the Assay is based on analyses performed with Waters IC-Pak Anion HC brand of L23 column. The typical retention time for etidronate peak is about 3 minutes.
(PA4: E. Gonikberg) RTS-40992-2; 40992-3

## Change to read:

## Dissolution $\langle 711\rangle$ -

Medium: water; 900 mL .
Apparatus 1: 100 rpm .
Time: 30 minutes.
Proedtre Determine the amount of $\mathrm{C}_{2} \mathrm{H}_{6} \mathrm{Na}_{2} \mathrm{O}_{7} \mathrm{P}_{2}$-dissolved, employing the proeedure set forth in the Asisty making any neeessary volumetric adjustments.
-Determine the amount of $\mathrm{C}_{2} \mathrm{H}_{6} \mathrm{Na}_{2} \mathrm{O}_{7} \mathrm{P}_{2}$ dissolved by employing the following method.
Mobile phase and Chromatographic system-Proceed as directed in the Assay for Etidronate Disodium.

## Standard solution-

 FOR PRODUCTS LABELED TO CONTAIN 200 MG OF ETIDRONATE DISODIUM-Transfer approximately 20 mg of USP Etidronic Acid Monohydrate RS to a $100-\mathrm{mL}$ volumetric flask, dissolve in 50 mL of water, add 2.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix.FOR PRODUCTS LABELED TO CONTAIN 400 MG OF ETIDRO-
NATE DISODIUM-Transfer approximately 20 mg of USP Etidronic Acid Monohydrate RS to a $50-\mathrm{mL}$ volumetric flask, dissolve in 25 mL of water, add 2.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix.

Test solution-Transfer a portion of the solution under test to an HPLC vial.

Procedure-Separately inject equal volumes (about 100 $\mu \mathrm{L}$ for products labeled to contain 200 mg of Etidronate Disodium, and about $50 \mu \mathrm{~L}$ for products labeled to contain 400 mg of Etidronate Disodium) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantities of $\mathrm{C}_{2} \mathrm{H}_{6} \mathrm{Na}_{2} \mathrm{O}_{7} \mathrm{P}_{2}$ dissolved, employing the procedure set forth in the Assay, making any necessary volumetric adjustments. ²S $_{\text {2S }}$ (USP28)
Tolerances-Not less than $70 \%$ ( $Q$ ) of the labeled amount of $\mathrm{C}_{2} \mathrm{H}_{6} \mathrm{Na}_{2} \mathrm{O}_{7} \mathrm{P}_{2}$ is dissolved in 30 minutes.

## Change to read:

## Assay-

Titrant and Standed preparation- Prepare as directed in the $-4 s$ say under Etidronate Disodium.
Assay preparation Weigh and finely powder not less than 20 fablets. Transfer an aceurately weighed portion of the powder, equivalent to about 200 me of etidrenate disoditm, to a 100 mL volumetric flask, and dilute with water to volume. Stir on a mag netic stirrer for about 10 minutes, and filter.
Procedure Proceed as directed for Procedure in the Assay under Etidrat Dis dium. Caleulate the quantity, in me, of $\mathrm{G}_{2} \mathrm{H}_{6} \mathrm{Na}_{2} \mathrm{O}_{7} \mathrm{P}_{2}$ in the pertion of Tablets taken by the formula:

$$
200\left(H_{4}+H_{s}\right),
$$

in which $Y_{t}$ and $Y_{s}$ are the volumes, in mL, of Titrant consumed by the Assaty preparation and the Standurd preparation, respectively.

- Mobile phase, Standard preparation, and Chromatographic system-Proceed as directed in the Assay under Etidronate Disodium.

Assay preparation-Weigh and finely powder not fewer than 20 tablets. Transfer an accurately weighed portion of the powder, equivalent to 160 to 170 mg of Etidronate Disodium, to a $200-\mathrm{mL}$ volumetric flask, and dilute with Mo bile phase to volume. Agitate the solution for at least 5 minutes, and pass through a $0.45-\mu \mathrm{m}$ nylon filter.

Procedure-Proceed as directed for Procedure in the $A s$ say under Etidronate Disodium. Calculate the quantity, in mg , of etidronate disodium $\left(\mathrm{C}_{2} \mathrm{H}_{6} \mathrm{Na}_{2} \mathrm{O}_{7} \mathrm{P}_{2}\right)$ in the portion of Tablets taken by the formula:

$$
C_{S} V_{U}(250.00 / 224.05)\left(r_{U} / r_{S}\right)
$$

in which 250.00 and 224.05 are the molecular weights of etidronate disodium and etidronic acid monohydrate, respectively; $C_{S}$ is the concentration, in mg per mL , of USP Etidronic Acid Monohydrate RS in the Standard preparation; $V_{U}$ is the volume, in mL , of the Assay preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP28)

## Briefing

Finasteride Tablets, USP 27 page 795. It is proposed to revise the Dissolution section to include separate tests for products labeled as $5-\mathrm{mg}$ Tablets and for products labeled as $1-\mathrm{mg}$ Tablets. The chromatographic procedure in the Dissolution test for products labeled as 1-mg Tablets was developed using a Zorbax SB-Phenyl brand of L11 column.
(BPC: M. Marques) RTS—41002-1; 41588-1

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: water; 900 mL
Apparatus 2: 50 rpm .
${ }^{\boldsymbol{■}} \mathrm{FOR}$ PRODUCTS LABELED AS 5-MG TABLETS: ${ }^{\text {2S }}$ (USP28)

## Time: 45 minutes.

Determine the amount of $\mathrm{C}_{23} \mathrm{H}_{36} \mathrm{~N}_{2} \mathrm{O}_{2}$ dissolved by employing the following method.

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and water ( $29: 21$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluting solution-Prepare a solution of acetonitrile and water (7:3).

Standard solution-Dissolve an accurately weighed quantity of USP Finasteride RS in Diluting solution, and dilute quantitatively, and stepwise if necessary, with Diluting solution to obtain a solution having a known concentration approximately equivalent to the sample under test.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 5-\mathrm{cm}$ column that contains packing L1. The column temperature is maintained at $45^{\circ}$. The flow rate is about 2 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the capacity factor $\left(k^{\prime}\right)$ is not less than 2.0; the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than 2.0\%.

Procedure-Separately inject equal volumes (about $200 \mu \mathrm{~L}$ ) of the solution under test and the Standard solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity of $\mathrm{C}_{23} \mathrm{H}_{36} \mathrm{~N}_{2} \mathrm{O}_{2}$ dissolved.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{23} \mathrm{H}_{36} \mathrm{~N}_{2} \mathrm{O}_{2}$ is dissolved in 45 minutes.

■ FOR PRODUCTS LABELED AS $1-M G ~ T A B L E T S: ~_{\text {P }}$
Time: 30 minutes.
Mobile phase-Prepare a degassed mixture of acetonitrile and water (11:9). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Diluting solution-Prepare a solution of water and acetonitrile (7:3).
Standard solution-Dissolve an accurately weighed quantity of USP Finasteride RS in Diluting solution, to obtain a solution having a known concentration of 0.1 mg per mL . Dilute this solution quantitatively, and stepwise if necessary, in $0.5 \%$ sodium lauryl sulfate to yield a solution containing 0.001 mg of finasteride per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L11. The column temperature is maintained at $45^{\circ}$. The flow rate is about 1.5 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 100 $\mu \mathrm{L}$ ) of the solution under test and the Standard solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity of finasteride $\left(\mathrm{C}_{23} \mathrm{H}_{36} \mathrm{~N}_{2} \mathrm{O}_{2}\right)$ dissolved.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{23} \mathrm{H}_{36} \mathrm{~N}_{2} \mathrm{O}_{2}$ is dissolved in 30 minutes. $\mathbf{m}^{2 S}$ (USP28)

## BRIEFING

Flucytosine, USP 27 page 798. Editorial revisions are proposed for the test for Fluorouracil to be consistent with USP style.
(PA7b: B. Davani) RTS-41389-1

## Change to read:

Fluorouracil-Dissolve 250 mg in 10 mL of a mixture of glacial acetic acid and water (8:2).
$\boldsymbol{m}_{(4: 1)} \cdot \boldsymbol{m}_{2 S}$ (USP28)
Apply $20 \mu \mathrm{~L}$ of this solution to a thin-layer chromatographic plate (see Chromatography $\langle 621\rangle$ ) coated with a $0.5-\mathrm{mm}$ layer of chromatographic silica gel mixture. To the same plate apply $20 \mu \mathrm{~L}$, in $10-\mu \mathrm{L}$ increments, of a + in 40,000
$\bullet_{0.025} \mathrm{mg}$ per $\mathrm{mL}_{\text {■ } 2 \text { (USP28) }}$
solution of USP Fluorouracil RS in a mixture of glacial acetic acid and water ( $4: 1$ ). Develop the chromatogram in a mixture of chloroform and glacial acetic acid (13:7) until the solvent front has moved not less than 14 cm from the origin. Remove the plate from the developing chamber, and allow the solvent to evaporate. Locate the spots on the plate by observing under short-wavelength UV radiation: any spot from the solution under test is not greater in size and intensity than the spot at the respective $R_{F}$ produced by the Standard solution, corresponding to not more than $0.1 \%$ of fluorouracil.

## BRIEFING

Fludarabine Phosphate, USP 27 page 800. It is proposed to revise the test for Chloride to reflect the procedure provided in the original proposal submitted by the manufacturer. The calculation of the formula in the Assay is also corrected.
(PA6: L. Evans) RTS-41590-1

## Change to read:

Chloride-not mere than 0.2\%
■Standard chloride solution-Transfer 82.4 mg of sodium chloride to a $100-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with water to volume. Transfer 1.0 mL of this solution to a $10-\mathrm{mL}$ volumetric flask, and dilute with water to volume. Transfer 2.0 mL of this solution to a test tube, add 13.0 mL of water, and mix.

Test solution-Transfer about 50.0 mg of fludarabine phosphate, accurately weighed, to a test tube, dissolve in 15 mL of water, and heat gently if necessary.

Procedure—Add 1.0 mL of nitric acid to the Standard chloride solution and the Test solution, and place each in separate colorless test tubes, containing 1.0 mL of silver nitrate TS. The Test solution shows less turbidity than the Standard chloride solution ( $0.2 \%$ ).■2S (USP28)

## Change to read:

## Assay-

Mobile phase-Prepare a mixture of filtered, degassed $10-\mathrm{mM}$ monobasic potassium phosphate and methanol ( $47: 3$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Fludarabine Phosphate RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, in Mobile phase to obtain a solution having a known concentration of 0.02 mg per mL .

Assay preparation-Transfer 50 mg of Fludarabine Phosphate, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix. Transfer 5.0 mL of the solution to a $250-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system-The liquid chromatograph is equipped with a $260-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column containing $5-\mu \mathrm{m}$ packing L1. The flow rate is 1.0 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the fludarabine phosphate peak. Calculate the quantity, in mg , of $\mathrm{C}_{10} \mathrm{H}_{13} \mathrm{FN}_{5} \mathrm{O}_{7} \mathrm{P}$ in the portion of Fludarabine Phosphate taken by the formula:

$$
\begin{gathered}
500 C\left(r_{t}+r_{s}\right), \\
-2500 C\left(r_{U} / r_{S}\right), \llbracket 2 S(U S P 28)
\end{gathered}
$$

in which $C$ is the concentration, in mg per mL , of USP Fludarabine Phosphate in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses for fludarabine in the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Fluvoxamine Maleate Tablets, page 1243 of PF 30(4) [JulyAug. 2004]. It is proposed to add a Dissolution test to this new monograph.
(BPC: M. Marques) RTS-40316-6

## Add the following:

## ■Fluvoxamine Maleate Tablets

» Fluvoxamine Maleate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fluvoxamine maleate $\left(\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right)$.

Packaging and storage-Preserve in tight containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Fluvoxamine Maleate $R S$.

Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Dissolution $\langle 711\rangle$ -
Medium: water; 900 mL , degassed.
Apparatus 2: 50 rpm .
Time: 30 minutes.
Procedure-Determine the amount of fluvoxamine maleate $\left(\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right)$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 246 nm on portions of the solution under test centrifuged at 2000 rpm for 10 minutes, suitably diluted with Me dium, if necessary, in comparison with a Standard solution having a known concentration of USP Fluvoxamine Maleate RS in the same Medium.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$ is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Related compounds-

Buffer solution, Mobile phase, Resolution solution, and Chromatographic system-Proceed as directed in the Assay.

Identification solution-Dissolve a quantity of maleic acid in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a concentration of about 0.35 mg per mL .
Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay stock preparation, prepared as directed in the Assay.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution, the Test solution, and the Identification solution into the chromatograph, record the chro-
matograms, and measure the responses for the major peaks. Calculate the percentage of impurities in the portion of Tablets taken by the formula:

$$
100(C / D) F\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Fluvoxamine Maleate RS in the Standard solution; $D$ is the expected concentration, in mg per mL , of fluvoxamine maleate
taking into account the labeled amount and the amount of sample taken to prepare the Test solution; $F$ is the response factor of each impurity as given in Table 1; $r_{i}$ is the individual peak area of each impurity in the Test solution; and $r_{s}$ is the peak area of fluvoxamine maleate in the Standard solution. The limits of impurities are specified in Table 1. [NOTE--Disregard any peak due to maleic acid or to the reagent blank.]

Table 1

| Compound name | Relative retention time | Response <br> Factor | Limit \% |
| :---: | :---: | :---: | :---: |
| Maleic acid | about 0.19 | - | - |
| 5-Methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(E)-O-[2-[(2-succinyl)amino]ethyl]oxime | about 0.50 | 1.0 | 0.8 |
| 5-Methoxy-4'-(trifluoromethyl)valerophenone ( $E$ )- $O$ -(2-aminoethyl)aminoethyl oxime maleate | about 0.67 | 1.4 | 0.2 |
| $Z$-isomer | about 0.79 | 1.0 | 0.5 |
| Fluvoxamine | 1.0 | - | - |
| 4'-(Trifluoromethyl)valerophenone (E)-O-2-(2-amino ethyl)aminoethyl oxime maleate | about 1.18 | 1.0 | 0.2 |
| (E)-O-2-(2-Aminoethyl)-4-(trifluoromethyl)- $\alpha$-phenylacetophenone oxime maleate | about 1.74 | 1.0 | 0.2 |
| 4'-(Trifluoromethyl)valerophenone( $E$ )-O-(2-aminoethyl) oxime maleate | about 2.00 | 1.0 | 0.2 |
| 5-Methoxy-4'-(trifluoromethyl)valerophenone oxime | about 3.45 | 0.6 | 0.2 |
| 5-Methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(E)-O-(2-aminoethyl] oxime maleic acid monoamide | about 4.3 | 1.0 | 0.2 |
| 5-Methoxy-4'-(trifluoromethyl)valerophenone ketone | about 4.2 | 0.3 | 0.2 |
| Unknown impurities | - | 1.0 | 0.1 |
| Total | - | - | 1.8 |

## Assay-

Buffer solution-Dissolve approximately 5 g of 1-pentanesulfonic acid sodium salt and 0.7 g of monobasic potassium phosphate in 620 mL of water. Adjust with phosphoric acid to a pH of $3.00 \pm 0.05$.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $62: 38$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Resolution solution-Transfer approximately 6 mg of fluvoxamine maleate to a $50-\mathrm{mL}$ volumetric flask. Heat the sample at $120^{\circ}$ for 10 minutes. Cool down to room temperature, and add 3.0 mL of 0.1 N hydrochloric acid. Heat the solution in a water bath for 10 minutes. Cool down to room temperature, add 50 mg of fluvoxamine maleate, and dissolve in 25 mL Mobile phase. Dilute with Mobile phase to volume, and mix.

Standard preparation-Dissolve an accurately weighed quantity of USP Fluvoxamine Maleate RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.05 mg per mL .

Assay stock preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg of fluvoxamine maleate, to a $500-\mathrm{mL}$ volumetric flask, add about 250 mL of Mobile phase, sonicate for about 15 minutes, shake by mechanical means for about 15 minutes, dilute with Mobile phase to volume, and mix. Centrifuge a portion of this solution for 10 minutes.

Assay preparation-Transfer 5.0 mL of the supernatant from the Assay stock preparation to a $100-\mathrm{mL}$ volumetric flask. Pass a portion of this solution through a filter having a $45-\mu \mathrm{m}$ or finer porosity, and use the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $234-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L7. The flow rate is about 1.7 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.19 for maleic acid, 0.5 for 5-methoxy-1-[4-(trifluoromethyl)phe-nyl]-1-pentanone-(E)-O-[2-[(2-succinyl)amino]ethyl]oxime, 0.79 for the $Z$-isomer, and 1.0 for fluvoxamine maleate; and the resolution, $R$, between the $Z$-isomer and fluvoxamine maleate is not less than 2.0 and not less that 5.0 between 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone- $(E)-O-[2-[(2$-succinyl)amino]ethyl]oxime and the $Z$-isomer. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the fluvoxamine maleate peaks. Calculate the quantity, in mg , of fluvoxamine maleate $\left(\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{~F}_{3} \mathrm{~N}_{2} \mathrm{O}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right)$ in the portion of Tablets taken by the formula:

$$
10,000 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Fluvoxamine Maleate RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively. $\quad$ 2S (USP28)

Briefing

Glucagon, USP 27 page 869, page 3260 of the Second Supplement, and page 1894 of $P F 29(6)$ [Nov.--Dec. 2003]. It is proposed to allow for the Assay to be repeated if the test fails to meet the confidence interval requirements. In the absence of any significant adverse comment, it is proposed to implement this revision via the First Interim Revision Announcement pertaining to USP 28-NF 23, with an official date of February 1, 2005.
(BNT: L. Callahan) RTS-41447-1

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■1S (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle — U S P$ Dextrose $R S$.

- USP Endotoxin RS.■1S (USP28)

USP Glucagon RS.

## Add the following:

-Other requirements-Where the label states that Glucagon is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Glucagon for Injection. Where the label states that Glucagon must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Glucagon for Injection.■1S (USP28)

## Change to read:

Assay-[NOTE-All buffers have a final pH of 7.4, unless otherwise indicated.]

HEPATOCYTE PREPARATION-
Calcium-free perfusion buffer with dextrose-Prepare a solution containing, in each L, 7.92 g of sodium chloride, 0.35 g of potassium chloride, 1.80 g of dextrose, 0.19 g of edetic acid, and 2.38 g of $N$-2-hydroxyethylpiperazine- $N$ '2-ethanesulfonic acid. Oxygenate prior to circulation.

Collagenase buffer-Prepare a solution containing, in each L, 3.62 g of sodium chloride, 23.83 g of N -2-hydroxyethylpipera-zine- $N^{\prime}$-2-ethanesulfonic acid, 0.35 g of potassium chloride, 0.52 g of calcium chloride, and 1.8 g of dextrose. Adjust to a pH
of 7.6, and oxygenate. Immediately before perfusion, dissolve a quantity of collagenase in this solution to obtain a concentration of $0.02 \%$ to $0.05 \%$.
Wash buffer-Prepare a solution containing, in each L, 7.92 g of sodium chloride, 0.35 g of potassium chloride, 0.19 g of edetic acid, 2.38 g of $N-2$-hydroxyethylpiperazine- $N^{\prime}-2$-ethanesulfonic acid, 0.22 g of calcium chloride, and 0.12 g of magnesium sulfate.

Incubation buffer-Prepare a solution containing, in each L, 6.19 g of sodium chloride, 0.35 g of potassium chloride, 0.22 g of calcium chloride, 0.12 g of magnesium sulfate, 0.16 g of monobasic potassium phosphate, 11.915 g of N -2-hydroxyethylpipera-zine- $N^{\prime}-2$-ethanesulfonic acid, and $1 \%$ bovine serum albumin. Adjust to a pH of 7.5 .

Test animals-Male Sprague-Dawley rats are maintained on a standard rat chow diet and freely given water. On the morning of the test, select a healthy rat weighing approximately 300 g , and administer 100 Units of Heparin Sodium subcutaneously.

Procedure-[NOTE-Conduct this procedure in the morning to ensure that the rat has optimal glycogen in its liver.] Anesthetize the rat with an appropriate anesthetic. Open the abdominal cavity, and isolate the portal vein. Insert an angiocatheter connected to a perfusion pump, and tie into the portal vein at the general location of the lienal branch. Start the perfusion ( 25 mL per minute) in situ with Calcium-free perfusion buffer with dextrose, equilibrated with oxygen, at a temperature of $37^{\circ}$. As the liver enlarges, cut the inferior vena cava to allow pressure equilibrium. [NOTE-About 300 mL of the perfusate is needed to clear the liver of red blood cells at a flow rate of 30 to 60 mL per minute.] Then circulate Collagenase buffer at a flow rate of 30 to 60 mL per minute for about $10 \mathrm{~min}-$ utes. The exact concentration of collagenase (within the range of $0.02 \%$ to $0.05 \%$ ) is determined empirically for each lot of enzyme. The concentration of collagenase is that necessary to consistently cause a breakdown of the liver about 10 minutes after initial entry of the Collagenase buffer into the liver. When the liver significantly increases in size, changes color and consistency, and starts to leak perfusate out of the lobes, change the system to the oxygenated prewarmed Wash buffer. About 100 mL of Wash buffer is needed to wash the liver of collagenase at a flow rate of 25 mL per minute. Surgically remove the liver from the animal and place in a prewarmed tray containing oxygenated Wash buffer $\left(37^{\circ}\right)$. Gently comb the liver with a stainless steel, fine-toothed comb to free the hepatocytes. Wash the hepatocytes with Wash buffer, and filter through cheesecloth (or a 150- $\mu \mathrm{m}$ mesh polyethylene net) into a plastic beaker. Centrifuge the cell suspension for about 2 minutes at about $25 \times g$ to form a loosely packed pellet. Discard the supernatant, and resuspend the pellet in Wash buffer. Repeat the washing procedure twice for a total of three washes. Resuspend the final pellet in 100 to 200 mL of Incubation buffer, depending on cell yield. [NOTE-If the Assay procedure is interrupted, cool the cells by collecting the cells in a beaker placed in ice. The cells are washed with ice-cold Wash buffer, and stored on ice until ready for use. At that point the cells are pelleted once more, and resuspended in ice-cold Incubation buffer.]

Suitability-The concentrations of cells may vary due to the collagenase activity and the viability of the hepatocytes. To check cell viability and to determine viable cell concentration, dilute duplicate $100-\mu \mathrm{L}$ aliquots of cell suspension with $400 \mu \mathrm{~L}$ of Wash buffer and $500 \mu \mathrm{~L}$ of isotonic $0.4 \%$ trypan blue. The aliquots are counted in a hemocytometer. The cells are suspended in Incubation buffer to obtain a viable cell concentration of not less than $3 \times 10^{6}$ per mL . Count several distinct fields. [NOTE-Viable cells are those cells that exclude the trypan blue.]

NEGATIVE CONTROL SOLUTION-Prepare a solution containing $0.5 \%$ bis(trimethylsilyl)acetamide (BSA) in sterile water.

INCUBATION FLASKS-Use $25-\mathrm{mL}$ conical flasks, the bottoms of which have been heated and pushed inward to form a conically raised center.
STANDARD PREPARATIONS_-In duplicate, dissolve a suitable quantity of USP Glucagon RS, accurately measured, in 0.01 N hydrochloric acid or other suitable diluent to obtain a solution containing 1.0 USP Glucagon Unit per mL.■2S (USP27) All dilutions
thereafter are made using $0.5 \%$ BSA (w/v) in water. Accurately dilute measured volumes of each solution with Negative control solution to obtain five concentrations-200, 100, 50, 25, and 12.5 micro-Units per mL - of each solution (Standard preparations). Pipet 0.2 mL of each Standard preparation into separate Incubation flasks. Pipet 0.2 mL of Negative control solution into each of two flasks (Negative control solutions 1 and 2). Then add the hepatocytes into each of the 12 flasks.

ASSAY PREPARATIONS-_Using accurately weighed quantities of Glucagon, proceed as directed for Standard preparations.

D-GLUCOSE DETERMINATION-
Standard stock solution-Transfer 2.0 g of USP Dextrose RS, accurately weighed, to a $200-\mathrm{mL}$ volumetric flask; and dissolve in and dilute with saturated benzoic
$\bullet{ }^{\text {acid }}{ }_{\bullet}$
solution to volume.
Standard solutions-Transfer suitable quantities of Standard stock solution to three flasks, and dilute with saturated benzoic acid solution to obtain solutions having known concentrations of 0.5 , 1.0 , and 1.5 times the typical sample glucose concentration.

Potassium ferrocyanide solution-Dissolve 1.25 g of trihydrate potassium ferrocyanide in 125 mL of Sterile Water for Injection. System suitability—Analyze the Potassium ferrocyanide solution, the Standard solutions, and five replicates of the middle Standard solution. Prepare a standard curve using the Standard solutions as directed for Procedure: the relative standard deviation of the standard curve is not more than $2.0 \%$; the response of the Potassium ferrocyanide solution is not more than 30 mg per L; and the relative standard deviation is not more than $2.0 \%$ for the replicate analyses of the middle Standard solution.

PROCEDURE-Dispense 5 mL of Hepatocyte preparation into the special incubation flasks in sequence from high glucagon concentration to low glucagon concentration, alternating the Standard preparations with the Assay preparations. The flasks are swirled in an orbiting water bath at 125 rpm at $30^{\circ}$ for approximately 30 to 60 minutes. [NOTE-The exact incubation time must be determined to optimize the signal-to-noise ratio.] Following incubation, place 0.5 - to $1.0-\mathrm{mL}$ aliquots, in duplicate, from each incubation flask into labeled tubes, and centrifuge at $12,500 \times g$. Determine the percentage of glucose concentration in each flask's supernatant.

To conform to the linear range of the instrument being used, it may be necessary to adjust by dilution each of the preparations. Use a glucose analyzer that has demonstrated appropriate specificity, accuracy, precision, and linear response over the range of concentrations being determined. [NOTE-A suitable analyzer may use an immobilized, oxidase-enzyme membrane or jacket-generating hydrogen peroxide, which is then detected at the electrode.] Perform the glucose analysis in the following sequence: Negative control solution 1, Standard preparations, Assay preparations, and Negative control solution 2. Determine the percentage of glucose against the Negative control solution for each preparation.

CALCULATIONS-
Linearity test-Use an analysis of variance (ANOVA) with one sample assayed against a standard, and using two replicates each, construct a table (see Table 1). Compare the value of the ratio MSNL/MSRES ${ }_{1}$ to a critical value obtained from a table for an $F$ distribution with $m-2$ and $3 m-3$ degrees of freedom, where $m$ is the number of dose levels for each preparation. If the ratio MSNL/ MSRES $_{1}$ does not indicate the presence of significant nonlinearity (ratio value is lower than the critical value), then proceed to the test for parallelism. If the ratio exceeds the critical value (significance level of 0.05 ), the nonlinearity is statistically significant and the test is repeated, discarding the results from either the highest or lowest dose of both the Standard preparations and the Assay preparations (four dose levels). If the ratio MSNL/MSRES ${ }_{1}$ does not indicate the presence of significant nonlinearity, then proceed to the test for parallelism.

Parallelism test-Compare the ratio MSNP/MSRES 2 to a critical value obtained from an $F$ distribution having 1 and $4 m-5$ degrees of freedom. If the ratio $\mathrm{MSNP}^{2} \mathrm{MSRES}_{2}$ does not indicate the presence of significant nonparallelism, then the assay is considered valid. Use the appropriate dose levels for the estimation of the relative potency.

Relative potency-Calculate the relative potency, $R$, of the Assay preparations as compared with the Standard preparations as follows.
(1) $X_{j}$ is defined as the $\log _{10}$ of the $j^{\text {th }}$ dose of the Standard preparations or the Assay preparations. The glucagon dose varies from 12.5 to $200 \times 10^{-6}$ USP Glucagon Units per mL . For ease in the subsequent calculations, these doses are respectively represented by 1 through 5 , as shown in the table below.

| $j$ | 1 | 2 | 3 | 4 | 5 |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Dose | 12.5 | 25 | 50 | 100 | 200 |
| $X_{j}$ | 1.10 | 1.40 | 1.70 | 2.00 | 2.30 |

(2) To differentiate between the Standard preparations and the Assay preparations in the calculations, the subscript $i$ will be used, with $i=1$ to designate the Standard preparations and $i=2$ to designate the Assay preparations. $Y_{i j k}$ will denote the glucose concentration associated with the $k^{\text {th }}$ replicate of the $j^{\text {th }}$ dose of the $i^{\text {th }}$ preparation. For example, $Y_{l j k}$ is the glucose concentration associated with the $k^{\text {th }}$ replicate of the $j^{\text {th }}$ dose of the appropriate Standard preparation; $Y_{l l k}$ is the glucose concentration associated with the $k^{\text {th }}$ replicate of dose 1 of the Standard preparation; and $Y_{2 l k}$ is the glucose concentration associated with the $k^{\text {th }}$ replicate of dose 1 of the Assay preparation. Dose 1 represents a glucose dose of $12.5 \times 10$ ${ }^{6}$ USP Glucagon Units per mL. Finally, $Y_{132}$ represents the glucose concentration associated with the $2^{\text {nd }}$ replicate of dose 3 for the Standard preparation.
(3) $Y_{S}$ and $Y_{t}$ denote the average glucose concentrations for the Standard preparations and the Assay preparations, respectively.
(4) Calculate the least-squares slope estimate, $b$, for a linear regression relating the $Y_{i j k}$ 's to the $X_{j}^{\prime}$ 's as follows: $b=S_{x y} / S_{x x}$, with $S_{x y}$ and $S_{x x}$ calculated using the equations in Table 2.
(5) The $\log$ potency, $M$, is calculated using $M=-1\left[\left(Y_{S}-Y_{t}\right) / b\right]$.
(6) $R=\operatorname{antilog}(M)$.
(7) Calculate the confidence limits (upper and lower) for the relative potency, $R$, using the value $s^{2}=$ MSRES $_{3}$ (see Table 1 and Table 2) as follows. Obtain $t$ from a table for a $t$ distribution having $4 m-4$ degrees of freedom. For the $95 \%$ limits, the $t$ values can be obtained from Table 9 under Design and Analysis of Biological Assays $\langle 111\rangle$.

NOTE-For confidence limits having other probability levels (i.e., $100(1-a) \%$ ), the right tail $t$ critical value having $a / 2$ area to its right is used.

$$
\begin{aligned}
& \text { Calculate } g=t^{2} S^{2} / b^{2} S_{x x} \\
& \qquad \text { and } F=(t s / b) \sqrt{(1 / m)(1-g)+\left(M^{2} / S_{x x}\right)},
\end{aligned}
$$

and calculate

$$
M_{L}=(M-F) /(1-g),
$$

and

$$
M_{U}=(M+F) /(1-g)
$$

where $M$ is the $\log$ potency and $M_{L}$ and $M_{U}$ are the log potency lower and upper confidence limits. The lower and upper confidence limits for the relative potency, $R$, are given by

$$
\begin{aligned}
& R L=\operatorname{antilog}\left(M_{L}\right) \\
& R U=\operatorname{antilog}\left(M_{U}\right)
\end{aligned}
$$

It meets the requirements if the potency is between 0.8 and 1.25 USP Glucagon Units per mg, and the confidence interval width at $P=0.95$ does not exceed $45 \%$ of the computed potency.
${ }^{\bullet}$ Repeat the assay if the confidence interval width exceeds $45 \%$ of the computed potency.

Table 1. ANOVA for the Rat Hepatocyte Assay for Glucagon

| Source | Degrees of <br> Freedom | SS (Sum of <br> Squares) | MS (Mean <br> Square) |
| :--- | :---: | :---: | :---: |
| Preparations | 1 | SSPREP | MSPREP |
| Replicates | 1 | SSREP | MSREP |
| Linear Slope $_{\text {Residual }_{3}}$ | 1 | SSLIN | MSLIN |
| Nonparallelism $_{\text {Residual }_{2}}$ | $1 m-4$ | SSRES $_{3}$ | MSRES $_{3}$ |
| Nonlinearity $_{\text {Residual }_{1}}$ | $4 m-5$ | SSNP $_{2}$ | MSNP $^{2}$ |
| TOTAL $^{2}$ | $3 m-2$ | SSNL $_{2}$ | MSRES $_{2}$ |

NOTES-This analysis pertains to one sample assayed against a standard, using two replicates each.

The number of dose levels for each preparation is denoted by $m$. Table 2 gives the equations for calculating the SS terms.
In each row of the ANOVA table, the MS is obtained by dividing the SS term by the degrees of freedom.

Table 2. Equations for Calculating the Sums of Squares in the Analysis of Variance*

$$
\begin{aligned}
& Y_{i .}=\sum \sum_{j k} y_{i j k} \\
& Y_{j}=\sum_{i k} y_{i j k} \\
& Y_{k}=\sum_{i j} \sum_{i j k} \\
& C F=\frac{\left(\sum_{\mathrm{ijk}} \sum \mathrm{y}_{\mathrm{ijk}}\right)^{2}}{4 \mathrm{~m}} \\
& S_{x y}^{s}=\sum_{j k} x_{\mathrm{x}_{\mathrm{j}} \mathrm{y}_{\mathrm{j} k}}-\frac{\left(\sum_{\mathrm{j}} \mathrm{x}_{\mathrm{j}}\right)\left(\mathrm{Y}_{1 . .}\right)}{m} \\
& S_{x y}^{\mathrm{T}}=\sum_{\mathrm{j} k} \mathrm{x}_{\mathrm{j}} \mathrm{y}_{2 \mathrm{jk}}-\frac{\left(\sum_{\mathrm{j}} \mathrm{x}_{\mathrm{j}}\right)\left(\mathrm{Y}_{2}\right)}{\mathrm{m}} \\
& S_{x y}=S_{x y}^{s}+S_{x y}^{\top} \\
& S_{x x}^{s}=2 \sum_{j} x_{j}^{2}-\frac{2\left(\sum_{j} x_{j}\right)^{2}}{m} \\
& S_{x x}^{\top}=S_{x x}^{s} \\
& S_{x x}=S_{x x}^{s}+S_{x x}^{\top} \\
& \text { SSPREP }=\frac{\sum_{i} Y_{i,}^{2}}{2 m}-C F \\
& \text { SSREP }=\frac{\sum_{k} Y^{2}{ }_{k}}{2 m}-C F \\
& \operatorname{SSLIN}=\frac{\left(\mathrm{S}_{\mathrm{xy}}\right)^{2}}{\mathrm{~S}_{\mathrm{xx}}} \\
& \mathrm{SST}=\sum_{\mathrm{i}, \mathrm{j}} \sum_{\mathrm{i}}^{\mathrm{ijk}} \mathrm{D}_{\mathrm{k}}-\mathrm{CF} \\
& \text { SSRES }_{3}=\text { SST }- \text { SSPREP }- \text { SSREP }- \text { SSLIN } \\
& \text { SSNP }=\frac{\left(S_{x y}^{s}\right)^{2}}{S_{x x}^{s}}+\frac{\left(S_{x y}^{T}\right)^{2}}{S_{x x}^{\top}}-\operatorname{SSLIN} \\
& \text { SSRES }_{2}=\text { SSRES }_{3}-\operatorname{SSNP} \\
& \operatorname{SSNL}=\frac{\sum_{j} Y_{j}^{2}}{4}-\operatorname{SSLIN}-\mathrm{CF} \\
& \text { SSRES }_{1}=\text { SSRES }_{2}-\text { SSNL }
\end{aligned}
$$

## Briefing

Hydrocodone Bitartrate, USP 27 page 919, page 3062 of the First Supplement, and page 1148 of the Fourth Interim Revision Announcement in PF 30(4) [May-June 2004]. It is proposed to resubmit the text that previously appeared in PF 28(1) [Jan.-Feb. 2002], which replaces the test for Ordinary impurities with a test for Related compounds. This impurity test uses a stability-indicating high-pressure liquid chromatographic method that resolves all known process impurities. The proposal from PF 29(1) [Jan.-Feb. 2003] that was postponed in the Fourth Interim Revision Announcement and will appear in USP 28 is hereby cancelled; it would have revised the Assay and added a new test for Related compounds.
(PA2: C. Anthony) RTS-41642-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Dihydrocodeine Bitartrate RS. USP Hydrocodone Bitartrate RS.
-USP Hydrocodone Bitartrate Related Compound A $R S$. п $^{\text {2S (USP28) }}$

## Delete the following:

日 Ordinary imptrities $\langle 466$ )-
Test solution: a mixture of methanel and water ( $1: 1$ ).
Standard solution: a mixture of methanol and water ( $1: 1$ ).
Elutat: a mixture of hexanes, ueetone, methanel, and ammo nitm hydroxide $(60: 40: 20: 1.5)$.
†isualization: 3, followed by overspraying with hydregen per oxide TS. [NOTE Gover the thin layer chromatographic plate with a glass plate stow fading of the spots. Exelude the rigin spet, if present, from the determination of the total impurities.] 12 (USP28)

## Add the following:

-Related compounds- [NOTE-Dry both the USP Hydrocodone Bitartrate RS and the Hydrocodone Bitartrate materials in vacuum at $105^{\circ}$ for 2 hours. Immediately transfer the dried materials to a desiccator containing phosphorus pentoxide. Weigh each dried material individually within 1 minute, and proceed with the Related compounds test.]

Solution A-Prepare a filtered and degassed mixture of 0.15 M monobasic sodium phosphate buffer, adjust with phosphoric acid to a pH of $3.3 \pm 0.1$.
Solution B-Prepare a filtered and degassed mixture of acetonitrile and Solution $A$ (50:50).

Mobile phase-Use variable mixtures of Solution A and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent: a mixture of methanol and water ( $50: 50$ ).
Benzophenone stock solution-Transfer about 16 mg of benzophenone, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with dehydrated alcohol to volume, and mix.

System suitability solution-Transfer about 25 mg of previously dried USP Hydrocodone Bitartrate RS to a $100-\mathrm{mL}$ volumetric flask, add about 25 mg of USP Dihydrocodeine Bitartrate RS, 17 mg of USP Hydrocodone Bitartrate Related Compound A RS, and 5 mL of phosphoric acid. Add 5.0 mL of Benzophenone stock solution, dilute with water, and mix.

Test solution-Transfer an accurately weighed quantity of previously dried Hydrocodone Bitartrate, equivalent to about 100 mg of hydrocodone bitartrate $\left(\mathrm{C}_{18} \mathrm{H}_{21} \mathrm{NO}_{3}\right.$. $\mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$ ), to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $278-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains a $5-\mu \mathrm{m}$ packing L7. The column temperature is maintained at $50^{\circ}$. The flow rate is about 2.2 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 95 | 5 | equilibrium |
| $0-17$ | $95 \rightarrow 90$ | $5 \rightarrow 10$ | linear gradient |
| $17-24$ | $90 \rightarrow 88$ | $10 \rightarrow 12$ | linear gradient |
| $24-40$ | $88 \rightarrow 30$ | $12 \rightarrow 70$ | linear gradient |
| $40-50$ | 30 | 70 | isocratic |
| $50-54$ | $30 \rightarrow 95$ | $70 \rightarrow 5$ | linear gradient |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the resolution, $R$, between hydrocodone and hydrocodone bitartrate related compound A is not less than 4.1; the capacity factor, $k^{\prime}$, is in the range of 17 to 20 for hydrocodone bitartrate; and the relative standard deviation, determined from analyte peaks, is not more than $15 \%$.

Procedure-Inject a volume ( $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each individual impurity in the portion of Hydrocodone Bitartrate taken by the formula:

$$
100\left(F r_{i} / r_{s}\right)
$$

in which $F$ is the relative response factor and is equal to 1.24 for dihydrocodeine bitartrate, 2.27 for hydrocodone bitartrate related compound A, and 13.73 for benzophenone; $r_{i}$ is the individual peak response of hydrocodone related compound A, dihydrocodeine bitartrate, and benzophenone in the Test solution; and $r_{s}$ is the sum of all peak responses. Not more than $0.5 \%$ each of hydrocodone bitartrate related compound A, dihydrocodeine bitartrate, and benzophenone is found; and the sum of all impurities is not more than $2.0 \%$.■2S (USP28)

## BRIEFING

Hydrogen Peroxide Concentrate, USP 27 page 935. It is proposed to revise the test for Acidity to specify that 25 mL of the diluted solution is titrated to be consistent with the same test under Hydrogen Peroxide Topical Solution.
(PA7b: B. Davani) RTS-41018-1

## Change to read:

Acidity-Dilute 25 g with water to 250 mL ,
■and mix thoroughly. Take 25 mL of the solution, $\mathbf{m}_{2 S}$ (USP28) add phenolphthalein TS, and titrate with 0.10 N sodium hydroxide: not more than 2.5 mL is required for neutralization.

## BRIEFING

Insulin, USP 27 page 981 and page 1906 of PF 29(6) [Nov.Dec. 2003]. It is proposed to change the dimensions of the column used in the test for Limit of high molecular weight proteins. The liquid chromatographic procedure was validated using a MacMod Zorbax GF250 brand of L20 column.
(BNT: L. Callahan) RTS-41635-1

## Change to read:

Labeling-Label it to indicate the one or more animal species to which it is related, as pork, as beef, or as a mixture of pork and beef. If the Insulin is purified, label it as such.
-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■1S (USP28)

## Change to read:

## Limit of high molecular weight proteins-

Arginine solution-Prepare a solution of L-arginine in water containing 1 mg per mL .

Mobile phase-Prepare a filtered and degassed mixture of Arginine solution, acetonitrile, and glacial acetic acid (65:20:15). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Resolution solution-Dissolve 4 mg of Insulin containing more than $0.4 \%$ high molecular weight proteins in 1 mL of 0.01 N hydrochloric acid. Store this solution in a refrigerator, and use within 7 days. [NOTE--Insulin containing the indicated percentage of high molecular weight proteins may be prepared by allowing Insulin to stand at room temperature for about 5 days.]

Test solution-Transfer about 4 mg of Insulin to a small vial, add 1 mL of 0.01 N hydrochloric acid, and mix to dissolve. Store in a refrigerator, and use within 7 days.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $276-\mathrm{nm}$ detector and a $7.8 \mathrm{~mm} \times 30 \mathrm{~cm}$

■9.4-mm $\times 25-\mathrm{cm}_{■ 2 \mathrm{~S}}$ (USP28)
column that contains packing L20. The flow rate is about 0.5 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the retention times are between 13 and 17 minutes for the polymeric insulin complexes, about 17.5 minutes for the covalent insulin dimer, and between 18 and 22 minutes for the insulin monomer, with salts eluting after the insulin monomer; and the ratio of the height of the covalent insulin dimer peak to the height of the valley between the covalent insulin dimer peak and the insulin monomer peak is not less than 2.0.

Procedure-Inject a volume (about $100 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the areas of the peak responses, disregarding any peaks having retention times greater than that of the insulin monomer. Calculate the percentage of high molecular weight proteins in the portion of Insulin taken by the formula:

$$
100 \Sigma r_{H} /\left(\Sigma r_{H}+r_{M}\right)
$$

in which $\Sigma r_{H}$ is the sum of the responses for all peaks having retention times less than that of the insulin monomer, and $r_{M}$ is the peak response of the insulin monomer: not more than $1.0 \%$ is found.

## Add the following:

-Other requirements-Where the label states that Insulin is sterile, it meets the requirements for Sterility under Insulin Injection.■1S (USP28)

Briefing

Insulin Human Injection, USP 27 page 984. On the basis of data and comments received for Insulin Injection, it is proposed to lower the limit of high molecular weight proteins.
(BNT: L. Callahan) RTS-41107-2

## Add the following:

-Limit of high molecular weight proteins-Proceed as directed in the test for Limit of high molecular weight proteins under Insulin Injection: not more than $1.7 \%$ is found.■2S (USP28)

## Change to read:

Other requirements-It meets the requirements under Injections $\langle 1\rangle$ and for $p H$, Zine emtent, and Limit of high moleculdr weight proteins under Insulin Injection.
$\square_{p H}$ and Zinc content.■2S (USP28)

## Briefing

Levothyroxine Sodium, USP 27 page 1084; Liothyronine Sodium, USP 27 page 1094; Liotrix Tablets, USP 27 page 1096. Because of the poor solubility of levothyroxine and liothyronine in the Mobile phase, it is proposed to modify the Standard preparation in the Assay. This change also affects the test for Limit of liothyronine. It also affects the Assay and test for Limit of liothyronine under Levothyroxine Sodium Tablets.
(PA4: E. Gonikberg) RTS-41634-1

## Change to read:

## Assay-

Mobile phase-Prepare a degassed and filtered mixture of water and acetonitrile ( $60: 40$ ) that contains 0.5 mL of phosphoric acid in each 1000 mL . Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation Transfer aceurately weighed quantities of USP Levothyroxine PS and USP Liothyronine PS to a-suitable eontainer, dissolve in and dilute quantitatively and stepurise with Mobile phase to obtain a solution having known concentrations of about $10 \mu \mathrm{~g}$ of levethyroxine per mL and $0.2 \mu \mathrm{~g}$ of liothyronine per mb.
-0.01 M Methanolic sodium hydroxide——Dissolve 400 mg of sodium hydroxide in 500 mL of water. Cool, add 500 mL of methanol, and mix.

Levothyroxine stock solution-Dissolve an accurately weighed quantity of USP Levothyroxine RS in 0.01 M Methanolic sodium hydroxide to obtain a solution having a known concentration of about 0.4 mg of levothyroxine per mL .

Liothyronine stock solution-Dissolve an accurately weighed quantity of USP Liothyronine RS in 0.01 M Methanolic sodium hydroxide to obtain a solution having a known concentration of about 0.4 mg of liothyronine per mL . Make a 1:100 dilution of this solution using Mobile phase.

Standard preparation-Transfer appropriate volumes of Levothyroxine stock solution and Liothyronine stock solution to a suitable container, and dilute quantitatively and stepwise, if necessary, with Mobile phase to obtain a solu-
tion having known concentrations of about $10 \mu \mathrm{~g}$ of levothyroxine per mL and $0.2 \mu \mathrm{~g}$ of liothyronine per mL . ${ }^{2 S}$ (USP28)

Assay preparation-Transfer an accurately weighed portion of about $100 \mu \mathrm{~g}$ of Levothyroxine Sodium into a centrifuge tube, add 2 glass beads, pipet 10 mL of Mobile phase into the tube, and mix using a vortex mixer for 3 minutes. Centrifuge to obtain a clear supernatant, filtering if necessary.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $225-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between the liothyronine and levothyroxine is not less than 5.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$ for levothyroxine.
Procedure-Separately inject equal volumes (about $100 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in $\mu \mathrm{g}$, of $\mathrm{C}_{15} \mathrm{H}_{10} \mathrm{I}_{4} \mathrm{~N}$ $\mathrm{NaO}_{4}$ in the portion of Levothyroxine Sodium taken by the formula:

$$
(798.85 / 776.87)(10 C)\left(r_{U} / r_{S}\right)
$$

in which 798.85 and 776.87 are the molecular weights of levothyroxine sodium and levothyroxine, respectively; $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Levothyroxine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the levothyroxine peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Briefing

Lidocaine Hydrochloride and Dextrose Injection, USP 27 page 1089 -See briefing under Alcohol in Dextrose Injection.
(PA1: K. Russo) RTS-41401-4

## Change to read:

Assay for dextrose-Determine the angular rotation of Injection in a suitable polarimeter tube at $25^{\circ}$ (see Optical Rotation-(781)). The observed ratation in degrees, multiplied by 1.04254 , im which $A$ is the ratio 200 divide by the length, in mm, of the polarimeter tube employed, represents the weight, in ${ }^{5}$, of $_{6} H_{42} \Theta_{6} \cdot H_{2} \Theta$ in 100 mL of the Injection.
-(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:

$$
(100 / 52.9)(198.17 / 180.16) A R,
$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees. $\quad$ 2S (USP28)

## Briefing

Liothyronine Sodium, USP 27 page 1094—See briefing under Levothyroxine Sodium. This change also affects the test for Limit of levothyroxine. It also affects the Assay and test for Limit of levothyroxine under Liothyronine Sodium Tablets.
(PA4: E. Gonikberg) RTS-41634-3

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of water and acetonitrile ( $60: 40$ ) that contains 0.5 mL of phosphoric acid in each 1000 mL . Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
standard preparation Transfer aceurately weighed quantities ef USP Liothyronine PS and USP Levethyroxine PS, and dissolve in and dilute quantitatively and stepwise with Mobile phase to obtain a solution having known concentrations of about 10 - g of li ethyronine per mL and 0.5 ug of levethyroxine per mL .

- 0.01 M Methanolic sodium hydroxide—Dissolve 400 mg of sodium hydroxide in 500 mL of water. Cool, add 500 mL of methanol, and mix.

Liothyronine stock solution-Dissolve an accurately weighed quantity of USP Liothyronine RS in 0.01 M Methanolic sodium hydroxide to obtain a solution having a known concentration of about 0.4 mg of liothyronine per mL .

Levothyroxine stock solution-Dissolve an accurately weighed quantity of USP Levothyroxine RS in 0.01 M Methanolic sodium hydroxide to obtain a solution having a known concentration of about 0.4 mg of levothyroxine per mL .Make a $1: 100$ dilution of this solution using Mobile phase.

Standard preparation-Transfer appropriate volumes of Liothyronine stock solution and Levothyroxine stock solution to a suitable container, and dilute quantitatively and stepwise, if necessary, with Mobile phase to obtain a solution having known concentrations of about $10 \mu \mathrm{~g}$ of liothyronine per mL and $0.5 \mu \mathrm{~g}$ of levothyroxine per mL . $\mathbf{m}^{2 S}$ (USP28) Assay preparation-Transfer an accurately weighed portion of $100 \mu \mathrm{~g}$ of Liothyronine Sodium to a centrifuge tube, add 2 glass beads, pipet 10 mL of Mobile phase into the tube, and mix using a vortex mixer for 3 minutes. Centrifuge to obtain a clear supernatant, filtering if necessary.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $225-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between the levothyroxine and liothyronine is not less than 5.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$ for liothyronine.

Procedure-Separately inject equal volumes (about $100 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in $\mu \mathrm{g}$, of $\mathrm{C}_{15} \mathrm{H}_{11} \mathrm{I}_{3} \mathrm{~N}$ $\mathrm{NaO}_{4}$ in the portion of Liothyronine Sodium taken by the formula:

$$
(672.96 / 650.97)(10 C)\left(r_{U} / r_{S}\right)
$$

in which 672.96 and 650.97 are the molecular weights of liothyronine sodium and liothyronine, respectively; $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Liothyronine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the liothyronine peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Liotrix Tablets, USP 27 page 1096-See Briefing under Levothyroxine Sodium.
(PA4: E. Gonikberg) RTS-41634-5

## Change to read:

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of water and acetonitrile ( $65: 35$ ) that contains 2 mL of trifluoroacetic acid in each 1000 mL of solution. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standud preparation Transfer aceurately weighed quantities ef USP Levothyroxine RS and USP Liothyrenine RS to a suitable eontainer, dissolve in and dilute quantitatively and stepwise with Mobile phase to obtain a solution having known concentrations of about $10 \mu \mathrm{~g}$ of levothyroxine per mL and $2.5 \mu \mathrm{~g}$ of liothyronine per mb.

- 0.01 M Methanolic sodium hydroxide—Dissolve 400 mg of sodium hydroxide in 500 mL of water. Cool, add 500 mL of methanol, and mix.

Levothyroxine stock solution-Dissolve an accurately weighed quantity of USP Levothyroxine RS in 0.01 M Methanolic sodium hydroxide to obtain a solution having a known concentration of about 0.4 mg of levothyroxine per mL.

Liothyronine stock solution-Dissolve an accurately weighed quantity of USP Liothyronine RS in 0.01 M Methanolic sodium hydroxide to obtain a solution having a known concentration of about 0.4 mg of liothyronine per mL . Make a 1:10 dilution of this solution using Mobile phase.

Standard preparation-Transfer appropriate volumes of Levothyroxine stock solution and Liothyronine stock solution to a suitable container, and dilute quantitatively and stepwise, if necessary, with Mobile phase to obtain a solution having known concentrations of about $10 \mu \mathrm{~g}$ of levothyroxine per mL and $2.5 \mu \mathrm{~g}$ of liothyronine per mL . ${ }^{2 S}$ (USP28)

Assay preparation-Transfer 20 Tablets to a $200-\mathrm{mL}$ volumetric flask, add 180 mL of Mobile phase, and sonicate for 15 minutes, occasionally swirling the flask to accelerate the disintegration of
the Tablets. Cool to room temperature, and dilute with Mobile phase to volume. Transfer a portion of the solution to a centrifuge tube, and centrifuge for 10 minutes at 5000 rpm . Quantitatively dilute a portion of the clear supernatant with Mobile phase to obtain concentrations of about $10.0 \mu \mathrm{~g}$ of levothyroxine sodium per mL and $2.5 \mu \mathrm{~g}$ of liothyronine sodium per mL .

Chromatographic system-Proceed as directed in the Assay under Levothyroxine Sodium.

Procedure-Proceed as directed for Procedure in the Assay under Levothyroxine Sodium. Calculate the quantity, in $\mu \mathrm{g}$, of levothyroxine sodium $\left(\mathrm{C}_{15} \mathrm{H}_{10} \mathrm{I}_{4} \mathrm{NNaO}_{4}\right)$ in the portion of Tablets taken by the formula:

$$
(798.86 / 776.87)(10 C)\left(r_{U} / r_{S}\right)
$$

in which 798.86 and 776.87 are the molecular weights of levothyroxine sodium and levothyroxine, respectively; $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Levothyroxine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the levothyroxine peak responses obtained from the Assay preparation and the Standard preparation, respectively.
Calculate the quantity, in $\mu \mathrm{g}$ of liothyronine sodium $\left(\mathrm{C}_{15} \mathrm{H}_{11} \mathrm{I}_{3} \mathrm{~N}\right.$ $\mathrm{NaO}_{4}$ ) in the portion of Tablets taken by the formula:

$$
(672.96 / 650.98)(10 C)\left(r_{U} / r_{S}\right),
$$

in which 672.96 and 650.98 are the molecular weights of liothyronine sodium and liothyronine, respectively; $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Liothyronine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the liothyronine peak responses obtained from the Assay preparation and the Standard preparation, respectively.

BRIEFING

Loperamide Hydrochloride Tablets, USP 27 page 1103 and page 122 of PF 30(1) [Jan.-Feb. 2004]. Because of the poor solubility of Loperamide Hydrochloride in water, it is proposed to modify the Standard preparation in the Assay.
(PA4: E. Gonikberg) RTS-41602-1

## Change to read:

Dissolution Proedtre for a Pooted Sample
-71S (USP28)
Medium: $\quad 0.01 \mathrm{~N}$ hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
Determine the amount of $\mathrm{C}_{29} \mathrm{H}_{33} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot \mathrm{HCl}$ dissolved by employing the following method.

Mobile phase and Chromatographic system-Proceed as directed in the Assay.

Procedure-
-Proceed as directed for Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets under Dissolution $\langle 711\rangle$. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. 1 (USP28)
Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of a filtered portion of the solution under test
-the pooled sample $_{\mathbf{m}_{1 S}(U S P 28)}$
into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $\mathrm{C}_{29} \mathrm{H}_{33} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot \mathrm{HCl}$ dissolved in comparison with a Standard solution having a known concentration of USP Loperamide Hydrochloride RS in the same Medium and similarly chromatographed. Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{29} \mathrm{H}_{33} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot \mathrm{HCl}$ is dissolved in 30 minutes:

- the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either $\mathrm{S}_{1}$ or $\mathrm{S}_{2}$. The quantity $Q$, is the amount of dissolved active ingredient, expressed as a percentage of the labeled content.

| Acceptance Table for a Pooled Sample |  |  |  |
| :---: | :---: | :---: | :---: |
| Number |  |  |  |
| Stage | Tested | Acceptance Criteria |  |
| $\mathrm{S}_{1}$ | 6 | Average amount dissolved is not less than $Q+10 \%$. |  |
| $\mathrm{S}_{2}$ | 6 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}\right)$ is equal to or greater than $Q+5 \%$. |  |
| $\mathrm{S}_{3}$ | 12 | Average amount dissolved $\left(\mathrm{S}_{1}+\mathrm{S}_{2}+\right.$ <br> $\mathrm{S}_{3}$ ) is equal to or greater than $Q$. | F <br> 10 <br> 0 <br> 8 <br> 8 |
| Change | read: | -1S (USP28) | \% 0 0 0 0 0 0 |
| Assay- <br> Buffer solution-Transfer 3.0 g of triethylamine hydrochloride and 1.0 mL of phosphoric acid to a 1-L flask, add 550 mL of water, |  |  |  |

-methanol to obtain a solution having a known concentration of about 2 mg per mL . Quantitatively dilute this solution with ${ }_{\text {2S (USP28) }}$
water to obtain a solution having a known concentration of about 0.2 mg per mL . Transfer 10.0 mL of this solution to a $250-\mathrm{mL}$ volumetric flask, add 5.0 mL of $5 \%$ phosphoric acid solution and 25 mL of methanol, dilute with water to volume, and mix.

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 16 mg of loperamide hydrochloride, to a $2000-\mathrm{mL}$ volumetric flask. Add 40 mL of $5 \%$ phosphoric acid solution and 200 mL of methanol, dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $214-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 8-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The flow rate is about 2 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of loperamide hydrochloride ( $\mathrm{C}_{29} \mathrm{H}_{33} \mathrm{ClN}_{2} \mathrm{O}_{2} \cdot \mathrm{HCl}$ ) in the portion of Tablets taken by the formula:

$$
2000 C\left(r_{U} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Loperamide Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Modafinil; Modafinil Tablets. Because there are no existing USP monographs for this drug substance and dosage form, new monographs are proposed based on a manufacturer's tests and acceptance criteria. The reverse phase HPLC procedures for the Related compounds and Assay tests were validated using an Inertsil ODS-2 brand of L1 column; modafinil elutes at approximately 3.9 minutes.
(PA1: K. Russo; PSD: C. Okeke; NL: C. Barnstein) RTS-39507-1; 39869-1

## Add the following:

## Modafinil


$\mathrm{C}_{15} \mathrm{H}_{15} \mathrm{NO}_{2} \mathrm{~S} \quad 273.35$

Acetamide, 2-[(diphenylmethyl)sulfinyl]-.
2-[(Diphenylmethyl)sulfinyl]-acetamide [68693-11-8].
» Modafinil contains not less than 98.0 percent and not more than 101.5 percent of $\mathrm{C}_{15} \mathrm{H}_{15} \mathrm{NO}_{2} \mathrm{~S}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in well-closed containers. Store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Modafinil RS. USP
Salicylic Acid RS.
Identification-Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
Water, Method $I\langle 921\rangle$ : not more than $0.2 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.

Particle size—Using suitable laser diffraction equipment, set the dry powder feed instrument to run 5 to 10 g of sample per run in the Fraunhofer mode. Adjust the feed ration to achieve a mean obscuration of 3 to 5 . Run a suitable check standard (e.g., garnet) to establish a practical, operational system. The sample is to be run in triplicate, separated by blank runs. The results of the individual runs are to be averaged for the mean, and all other parameters required: the relative standard deviation for each specified volume of sample is not more than $10 \%$; not less than $50 \%$ of the particles are less than $45 \mu \mathrm{~m}$, not less than $80 \%$ of the particles are less than $110 \mu \mathrm{~m}$, and not less than $95 \%$ of the particles are less than $220 \mu \mathrm{~m}$.

Heavy metals, Method $I\langle 231\rangle$ —Dissolve the sample in methanol and water solution ( $60: 40$ ): not more than $0.002 \%$.

## Related compounds-

Buffer, Mobile phase, and System suitability prepara-tion-Prepare as directed in the Assay.

Test solution-Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed under Assay. Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the relative retention times are listed in the table below; the resolution, $R$, between salicylic acid and modafinil is not less than 1.3; the tailing factor is not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$ based on the modafinil peak.

|  | Relative Re- <br> tention Time <br> (relative to <br> modafinil) |
| :--- | :---: |
| Impurity | 1.1 |
| Salicylic acid* $_{\text {Modafinil acid [2-[(diphenylmethyl)sul- }}$ | 1.4 |
| Minyl]acetic acid] | 1.7 |
| sulfonyl]acetamide] <br> Modafinil ester [2-[(diphenylmethyl)sul- <br> finyl]acetic acid methyl ester] | 3.0 |

* Salicylic acid is used for calculating resolution and is not a potential impurity.

Procedure-Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each related compound in the portion of Modafinil taken by the formula:

$$
100(1 / F)\left(r_{i} / r_{s}\right)
$$

in which $F$ is the relative response factor for an impurity ( $F$ is 0.90 for modafinil sulfone; $F$ is 1 for all other known and unknown impurities); $r_{i}$ is the individual peak response of each impurity; and $r_{s}$ is the sum of the responses of all the peaks: not more than $0.5 \%$ of any individual known impurity is found, not more than $0.05 \%$ of any individual unknown impurity is found, and not more than $1.0 \%$ of total impurities is found.

Organic volatile impurities, Method $V\langle 467\rangle$ : meets the requirements.
Solvent: $n$-methylpyrrolidone.

Assay-
Buffer-Dissolve 6.8 g of potassium dihydrogen phosphate in 500 mL of water in a $1000-\mathrm{mL}$ flask. Dilute with water to volume, and mix. Adjust with phosphoric acid to a pH of 2.3.

Mobile phase-Prepare a filtered and degassed mixture of Buffer and acetonitrile ( $65: 35$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare a mixture containing water and acetonitrile ( $65: 35$ ), and mix.

System suitability preparation-Dissolve suitable quantities of USP Modafinil RS and USP Salicylic Acid RS in Diluent to obtain a solution containing about 0.005 mg per mL and 0.05 mg per mL , respectively.

Standard preparation-Dissolve an accurately weighed quantity of USP Modafinil RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 0.1 mg per mL .

Assay preparation-Transfer about 100 mg of Modafinil, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix. Dilute 5.0 mL of this solution with Diluent to 50 mL , and mix well.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the relative reten-
tion times are about 1.1 for salicylic acid and 1.0 for modafinil; the resolution, $R$, between modafinil and salicylic acid is not less than 1.3; the tailing factor of the modafinil peak is not more than 1.5; and the relative standard deviation for replicate injections is not more than $2.0 \%$ based on the modafinil peak.
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the modafinil peaks. Calculate the quantity, in mg, of $\mathrm{C}_{15} \mathrm{H}_{15} \mathrm{NO}_{2} \mathrm{~S}$ in the portion of Modafinil taken by the formula:

$$
1000 C\left(r_{U} / r_{s}\right)
$$

in which 1000 is the dilution factor for the Assay preparation; $C$ is the concentration, in mg per mL , of USP Modafinil RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP28)

[^241]
## Add the following:

## Modafinil Tablets

» Modafinil Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of modafinil $\left(\mathrm{C}_{15} \mathrm{H}_{15} \mathrm{NO}_{2} \mathrm{~S}\right)$.

Packaging and storage-Preserve in tight containers. Store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Modafinil RS. USP Salicylic Acid RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$-Grind 1 Tablet and add 50 mL each of dichloromethane and water. Shake the mixture and allow the layers to separate. Filter a portion of the upper (dichloromethane) layer and evaporate to dryness, using a stream of nitrogen if necessary. Prepare a potassium bromide pellet of the residue. To prepare the Reference Standard potassium bromide dispersion, transfer a quantity (in mg ) of USP Modafinil RS, equivalent to the labeled amount of modafinil, to a suitable container, and proceed as directed above beginning with "add 50 mL each of dichloromethane and water."

## Dissolution $\langle 711\rangle$ -

Medium: $\quad 0.1 \mathrm{~N}$ hydrochloric acid; 900 mL .
Apparatus 2: 50 rpm.
Time: 30 minutes.
Procedure-Determine the amount of $\mathrm{C}_{15} \mathrm{H}_{15} \mathrm{NO}_{2} \mathrm{~S}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 222 nm on filtered portions of the solution under test, suitably diluted with Medium if
necessary, in comparison with a Standard solution having a known concentration of USP Modafinil RS in the same Medium.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{15} \mathrm{H}_{15} \mathrm{NO}_{2} \mathrm{~S}$ is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

## Related compounds-

Buffer, Mobile phase, and System suitability prepara-tion-Prepare as directed in the Assay under Modafinil. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare as directed in the Assay.
Test solution-Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay. Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the relative retention times are presented in the table below; the resolution, $R$, between modafinil and salicylic acid is not less than 1.3; and the relative standard deviation for replicate injections is not more than $2.0 \%$ based on the modafinil peak.

|  | Relative Re- <br> tention Time <br> (relative to <br> modafinil) |
| :--- | :---: |
| Impurity | 1.1 |
| Salicylic acid* | 1.4 |
| Modafinil acid [2-[(diphenylmethyl)sul- <br> finyl]acetic acid] |  |


|  | Relative Re- <br> tention Time <br> (relative to <br> modafinil) |
| :--- | :---: |
| Impurity | 1.7 |
| Modafinil sulfone [2-[(diphenylmethyl) <br> sulfonyl]acetamide] |  |
| Modafinil ester [2-[(diphenylmethyl)sul- <br> finyl]acetic acid methyl ester] | 3.0 |

* Salicylic acid is used for calculating resolution and is not a potential impurity.

Procedure-Inject a volume (about $5 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$
100(1 / F)\left(r_{i} / r_{s}\right)
$$

in which $F$ is the relative response factor for an impurity ( $F$ is 0.90 for modafinil sulfone; $F$ is 1 for all other known and unknown impurities); $r_{i}$ is the peak response for each impurity; and $r_{s}$ is the sum of the responses of all the peaks: not more than $0.5 \%$ of any individual impurity is found, not more than $0.1 \%$ of any individual unknown impurity is found, and not more than $1.5 \%$ of total impurities is found.

## Assay-

Buffer, Mobile phase, and System suitability prepara-tion-Prepare as directed in the Assay under Modafinil.

Diluent-Prepare a mixture containing water, acetonitrile, and acetic acid ( $65: 35: 1$ ), and mix.

Standard preparation-Dissolve an accurately weighed quantity of USP Modafinil RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 0.4 mg per mL .

Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of modafinil, to a $250-\mathrm{mL}$ volumetric flask, add 200 mL of Diluent, and sonicate for about 5 minutes with intermittent manual shaking. Dilute with Diluent to volume, and mix. Pass a portion of this solution through a filter having a $0.45-\mu \mathrm{m}$ or finer porosity, and use the filtrate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the relative retention times are about 1.1 for salicylic acid and 1.0 for modafinil; the resolution, $R$, between modafinil and salicylic acid is not less than 1.3 ; the tailing factor is not more than 1.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$ based on the modafinil peak.

Procedure-Separately inject equal volumes (about $5 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure
the responses for the modafinil peaks. Calculate the quantity, in mg , of modafinil $\left(\mathrm{C}_{15} \mathrm{H}_{15} \mathrm{NO}_{2} \mathrm{~S}\right)$ in the portion of Tablets taken by the formula:

$$
250 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Modafinil RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. ${ }^{\mathbf{n} 2 \mathrm{~S}}$ (USP28)

BRIEFING

Morphine Sulfate, USP 27 page 1263 and page 3277 of the Second Supplement. On the basis of comments received concerning revisions proposed in PF 29(6) [Nov.-Dec. 2003], further revisions to the Packaging and storage are proposed, and the proposed revisions to the Labeling, Reference standards, and Other requirements sections are hereby canceled.
(PA2: C. Anthony) RTS-41188-2

## Change to read:

Packaging and storage-Preserve in tight, light-resistant containers. Store at $25^{\circ}$, exeursions permitted between $15^{\circ}$ and


- Store up to $40^{\circ}$ as permitted by the manufacturer.■2S (USP28)
protein standard solution used in the Standard preparations. The albumin standard currently cited is no longer available from the source indicated.
(RMI: A.Wilk) RTS—41561-1
(Current title-not to change until February 1, 2005)
Monograph title change-to become official February 1, 2005
See Perflutren Protein-Type A Microspheres Injectable
Suspension


## Change to read:

## Assay for protein-

Diluted antifoam reagent-Transfer $100 \mu \mathrm{~L}$ of antifoam reagent ${ }^{8}$ to a suitable container, and dilute with water to 10 mL .
Blank preparation-Transfer $500 \mu \mathrm{~L}$ of Sodium Chloride Injection to a culture tube. Dilute the contents of the tube with water to 2 mL , and add $10 \mu \mathrm{~L}$ of Diluted antifoam reagent.

Standard preparations-Transfer 25-, 50-, 62.5-, $75-$, and $100-$ $\mu \mathrm{L}$ aliquots of protein standard solution ${ }^{9}$ containing 8 g per dL into separate tubes. Dilute the contents of each tube with water to 2.00 mL , and add $10 \mu \mathrm{~L}$ of the Diluted antifoam reagent to each tube. During the Procedure the addition of 3.0 mL of biuret reagent TS to each of the tubes produces Standard preparations with protein concentrations of $0.4,0.8,1.0,1.2$, and 1.6 mg per mL .

Assay preparation-Equilibrate each container of Perflutren Protein-Type A Microspheres for Injection to room temperature, and mix each for at least 5 minutes to ensure a homogenous suspension. Vent the container, and transfer $500-\mu \mathrm{L}$ aliquots into separate tubes. Dilute the contents of each tube with water to 2 mL , and add $10 \mu \mathrm{~L}$ of Diluted antifoam reagent.

Procedure-To each of the tubes containing the Blank preparation, Standard preparations, and Assay preparation add 3.0 mL of biuret reagent TS, mix, and allow to stand for 30 minutes, accurately timed, for maximum color development. The Blank preparation, Standard preparations, and Assay preparation are treated identically. Using the Blank preparation, set the absorbance equal to zero. Determine the absorbance of each of the Standard preparations and the Assay preparation in $1-\mathrm{cm}$ cells with a suitable spectrophotometer at a wavelength of 540 nm . Using linear regression, analyze the data obtained for each of the Standard preparations. Calculate the correlation coefficient, slope, and $y$-intercept values: the correlation coefficient is not less than 0.995 . Calculate the quantity, in mg , of protein in each mL of the Perflutren ProteinType A Microspheres for Injection by the formula:

$$
10\left[\left(A_{U}-y \text {-intercept }\right) / \text { slope }\right]
$$

in which 10 is the dilution factor; and $A_{U}$ is the absorbance of the Assay preparation: the calculated quantity of protein in the Perflutren Protein-Type A Microspheres for Injection is between 8 mg per mL and 12 mg per mL .

Perflutren Protein-Type A Microspheres for Injection, USP 27 page 1446; Perflutren Protein-Type A Microspheres Injectable Suspension, USP 27 page 1448. It is proposed to revise footnote 9 in the Assay for protein to identify a new source for the
${ }^{8}$ Available as Antifoam Reagent, catalog number 2210, from Dow Corning Corporation, Midland, MI.
${ }^{9}$ Available Albumin Standard (8 g/d $/$ U), eataleg number A 1533 , frem Sigma-Chemieal Co., St. Louis, MO.

- Available as Bovine Serum Albumin, SRM 927c, Standard Reference Materials, National Institute of Standards and Technology, Gaithersburg, MD. $\quad$ 2S (USP28)

Perflutren Protein-Type A Microspheres Injectable Suspen-sion-See briefing under Perflutren Protein-Type A Microspheres for Injection.
(RMI: A. Wilk) RTS-41561-1

# Perflutren Protein-Type A Microspheres Injectable Suspension 

(Monograph under this new title-to become official February
1, 2005)
(Current monograph title is Perflutren Protein-Type A
Microspheres for Injection)

## Change to read:

## Assay for protein-

Diluted antifoam reagent-Transfer $100 \mu \mathrm{~L}$ of antifoam reagent ${ }^{8}$ to a suitable container, and dilute with water to 10 mL .

Blank preparation-Transfer $500 \mu \mathrm{~L}$ of Sodium Chloride Injection to a culture tube. Dilute the contents of the tube with water to 2 mL , and add $10 \mu \mathrm{~L}$ of Diluted antifoam reagent.

Standard preparations-Transfer $25-$, $50-$, $62.5-$ - $75-$, and 100$\mu \mathrm{L}$ aliquots of protein standard solution ${ }^{9}$ containing 8 g per dL into separate tubes. Dilute the contents of each tube with water to 2.00 mL , and add $10 \mu \mathrm{~L}$ of the Diluted antifoam reagent to each tube. During the Procedure, the addition of 3.0 mL of biuret reagent TS to each of the tubes produces Standard preparations with protein concentrations of $0.4,0.8,1.0,1.2$, and 1.6 mg per mL .

Assay preparation-Equilibrate each container of Injectable Suspension to room temperature, and mix each for at least 5 min utes to ensure a homogeneous suspension. Vent the container, and transfer $500-\mu \mathrm{L}$ aliquots into separate tubes. Dilute the contents of each tube with water to 2 mL , and add $10 \mu \mathrm{~L}$ of Diluted antifoam reagent.

Procedure-To each of the tubes containing the Blank preparation, Standard preparations, and Assay preparation add 3.0 mL of biuret reagent TS, mix, and allow to stand for 30 minutes, accurately timed, for maximum color development. The Blank preparation, Standard preparations, and Assay preparation are treated identically. Using the Blank preparation, set the absorbance equal to zero. Determine the absorbance of each of the Standard preparations and the Assay preparation in $1-\mathrm{cm}$ cells with a suitable spectrophotometer at a wavelength of 540 nm . Using linear regression, analyze the data obtained for each of the Standard preparations. Calculate the correlation coefficient, slope, and $y$-intercept
values: the correlation coefficient is not less than 0.995 . Calculate the quantity, in mg , of protein in each mL of the Injectable Suspension by the formula:

$$
10\left[\left(A_{U}-y \text {-intercept }\right) / \text { slope }\right],
$$

in which 10 is the dilution factor; and $A_{U}$ is the absorbance of the Assay preparation: the calculated quantity of protein in the Injectable Suspension is between 8 and 12 mg per mL .

BRIEFING

Potassium Chloride in Dextrose Injection, USP 27 page 1516-See briefing under Alcohol in Dextrose Injection.
(PA1: K. Russo) RTS-41401-9

## Change to read:

» Potassium Chloride in Dextrose Injection is a sterile solution of Potassium Chloride and Dextrose in Water for Injection. It contains not less than 95.0 percent and not more than 110.0 percent of the labeled amount of

- Potassium Chloride ${ }_{\text {n2S }}$ (USP28)
$(\mathrm{KCl})$ and not less than 95.0 percent and not more than 105.0 percent of the labeled amount of
-dextrose ${ }_{\text {■2S }}{ }^{\text {(USP28) }}$
$\left(\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}\right)$. It contains no antimicrobial agents.


## Change to read:

Assay for dextrose-Transfer an accurately measured volume of Injection, containing between 2 and 5 g of dextrose, to a $100-\mathrm{mL}$ volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. Determine the angular rotation in a suitable polarimeter tube at $25^{\circ}$ (see Optical Rotion (781)). The observed rotation, in degrees, multiplied by 1.04254 , in which 4 is the ratio 200 divided by the length, in mm, of the polarimeter tube employed, represents the weight, in of, of $\mathrm{G}_{6} \mathrm{H}_{42} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the wot tme of Injection taken.

[^242]■(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:

$$
(100 / 52.9)(198.17 / 180.16) A R
$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees.■2S (USP28)

## BRIEFING

Potassium Chloride in Dextrose and Sodium Chloride Injection, USP 27 page 1517-See briefing under Alcohol in Dextrose Injection.
(PA1: K. Russo) RTS-41401-8

## Change to read:

Assay for dextrose-Transfer an accurately measured volume of Injection, containing between 2 g and 5 g of dextrose, to a $100-\mathrm{mL}$ volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. Determine the angular rotation in a suitable polarimeter tube $25^{\circ}$ (se-Optind Rot (784)). The observed retation, in degrees, multiplied by $1.0425 A$, in whieh $A$ is the ratio 200 divided by the length, in mm, of the polarimeter tube employed, represents the weight, in of, of $\mathrm{G}_{6} \mathrm{H}_{42} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the wh ume of Injection taken.
-(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage (g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:
$(100 / 52.9)(198.17 / 180.16) A R$,
in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm; and $R$ is the observed rotation, in degrees. $\quad$ 2S (USP28)

BRIEFING

Prednisolone, USP 27 page 1537 and page 1440 of $P F$ 28(5) [Sept-Oct. 2002]. It is proposed to resubmit the proposal that previously appeared in PF 28(5) to replace the test for Ordinary impurities with a test for Chromatographic purity that provides superior separation and more rigid acceptance criteria for the limit of impurities. It is also proposed to cancel text postponed indefinately in USP 27.
(PA1: C. Anthony) RTS-41660-1

## Add the following:

## -Chromatographic purity-

Solution $A$-Prepare a filtered and degassed mixture of water and acetonitrile (77:23).

Solution B-Prepare a filtered and degassed mixture of water and acetonitrile (60:40).

Mobile phase—Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent: a mixture of water and acetonitrile (1:1).
Standard solution-Dissolve an accurately weighed quantity of USP Prednisolone RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 0.01 mg per mL .

System suitability solution-Dissolve an accurately weighed quantity of USP Prednisolone RS and hydrocortisone in Diluent to obtain a solution having a known concentration of about 1 mg per mL and 0.06 mg per mL , respectively.
Test solution-Transfer about 25 mg of Prednisolone, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $40^{\circ}$. The chromatograph is programmed as follows.

| Time | Solution A <br> (minutes) | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 100 | 0 | equilibration |
| $0-25$ | 100 | 0 | isocratic |
| $25-45$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| $45-60$ | 0 | 100 | isocratic |
| $60-61$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $61-100$ | 100 | 0 | re-equilibration |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times for prednisolone and hydrocortisone are about 1.0 and 1.06 , respectively; and the height of the smallest peak is not less than 2 times the height of the valley between the prednisolone and hydrocortisone peaks. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $5.0 \%$ for the prednisolone peak.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and Test solution into the chromatograph, record the chromatograms, and measure the re-
sponses for the major peaks. Calculate the percentage of each impurity in the portion of Prednisolone taken by the formula:

$$
2500(C / W)\left(r_{i} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Prednisolone RS in the Standard solution; $W$ is the weight, in mg , of prednisolone used to prepare the Test solution; $r_{i}$ is the peak response for each impurity in the Test solution; and $r_{s}$ is the peak response obtained from the Standard solution: no impurity greater than $1.0 \%$ and only one peak greater than $0.5 \%$ is found; and not more than $2.0 \%$ of total impurities is found. ${ }^{2 S}$ (USP28)

## Delete the following:

- Ordinary imptrities- 466 ) -

Solvent: a mixture of aleohol and water (1:1).
Eltunt: amixture of toluene andisepropyl aleohel $(70: 30)$, in
a nenequilibrated chamber.
Yistulization: teehnique-1.■2S (USP28)

## BRIEFING

Prednisolone Acetate, USP 27 page 1540, page 3295 of the Second Supplement, and page 1564 of PF 29(5) [Sept.-Oct. 2003]. It is proposed to delete test $C$ under Identification to avoid inhalation of ethyl acetate.
(PA1: C. Anthony) RTS-41625-1

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■1S (USP28)

## Change to read:

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ -
Solution: $10 \mu \mathrm{~g}$ per mL.
Medium: methanol.
Absorptivities at 242 nm , calculated on the dried basis, do not differ by more than $2.5 \%$.

C: To about 50 mg entained in a test tube add 2 mL of aleo
hol and 2 mL of dilute sulfaric acid ( 1 in -3.5 ), and boil gently for about 1 minte: the oder of ethylacetate is pereeptible.

■ ${ }^{\text {2S }}$ (USP28)

## Add the following:

-Other requirements-Where the label states that Prednisolone Acetate is sterile, it meets the requirements for Sterility under Prednisolone Acetate Injectable Suspension.■1S (USP28)

## Briefing

Prilocaine. Because there is no existing USP monograph for this drug substance, a new monograph is proposed. The tests for Limit of prilocaine related compound $A$ and Related compounds were validated using a Symmetry C18 brand of L1 column. Typical retention times are approximately 9,24 , and 28 minutes for $o$-toluidine (prilocaine related compound A), prilocaine, and (RS)-N-(4-methylphenyl)-2-(propylamino)propanamide (prilocaine related compound B), respectively.
(PA1: K. Russo; NL: C. Barnstein; PSD: C. Okeke) RTS-41125-1; 41125-2; 41125-3

## Add the following:

## © Prilocaine


$\mathrm{C}_{13} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{O} \quad 220.31$
Propranamide, $N$-(2-methylphenyl)-2-(propylamino).
2-(Propylamino)-o-propionotoluidide.
(RS)-N-(2-methylphenyl)-2-(propylamino)propanamide [721-50-6].
» Prilocaine contains not less than 99.0 percent and not more than 101.0 percent of $\mathrm{C}_{13} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{O}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in well-closed containers and store below $25^{\circ}$.

USP Reference standards $\langle 11\rangle —$ USP Prilocaine RS. USP Prilocaine Related Compound A RS. USP Prilocaine Related Compound B RS.

Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$-Because of the low melting point of prilocaine, the mortar, pestle, and potassium bromide must be at ambient temperature. Record the IR spectrum using the diffuse reflectance technique.

Melting range, Class $1 a\langle 741\rangle$ : between $36^{\circ}$ and $39^{\circ}$, without previous drying.

Water, Method Ia $\langle 921\rangle$ : not more than $0.5 \%$, determined on 1.00 g of sample.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Limit of prilocaine related compound A-
Mobile phase-Prepare as directed under Related compounds.
Standard solution-Dissolve an accurately weighed quantity of USP Prilocaine Related Compound A RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $1.3 \mu \mathrm{~g}$ per mL .

Test solution-Transfer about 100 mg of Prilocaine, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )Use the system as described under Related compounds. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the signal-to-noise ratio of the major peak should be greater than 10 .
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks: any peak corresponding to prilocaine related compound A (o-toluidine) in the Test solution is not greater than the response of the major peak in the Standard solution $(0.01 \%)$.

## Related compounds-

Buffer-Dilute 1.3 mL of a 1 M sodium phosphate monobasic solution ( 1.38 g diluted with water to 10 mL ) and 32.5 mL of a 0.5 M anhydrous disodium hydrogen phosphate solution ( 7.1 g diluted with water to 100 mL ) with water to 1 L. The pH of this solution is 8.0. Make adjustments as needed.

Mobile phase—Prepare a degassed mixture of Buffer and acetonitrile ( $73: 27$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
System suitability solution-Dissolve accurately weighed quantities of USP Prilocaine RS and USP Prilocaine Related Compound B RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having known concentrations of about $2.5 \mu \mathrm{~g}$ per mL and $3.0 \mu \mathrm{~g}$ per mL , respectively.

Test solution-Transfer about 25 mg of Prilocaine, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $240-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.19 for prilocaine related compound B and 1.0 for prilocaine; the resolution, $R$, between prilocaine and prilocaine related compound $B$ is not less than 3.0 ; and the signal-to-noise ratio for the prilocaine peak is not less than 10 .

Procedure-Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Run the chromatograms for at least 1.5 times the retention of prilocaine. Check the stability of the baseline by injecting Mobile phase. Calculate the percentage of each impurity in the portion of Prilocaine taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the individual peak response of each impurity; and $r_{s}$ is the sum of the responses of all the peaks: not more than $0.2 \%$ of any individual impurity is found; not more than one impurity exceeds $0.1 \%$, and not more than $0.5 \%$ of total impurities is found.

Assay—Dissolve 400 mg of Prilocaine, accurately weighed, in 50 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Each mL of 0.1 perchloric acid is equivalent to 22.03 mg of $\mathrm{C}_{13} \mathrm{H}_{20}$ $\mathrm{N}_{2} \mathrm{O}$. ${ }^{2 S}$ (USP28)

Propofol, page 3296 of the Second Supplement. It is proposed to revise the Packaging and storage statement to indicate storage at room temperature rather than restricting the excursions to between $15^{\circ}$ and $30^{\circ}$. The Labeling statement is revised to specify that the labeling only needs to indicate a Related compounds test other than Test 1. It is proposed to revise the preparation of the Resolution solution for Test 1 by changing the name of USP Propofol Resolution RS to USP Propofol Resolution Mixture RS and adding USP Propofol Related Compound C RS [2-(1-methylethoxy)-1,3-bis(1methylethyl)benzene]. The preparation of System suitability solution 2 in Related compounds Test 2 is revised to indicate use of individual related compound reference standards rather than USP Propofol for System Suitability RS, originally intended as a mixture; and the Procedure for Test 2 is revised to delete the reference to the limit of 2-(1-methylethoxy)-1,3-bis(1-methylethylbenzene), since 2,6-diisopropylphenylisopropyl ether is already listed and these are two names for the same related compound. The USP Reference standards section is revised to reflect the changes in the procedures.
(PA1: K. Russo; PSD: C. Okeke; NL: C. Barnstein) RTS-41122-1; 41592-1; 41592-2; 41592-3

## Change to read:

Packaging and storage-Preserve in tight light resistant
■ $\quad$ 2S (USP28)
containers under an atmosphere of inert gas,
■and protect from light.m2S.(USP28)
Store at $25^{\circ}$, exeursions permitted between $15^{\circ}$ and $30^{\circ}$.
${ }^{\text {■ }}$ room temperature. $\quad$ 2S (USP28)

## Change to read:

Labeling-The labeling indicates the Related compounds test with which the article complies

■if a test other than Test 1 is used.■2S (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Propofol RS. USP Propofol Related Compound A RS. USP Propofol Related Compound B
 bility RS.

- USP Propofol Related Compound C RS. USP Propofol

Resolution Mixture $R S_{\mathbf{■}^{\text {2S }} \text { (USP28) }}$

## Change to read:

Related compounds-[NOTE-On the basis of knowledge of the manufacturing process, either (1) Related compounds Test 1 is performed in conjunction with the Limit of propofol related compound A, Limit of propofol related compound B Test 1, and Assay Test 1 procedures; or (2) Related compounds Test 2 is performed in conjunction with the Limit of propofol related compound B Test 2 and the Assay Test 2 procedures.]

TEST 1-
Resolution solution-Dissolve an accurately weighed quantity of USP Propefol Resolution PS
-USP Propofol Resolution Mixture $\mathrm{RS}_{\mathbf{m}^{2 S}}$ (USP28)
in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a concentration of about 100 mg per mL .
Standard solution-Dissolve an accurately weighed quantity of USP Propofol RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a concentration of about 0.1 mg per mL .

Test solution - Transfer about 1000 mg of Propofol, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with methanol to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )——Proceed as directed under Assay Test 1, except to chromatograph the Standard solution six times and chromatograph the Resolution solution: the relative retention time is about 0.18 for 2,6-diisopropylphenyl isopropylether, 1.0 for propofol, and about 1.1 for 2-isopropyl-6- $n$-propylphenol; the resolution, $R$, between propofol and 2-isopropyl-6-n-propylphenol is not less than 2. Chromatograph the Standard solution six times, and record the peak responses as directed for Procedure: the column efficiency determined from the propofol peak is not less than 5000 theoretical plates; and the relative standard deviation for replicate injections is not more than $3.5 \%$.
Procedure-Separately inject equal volumes (about $1.0 \mu \mathrm{~L}$ ) of the Resolution solution, the Standard solution, and the Test solution into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of each impurity in the portion of Propofol taken by the formula:

$$
0.1\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the peak response for propofol obtained from the Standard solution: not more than $0.1 \%$ of 2,6-diisopropylphenyl isopropylether is found; not more than $0.1 \%$ of each other individual impurity is found; and not more than $0.3 \%$ of total impurities is found.

TEST 2-
Mobile phase-Prepare as directed in Assay Test 2.
System suitability solution 1-Transfer $5 \mu \mathrm{~L}$ of USP Propofol RS and $15 \mu \mathrm{~L}$ of USP Propofol Related Compound B RS to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with hexane to volume, and mix.

System suitability solution 2- Pissolve 1 mL of USP Propefor for System Sutability RS with hewane to make- 10 -mL.
-Dissolve an accurately weighed quantity of USP Propofol Related Compound A RS and accurate volumes of the propofol that is under test and USP Propofol Related Compound $C R S$ in hexane, and dilute quantitatively, and stepwise if necessary, with hexane to obtain a solution hav-
ing known concentrations of 0.25 mg propofol related compound A per $\mathrm{mL}, 100 \mu \mathrm{~L}$ of propofol per mL , and $5 \mu \mathrm{~L}$ of propofol related compound C per mL. $\mathbf{n}_{2 \text { S }}$ (USP28)

Test solution-Transfer about 1000 mg of Propofol, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with hexane to volume, and mix.

Reference solution-Dilute 1 mL of the Test solution with hexane to 100 mL , and mix. Dilute 1 mL of this solution with hexane to 10 mL , and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—Proceed as directed in Assay Test 2. Chromatograph System suitability solution 1 and System suitability solution 2, and record the peak responses as directed for Procedure: the relative retention times are about 0.8 for propofol related compound B from System suitability solution 1, 0.5 for 2-(1-methylethoxy)-1,3-bis(1-methylethylbenzene), 1.0 for propofol, and 5.0 for propofol related compound A from System suitability solution 2; the resolution, $R$, between propofol related compound B and propofol is at least 4.0.

Procedure-Separately inject a volume (about $10 \mu \mathrm{~L}$ ) of the Test solution and the Reference solution into the chromatograph, record the chromatogram, and measure all peak responses. Calculate the percentage of each impurity in the portion of Propofol taken by the formula:

$$
0.1\left(r_{i} / r_{S}\right)(1 / F)
$$

in which $r_{i}$ is the peak response for each impurity obtained from the Test solution; $r_{S}$ is the peak response for propofol obtained from the Reference solution; and $F$ is the response factor. $F$ is 0.2 for 2,6diisopropylphenylisopropyl ether and 4.0 for propofol related compound A: more than $0.2 \%$ of 2 ( 1 methylethoxy) 1,3 bis ( $1-$ methylethylbenzene) is found;

## ■ ${ }^{\text {■ }}$ (USP28)

not more than $0.2 \%$ of 2,6-diisopropylphenylisopropyl ether is found; not more than $0.01 \%$ of propofol related compound A is found; not more than $0.05 \%$ of each of the other individual impurities is found; and not more than $0.3 \%$ of total impurities is found.
remaining stock solution for the Assay for sodium and potassium, the Assay for chloride, the Assay for bicarbonate, and the Assay for citrate.] Determine the angular rotation in a suitable polarimeter tube at $25^{\circ}$ (see-9ptical Rotation- 781 ) ). Caleulate the quantity, in $\frac{5}{2}$, of anhydrous dextrese $\left(\mathrm{C}_{6} \mathrm{H}_{42} \mathrm{O}_{6}\right)$ in the unit dose container er containers taken or in the portion of powder taken from the mul tiple unit container, by the formula:

## $(200152.7)(a t)$,

in which 52.7 is the specifie rotation of anhydrous dextrose, a is the eerrected observed rotation, in degrees, and $l$ is the length, in dm, of the pelarimeter tabe. Where the-Oral-Rehydration-Salts is lat beledtocentain Dextrose-Menehydrate, ealeulate the quantity of dextrese menehydrate $\left(\mathrm{C}_{6} \mathrm{H}_{42} \Theta_{6} \cdot \mathrm{H}_{2} \Theta\right)$ by the same formula, substituting the figure 47.9, the specific rotation of dextrose monohy Arate, in place of 52.7.
-(see Optical Rotation $\langle 781\rangle$ ). Where the Oral Rehydration Salts is labeled to contain anhydrous dextrose, calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6}$ in the portion of Oral Rehydration Salts taken by the formula:
(100/52.9)AR,
in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; $A$ is 100 mm divided by the length of the polarimeter tube, in mm; and $R$ is the observed rotation, in degrees. Where the Oral Rehydration Salts is labeled to contain dextrose monohydrate, calculate the percentage (g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Oral Rehydration Salts taken by the formula:

$$
(100 / 52.9)(198.17 / 180.16) A R
$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees. $\quad$ 2S (USP28)

Ringer's and Dextrose Injection, USP 27 page 1657 and page 1293 of PF 30(4) [July-Aug. 2004]-See briefing under Alcohol in Dextrose Injection.
(PA1: K. Russo) RTS-41401-10

## Change to read:

Labeling-The label states the total osmolar concentration in mOsmol per liter. Where the contents are less than 100 mL , the label alternatively may state the total osmolar concentration in mOsmol per mL . The label ineludes also the warning "Not for use in the treatment of lactic acidosis."

■.1S(USP28)

## Change to read:

Assay for dextrose-Transfer an accurately measured volume of Injection, containing 2 to 5 g of dextrose, to a $100-\mathrm{mL}$ volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. Determine the angular rotation in a suitable polarimeter tube at $25^{\circ}$ (see-9ptical Rotation (781)). The observed fotation, in degrees, multiplied by $1.0425 A$, in which $A$ is the ratio 200 -divided by the length, in mm, of the pelarimeter tube-em ployed, represents the weight, in $\frac{5}{5}, \mathrm{of}_{6} \mathrm{H}_{4} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the volume of Injection taken.
-(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:

$$
(100 / 52.9)(198.17 / 180.16) A R
$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm; and $R$ is the observed rotation, in degrees. $\mathbf{m}^{2 S}$ (USP28)

Briefing

Simvastatin, USP 27 page 1692. It is proposed to revise the Packaging and storage section based on the current manufacturer's requirements.
(PA4: E. Gonikberg; PSD: C. Okeke) RTS-41487-1

## Change to read:

Packaging and storage-Preserve in well-closed containers. tur der nitregen

- Store between $15^{\circ}$ and $30^{\circ}$, or under refrigeration. $\quad$ 2S (USP28)


## BRIEFING

Sodium Chloride and Dextrose Tablets, USP 27 page 1702See briefing under Alcohol in Dextrose Injection.
(PA1: K. Russo) RTS-41401-11

## Change to read:

Assay for dextrose-Dissolve not fewer than 10 Tablets, containing from 2 to 5 g of dextrose, in about 75 mL of water in a $100-\mathrm{mL}$ volumetric flask, add several drops of 6 N ammonium hydroxide, dilute with water to volume, and mix. After 30 minutes, filter through a dry filter, and determine the angular rotation in a 200 mm tube at $25^{\circ}$, retaining the excess of the solution for the $A$ ssaty for sodiun ehtoride. The observed rotation in degrees, multiplied by 1.0425 , represent the weight, in of, of $_{6} \mathrm{H}_{42} \Theta_{6} \cdot \mathrm{H}_{2} \Theta$ in the spec mmen taken.
-suitable polarimeter tube (see Optical Rotation $\langle 781\rangle$ ), retaining the excess of the solution for the Assay for sodium chloride. Calculate the percentage ( g per 100 mL ) of
$\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:
$(100 / 52.9)(198.17 / 180.16) A R$,
in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees. $\quad$ 2S (USP28)

## BRIEFING

Soybean Oil, USP 27 page 1718 and page 3084 of the First Supplement; Sesame Oil, NF 22 page 2926 and page 608 of $P F$ $30(2)$ [Mar.-Apr. 2004]. On the basis of comments received, it is proposed to revise the Definition and add a Labeling section to include the use of a suitable antioxidant.
(EMC: C. Sheehan; NL: W. Paul) RTS-41628-1

## Change to read:

» Soybean Oil is the refined fixed oil obtained from the seeds of the soya plant -Glycine max Merr. (Fabaceae). $\mathbf{m S ~}^{1 \mathrm{~S}}$ (USP27)
-It may contain suitable antioxidants. ${ }^{\text {ens }}$ (USP28)

## Add the following:

-Labeling-Label it to indicate the name and quantity of any added antioxidant. ${ }^{2 S}$ (USP28)

## Briefing

Testosterone Enanthate, USP 27 page 1793. On the basis of historical data, it is proposed to change the limit of Water from $0.05 \%$ to $0.5 \%$.
(PA1: C. Anthony) RTS-41611-1

## Change to read:

Water, Method $I\langle 921\rangle$ : not more than $0.05 \%$.
$-0.5 \%$. ${ }^{-}$2S (USP28)

## BRIEFING

Tetracaine Hydrochloride in Dextrose Injection, USP 27 page 1799-See briefing under Alcohol in Dextrose Injection.
(PA1: K. Russo) RTS-41401-12

## Change to read:

Assay for dextrose-Determine the angular rotation of Injection in a suitable polarimeter tube (see Optical Rotation $\langle 781\rangle$ ). The ebserved retation, in degrees, multiplied by $9.452 A$, in whieh $A$ is the ratio of 200 divided by the length, in mm, of the polarimeter tube employed, represents the weight, in mg, of dextrese $\left(\mathrm{C}_{6} \mathrm{H}_{42} \Theta_{6}\right)$ in each mL of the Injection.
-Calculate the percentage (g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6}$ in the portion of Injection taken by the formula:
(100/52.9)AR,
in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; $A$ is 100 mm divided by the length of the polarimeter tube, in mm; and $R$ is the observed rotation, in degrees. $\mathbf{L S S}_{\text {(USP28) }}$

Theophylline in Dextrose Injection, USP 27 page 1815-See briefing under Alcohol in Dextrose Injection.
(PA1: K. Russo) RTS-41401-13

## Change to read:

Assay for dextrose-Transfer an accurately measured volume of Injection, containing 2 to 5 g of dextrose, to a $100-\mathrm{mL}$ volumetric flask. Add 0.2 mL of 6 N ammonium hydroxide, dilute with water to volume, and mix. Determine the angular rotation in a suitable polarimeter tube at $25^{\circ}$ (see -iptied Rotan (781)). The observed retation, in degrees multiplied by 1.04254 , in which 4 is the ratio 200 divide by the length, in mm, of the pelarimeter tube em ployed, represents the weight, ing, $\mathrm{of}_{6} \mathrm{H}_{+2} \Theta_{6} \cdot \mathrm{H}_{2} \Theta$ in the volume of Injection taken.
-(see Optical Rotation $\langle 781\rangle$ ). Calculate the percentage ( g per 100 mL ) of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \cdot \mathrm{H}_{2} \mathrm{O}$ in the portion of Injection taken by the formula:

$$
(100 / 52.9)(198.17 / 180.16) A R
$$

in which 100 is percent; 52.9 is the midpoint of the specific rotation range for anhydrous dextrose, in degrees; 198.17 and 180.16 are the molecular weights for dextrose monohydrate and anhydrous dextrose, respectively; $A$ is 100 mm divided by the length of the polarimeter tube, in mm ; and $R$ is the observed rotation, in degrees. $\quad$ 2S (USP28)

## BRIEFING

Tiagabine Hydrochloride, USP 27 page 1841 and page 3305 of the Second Supplement. It is proposed to revise the test for Chromatographic purity to add the names of the impurities listed by retention times in the table of Relative Response Factors.
(PA3: S. Salado) RTS-41610-1

## Change to read:

## Chromatographic purity-

Solution A-Use a filtered and degassed solution of water adjusted with phosphoric acid to a pH of 2.3 .
Solution B-Use filtered and degassed acetonitrile.
Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard stock solution-Dissolve an accurately weighed quantity of USP Tiagabine Hydrochloride RS in water to obtain a solution having a known concentration of about 1 mg per mL .
Standard solution-Dilute a portion of the Standard stock solution quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.001 mg per mL .

Resolution solution-Dissolve an accurately weighed quantity of -USP Tiagabine Related Compound $\mathrm{A} \mathrm{RS}_{\text {I2S }}$ (USP27) in water to obtain a solution having a known concentration of about 1 mg per mL. Transfer 1.0 mL of this solution and 1.0 mL of the Standard stock solution to a $10-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Test solution-Transfer about 100 mg of Tiagabine Hydrochloride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 75 | 25 | equilibration |
| $0-30$ | $75 \rightarrow 45$ | $25 \rightarrow 55$ | linear gradient |
| $30-40$ | $45 \rightarrow 10$ | $55 \rightarrow 90$ | linear gradient |
| $40-45$ | 10 | 90 | isocratic |

Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between tiag-
 is not less than 9.0; chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.
Interference check-Inject water as the blank: no interfering peaks are observed.
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of each impurity in the portion of Tiagabine Hydrochloride taken by the formula:

$$
100 F\left(r_{i} / r_{s}\right)
$$

in which $F$ is the relative response factor (see the accompanying table for values) for each impurity; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{s}$ is the sum of the responses of all the peaks, excluding the solvent peaks. (See the accompanying table for limits of individual impurities.) Not more than $1.0 \%$ of total impurities is found.

Relative Response Factors

| ${ }^{\text {- }}$ Compound ${ }^{\text {Name }}{ }_{\text {m2S }}$ (USP28) | Relative Retention Time <br> $\mathbf{n}^{(\text {approximated })}{ }_{\text {ne (USP28) }}$ | $F$ | Limit (\%) |
| :---: | :---: | :---: | :---: |
| -(R)-1-[4,4-Bis(3-methyl-2-thienyl)-3,4-dihydroxybutyl]-3-piperidinecarboxylic acid | 0.51 | 0.75 | 0.2 |
| $\begin{aligned} & \text { (R)-1-[4,4-Bis(3-methyl-2-thienyl)-3-oxybutyl]-3-piperidine- } \\ & \quad \text { carboxylic } \operatorname{acid}^{\square 2 S}(U S P 28) \end{aligned}$ | 0.79 | 0.63 | 0.1 |
| $\begin{aligned} & (R) \text {-1-[4-(3-Methyl-2-thienyl)-4-(2-thienyl)-3-butenyl]-3-piperi- } \\ & \quad \text { dinecarboxylic acid } \\ & \mathbf{m}^{2 S}(U S P 28) \end{aligned}$ | 0.93 | 1.00 | 0.1 |
| -Tiagabine | 1.0 | - | -2S (USP28) |
| $\begin{aligned} & (R) \text {-Methyl 1-[[4-( } x \text {-methyl-2-thienyl)-4-( } y \text {-methyl-2-thienyl)]-3- } \\ & \text { butenyl]-3-piperidinecarboxylic acid }{ }_{\mathbf{2 S}(U S P 28)} \end{aligned}$ | 1.13 | 1.00 | 0.6 |
| $\begin{aligned} & (R) \text {-Methyl 1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidine- } \\ & \text { carboxylate }_{\boldsymbol{\omega S} \text { (USP28) }} \end{aligned}$ | 1.32 | 1.01 | 0.2 |
| -Tiagabine related compound $\mathrm{A}_{\boxed{\square} 2 \mathrm{~S}}$ (USP28) | 1.39 | 1.04 | 0.2 |
| -4,4-Bis(3-methyl-2-thienyl)-3-buten-1-ol $\mathbf{L 2 S}_{\text {(USP28) }}$ | 1.98 | 0.97 | 0.2 |
| - Bis(3-methyl-2-thienyl)methanone $\mathbf{\square}^{2 S}$ (USP28) | 2.27 | 0.39 | 0.1 |
| -4,4-Bis(3-methyl-2-thienyl)-3-buten-1-ol, methanesulfonate $_{\text {m }}$ (USP28) | 2.33 | 0.96 | 0.1 |
| $\mathbf{- 2 , 2 - B i s ( 3 - m e t h y l - 2 - t h i e n y l ) t e t r a h y d r o f u r a n ~}_{\mathbf{L 2 S}^{2 S} \text { (USP28) }}$ | 2.54 | 0.94 | 0.1 |
| - Any unknown impurity $_{\mathbf{m}_{2 S} \text { (USP28) }}$ | - | 1.00 | 0.1 |

## Briefing

Water for Injection, USP 27 page 1949 and page 3087 of the First Supplement. The Pharmaceutical Waters Expert Committee proposes, with the concurrence of the Analytical Microbiology Expert Committee, a revision in the test for Bacterial endotoxins to harmonize with the European Pharmacopoeia and to be consistent with the language in Bacterial Endotoxins Test $\langle 85\rangle$.
(PW: F. Barletta; AMB: D. Porter) RTS—41213-2; 41215-1

## Change to read:

" Water for Injection is water purified by distillation or $\Delta$ a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms. $\triangle$ USP27 It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or comparable regulations of the European Union, Japan,
-or the World Health Organization's Guidelines
for Drinking Water Quality.n2S (USP28)
It contains no added substance.
NOTE-Water for Injection is intended for use in the preparation of parenteral solutions. Where used for the preparation of parenteral solutions subject to final sterilization, use suitable means to minimize microbial
growth, or first render the Water for Injection sterile and thereafter protect it from microbial contamination. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Water for Injection sterile and, thereafter, protect it from microbial contamination. The tests for Total organic carbon and Water conductivity apply to Water for Injection produced on site for use in manufacturing. Water for Injection packaged in bulk for commercial use elsewhere meets the requirement of the test for Bacterial endotoxins as indicated below and the requirements of all the tests under Sterile Purified Water, except $L a-$ beling.

## Change to read:

Bacterial endotoxins $\langle 85\rangle$ - It contains
$\boldsymbol{- l}^{\text {lesS }}{ }_{\text {2S }}$ (USP28)
than 0.25 USP Endotoxin Unit per mL.

Pure Steam. During the Open Conference held in New Orleans in May 1998, it was concluded that there is no universally accepted standard for Pure Steam and it was recommended that the USP address this issue. The Pharmaceutical Waters Expert Committee proposes this new monograph and encourages public comment. The Committee has assigned specific requirements to the steam or vapor phase while the testing is performed on the condensate, which must meet the requirements for Water for Injection (WFI). Comments should be addressed to Frank Barletta, the Committee Liaison.

$$
\text { (PW: F. Barletta) } \quad \text { RTS }-41332-1
$$

## Add the following:

## ■ Pure Steam

NOTE-For microbiological guidance see general information chapter Water for Pharmaceutical
Purposes $\langle 1231\rangle$.
» Pure Steam is water that has been heated above $100^{\circ}$ and vaporized in a manner which prevents source water entrainment. It is prepared from water complying with the U.S. Environmental Protection Agency National Primary Drinking Water Regulations or drinking water regulations of the European Union, Japan or the WHO drinking water guidelines. It contains no added substance. The level of steam saturation or dryness, and the amount of non-condensable gases are to be determined by the Pure Steam application.

NOTE-Pure Steam quality is difficult to assess in its vapor state; therefore the attributes of its condensate are used to indirectly test its quality. The process used to create and collect the condensate for analysis must not adversely impact these quality attributes.

USP Reference standards $\langle 11\rangle$ —USP 1,4 Benzoquinone RS. USP Endotoxin RS. USP Sucrose RS.

Bacterial endotoxins $\langle 85\rangle$-The condensate contains less than 0.25 USP Endotoxin Unit per mL.

Total Organic Carbon $\langle 643\rangle$ : the condensate meets the requirement.

Water Conductivity $\langle 645\rangle$ : the condensate meets the re-
quirement.■2S (USP28)

## Briefing

Small Intestinal Submucosa Wound Matrix, page 538 of $P F$ 30(2) [Mar.-Apr. 2004]. On the basis of comments and data received, it is proposed to simplify the preparation of the Test solution in the test for Fibroblast growth factor-2 content. This proposed new preparation procedure is less time consuming and results in lower loss of material during the tissue extraction process. Interested parties are invited to submit comments.
(GCT: I. DeVeau) RTS-41434-1

## Add the following:

## ■Small Intestinal Submucosa Wound Matrix

» Small Intestinal Submucosa Wound Matrix is a biologically derived, collagen-based wound care product, translucent and off-white in color. It is obtained from the small intestinal submucosa layer of the domestic pig (Sus scrofa L.). This layer has been mechanically separated from the adjoining layers of the intestine to remove the serosal, mucosal, and muscular elements. The isolated submucosa is chemically cleaned, decellularized, freeze-dried, and terminally sterilized. Small Intestinal Submucosa Wound Matrix also undergoes a viral inactivation; the inactivation method is validated using parvovirus, reovirus, pseudorabies virus, and leukemia retrovirus as the test viruses. By dried weight, Small Intestinal Submucosa Wound Matrix consists of about 70 percent protein, about 20 percent carbohydrate, and about 7 percent lipid. The protein component is primarily
collagen type I (approximately 90 percent), with minor amounts of elastin and collagen type III, collagen type IV, and collagen type VI. In addition to these components, additional extracellular matrix components, such as glycosaminoglycans and basic fibroblast growth factor, are also retained.

Packaging and storage-Package in single-use, peel-open pouches that are gas permeable for sterilization purposes. Store under clean, dry conditions at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-The package is labeled to indicate the dimensions of the enclosed Small Intestinal Submucosa Wound Matrix, the expiry date, required storage conditions, and the lot number. The label indicates that the Wound Matrix is sterile if the package is intact, and that the Wound Matrix is designed for single patient, one-time use.

USP Reference standards $\langle 11\rangle$ —USP Endotoxin RS.
USP Authentic Visual References-USP Cultured Rat Pheochromocytoma Reference Photomicrographs. These photomicrographs represent examples of normal and differentiated rat pheochromocytoma cells and are used to assist in ascertaining bioactivity.

Bacterial endotoxins $\langle 85\rangle$-Immerse $70 \mathrm{~cm}^{2}$ of Small Intestinal Submucosa Wound Matrix in 40 mL of LAL Reagent Water. Extract for 60 minutes at $37^{\circ}$ with shaking. Remove a $100-\mu \mathrm{L}$ aliquot to measure the amount of bacterial endotoxins. It contains not more than 20.0 USP Endotoxin Units per $70 \mathrm{~cm}^{2}$.

Sterility $\langle 71\rangle$ : meets the requirements.

## Fibroblast growth factor-2 content-

8M Urea Dissolve-480.4g of urea in about 700 mL of water. Dilute with water to - L. [Cattion Urea is highly toxic. Avoid skin comtact.]

Extraction buffer Mix 250 mL of 8 M Urea and 750 mL of water. To this solution add 6.0 g of tromethamine and 2.5 of heparin, and mix to dissolve.

N Ethylmateimide solution Dissolve 25 g of N ethylmateimide in 90 mL of aleohel. Dilute with aleohel to 100 mL . Phenylmethylsulfomylfturide solution- Dissolve-3.5 gof phenylmethylsulfonyl fluride in 100 mL of alcohel with gentle heating. [Caution Phenylmethylsulfonyl flurride is highly toxic. Avid skin contact and inhaling dust and va pers.]

Benzamidine hydrochloride solution- Dissolve-15.7g of benzamidine hydrochloride hydrate in $90-\mathrm{mL}$ of water. Di lete with water to 100 mL .

> IgG: agarose suspension Prepare a-suspension cen
taining 5-10-10 mg of human immeneghebulin G: agarese in 0.5 M sodium chloride with $0.01 \%$ thimerisal. ${ }^{+}$

Ealibrator diltent Prepare an aqueous buffered protein solution, with preservative, suitable for the performance of ELISA (see Biotechnology Derived Products $\langle 1045$ ).).²

IgG: agarese diluent Remove an aliquot of the IfG: agatiose suspension, allow the agarese beads to settle, and discard the supernatant. Measure the volume of the remaining agarese gel, add anequal volume of Calibrator dil went, and mix the slurry for 1 hour at $4^{\circ}$. Prepare immediately before use.

Sterile PBS solution-Prepare a sterile solution that contains 8065.0 mg and 200.0 mg of sodium chloride and potassium chloride, respectively, per L of 0.01 M sodium phosphate buffer, pH 7.4 .

Test solution Pulverize the Small-Intestinal Submueosa Wound Matrix in liquid nitrogen using a mortar and pestle that has been prechilled to- $80^{\circ}$. Transfer 10 of powdered tissue to 100 mL of Extraction buffer. Mix 0.5 mL each of A Ethylmateimide solution, Phenylmethylsulfonyl flumide soltuien, and Benzamidine hydrechloride soltaion, and ad just to a pH of 7.4 using sterile selutions of either $0.5 \mathrm{M}-\mathrm{se}$ dium hydroxide or 0.5 M hydrochloric acid. Extract the powdered Small Intestinal Submueosa-Wound Matrix with censtant stirring at $4^{\circ}$ for 24 hours. Centrifuge the extract at $12,000 \times 8$ for 30 minntes at $4^{\circ}$. Place the supernatant inte dialysis tubing with a molecular weight eut offof 3500 dat tons; dialyze at $4^{\circ}$ with stirring against about 20 Lof water. Change the dialysis water 3 times a day for 2 days. Colleet the solution frem the dialysis tubing, and centrifuge at $12,000 \times$ of for 30 minutes at $4^{\circ}$. Lyophilize the supernatant and reconstitute the lyophilisate in water, with vortexing, to aconeentration of 10 mg per mL . Centrifuge at $5000 \times 8$ for 3 minttes, and diseard the pellet. Add $50 \mu \mathrm{H}$ of $I \mathrm{~g} G$ : agarose diluent to the lyophilisate solution, and mix for 4 heur at $4^{\circ}$. Centriftuge at $12,000 \times \frac{8}{}$ for 5 mintes at $4^{\circ}$, recover the supernatant, and store at $4^{\circ}$. Usewithin 24 hours ef preparation. Obtain a $1-\mathrm{cm}^{2}$ sample of Small Intestinal Submucosa Wound Matrix, weigh, and submerge in 400 $\mu \mathrm{L}$ of Sterile PBS solution. Pulverize the tissue for 90 seconds using a tissue grinder, intermittently checking to be sure the tissue remains immersed in the Sterile PBS solution and becomes homogenized. Centrifuge at $12,000 \times g$ for 5 minutes at $4^{\circ}$. Use immediately upon preparation. [NOTE-

[^243]The Test solution may be stored for short periods at $4^{\circ}$ or on ice.]

Procedure-Examine duplicate aliquots of the Test solution by a suitably sensitive ELISA method: ${ }^{1}$ the analysis is considered valid if the ELISA kit generates a linear standard curve with the square of the correlation coefficient $\left(r^{2}\right)$ not less than 0.95 , and if the duplicate aliquots of the Test solution yield results that are within $20 \%$ of each other. The average content of fibroblast growth factor-2 is not less than $10,000 \mathrm{pg}$ per g of Small Intestinal Submucosa Wound Matrix.

## Glycosaminoglycan content-

1,9-Dimethylmethylene blue solution-Mix 95 mL of 0.1 M hydrochloric acid in 500 mL of water. Add 16 mg of 1,9-dimethylmethylene blue, 3.04 g of aminoacetic acid, and 2.37 g of sodium chloride. Dilute with water to 1 L and adjust to a pH of 3.0 using sterile solutions of either 1.0 M sodium hydroxide or 1.0 M hydrochloric acid. Store in lowactinic glassware.

Sterile PBS solution -Prepare - sterile solution that eontains 8065.0 mg and 200.0 mg of sodium chloride and $\mathrm{pe}-$ fassitum ehloride, respectively, per L of 0.01 M soditum phesfer, pH 7.4. Prepare as directed under Fibroblast growth factor-2 content.

Proteinase K solution-Prepare a solution of Tritirachium album proteinase K in water having an activity of 600 units per mL.
Stock heparin standard solution-Prepare a solution containing 1 mg of heparin per mL of water.

Heparin standard curve solutions-Using the Stock heparin standard solution, prepare three solutions containing $20 \mu \mathrm{~g}$ per $\mathrm{mL}, 50 \mu \mathrm{~g}$ per mL , and $100 \mu \mathrm{~g}$ per mL of heparin, respectively.

[^244]Blank solution-Use water.
Test solution-Prepare test samples in duplicate. Accurately weigh about 25 mg of Small Intestinal Submucosa Wound Matrix and cut into small pieces (roughly $2 \mathrm{~mm} \times 2$ mm ). Transfer to a $1.5-\mathrm{mL}$ microcentrifuge tube, and add $180 \mu \mathrm{~L}$ of Sterile PBS solution and $20 \mu \mathrm{~L}$ of Proteinase $K$ solution. Mix, and incubate the sample at $56^{\circ}$ for 15 min utes; during the incubation mix intermittently on a vortex mixer. Cool the sample to room temperature. Dilute with water to obtain a concentration of 12.5 mg of digested Small Intestinal Submucosa Wound Matrix per mL.
Collagen control solution-Accurately weigh about 25 mg of a bovine collagen, type I, that contains less than 1 $\mu \mathrm{g}$ of glycosaminoglycan per mg . Transfer to a $1.5-\mathrm{mL}$ microcentrifuge tube, and add $180 \mu \mathrm{~L}$ of Sterile PBS solution and $20 \mu \mathrm{~L}$ of Proteinase $K$ solution. Mix, and incubate the sample at $56^{\circ}$ for 15 minutes; during the incubation mix intermittently on a vortex mixer. Cool the sample to room temperature. Dilute with water to obtain a concentration of 12.5 mg of digested bovine collagen per mL .
Procedure (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ )-To triplicate $100-\mu \mathrm{L}$ aliquots each of Heparin standard curve solutions, Blank solution, Test solution, and Collagen control solution, add 2.5 mL of 1,9-Dimethylmethylene blue solution. Mix on a vortex mixer for 1 second and immediately read the absorbance at 525 nm . Generate a standard curve of absorbance versus concentration using the averages of each Heparin standard curve solution, correcting for the blank, and calculate the regression line and regression coefficient. The concentration of glycosaminoglycan in the Test solution and Collagen control solution is determined directly from the regression line. If the absorbance of the Test solution is greater than the highest Heparin standard curve solution, then dilute the Test solution appropriately, and repeat the Procedure beginning with "To trip-
licate $100-\mu \mathrm{L}$ aliquots." The test is considered valid if the regression curve has a square of the correlation coefficient ( $r^{2}$ ) not less than 0.95 ; the triplicate aliquots of the Test solution and Collagen control solution yield results that are within $20 \%$ of each other, respectively; and the average glycosaminoglycan content of the Test solution is statistically greater than the Collagen control solution using one-tailed, unequal variances, $t$-test at $\alpha=0.05$. The average glycosaminoglycan content of the Test solution is not less than $2 \mu \mathrm{~g}$ per mg.

## Metabolic activity assessment-

Dulbecco's modified Eagle's tissue culture medium-Prepare a solution that contains the components included in the following Table 1:

Table 1

|  | Content |
| :--- | :---: |
| Component | (mg per L) |.

Table 1 (Continued)

\left.| Component |  |
| :--- | :---: |
|  | Content |
| (mg per L) |  |$\right]$

Procedure-Remove three $12-\mathrm{mm}$ diameter circular sections of Small Intestinal Submucosa Wound Matrix, using the appropriate size biopsy punch. Immerse each section into individual wells of a 12-well cell culture plate (dimension of each well is about 22 to 23 mm in diameter and about 17 to 18 mm in depth), each containing 1 mL of Dulbecco's modified Eagle's tissue culture medium. Prepare a positive control by harvesting a full-thickness section of porcine jejunum immediately following slaughter. Rinse the section of jejunum in $37^{\circ}$ isotonic sodium chloride solution for 5 min utes to remove intestinal debris. Using scissors, split open the section of jejunum to form a sheet. Remove three 12mm diameter circular sections of jejunum, using the appropriate size biopsy punch. Immerse each section into individual wells of a 12-well cell culture plate, each well containing 1 mL of Dulbecco's modified Eagle's tissue culture medium. Treat these positive control wells in the same manner as the test wells. Prepare a blank solution using 1 mL of Dulbecco's modified Eagle's tissue culture medium. Allow sections to hydrate for 5 minutes, add $50 \mu \mathrm{~L}$ of MTT reagent to each of the sections and the blank, and mix. Incubate for 3 hours at $37^{\circ}$ in an atmosphere containing $5 \%$ carbon dioxide. Add $100 \mu \mathrm{~L}$ of Detergent reagent to each well, and mix. Leave the samples at ambient temperature in the dark for 2 hours. Measure the absorbance of the resulting solution at 570 nm , adjusting for the blank. For the test to be valid, the average absorbance in the positive control wells is greater than 0.100 . The average absorbance reading for the Small Intestinal Submucosa Wound Matrix wells is less than 0.100 . Bioactivity-
NOTE—Aseptic cell culture techniques should be employed throughout the performance of this test.

Modified RPMI-1640 culture medium-Prepare a sterile solution that contains the components included in the following Table 2:

Table 2

| Component | Content <br> $(\mathrm{mg}$ per L) |
| :--- | :---: |
| Calcium chloride | 264.9 |
| Ferric nitrate, nonahydrate | 0.10 |
| Potassium chloride | 400.0 |
| Magnesium sulfate, heptahydrate | 200.0 |
| Sodium chloride | $6,400.0$ |
| Sodium bicarbonate | $3,700.0$ |
| Sodium phosphate, monobasic, | 125.0 |
| monohydrate |  |
| Glucose | $4,500.0$ |
| Phenol red | 15.0 |
| Sodium pyruvate | 110.0 |
| L-Arginine hydrochloride | 84.0 |
| L-Cystine | 48.0 |
| Aminoacetic acid | 30.0 |
| L-Histidine hydrochloride, | 42.0 |
| monohydrate |  |
| L-Isoleucine | 104.8 |
| L-Leucine | 104.8 |
| L-Lysine hydrochloride | 146.2 |
| L-Methionine | 30.0 |
| L-Phenylalanine | 66.0 |
| L-Serine | 42.0 |
| L-Threonine | 95.2 |
| L-Tryptophan | 16.0 |
| L-Tyrosine | 72.0 |
| L-Valine | 93.6 |
| L-Calcium pantothenate | 4.0 |
| Choline chloride | 4.0 |
| Folic acid | 4.0 |

Table 2 (Continued)

|  | Content <br> (mg per L) |
| :--- | :---: |
| Component | 7.0 |
| Inositol | 4.0 |
| Nicotinamide | 4.0 |
| Pyridoxine hydrochloride | 0.40 |
| Riboflavin | 4.0 |
| Thiamine hydrochloride | 2383.0 |
| Sodium 1-heptanesulfonic acid |  |

Penicillin-streptomycin solution-Prepare a suitable buffered solution containing 10,000 USP Penicillin Units of penicillin per mL and 10 mg of streptomycin per $\mathrm{mL} .{ }^{4}$
PC12 cell line culture medium-Mix 420 mL of Modified RPMI-1640 culture medium, 50 mL of horse serum, ${ }^{5} 25 \mathrm{~mL}$ of fetal bovine serum, ${ }^{6}$ and 5 mL of Penicillin-streptomycin solution. Sterilize by passing through a $0.22-\mu \mathrm{m}$ filter.
Sterile PBS solution-Prepare as directed under Gly Fibroblast growth factor-2 content.
Rat tail collagen solution-Prepare a suspension containing 0.2 mg of rat tail collagen, type I, in sterile water.

Cell culture apparatus-Prepare by adding a sufficient volume of Rat tail collagen solution to completely cover the bottom of each well of a 12 -well cell culture plate (dimension of each well is about 22 to 23 mm in diameter and about 17 to 18 mm in depth). Incubate under sterile condi-

[^245]tions for 2 hours at $37^{\circ}$ or overnight at room temperature. Remove the Rat tail collagen solution by aspiration. Rinse with Sterile PBS solution that has been preheated to $37^{\circ}$.

PC12 cells-Use cultured rat pheochromocytoma cells (ATCC CRL-1721).

Cultivation of PC12 cells-Starting from a frozen culture, prewarm PC12 cell line culture medium to $37^{\circ}$. Add 15 mL of prewarmed PC12 cell line culture medium to a T-75 culture flask. Place a single vial containing the frozen PC12 cells in a $37^{\circ}$ water bath with gentle agitation until they start to thaw (about 1 minute). Complete the thawing procedure by slowly rotating the vial between the hands. Rinse the outside of the vial with 70 percent alcohol. Transfer the contents of the vial to the T-75 flask, and mix. Incubate the cells overnight at $37^{\circ}$ in a $5 \%$ carbon dioxide atmosphere. Transfer the contents of the T-75 culture flask to a sterile centrifuge tube, centrifuge at $200 \times g$ for 5 minutes at $37^{\circ}$, and discard the supernatant. Resuspend the cells in 15 mL of PC12 cell line culture medium, and transfer the contents back into the T-75 culture flask. Incubate the cells at $37^{\circ}$ in a $5 \%$ carbon dioxide atmosphere for 3 days.

Cell feeding-At the end of 3 days, the cells will need to be fed for optimal growth. To feed the cells, remove a flask of cells from the incubator, tightening the cap in the process. Examine the T-75 flask under the microscope and check for microbial contamination and confluency. If there is microbial contamination, then discard the flask. If the cells appear confluent, follow the instructions below for perpetuating the PC12 cell line (see Culture perpetuation). Otherwise, harvest the cells from the flask by pipeting the contents of the flask across the bottom of the flask several times. Transfer the cell suspension to a sterile $50-\mathrm{mL}$ centrifuge tube. Centrifuge the cells at $200 \times g$ for 5 minutes at $37^{\circ}$, and discard the supernatant. Resuspend the cells in 13 mL of PC12 cell line culture medium, prewarmed to $37^{\circ}$. Transfer
the cell suspension back to the T-75 flask, and mix. Loosen the cap of the flask, and return to the incubator; incubate the cells at $37^{\circ}$ in a $5 \%$ carbon dioxide atmosphere for another 3 to 7 days.

Culture perpetuation-To perpetuate a line of PC12 cells for culture, examine under the microscope a T-75 flask containing cells and check for microbial contamination and confluency. If there is microbial contamination, discard the flask and use another. If the cells do not appear confluent, then follow the instructions above for feeding the PC12 cell line (see Cell feeding), beginning with "Otherwise, harvest the cells from the flask by pipeting the contents of the flask across the bottom of the flask several times." If the cells are confluent and there is no contamination, harvest the cells from the flask by pipeting the contents of the flask across the bottom of the flask several times to loosen up the cells from their attachment to the bottom of the flask and to break up cell clusters. Check under the microscope prior to proceeding to ensure that most of the cells have detached from the plastic. Transfer the cell suspension to a sterile $50-\mathrm{mL}$ centrifuge tube, and centrifuge the cells at $200 \times$ $g$ for 5 minutes at $37^{\circ}$. Discard the supernatant and resuspend the cells with 10 mL of PC12 cell line culture medium, prewarmed to $37^{\circ}$. Dispense an equal amount of the cell suspension into each of three to five T-75 flasks, each flask containing 10 mL of PC12 cell line culture medium, prewarmed to $37^{\circ}$, and mix. Return the passed cells to the incubator, being sure to loosen the cap of the flasks. Incubate the cells at $37^{\circ}$ in a $5 \%$ carbon dioxide atmosphere. Feed the cells after 3 days as directed above, beginning with "To feed the cells, remove a flask of cells from the incubator, tightening the cap in the process." [NOTE-To perform the test for Bioactivity, cells that have undergone more than 15 passages after obtaining them from ATCC should not be used.]

Positive control solution-Prepare a solution containing about 10 ng of fibroblast growth factor-2 per mL of PC12 cell line culture medium.

Negative control solution-Use PC12 cell line culture medium.
Test solution-Immerse $70 \mathrm{~cm}^{2}$ of Small Intestinal Submucosa Wound Matrix in sterile water for 5 minutes. Remove the Small Intestinal Submucosa Wound Matrix, and blot excess water using sterile gauze. Weigh the rehydrated Small Intestinal Submucosa Wound Matrix to the nearest 0.1 g and add Modified RPMI-1640 culture medium at a ratio of 7.5 mL of Modified RPMI-1640 culture medium for each 1.0 g of Small Intestinal Submucosa Wound Matrix. Incubate for 24 hours at $37^{\circ}$ with constant shaking. Remove the Small Intestinal Submucosa Wound Matrix, and pass the solution through a $0.22-\mu \mathrm{m}$ filter. Add sufficient quantities of sterile horse serum and sterile fetal bovine serum to concentrations of $10 \%$ and $5 \%$, respectively, and add a sufficient quantity of Penicillin-streptomycin solution such that there are 100 USP Penicillin Units and 0.1 mg of streptomycin per mL. Adjust the pH of the Test solution to 7.4, using a sterile solution of either 1.0 M sodium hydroxide or 1.0 M hydrochloric acid.

Procedure-Harvest a flask of confluent PC12 cells by centrifuging at $200 \times g$ for 5 minutes. Remove the supernatant by aspiration, and resuspend the pellet to obtain a concentration of about $1 \times 10^{6}$ cells per mL of PC12 cell line culture medium. Add to each of three wells of the Cell culture apparatus 1.0 mL of Negative control solution. To a second set of three wells add to each 1.0 mL of Positive control solution, and to a third set of three wells add to each 1.0 mL of Test solution. Add to each well about 20,000 cells, mix by gentle rocking, and incubate for 48 hours at $37^{\circ}$. For each well, count three random microscopic fields of cells using a microscope with a $10 \times$ ocular lens and a
$20 \times$ objective lens. Each field should have at least 20 cells; avoid large clumps of cells where individual cell bodies cannot be ascertained. Determine the total number of cells in the field and, using USP Cultured Rat Pheochromocytoma Reference Photomicrographs of normal and differentiated rat pheochromocytoma cells for comparison, determine the total number of cells that have formed at least one neurite-like extension at least twice the diameter of a normal, undifferentiated cell body. For each experimental group, record the total number of cells counted and the total number of cells differentiated across all three wells, and calculate the total percentage of cells that have differentiated. For a test to be valid, the following criteria must be met: (1) none of the wells are microbially contaminated; (2) the weighted percentage of differentiated cells across the Negative control solution wells is less than $5 \%$; (3) the weighted percentage of differentiated cells across the Positive control solution wells is greater than $6 \%$; and (4) the weighted percentage of differentiated cells across the Negative control solution wells is statistically less than the weighted percentage of differentiated cells across the Positive control solution wells, using a one-sided, two-sample test for proportions at $\alpha=0.05$. The weighted percentage of differentiated cells incubated in the Test solution wells is statistically greater than those incubated in the Negative control solution wells, using a one-sided, two-sample test for proportions at $\alpha=0.05 \cdot \mathbf{@ L S}^{\text {(USP28) }}$

## Briefing

Excipients, USP and NF Excipients, Listed by Category, $N F$ 22 page 2809, page 3355 of the Second Supplement, and page 1317 of PF 30(4) [July-Aug. 2004]. The proposed revision complements the proposed new monograph, Myristic Acid, that appears elsewhere in this number of PF.
(EMC) RTS-41326-1

## Change to read:

Acidifying Agent
Acetic Acid
Acetic Acid, Glacial
Gitric Acid
${ }^{\Delta}$ Citric Acid, Anhydrous $\mathbf{\Delta N F 2 3}$
${ }^{\mathbf{\Delta}}$ Citric Acid Monohydrate $\mathbf{\Delta N F 2 3}$
Fumaric Acid
Hydrochloric Acid
Hydrochloric Acid, Diluted
Malic Acid
Nitric Acid
Phosphoric Acid
Phosphoric Acid, Diluted
Propionic Acid
Sulfuric Acid
Tartaric Acid

## Change to read:

Antifoaming Agent
Dimethicone

- Myristic Acid $_{\text {■2S (NF23) }}$
- Palmitic Acid ${ }_{\text {■1S (NF23) }}$ Simethicone


## Change to read:

Antimicrobial Preservative
Benzalkonium Chloride
Benzalkonium Chloride Solution
Benzethonium Chloride
Benzoic Acid
Benzyl Alcohol
Butylparaben
${ }^{\mathbf{\Delta}}$ Cetrimonium Bromide $\mathbf{A N F 2 2}$
Cetylpyridinium Chloride
Chlorobutanol
Chlorocresol
Cresol
Ethylparaben
Methylparaben
Methylparaben Sodium
Phenol
$\mathbf{\Delta}_{2}$-Phenoxyethanol $\mathbf{\Delta N F 2 3}$
Phenylethyl Alcohol
Phenylmercuric Acetate

Phenylmercuric Nitrate
Potassium Benzoate
Potassium Sorbate
Propylparaben
Propylparaben Sodium
Sodium Benzoate
Sodium Dehydroacetate
Sodium Propionate
Sorbic Acid
Thimerosal
Thymol

## Change to read:

## Antioxidant

Ascorbic Acid
Ascorbyl Palmitate
Butylated Hydroxyanisole
Butylated Hydroxytoluene
Hypophosphorous Acid
Monothioglycerol
Potassium Metabisulfite
Propyl Gallate
Sodium Formaldehyde Sulfoxylate
Sodium Metabisulfite
${ }^{\mathbf{4}}$ Sodium Sulfite ${ }_{\mathbf{\Delta} N F 23}$
Sodium Thiosulfate
Sulfur Dioxide
Tocopherol
Tocopherols Excipient

## Change to read:

Buffering Agent
Acetic Acid
${ }^{\Delta}$ Adipic Acid ${ }_{\mathbf{A} N F 23}$
Ammonium Carbonate
Ammonium Phosphate
Boric Acid
Gitrie Acid
${ }^{\Delta}$ Citric Acid, Anhydrous $\mathbf{\Delta N F 2 3}$
${ }^{\boldsymbol{\Delta}}$ Citric Acid Monohydrate $\mathbf{\Delta N F 2 3}$
Lactic Acid
Phosphoric Acid
Potassium Citrate
Potassium Metaphosphate
Potassium Phosphate, Monobasic
Sodium Acetate
Sodium Citrate
Sodium Lactate Solution
Sodium Phosphate, Dibasic
Sodium Phosphate, Monobasic
${ }^{\boldsymbol{\Delta}}$ Succinic Acid $_{\mathbf{\Delta N F 2 3}}$

## Change to read:

## Coating Agent

-Ammonio Methacrylate Copolymer ${ }_{1 S}{ }_{\text {(NF23) }}$

- Ammonio Methacrylate Copolymer Dispersion ${ }_{\text {US }}$ (NF22)

Carboxymethylcellulose, Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate

Cellulose Acetate Butyrate
${ }^{\mathbf{\Delta}}$ Cellaburate $\mathbf{\Delta N F 2 3}$
Cellulose Acetate Phthalate (see Cellacefate)


- Corn Syrup Solids ${ }_{\text {■ }}$ (NF23)

Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose ${ }^{\Delta}$ (see Hypromellose) ANF22
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
${ }^{\text {a }}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) $\mathbf{A N F 2 2}^{\text {a }}$
-Hypromellose Acetate Succinate $_{\text {■1S (NF23) }}$
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate
Shellac
$\square_{\text {©Starch, }}$ Pregelatinized Modified $\mathbf{I S ~ ( N F 2 3 ) ~}$
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

## Change to read:

## Emollient

Alkyl (C12-15) Benzoate

-Polydecene $\mathbf{I I S}_{1 \text { (NF23) }}$

## Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Cholesterol
Diethanolamine (Adjunct)
Diethylene Glycol Stearates ${ }_{\text {1S }}$ (NF22)
${ }^{\text {Dethylene Glycol Stearates }}$ IS (NF22)
${ }_{\Delta}^{\Delta}$ Glyceryl Distearate ${ }_{\text {ANF22 }}$
${ }_{\Delta}^{\Delta}$ Glyceryl Monolinoleate ${ }_{\text {ANF22 }}$
${ }^{\Delta}$ Glyceryl Monooleate ${ }_{\mathbf{A} N F 22}$
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 40 Stearate

- Polyoxyl Lauryl Ether ${ }_{\text {1S (NF22) }}$
-Polyoxyl Stearyl Ether. 1 (NF22)
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
${ }^{-}$Sodium Cetostearyl Sulfate ${ }_{\text {1S }}$ (NF22)
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Stearic Acid
Trolamine
Wax, Emulsifying


## Change to read:

## Flavors and Perfumes

Anethole
Benzaldehyde
Ethyl Vanillin

- Maltol $_{\text {■ }}$ S (NF23)

Menthol
Methyl Salicylate
Monosodium Glutamate
Peppermint
Peppermint Oil
Peppermint Spirit
Rose Oil
Rose Water, Stronger
Thymol
Vanillin

## Change to read:

## Humectant

${ }^{\text {E }}$ Corn Syrup Solids $\mathbf{■ 1 S}^{\text {(NF23) }}$
Glycerin
Hexylene Glycol
Propylene Glycol
Sorbitol
$\bullet^{\bullet}$ Sorbitol, Anhydrized Liquid ${ }_{\text {1S (NF23) }}$

- Tagatose $_{\text {■2S (NF23) }}$


## Change to read:

[^246]Oleoyl Polyoxylglycerides $_{\text {© }}$ (NF23)
Ointment, Yellow
Polyethylene Glycol Ointment
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White

- Polydecene $\boldsymbol{n}_{\text {1S }}$ (NF23)

Rose Water Ointment
Squalane
Stearoyl Marerogelgyeerides
■Stearoyl Polyoxylglycerides $_{\mathbf{m}_{1 S} \text { (NF23) }}$
Vegetable Oil, Hydrogenated, Type II

## Change to read:

## Plasticizer

Acetyltributyl Citrate
Acetyltriethyl Citrate
Castor Oil
Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin
Polyethylene Glycol
Propylene Glycol
$\square_{\text {Sorbitol, Anhydrized Liquid }}^{\mathbf{m}_{1 S}(N F 23)}$
Triacetin
Tributyl Citrate
Triethyl Citrate

## Change to read:

## Polymer Membrane

-Ammonio Methacrylate Copolymer ${ }_{\text {1S (NF23) }}$
-Ammonio Methacrylate Copolymer Dispersion $_{\text {(NF22) }}$
Cellulose Acetate
Cellulose-Acetate Butyrate
${ }^{\boldsymbol{4}}$ Cellaburate $_{\Delta \text { NF23 }}$
Change to read:
Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)
${ }^{\mathbf{\Delta}}$ Sodium Tartrate ${ }_{\mathbf{\Delta N F 2 3}}$

## Change to read:

## Solvent

Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol
Gapryloraproyl Macrogelglyeerides
$\square_{\text {Caprylocaproyl }}$ Polyoxylglycerides IS (NF23) $^{\text {( }}$
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether

Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
■Lauroyl Macrogolglycerides ${ }_{\text {■ } 1 \mathrm{~S}(\text { NF23 }}$
Lineoy Macrogolglyeerides
■Lineoyl Polyoxylglycerides $_{\text {■ } 1 \mathrm{~S} \text { (NF23) }}$
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Oleqyl Maregolgyyerides
$\square_{\text {Oleoyl Polyoxylglycerides }}^{\mathbf{■}_{1 S}(\text { NF23 })}$
Peanut Oil

- Polydecene $_{\text {1S (NF23) }}$

Polyethylene Glycol
Propylene Glycol
Sesame Oil
Steareyl Macregolglywerides
■Stearoyl Polyoxylglycerides $_{\text {■ }_{1 S} \text { (NF23) }}$
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

## Change to read:

Suspending and/or Viscosity-increasing Agent
Acacia
Agar
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
-Carbomer Homopolymer ${ }_{\text {1S (NF23) }}$
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium
${ }^{\text {- }}$ Corn Syrup Solids ${ }_{\text {■ }}$ (NF23)
Dextrin
Gelatin
${ }_{\text {■Gellan }}$ Gum $_{\text {■1S (NF22) }}$
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose ${ }^{\Delta}$ (see Hypromellose) $\mathbf{A N F 2 2}^{2}$
${ }^{\Delta}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) $\mathbf{a N F 2 2}^{\text {an }}$
Magnesium Aluminum Silicate
Methylcellulose
Pectin

Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate

-Starch, $^{\text {Potato }}{ }_{\text {1S (NF23) }}$
${ }^{\mathbf{4}}$ Starch, Tapioca $\mathbf{A N F 2 2}$

- Starch, Wheatı1S (NF23)

Tragacanth
Xanthan Gum

## Change to read:

## Sweetening Agent

${ }^{\boldsymbol{\Delta}}$ Acesulfame Potassium $\mathbf{A N F 2 3}$
Aspartame
${ }^{\Delta}$ Aspartame Acesulfame $\mathbf{A N F 2 2}$
${ }^{-}$Corn Syrup Solids ${ }_{\text {■ }}$ (NF23)
Dextrates
Dextrose
Dextrose Excipient
Fructose
${ }^{\mathbf{4}}$ Galactose $\mathbf{\Delta N F 2 3}$
${ }^{-}$Maltose M2S (NF22) $^{\text {Mannt }}$
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

- Tagatose $_{\text {■2S (NF23) }}$


## Change to read:

## Tablet Binder

Acacia
Alginic Acid
-Ammonio Methacrylate Copolymer ${ }_{\text {1S (NF23) }}$
${ }^{-}$Ammonio Methacrylate Copolymer Dispersion_(NF22)
${ }^{\mathbf{\Delta}}$ Carbomer Homopolymer ${ }_{\mathbf{A} N F 23}$
Carboxymethylcellulose, Sodium
Cellulose, Microcrystalline

${ }^{-}$Corn Syrup Solids ${ }_{\text {■ }}$ IS (NF23)
Dextrin
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
Hydroxypropyl Methylcellulose ${ }^{\mathbf{\Delta}}$ (see Hypromellose) $\mathbf{\Delta N F 2 2}$
${ }^{\mathbf{\Delta}}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) $\mathbf{A N F 2 2}^{\text {a }}$

${ }^{-}$Maltose ${ }_{\text {2S }}{ }^{\text {(NF22) }}$
Methylcellulose
Polyethylene Oxide
Povidone
${ }^{\mathbf{\Delta}}$ Starch, Corn $_{\mathbf{\Delta N F} 23}$
${ }^{\boldsymbol{\Delta}}$ Starch, Potato $\mathbf{A N F 2 3}$
Starch, Pregelatinized
$\square_{\text {©Starch, Pregelatinized Modified }}^{\text {IS (NF23) }}$
${ }^{\boldsymbol{4}}$ Starch, Tapioca ${ }_{\mathbf{A F F 2 2}}$
${ }^{\boldsymbol{\Delta}}$ Starch, Wheat ${ }_{\Delta N F 23}$
Syrup

## Change to read:

Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered
${ }^{\text {- Corn Syrup Solids }}{ }_{\text {■1S (NF23) }}$
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose
$\mathbf{m a l t o s e}_{\mathbf{■ 2 S}}$ (NF22)
Mannitol
Sorbitol
Stareh
${ }^{\mathbf{\Delta}}$ Starch, $\operatorname{Corn}_{\mathbf{\Delta N F 2 3}}$
${ }^{\Delta}$ Starch, Potato ${ }_{\mathbf{4} N F 23}$
Starch, Pregelatinized

${ }^{\mathbf{\Delta}}$ Starch, Tapioca $\mathbf{\Delta N F 2 2 ~}$
${ }^{\mathbf{4}}$ Starch, Wheat ${ }_{\text {aNF23 }}$

## Sucrose

Sugar, Compressible
Sugar, Confectioner's
${ }^{\mathbf{4}}$ Starch, $^{\text {Potato }}{ }_{\mathbf{\Delta N F 2 3}}$
Starch, Pregelatinized
$\square_{\text {Starch, }}$ Pregelatinized Modified ${ }_{\text {■S (NF23) }}$
${ }^{\boldsymbol{4}}$ Starch, Tapioca $\mathbf{A N F 2 2}^{2}$
${ }^{\mathbf{\Delta}}$ Starch, Wheat ${ }_{\Delta N F 23}$

## Change to read:

## Tonicity Agent

${ }^{\text {- Corn Syrup Solids }}{ }_{\text {■1S (NF23) }}$
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

## Change to read:

## Vehicle

FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound

- Corn Syrup Solids_(NF23)

Peppermint Water
Sorbitol Solution
Syrup
OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
-Polydecene_ $_{\text {1S (NF23) }}$
Safflower Oil
Sesame Oil
Soybean Oil
Squalane
SOLID CARRIER
Sugar Spheres

## STERILE

Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

## Change to read:

Tablet Disintegrant
Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone

- Maltose $_{\text {п2S (NF22) }}$

Polacrilin Potassium
Sodium Starch Glycolate
Stareh
${ }^{\boldsymbol{\Delta}}$ Starch, Corn $_{\mathbf{\Delta N F 2 3}}$

## DIETARY SUPPLEMENTS— MONOGRAPHS

## BRIEFING

> Chromium Picolinate Tablets. Because there is no existing $U S P$ monograph for this dietary supplement, a new monograph, based on validation data received, is being proposed.
(DSN: L. Evans; PSD: C. Okeke; NL: C. Barnstein) RTS-40078-1; 40078-2; 40078-3; 41479-1

## Add the following:

## ■Chromium Picolinate Tablets

## » Chromium Picolinate Tablets contain not less

 than 95.0 percent and not more than 125.0 percent of the labeled amount of chromium $(\mathrm{Cr})$.Packaging and storage-Preserve in well-closed containers, and store at controlled room temperature.

## Identification-

Test solution-Use the Assay preparation.
Procedure-The Test solution gives a positive test for chromium, determined at 357.9 nm using an atomic absorption spectrophotometer as directed for Procedure in the $A s$ say.

Disintegration and dissolution $\langle 2040\rangle$ : meet the requirements for Disintegration only.

Weight variation $\langle 2091\rangle$ : meet the requirements.

Assay-
Standard stock preparation 1-Transfer about 2.829 g of potassium dichromate, previously dried at $120^{\circ}$ for 4 hours and accurately weighed, to a $1000-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix to obtain a solution having a known concentration of about $1000 \mu \mathrm{~g}$ of chromium per mL . Store in a polyethylene bottle.

Standard stock preparation 2-Transfer 10.0 mL of Standard stock preparation 1 to a $1000-\mathrm{mL}$ volumetric flask, add 50.0 mL of 6 N hydrochloric acid, dilute with water to volume, and mix to obtain a solution having a known concentration of about $10 \mu \mathrm{~g}$ of chromium per mL .

Standard preparations-Transfer 10.0 mL and 20.0 mL of Standard stock preparation 2 to separate $100-\mathrm{mL}$ volumetric flasks, and transfer 15.0 mL and 20.0 mL of Standard stock preparation 2 to separate $50-\mathrm{mL}$ volumetric flasks. Dilute the contents of each of the four flasks with 0.125 N hydrochloric acid to volume, and mix to obtain solutions having known concentrations of about 1.0, 2.0, 3.0, and $4.0 \mu \mathrm{~g}$ of chromium per mL .
Assay preparation-Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 Tablets, to a porcelain crucible, heat the crucible in a muffle furnace maintained at about $550^{\circ}$ for 6 to 12 hours, and cool. Add about 60 mL of hydrochloric acid, and boil gently on a hot plate or steam bath for 30 minutes, intermittently rinsing the inner surface of the crucible with 6 N hydrochloric acid. Cool, and quantitatively transfer the contents of the crucible to a $100-\mathrm{mL}$ volumetric flask. Rinse the crucible with small portions of 6 N hydrochloric acid, and add the rinsings to the flask. Dilute with water to volume, mix, and filter, discarding the first 5 mL of the filtrate. Dilute this solution quantitatively, and
stepwise if necessary, with 0.125 N hydrochloric acid to obtain a solution having a concentration of about $1 \mu \mathrm{~g}$ of chromium per mL .

Procedure-Concomitantly determine the absorbances of the Standard preparations and the Assay preparation at the chromium emission line at 357.9 nm with an atomic absorption spectrophotometer (see Spectrophotometry and LightScattering $\langle 851\rangle$ ) equipped with a chromium hollow-cathode lamp and an air-acetylene flame, using 0.125 N hydrochloric acid as the blank. Plot the absorbances of the Standard preparations versus concentration, in $\mu \mathrm{g}$ per mL , of chromium, and draw the straight line best fitting the four plotted points. From the graph so obtained, determine the concentration, $C$, in $\mu \mathrm{g}$ per mL , of chromium in the Assay preparation. Calculate the quantity, in $\mu \mathrm{g}$, of chromium $(\mathrm{Cr})$ in the portion of Tablets taken by the formula:

## $C D$,

in which $C$ is as defined above; and $D$ is the dilution factor used to prepare the Assay preparation.■2S (USP28)

## BRIEFING

Lysine Hydrochloride Tablets. Because there is no existing USP monograph for this dietary supplement, a new monograph, based on validation data received, is being proposed.
(DSN: L. Evans; PSD: C. Okeke; NL: C. Barnstein) RTS-41480-1

## Add the following:

## ■ Lysine Hydrochloride Tablets

## » Lysine Hydrochloride Tablets contain not less

 than 90.0 percent and not more than 120.0 percent of the labeled amount of $\mathrm{C}_{6} \mathrm{H}_{14} \mathrm{~N}_{2} \mathrm{O}_{2} \cdot \mathrm{HCl}$, as Llysine hydrochloride.Packaging and storage-Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP L-Lysine Hydrochloride RS.

Thin-layer chromatographic identification test $\langle 201\rangle$ -
Test solution-Powder and transfer a portion of Tablets equivalent to about 40 mg of lysine hydrochloride to a $100-\mathrm{mL}$ volumetric flask. Dilute with water to volume, mix, and filter. Use the filtrate.

Standard solution-Dissolve an accurately weighed quantity of USP L-Lysine Hydrochloride RS in water to obtain a solution having a known concentration of about 0.4 mg per mL .
Developing solvent system-Prepare a mixture of isopropyl alcohol and ammonium hydroxide ( $70: 30$ ).

Spray reagent-Dissolve 0.2 g of ninhydrin in 100 mL of a mixture of butyl alcohol and 2 N acetic acid ( $95: 5$ ).
Procedure-Proceed as directed in the chapter. Dry the plate between $100^{\circ}$ and $105^{\circ}$ until the ammonia disappears completely. Spray with Spray reagent, and heat between $100^{\circ}$ and $105^{\circ}$ for about 15 minutes. Examine the plate under white light.

## Disintegration and dissolution of dietary supplements

$\langle 2040\rangle$ : meet the requirements for Disintegration only, 20 minutes.

Weight variation of dietary supplements $\langle 2091\rangle$ : meet the requirements.

Assay-Weigh and finely powder not fewer than 20 Tablets. Transfer about 75 mg of Lysine Hydrochloride, accurately weighed, to a $125-\mathrm{mL}$ flask, and dissolve in 5 mL of mercuric acetate TS with gentle heating. Cool, then add 50 mL of glacial acetic acid and 3 drops of crystal violets TS, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 9.133 mg of $\mathrm{C}_{6} \mathrm{H}_{14} \mathrm{~N}_{2} \mathrm{O}_{2} \cdot \mathrm{HCl}_{\text {. }}{ }^{2 S}$ (USP28)

## MONOGRAPHS (NF)

[^247]
## Briefing

Myristic Acid. Because there is no existing $N F$ monograph for this excipient, a new monograph based on the Myristic Acid monograph in the Food Chemical Codex, 5th Edition, page 297, is being proposed.
(EMC: D. Bempong) RTS-41326-1

## Add the following:

## ■Myristic Acid

$\mathrm{C}_{14} \mathrm{H}_{28} \mathrm{O}_{2} \quad 228.37$
Tetradecanoic acid [544-63-8].
» Myristic Acid is obtained from coconut oil and other fats. It contains not less than 97.0 percent of $\mathrm{C}_{14} \mathrm{H}_{28} \mathrm{O}_{2}$.

Packaging and storage-Preserve in well-closed containers. No storage requirements specified.

USP Reference standards $\langle 11\rangle$ —USP Myristic Acid RS.
Congealing temperature $\langle 651\rangle$ : between $48^{\circ}$ and $55.5^{\circ}$.
Acid value $\langle 401\rangle$ : between 242 and 249.
Iodine value $\langle 401\rangle$ : not more than 1.0.
Saponification value $\langle 401\rangle$ : between 242 and 251.
Unsaponifiable matter $\langle 401\rangle$ : not more than $1 \%$.
Water, Method $I\langle 921\rangle$ : not more than $0.2 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.

Limit of lead- [NOTE-Select reagents having as low a lead content as practicable, and store all solutions in high-density polyethylene containers. Rinse all plastic and glassware thoroughly with warm, 8 N nitric acid followed by deionized water.]

Standard stock solution-Dissolve about 160 mg of lead nitrate, accurately weighed, in 100 mL of water containing 1 mL of nitric acid. Dilute with water to 1000 mL , and mix.

Standard solutions-[NOTE-Prepare these solutions on the day of use.] Transfer 10.0 mL of Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. Each mL of this solution contains the equivalent of about $10 \mu \mathrm{~g}$ of lead. Dilute accurately measured volumes of the diluted Standard stock solution with water to obtain solutions having known concentrations of about $1 \mu \mathrm{~g}, 2 \mu \mathrm{~g}$, and $5 \mu \mathrm{~g}$ of lead per mL .

Test solution-Transfer about 5 g of Myristic Acid, accurately weighed, to an evaporating dish. Add 5 mL of a $25 \%$ sulfuric acid solution, and distribute the sulfuric acid uniformly through the sample. Within a hood, place the dish on a steam bath to evaporate most of the water. Place the dish on a burner, and slowly pre-ash the sample by expelling most of the sulfuric acid. Place the dish in a muffle furnace that has been set at $525^{\circ}$, and ash the sample until the residue appears free from carbon. Prepare a blank by ashing 5 mL of a $25 \%$ sulfuric acid solution. Cool, and cautiously wash down the inside of each evaporation dish with water. Treat both the sample and the blank as follows. Add 5 mL of 1 N hydrochloric acid. Place each dish on a steam bath, and evaporate to dryness. To each dish add 1.0 mL of 3 N hydrochloric acid and approximately 5 mL of water, and heat briefly on a steam bath to dissolve any residue. Transfer each solution quantitatively to a $10-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Procedure-Using a suitable atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) equipped with a lead electrodeless discharge lamp, an air-acetylene flame, and a suitable burner head, perform a blank determination with water, following the manufacturer's operating instructions. Concomitantly determine the absorbances of the blank, the Standard solutions, and the Test solution at the lead emission line of 283.3 nm , using a slit-width of 0.7 nm . Determine the corrected absorbance values by subtracting the absorbance of the blank from the absorbance of each of the Standard solutions and from the absorbance of the Test solution. Prepare a standard curve by plotting the corrected absorbance values of the Standard solutions versus their corresponding concentration, in $\mu \mathrm{g}$ per mL . From the calibration curve, determine the lead concentration in the Test solution. Calculate the lead content, in $\mu \mathrm{g}$ per g , in the portion of Myristic Acid taken by the formula:

$$
10 C / W_{s}
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of lead from the standard curve; and $W_{S}$ is the weight, in g , of Myristic Acid taken: not more than $2 \mu \mathrm{~g}$ per g is found.

## Assay-

Resolution solution-Proceed as directed for the System Suitability Solution in Fatty Acid Composition under Fats and Fixed Oils $\langle 401\rangle$, except that only stearic acid and palmitic acid are used.

Standard preparation-Prepare as directed for the Assay preparation using 100 mg of USP Myristic Acid RS instead of the substance to be examined.

Assay preparation-Proceed as directed for the Test Solution in Fatty Acid Composition under Fats and Fixed Oils $\langle 401\rangle$.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
Prepare as directed for Fatty Acid Composition under Fats and Fixed Oils $\langle 401\rangle$. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between methyl stearate and methyl palmitate is not less than 1.5.

Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and identify the methyl myristate peak in the chromatogram obtained from the Assay preparation by comparing the retention times of the peaks in that chromatogram with those in the chromatogram obtained from the Standard preparation. Measure the responses for all of the peaks in the chromatogram obtained from the Assay preparation, excluding the solvent peak, and calculate the percentage of $\mathrm{C}_{14} \mathrm{H}_{28} \mathrm{O}_{2}$ in the portion of Myristic Acid taken by the formula:

## 100A/B,

in which $A$ is the the methyl myristate peak response; and $B$ is the sum of the responses of all the peaks in the chromatogram, except the solvent peak. $\mathbf{D S S}_{\text {2 (NF23) }}$

## Add the following:

-USP Reference standards $\langle 11\rangle$ —USP Polyoxyl 35 Castor Oil RS. $\mathbf{■ S ~}_{\text {2S (NF23) }}$

## Change to read:

## Identification-

A: Bissolve about 0.1 g in 1 mL of water, add 9 mL of sodium ehloride-solation (1-in 20), and heat in a water bath: the-selution becomes turbid at a temperature between $65^{\circ}$ and $85^{\circ}$ and becomes elear on cooling to $40^{\circ}$.

- Infrared Absorption $\langle 197 \mathrm{~F}\rangle$. ${ }^{2 S}$ (NF23

B: Dissolve about 0.1 g in 10 mL of alcoholic potassium hydroxide TS, boil for about 3 minutes, and evaporate to dryness. Mix the residue with 5 mL of water: it dissolves, yielding a clear solution. Add a few drops of glacial acetic acid: a white precipitate is formed.
C: To a solution (1 in 20) add bromine TS, dropwise: the bromine is decolorized.

Briefing

Sesame Oil, NF 22 page 2926 and page 608 of PF 30(2) [Mar.Apr. 2004]-See briefing under Soybean Oil.
(EMC: C. Sheehan; NL: W. Paul) RTS-41628-2

## Change to read:

» Sesame Oil is the refined fixed oil obtained from the seed of one or more cultivated varieties of Sesamum indicum Linné (Fam. Pedaliaceae).
-It may contain suitable antioxidants.■2S (NF23)

## Add the following:

-USP Reference standards $\langle 11\rangle$ —USP Sesame Oil Related Compound A RS. USP Sesame Oil Related Compound B RS.■1S (NF23)

## Add the following:

-Labeling-Label it to indicate the name and quantity of any added antioxidant. $\quad$ 2S (NF23)

## Change to read:

Triglyceride composition-
Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and methylene chloride ( $60: 40$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

NOTE-The fatty acid radicals are designated as linoleic (L), oleic $(\mathrm{O})$, palmitic $(\mathrm{P})$, and stearic (S), and the common abbreviations for triglycerides used are as follows: trilinolein (LLL), 1,2-dilino-leoyl-3-oleoyl-rac-glycerol (OLL), 1,2-dilinoleoyl-3-palmitoyl-rac-glycerol (PLL), 1,2-dioleoyl-3-linoleoyl-rac-glycerol (OOL), 1-palmitoyl-2-oleoyl-3-linoleoyl-rac-glycerol (POL), triolein (OOO), 1-linoleoyl-2-oleoyl-3-stearoyl-rac-glycerol (SOL), and 1,2-dioleoyl-3-palmitoyl-rac-glycerol (POO).

System suitability solution - Transfer abut 30 mg each of OLL and PLL, aceurately weighed, to a 10 mL volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.
-Dissolve an accurately weighed quantity of USP Sesame
Oil Related Compound A RS and USP Sesame Oil Related
Compound B RS in Mobile phase to obtain a solution having a known concentration of about 3 mg of each per mL . [nOTE--USP Sesame Oil Related Compound A RS is OLL and USP Sesame Oil Related Compound B RS is PLL]. ${ }^{1 S}$ (NF23)

Test solution-Transfer about 200 mg of Oil, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The chromatograph is equipped with a refractive index detector and two $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ columns in series that contain packings L1 and are maintained at a constant temperature of about $30^{\circ}$. The flow rate is about 1.0 mL per minute. Chromatograph the System suitability solution, and record the peak areas as directed for Procedure: the relative retention times are about 0.93 for OLL and 1.0 for PLL; the resolution, $R$, between OLL and PLL is not less than 1.8; the relative standard deviation for replicate injections, determined from peak areas, is not more than $1.5 \%$; and the relative standard deviation for replicate injections, determined from peak area ratios of OLL to PLL, is not more than $2.2 \%$.

Procedure-Inject about $20 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure the areas for the eight major triglyceride peaks, eluting from 0 to about $40 \mathrm{~min}-$ utes, with relative retention times stated in the table below and in the order specified. Calculate the percentage of each of these triglycerides in the portion of Oil taken by the formula:

$$
100(A / B)
$$

in which $A$ is the peak area for each individual triglyceride; and $B$ is the sum of the areas of all the peaks, excluding the solvent peak.

| Triglyceride | Relative Retention Time | Composition (\%) |
| :---: | :---: | :---: |
| LLL | 0.55 | 7.0 to 19.0 |
| OLL | 0.65 | 13.0 to 30.0 |
| PLL | 0.69 | 5.0 to 9.0 |
| OOL | 0.77 | 14.0 to 25.0 |
| POL | 0.82 | 8.0 to 16.0 |
| OOO | 0.93 | 5.0 to 14.0 |
| SOL | 0.97 | 2.0 to 8.0 |
| POO | 1.0 | 2.0 to 8.0 |

## Briefing

Anhydrized Liquid Sorbitol, page 993 of $P F$ 30(3) [May-June 2004]. It is proposed to adopt Sorbitol Sorbitan Solution as the title of this proposed new monograph, which first appeared with the name Anhydrized Liquid Sorbitol in a Pharmacopeial Preview in PF 28(3) [May-June 2002] and under In-Process Revision in PF 29(1) [Jan.-Feb. 2003] and subsequently, under In-Process Revision in PF 29(4) [July.-Aug. 2003]. The Expert Committee on Nomenclature and Labeling has proposed Sorbitol Sorbitan Solution as the title of the monograph for this excipient, which is proposed for inclusion in the Second Supplement to USP 28-NF 23, but with an official date of August 1,2010, which is sixty months later than the August 1, 2005, official date of the Second Supplement. The sixty month extension will provide the time deemed necessary for labeling changes to be made for the article and the numerous preparations in which it is an ingredient, and for practitioners, consumers, and regulatory agencies to become familiar with the terminology.
(EMC: C. Sheehan; NL: C. Barnstein) RTS-41545-1

## Add the following:

## ■Anhydrized Liquid-Sorbitol Sorbitol Sorbitan Solution

(Monograph under this new title - to become official August 1, 2010)
(Currently there is no official monograph for this article)

## " Anhydrized Liquid Sorbitel Sorbitol Sorbitan

Solution is a water solution containing, on the anhydrous basis, not less than 25.0 percent of D-sorbitol $\left(\mathrm{C}_{6} \mathrm{H}_{14} \mathrm{O}_{6}\right)$ and not less than 15.0 percent of 1,4-sorbitan $\left(\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{5}\right)$. The amounts of total sugars, other polyhydric alcohols, and any other hexitol anhydrides, if detected, are not included in the requirements or in the calculated amount under Other Impurities.

Packaging and storage-Prese in tightentrens. Preserve in well-closed containers. Po nore $20^{\circ}$. No storage requirements specified.

Labeling-The labeling indicates the percentage content, on the anhydrous basis, of D-sorbitol and 1,4-sorbitan.

USP Reference standards $\langle 11\rangle — U S P$ Sorbitol RS. USP

## 1,4-Sorbitan RS.

## Identification-

A: Dissolve Prepare a solution containing 1.4 g of Ant hydrized Liquid Sorbitel Sorbitol Sorbitan Solution in 75 mL of water. Transfer 3 mL of this solution to a $15-\mathrm{cm}$ test tube, add 3 mL of freshly prepared catechol solution (1 in 10 ), and mix. Add 6 mL of sulfuric acid, mix again, then gently heat the tube in a flame for about 30 seconds: a deep pink or wine-red color appears.
B: The retention times of the major peaks in the chromatogram of the Assay preparation correspond to those in the chromatogram of the Standard preparation, as obtained in the Assay.

Microbial limits $\langle 61\rangle$ —The total aerobic microbial count using the Plate Method is not more than 1000 cfu per mL. The total combined molds and yeasts count is not more than 100 cfu per mL.
$\mathbf{p H}\langle 791\rangle$ : between 4.0 and 7.0 , in a $14 \%(\mathrm{w} / \mathrm{w})$ solution of Anhydrized Liquid Sorbitel Sorbitol Sorbitan Solution in carbon dioxide-free water.

Water, Method I $\langle 921\rangle$ : not more than 31.5\%.
Residue on ignition $\langle 281\rangle$ : not more than $0.20 \%$, calculated on the anhydrous basis. Determine on a $2-\mathrm{g}$ portion, accurately weighed.

Reducing sugars-To an amount of Anhydrized Liquid Serbitel Sorbitol Sorbitan Solution, equivalent to 3.3 g , on the anhydrous basis, add 3 mL of water, 20.0 mL of cupric citrate TS, and a few glass beads. Proce in the test for Reducing sugats under Mannitol, beginning with "Heat that beiling begins." Heat so that boiling begins after 4 minutes, and maintain boiling for 3 minutes. Cool
rapidly, and add 40 mL of diluted acetic acid, 60 mL of water, and 20.0 mL of 0.05 N iodine VS. With continuous shaking, add 25 mL of a mixture of 6 mL of hydrochloric acid and 94 mL of water. When the precipitate has dissolved, titrate the excess of iodine with 0.05 N sodium thiosulfate VS using 2 mL of starch TS, added towards the end of the titration, as an indicator. Not less than 12.8 mL of 0.05 N sodium thiosulfate VS is required, corresponding to not more than $0.3 \%$ of reducing sugars, on the anhydrous basis, as glucose. The amount determined in this test is not included in the calculated amount under

## Other Impurities.

## Limit of nickel-

Test solution-Dissolve 20.0 g of Anhydrized Liquid Sor bitol Sorbitol Sorbitan Solution in diluted acetic acid, and dilute with diluted acetic acid to 100.0 mL . Add 2.0 mL of a saturated solution of ammonium pyrrolidine dithiocarbamate (about 10 g of ammonium pyrrolidine dithiocarbamate per L ) and 10.0 mL of methyl isobutyl ketone, and shake for 30 seconds. Protect from bright light. Allow the two layers to separate, and use the methyl isobutyl ketone layer.

Blank solution-Prepare as directed for the Test solution, except to omit the use of Anhydrize Liquid Sorbited Sorbitol Sorbitan Solution. Quantities should be increased five fold to ensure that a sufficient volume of Blank solution is available.
Standard solutions-Prepare as directed for the Test solution, except to prepare three solutions by adding $0.5 \mathrm{~mL}, 1.0$ mL , and 1.5 mL of nickel standard solution TS.

Procedure-Procee as directed in the test for Nickel under Mat Set the instrument to zero using the Blank solution. Concomitantly determine the absorbances of the Standard solutions and the Test solution at least three times each, at the wavelength of maximum absorbance at 232.0
nm , with a suitable atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) equipped with a nickel hollow-cathode lamp and an air-acetylene flame. Record the average of the steady readings for each of the Standard solutions and the Test solution. Between each measurement, aspirate the Blank solution, and ascertain that the reading returns to zero. Plot the absorbances of the Standard solutions and the Test solution versus the added quantity of nickel. Extrapolate the line joining the points on the graph until it meets the concentration axis. The distance between this point and the intersection of the axes represents the concentration of nickel in the Test solution. Not more than $1 \mu \mathrm{~g}$ per g, calculated on the anhydrous basis, is found.

Assay-
Mobile phase-Use degassed water.
Resolution solution-Dissolve sorbitol, 1,4-sorbitan, isosorbide, and mannitol in water to obtain a solution having concentrations of about 10 mg per $\mathrm{g}, 4 \mathrm{mg}$ per $\mathrm{g}, 4 \mathrm{mg}$ per g , and 1 mg per g , respectively.
Standard preparation-Dissolve accurately weighed quantities of USP Sorbitol RS and USP 1,4-Sorbitan RS in water to obtain a solution having concentrations of about 10 mg per g and 4 mg per g , respectively.
Assay preparation-Dissolve about 0.40 g of Anhydrized Liquid Sorbitel Sorbitol Sorbitan Solution, accurately weighed, in water, and dilute with water to about 20 g . Accurately record the final solution weight, and mix thoroughly.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a refractive index detector that is maintained at a constant temperature of
about $35^{\circ}$, and a $7.8-\mathrm{mm} \times 10-\mathrm{cm}$ column that contains packing L34. The column temperature is maintained at about $50^{\circ}$, controlled within $\pm 2^{\circ}$, and the flow rate is about 0.6 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the 1,4 -sorbitan and isosorbide is not less than 2.0. Chromatograph the Standard preparation, and record the peak responses for 1,4 -sorbitan and sorbitol as directed for Procedure: the relative retention times are about 0.35 for 1,4 -sorbitan, 0.43 for isosorbide, 0.7 for mannitol, and 1.0 for sorbitol; and the relative standard deviation for replicate injections is not more than $2.0 \%$ for each analyte.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Separately calculate the percentages, on the anhydrous basis, of 1,4-sorbi$\tan$ and sorbitol in the portion of Anhydrized Liquid Sorbitel Sorbitol Sorbitan Solution taken by the formula:

$$
\left[10,000\left(C_{S} / C_{U}\right)\left(r_{U} / r_{s}\right)\right] /(100-W)
$$

in which $C_{S}$ is the concentration, in mg per g , of the appropriate USP Reference Standard in the Standard preparation; $C_{U}$ is the concentration, in mg per g , of the Ambydrized Liq wid Sorbital Sorbitol Sorbitan Solution in the Assay preparation; $r_{U}$ and $r_{S}$ are the peak responses of the corresponding analyte obtained from the Assay preparation and the Standard preparation, respectively; and $W$ is the percentage obtained in the test for Water: $\quad$ 2S (NF23)

## Briefing

Tapioca Starch, NF 22 page 2940, page 3181 of the First Supplement, and page 1336 of PF 30(4) [July-Aug. 2004]. On the basis of comments received, it is proposed to revise the sample size in the test for Iron $\langle 241\rangle$.
(EMC: C. Sheehan) RTS-41473-1

## Change to read:

Packaging and storage-Preserve in well-closed containers.

- No storage requirements specified.■1S (NF23)


## Delete the following:

Botanic eharaeteristies Examine Tapioca-Stareh under a mi eroseope, using not less than $20 x$ magnifieation and using slye erin as the mounting agent: it appears as spherieal granules with ene trumeated side, typieally having a 5 to $35 \mathrm{\mu m}$ diameter and having cireular or several rayed central clefts.a1S (NF23)

## Change to read:

## Identification-

A: Suspend 1 g of Tapieen Stareh in 50 mL of water, beil for 4 minute, and cool: a thin, cloudy mueilage is formed.

B: To 10 mL of the mucilage obtained in Identification test $A$ add 0.04 mL each of iodine and potassium iodide $T S$ : a reddish riolet to dark blue color is produred, which disappears on heating and reappears on cooling.
-A: Examine Tapioca Starch under a microscope, using not less than $20 \times$ magnification and using glycerin as the mounting agent: it appears as spherical granules with one truncated side, typically having a 5 - to $35-\mu \mathrm{m}$ diameter and having circular or several-rayed central clefts.

B: Suspend 1 g of Tapioca Starch in 50 mL of water, boil for 1 minute, and cool: a thin, cloudy mucilage is formed.

C: To 1 mL of the mucilage obtained in Identification test $B$ add 0.05 mL of iodine and potassium iodide TS 2: an orange-red to dark blue color, which disappears on heating, is produced. $\quad$ (NS (NF23)

## Change to read:

Iron $\langle 241\rangle$ : $0.002 \%$, the Test Preparation being prepared as follows. Shake 0.25 g
$-0.75 \mathrm{~g}_{\mathrm{m} 2 \mathrm{~S}}{ }_{\text {(NF23) }}$
of Tapioca Starch with 15 mL of 0.1 N hydrochloric acid, and filter. Use 10 mL of this solution as the Test Preparation.


#### Abstract

\section*{BRIEFING}

Tagatose. Because there is no existing $N F$ monograph for this excipient, a new monograph is proposed based on a manufacturer's tests and acceptance criteria. The liquid chromatographic procedure in the Assay was validated using a Biorad Aminex HPX87 C brand of L19 column; tagatose peak elutes at approximately 32 minutes. (EMC: E. Gonikberg; AMB: D. Porter) RTS-41251-1


## Add the following:

## ©Tagatose


$\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6} \quad 180.16$ [87-81-0].
d-Tagatose.
D-lyxo-Hexulose.
» Tagatose is a ketohexose, an epimer of D-fructose inverted at $\mathrm{C}-4$. It is obtained from D-galactose by isomerization under alkaline conditions in the presence of calcium. It contains not less than 98.0 percent of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6}$, calculated on the dried basis.

Packaging and storage-Preserve in well-closed containers, and store at room temperature.

USP Reference standards $\langle 11\rangle$ —USP Tagatose RS.

## Identification-

A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.
B: It meets the requirements of the test for Specific rotation $\langle 781 \mathrm{~S}\rangle$.

C: Add 3 mL of a solution ( 1 in 5 ) to 5 mL of hot alkaline cupric tartrate TS: a copious red precipitate of cuprous oxide is formed.

Melting range, Class $1\langle 741\rangle$ : between $133^{\circ}$ and $144^{\circ}$.
Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $-4^{\circ}$ and $-5.6^{\circ}$.
Test solution: 10 mg per mL , in water.
Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absence of Salmonella species and Escherichia coli. The total aerobic microbial count does not exceed 1000 cfu per g , and the total combined molds and yeasts count does not exceed 100 cfu per g.

Loss on drying $\langle 731\rangle$ —Dry it at $102^{\circ}$ for 2 hours: it loses not more than $0.5 \%$ of its weight.

Total ash $\langle 561\rangle$ : not more than $0.1 \%$, determined on a $1.0-\mathrm{g}$ specimen.

## Limit of lead-

Test solution-Accurately weigh about 2.5 g of Tagatose, and dissolve in a mixture of 4 mL of sulfuric acid and 5 mL of hydrochloric acid. Transfer the solution to a $50-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Standard lead solution-Dissolve 1.60 g of lead nitrate in diluted nitric acid ( 10 mL of nitric acid diluted with 20 mL water, boiled to remove nitrous fumes, and cooled), and di-
lute with water to 1000 mL . Dilute 10.0 mL of this solution with water to 500 mL . This solution contains the equivalent of $20 \mu \mathrm{~g}$ of lead per mL .
Calibration solutions-To a series of $100-\mathrm{mL}$ volumetric flasks, pipet $0,1,2,3,4$ and 5 mL of the Standard lead solution, and dilute to about 50 mL . Add 8 mL of sulfuric acid and 10 mL of hydrochloric acid to each flask, shake to dissolve, and dilute with water to volume. These solutions contain $0,0.2,0.4,0.6,0.8$ and $1.0 \mu \mathrm{~g}$ of lead per mL .

Procedure-Concomitantly determine the absorbances of the Calibration solutions and the Test solution at the wavelength of maximum absorbance at 283.3 nm , with a suitable atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) using an air-acetylene flame. Plot the absorbances of the Calibration solutions versus the concentration of lead. Using this graph, determine the concentration of lead in the Test solution. Not more than $1 \mu \mathrm{~g}$ per g is found.

## Assay-

Mobile phase-Prepare a solution in water containing 50 mg of calcium acetate per L .

Standard preparation-Dissolve an accurately weighed quantity of USP Tagatose RS in water to obtain a solution having a known concentration of about 5 mg per mL . Pass through a $0.2-\mu \mathrm{m}$ filter.

Assay preparation-Transfer about 50 mg of Tagatose, previously dried, to a $10-\mathrm{mL}$ volumetric flask, and dissolve in about 8 mL of water. Dilute with water to volume, and pass through a $0.2-\mu \mathrm{m}$ filter.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a refractive index detector and a $7.8-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains $9-\mu \mathrm{m}$ packing L19. The column temperature is maintained at $85^{\circ}$. The flow rate is about 0.6 mL per minute. Chromat-
ograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{6} \mathrm{H}_{12} \mathrm{O}_{6}$ in the portion of Tagatose taken by the formula:

$$
10 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Tagatose RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.n2S (NF23)

## GENERAL CHAPTERS

## General Tests and Assays

## General Requirements for Tests and Assays

〈11〉 USP Reference Standards, USP 27 page 2111, page 3310 of the Second Supplement, the Third Interim Revision Announcement on page 785 of PF 30(3) [May-June 2004], the Fourth Interim Revision Announcement on page 1150 of PF 30(4) [July-Aug. 2004], page 793 of $P F$ 26(3) [May-June 2000], page 1101 of $P F$ 26(4) [July-Aug. 2000], page 1832 of $P F 27$ (1) [Jan.-Feb. 2001], page 3071 of $P F 27(5)$ [Sept.-Oct. 2001], page 433 of $P F 28$ (2) [Mar.-Apr. 2002], page 839 of $P F$ 28(3) [May-June 2002], page 1224 of $P F 28(4)$ [July-Aug. 2002], page 1468 of $P F 28(5)$ [Sept.Oct. 2002], page 1913 of $P F 28(6)$ [Nov.-Dec. 2002], page 710 of

PF 29(3) [May-June 2003], page 1137 of $P F$ 29(4) [July-Aug. 2003], page 1601 of $P F$ 29(5) [Sept.-Oct. 2003], page 2022 of $P F$ 29(6) [Nov.-Dec. 2003], page 211 of $P F 30(1)$ [Jan.-Feb. 2004], page 613 of $P F$ 30(2) [Mar.-Apr. 2004], page 998 of $P F$ 30(3) [May-June 2004], and page 1338 of PF 30(4) [July-Aug. 2004].

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(HDQ) RTS-40992-1; 41251-1; 41357-1; 41354-1; 41356-1; 41355-1; 39507-4; 41592-2
```


## Add the following:

-USP 4-Aminophenol RS-[To come.] $]_{\text {■2S (USP28) }}$

## Add the following:

## -USP Etidronate Disodium Related Compound A RS

 [sodium phosphite dibasic pentahydrate] ( $\mathrm{Na}_{2}$ $\mathrm{HPO}_{3} \cdot 5 \mathrm{H}_{2} \mathrm{O} \diamond 216.04 \diamond$ CAS-13708-85-5)—Do not dry. ${ }^{\text {2S }}$ (USP28)
## Add the following:

-USP Modafinil RS—[To come.] $]_{\text {2S (USP28) }}$

## Add the following:

-USP Phenol RS-[To come.] $]_{\text {2S }}$ (USP28)

## Add the following:

-USP Prilocaine RS—[To come.] $]_{\text {2S (USP28) }}$

## Add the following:

-USP Prilocaine Related Compound A RS [ $o$-toluidine hydrochloride] $\left(\mathrm{CH}_{3} \mathrm{C}_{6} \mathrm{H}_{4} \mathrm{NH}_{2} \mathrm{HCl} \diamond 143.62 \triangleleft\right.$ CAS-636-
21-5). $\mathbf{\square}$ 2S (USP28)

## Add the following:

-USP Prilocaine Related Compound B RS [(RS)-N-(4-methylphenyl)-2-(propylamino)propanamide] $\left(\mathrm{C}_{13} \mathrm{H}_{20} \mathrm{~N}_{2} \mathrm{O} \triangleleft\right.$ 220.31). ${ }^{\text {■S }}$ (USP28)

## Change to read:

-USP Propofol Resolution

- Mixture $_{\text {a2S }}$ (USP28)

RS [propofol and 2-isopropyl-6-n-propylphenol]. $\mathbf{n}^{2 S}$ (USP27)

## Add the following:

${ }^{\bullet}$ USP Propofol Related Compound C RS [2-(1-methyl-ethoxy)-1,3-bis(1-methylethyl)benzene] (C14 $\left.\mathrm{H}_{22} \mathrm{O} \diamond 206.32\right)_{\bullet 2}($ USP28)

## Delete the following:

=USP Propofolfor System Suitability RS [propefol, 3, 3' 5,5' tet raisopropyldiphenol and 2 ( 1 methylethoxy) 1,3 bis( 1 methy tethyl)benzene]. 2 2S (USP28)

## Add the following:

-USP Tagatose RS—Dry at $102^{\circ}$ for 2 hours before using.■2S (USP28)

## Biological Tests and Assays

## BriEfing

$\langle\mathbf{1 2 1}\rangle$ Insulin Assays, USP 27 page 2193. On the basis of information received, it is proposed to modify the calculation for potency and the statistics used to calculate the confidence interval. Several other changes have been made to clarify the procedure.
(BNT: L. Callahan) RTS—32750-1; 41659-1

## Change to read:

The most prominent manifestation of insulin activity, an abrupt decrease in blood glucose, was the basis for biologic assay from the time of the
$\boldsymbol{m}_{\text {its }}^{\boldsymbol{m 2 S}}$
first clinical use. of insulim
-2S (USP28)
The procedure, although relatively cumbersome, has the great merit of accurately reflecting the effect on the diabetic patient. The advent of practical yet sophisticated physicochemical methods (e.g., liquid chromatography) to measure insulin potency quantitatively has resulted in a more accurate and precise compendial test for insulin and insulin products. However, the bioidentity of insulin and insulin products cannot be assessed by these methods. Thus, a qualitative test in rabbits is included in this chapter, and its use is called for in the appropriate monographs.

The Rabbit Blood Sugar Method-Quantitative is used to determine the potency of Insulin Reference Standards, for the validation of the stability of new insulin preparations, and to determine the specific activities of insulin analogs.

## Change to read:

## RABBIT BLOOD SUGAR METHODQUANTITATIVE

USP Reference Standards $\langle 11\rangle$ —USP Dextrose RS. USP Insulin RS. USP Insulin (Beef) RS. USP Insulin Human RS. USP Insulin (Pork) RS.
-Diluent-Prepare an aqueous solution containing $0.1 \%$ to $0.25 \%(\mathrm{w} / \mathrm{v})$ of either cresol or phenol, $1.4 \%$ to $1.8 \%$ $(\mathrm{w} / \mathrm{v})$ of glycerin, and sufficient hydrochloric acid to produce a pH between 2.5 and 3.5, unless otherwise directed in the individual monograph.■2S (USP28)

Standard Stock Solution-Dissolve either a suitable quantity of accurately weighed USP Insulin RS or a vial of lyophilized USP Insulin RS of the appropriate species in suffienter timing $0.1 \%$ 0- $0.25 \%$ (w) of either phenol or cresel, $1.4 \%$ to . $8 \%$ (w/v) of glyeerin, and sufficient hydrochloric acid

- Diluent ${ }_{\text {■2S }}$ (USP28)
to make a Standard Stock Solution containing 40 USP Insulin Units per mL and having a pH between 2.5 and 3.5 , unless otherwise directed in the individual monograph. Store in a cold place, protected from freezing, and use within 6 months.

Standard Solutions-Dilute portions of the Standard Stock Solution
$\mathbf{■}_{\text {With }}$ Diluent ${ }_{\text {■2S }}{ }_{\text {(USP28) }}$
to make two solutions, one to contain 1.0 USP Insulin Unit per mL (Standard Solution 1), and the other to contain 2.0 USP Insulin Units per mL (Standard Solution 2). Use as diluent a solution entaining $0.1 \%$ to $0.25 \%$ (w/v) of either eresolor phend, $1.4 \%$ to $1.8 \%$ (w/v) of glyeerin, and sufficient hydrochloric acid to produre a pH between 2.5 and 3.5 , unless otherwise directed in the individual monegraph.

■ ${ }^{\text {2S }}$ (USP28)
-Assay Stock Solution-Proceed as directed under Standard Stock Solution except use a suitable quantity of the preparation under test in place of USP Insulin RS. The $A s-$ say Stock Solution contains about 40 USP Insulin Units per mL.■2S (USP28)

Assay Solutions- Dilute volumes of the preparation under test with Stal Stock Solution to obtain a solution containing 1.0 USP Insulin Unit per mL (Assay Solution 1), and a second solution containing 2.0USP Insulin Units per mL (Assay Solution 2). th the ease of neutral insulin injection, adjust to a pH of 2.5 to 3.5 prior to making the dilutions.
-Dilute portions of the Assay Stock Solution with Diluent to make two dilutions of the preparation under test, one of which may be expected, on the basis of the assumed poten-
cy, to contain 1.0 USP Insulin Unit per mL (Assay Solution 1), and the other to contain 2.0 USP Insulin Units per mL (Assay Solution 2). In the case of neutral insulin injection, adjust to a pH of 2.5 to 3.5 prior to making the dilutions. $\mathbf{m}^{2 S}$ (USP28)

Doses of the Solutions To Be Injected-Select on the basis of trial or experience the dose of the dilutions to be injected, the volume of which usually will be between 0.30 mL and 0.50 mL . For each animal the volume of the Standard Solution is the same as that of the Assay Solution.

Preparation of Animal-Select suitable, healthy rabbits each weighing not less than 1.8 kg . Keep the rabbits in the laboratory for not less than 1 week before use in the assay, maintaining them on an adequate uniform diet, with water available at all times.
Procedure-Divide the rabbits into four equal groups of preferably not less than six rabbits each. On the preceding day, approximately 20 hours before the assay, provide each rabbit with an amount of food that will be consumed within 6 hours. Follow the same feeding schedule before each test day. During the assay, withhold all food until after the final blood specimen is taken. Handle the rabbits with care in order to avoid undue excitement, and inject subcutaneously the doses indicated in the following design
-(see Table 1), ${ }_{\text {\#2S }}$ (USP28)
the second injection being made on the day after the first injection, or not more than 1 week later.
-The time between the first and second injection is the same for all rabbits.

Table 1

| Group | First Injection |
| :--- | :--- | Second Injection

Anticoagulant Solution-Dissolve 1 g of edetate sodium and 200 mg of sodium fluoride in 1 L of water, and mix.
Dextrose Standard Preparations-Transfer known concentrations of USP Dextrose RS to suitable vessels, and dilute quantitatively and stepwise with Anticoagulant Solution (1:9) to obtain a range of Dextrose Standard Solutions containing between 20 and 100 mg per 100 mL , having known concentrations similar to the concentrations in the rabbit blood samples.
Test Preparations-Pipet into separate, suitable vessels 0.1 mL of each Blood Sample and 0.9 mL of Anticoagulant Solution.
Procedure-Subject the Test Preparations to dialysis across a semipermeable membrane for a sufficient time so that the dextrose passes through the membrane into a saline TS solution containing glucose oxidase, horseradish peroxidase, 3-methyl-2-benzothiazolinone hydrazone hydrochloride TS, and $N, N$-dimethylaniline. The absorbances of the Test Preparations are determined at 600 nm in a recording colorimeter. The absorbances of the Dextrose Standard Preparations are similarly determined at the start and the end of each run.

Calculation-Calculate the response of each rabbit to each injection from the sum of the two blood-sugar values, and subtract
 2,

■ 2 S (USP28)
disregarding the chronological order in which the responses were observed, to obtain the individual differences, $y$, as shown in the acempanying table
-Table 2.n2S (USP28)
When the data for one or more rabbits are missing in an assay, allow for differences in the sizes of the groups by suitable means (see Replacement of Missing Values under Design and Analysis of Biologieal Assay: $\langle(14\rangle$ ).
-do not use the confidence interval formulas given here, but seek statistical help. The data can still be analyzed with proper analysis of variance. $\quad$ 2S (USP28)

When the number of rabbits, $f$, carried through the assay is the same in each group, total the $y$ 's in each group and compute $T_{a}=-$ $T_{1}+T_{2}+T_{3}-T_{4}$ and $T_{b}=T_{1}+T_{2}+T_{3}+T_{4}$. The logarithm of the relative potency of the test dilutions is $M^{4}=0.301 T_{a} / T_{b}$. The potency of the injection in USP Units per mE
$\mathbf{- m g}_{\text {. } 2 \mathrm{~S}}$ (USP28)
equals the antilog $\left(\log R+M^{\prime}\right)$, where $R=v_{S} / v_{U}$, in which $v_{S}$ is the number of USP Units per mL of the Standard dilution and $v_{U}$ ithe number of of injection per mL of the Assay dilution.
$\boldsymbol{\square}_{\text {is }}$ the number of mg of insulin per mL of the corresponding

-Determine the $95 \%$ confidence interval for the log-relative potency using Fieller's Theorem (see Appendix and Design
and Analysis of Biological Assays (111〉). ${ }^{2}$ 2S (USP28)
If the confidence interval is more than 0.082 , which corresponds at $P=0.95$ to confidence limits of about $\pm 10 \%$ of the computed potency, repeat the assay until the combined data of the two or more assays, redetermined as described in Combination of Independent Assays under Design and Analysis of Biological Assays $\langle 111\rangle$, meet this acceptable limit.

Table 2

| Group | Differences | Individual <br> Response (y) | Total <br> Response ( $T$ ) | -Standard Deviations of <br> Differences $(S)_{\text {2S (USP28) }}$ |
| :---: | :---: | :---: | :---: | :---: |
| 1 | Standard Solution 2 - Assay Solution 1 | $y_{1}$ | $T_{1}$ | ${ }^{\square} S_{1 ■ 2 S}$ (USP28) |
| 2 | Assay Solution 2 - Standard Solution 1 | $y_{2}$ | $T_{2}$ | $S^{-1 / 2 S}$ (USP28) |
| 3 | Assay Solution 2 - Standard Solution 1 | $y_{3}$ | $T_{3}$ | $S^{-1 / 2 S}$ (USP28) |
| 4 | Standard Solution 2 - Assay Solution 1 | $y_{4}$ | $T_{4}$ | ${ }^{-} S_{4!2 \mathrm{~S}}$ (USP28) |

## Add the following:

-Appendix—Fieller's Theorem for Determining the

## Confidence Interval for a Ratio

This version of Fieller's Theorem is for the case where the numerator and denominator are uncorrelated. The equation assumes the numerator and denominator are normally distributed and the groups of rabbits are equal-sized.

Then, the $95 \%$ confidence interval for the ratio is:

$$
(L, U)=\frac{M^{\prime} \pm \frac{t}{T_{B}} \sqrt{(1-g) S_{N}^{2}+\left(M^{\prime}\right) S_{D}^{2}}}{1-g}, \quad S_{N}=0.301 \sqrt{k} \sqrt{S_{1}^{2}+S_{2}^{2}+S_{3}^{2}+S_{4}^{2}},
$$

where $f$ (degrees of freedom in the standard errors) $=4(k-$ 1 ), where $k$ is the number of rabbits in a group, $t$ is the upper 97.5 percentile of the $t$-distribution with $f$ degrees of freedom, and

$$
g=\frac{t^{2} S_{D}^{2}}{T_{B}^{2}}
$$

If $g \geq 1$, the denominator is not significantly different from 0 and the formula does not work.

$$
S_{D}=\sqrt{k} \sqrt{S_{1}^{2}+S_{2}^{2}+S_{3}^{2}+S_{4}^{2}} \cdot \mathbf{m S}_{(U S P 28)}
$$

# Chemical Tests and Assays 

## OTHER TESTS AND ASSAYS

## Briefing

$\langle 341\rangle$ Antimicrobial Agents-Content, USP 27 page 2210 and page 3104 of the First Supplement. In the General Gas Chromatographic Method, it is proposed to revise the Standard Preparation under Chlorobutanol and the Internal Standard Solution and the Standard Preparation under Phenol to include the use of USP Chlorobutanol RS and USP Benzyl Alcohol RS and USP Phenol RS, respectively. In the Polarographic Method, it is proposed to revise the Standard Preparation under Thimerosal to include the use of USP Thimerosal RS.
(PA7b: B. Davani) RTS-41357-1

## Change to read:

## GENERAL GAS CHROMATOGRAPHIC METHOD

The general procedures set forth in the following paragraphs are applicable to the quantitative determination of benzyl alcohol, chlorobutanol, phenol, and the methyl, ethyl, propyl, and butyl esters of $p$-hydroxybenzoic acid, the latter being treated as a group, the individual members of which, if present, are capable of separate determination. Prepare the Internal Standard Solution and the Standard Preparation for each agent as directed individually below. Unless otherwise directed below, prepare the Test Preparation from accurately measured portions of the Internal Standard Solution and the sample under test, of such size that the concentration of the agent and the composition of the solvent correspond closely to the concentration and composition of the Standard Preparation. Suggested operating parameters of the gas chromatograph apparatus are given in the accompanying table, the carrier gas being helium or nitrogen, and the detector being the flame-ionization type.

Suggested Operating Parameters of Gas Chromatograph Apparatus

|  | Column Size |  | Column <br> Packing <br> Phases and <br> Support | Flow <br> Rate, <br> mL per <br> min. | Column <br> Temper- <br> ature |
| :--- | :---: | :---: | :---: | :---: | :---: |
| Benzyl <br> Alcohol | 1.8 m | 3 mm | $5 \%$ G16/ <br> Length | 50 | $140^{\circ}$ |
| S1A <br> Cloro- <br> butanol | 1.8 m | 2 mm | $5 \%$ G16/ <br> S1A | 20 | $110^{\circ}$ |

Suggested Operating Parameters of Gas Chromatograph Apparatus (Continued)

| Agent | Column Size |  | Column <br> Packing Phases and Support | Flow Rate, mL per min. | Column Temperature |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  | Length | ID |  |  |  |
| Phenol | 1.2 m | 3 mm | 5\% G16/ | 50 | $145^{\circ}$ |
|  |  |  | S1A |  |  |
| Parabens | 1.8 m | 2 mm | 5\% G2/ | 20 | $150^{\circ}$ |
|  |  |  | S1A |  |  |

## Benzyl Alcohol

Internal Standard Solution-Dissolve about 380 mg of phenol in 10 mL of methanol contained in a $200-\mathrm{mL}$ volumetric flask. Add water to volume, and mix.

Standard Preparation-Dissolve about 180 mg of ©USP Benzyl Alcohol RS, ${ }^{1 S}$ (USP27) accurately weighed, in 20.0 mL of methanol contained in a $100-\mathrm{mL}$ volumetric flask. Add Internal Standard Solution to volume, and mix.

Procedure-Separately inject equal volumes (about $5 \mu \mathrm{~L}$ ) of the Standard Preparation and the Test Preparation into the chromatograph, record the chromatograms with the apparatus adjusted to the parameters set forth in the accompanying table, and measure the areas under the peaks for benzyl alcohol and phenol. Calculate the content, in mg per mL , of benzyl alcohol $\left(\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{O}\right)$ in the specimen taken by the formula:

$$
100(C / V)\left(p_{1} / p_{2}\right)\left(P_{2} / P_{1}\right),
$$

in which $C$ is the concentration, in mg per mL , of benzyl alcohol in the Standard Preparation; $V$ is the volume, in mL , of the specimen under test used in preparing each 100 mL of the Test Preparation; $p_{1}$ and $p_{2}$ are the peak areas for benzyl alcohol and phenol, respectively, obtained from the Test Preparation; and $P_{1}$ and $P_{2}$ are the peak areas of benzyl alcohol and phenol, respectively, obtained from the Standard Preparation.

## Chlorobutanol

Internal Standard Solution-Transfer about 140 mg of benzaldehyde to a $100-\mathrm{mL}$ volumetric flask, add 10 mL of methanol, and swirl to dissolve. Dilute with water to volume, and mix.

Standard Preparation-Transfer about 125 mg of ehlorebuta n@l,
-USP Chlorobutanol RS, ${ }_{\text {W2S (USP28) }}$
accurately weighed, to a $25-\mathrm{mL}$ volumetric flask. Add 2 mL of methanol, swirl to dissolve, dilute with water to volume, and mix. Transfer 5.0 mL of this solution and 5.0 mL of Internal Standard Solution to a $25-\mathrm{mL}$ flask, and mix to obtain a solution having a known concentration of about 2.5 mg of chlorobutanol per mL .

Test Preparation-Quantitatively dilute, if necessary, an accurately measured volume of the specimen under test with methanol to obtain a solution containing not more than about 5.0 mg of chlorobutanol per mL. Combine 3.0 mL of this solution with 3.0 mL of Internal Standard Solution, and mix.

Chromatographic System (see Chromatography $\langle 621\rangle$ ) -[NOTE-See accompanying table for column dimensions, column packing phase and support, flow rate, and column temperature.] The injection port temperature is maintained at $180^{\circ}$, and the detector is maintained at $220^{\circ}$. Chromatograph the Standard Preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.8 for benzaldehyde and
1.0 for chlorobutanol; the resolution, $R$, between benzaldehyde and the chlorobutanol is not less than 2.0 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard Preparation and the Test Preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg , of chlorobutanol $\left(\mathrm{C}_{4} \mathrm{H}_{7} \mathrm{Cl}_{3} \mathrm{O}\right)$ in each mL of the specimen under test by the formula:

$$
C(L / D)\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of chlorobutanol, calculated on the anhydrous basis, in the Standard Preparation; $L$ is the labeled quantity, in mg , of chlorobutanol in each mL of the specimen under test; $D$ is the concentration, in mg per mL , of chlorobutanol in the Test Preparation, based on the volume of specimen under test taken and the extent of dilution; and $R_{U}$ and $R_{S}$ are the ratios of the chlorobutanol peak to the benzaldehyde peak obtained from the Test Preparation and the Standard Preparation, respectively.

## Phenol

Internal Standard Solution-Pipet 1 mL of
■USP Benzyl Alcohol RS ${ }_{\text {n2S }}$ (USP28)
into a $500-\mathrm{mL}$ volumetric flask, add methanol to volume, and mix.
Standard Preparation-Dissolve about 75 mg of phenel,
-USP Phenol RS, ${ }_{\text {■ }}$ 2S (USP28)
accurately weighed, in 7.5 mL of methanol contained in a $100-\mathrm{mL}$ volumetric flask. Add 20.0 mL of Internal Standard Solution, then add water to volume, and mix.

Procedure-Separately inject equal volumes (about $3 \mu \mathrm{~L}$ ) of the Standard Preparation and the Test Preparation into the chromatograph, record the chromatograms with the apparatus adjusted to the parameters set forth in the accompanying table, and measure the areas under the peaks for phenol and benzyl alcohol Calculate the content, in mg per mL , of phenol $\left(\mathrm{C}_{6} \mathrm{H}_{6} \mathrm{O}\right)$ in each mL of the specimen taken by the formula:

$$
100(C / V)\left(p_{1} / p_{2}\right)\left(P_{2} / P_{1}\right)
$$

in which $C$ is the concentration, in mg per mL , of phenol in the Standard Preparation; $V$ is the volume, in mL , of the specimen under test used in preparing each 100 mL of the Test Preparation; $p_{1}$ and $p_{2}$ are the peak areas for phenol and benzyl alcohol, respectively, obtained from the Test Preparation; and $P_{1}$ and $P_{2}$ are the peak areas of phenol and benzyl alcohol, respectively, obtained from the Standard Preparation.

## Methylparaben and Propylparaben

Internal Standard Solution-Place about 200 mg of benzophenone in a $250-\mathrm{mL}$ volumetric flask, dilute with ether to volume, and mix.

Standard Preparation-Place 100 mg of -USP Methylpara-
 each accurately weighed, in a $200-\mathrm{mL}$ volumetric flask, dilute with Internal Standard Solution to volume, and mix. Place 10 mL of this solution in a $25-\mathrm{mL}$ conical flask, and proceed as directed for Test Preparation, beginning with "Add 3 mL of pyridine."

Test Preparation-Pipet 10 mL of the specimen under test and 10 mL of the Internal Standard Solution into a small separator. Shake vigorously, allow the layers to separate, draw off the aqueous layer into a second separator, and transfer the ether layer into a small flask through a funnel containing anhydrous sodium sulfate. Extract the aqueous layer with two $10-\mathrm{mL}$ portions of ether, also
filtering the extracts through the anhydrous sodium sulfate. Evaporate the combined extracts under a current of dry air until the volume is reduced to about 10 mL , then transfer the residue to a 25 mL conical flask. Add 3 mL of pyridine, complete the evaporation of the ether, and boil on a hot plate until the volume is reduced to about 1 mL . Cool, and add 1 mL of a suitable silylation agent, such as bis(trimethylsilyl)trifluoroacetamide, bis(trimethylsilyl)acetamide, or a mixture of hexamethyldisilazane and trimethylchlorosilane [2:1 or $3: 1(\mathrm{v} / \mathrm{v})]$. Mix, and allow to stand for not less than 15 minutes.

Procedure-Separately inject equal volumes $(2 \mu \mathrm{~L})$ of the silanized solution from the Standard Preparation and the Test Preparation into the chromatograph, record the chromatograms with the apparatus adjusted to the parameters set forth in the accompanying table, and measure the areas under the peaks for methylparaben, propylparaben, and benzophenone. Calculate the content, in $\mu \mathrm{g}$ per mL , of methylparaben $\left(\mathrm{C}_{8} \mathrm{H}_{8} \mathrm{O}_{3}\right)$ in the sample under test by the formula:

$$
10\left(C_{M} / V\right)\left(p_{1} / p_{3}\right)\left(P_{3} / P_{1}\right)
$$

in which $C_{M}$ is the concentration, in $\mu \mathrm{g}$ per mL , of methylparaben in the Standard Preparation; $V$ is the volume, in mL , of the specimen taken; $p_{1}$ and $p_{3}$ are the peak areas for methylparaben and benzophenone, respectively, obtained from the Test Preparation; and $P_{1}$ and $P_{3}$ are the peak areas of methylparaben and benzophenone, respectively, obtained from the Standard Preparation. Similarly, calculate the content, in $\mu$ g per mL , of propylparaben $\left(\mathrm{C}_{10} \mathrm{H}_{12} \mathrm{O}_{3}\right)$ in the specimen under test by the formula:

$$
10\left(C_{P} / V\right)\left(p_{2} / p_{3}\right)\left(P_{3} / P_{2}\right)
$$

in which $C_{P}$ is the concentration, in $\mu \mathrm{g}$ per mL , of propylparaben in the Standard Preparation; $V$ is the volume, in mL , of the specimen taken; $p_{2}$ and $p_{3}$ are the peak areas for propylparaben and benzophenone, respectively, obtained from the Test Preparation; and $P_{2}$ and $P_{3}$ are the peak areas of propylparaben and benzophenone, respectively, obtained from the Standard Preparation.

Ethylparaben and butylparaben may be determined in a similar manner.

## Change to read:

## POLAROGRAPHIC METHOD

## Phenylmercuric Nitrate

Standard Preparation-Dissolve about 100 mg of phenylmercuric nitrate, accurately weighed, in sodium hydroxide solution (1 in 250 ) contained in a $1000-\mathrm{mL}$ volumetric flask, warming if necessary to effect solution, add the sodium hydroxide solution to volume, and mix. Pipet 10 mL of this solution into a $25-\mathrm{mL}$ volumetric flask, and proceed as directed under Test Preparation, beginning with "add 2 mL of potassium nitrate solution (1 in 100)."

Test Preparation-Pipet 10 mL of the specimen under test into a $25-\mathrm{mL}$ volumetric flask, add 2 mL of potassium nitrate solution ( 1 in 100) and 10 mL of pH 9.2 alkaline borate buffer (see under Buffer Solutions in the section Reagents, Indicators, and Solutions), and adjust to a pH of 9.2, if necessary, by the addition of 2 N nitric acid. Add 1.5 mL of freshly prepared gelatin solution ( 1 in 1000), then add the pH 9.2 alkaline borate buffer to volume, and mix.

Procedure-Pipet a portion of the Test Preparation into the polarographic cell, and deaerate by bubbling nitrogen through the solution for 15 minutes. Insert the dropping mercury electrode of a suitable polarograph (see Polarography $\langle 801\rangle$ ), and record the polarogram from -0.6 to -1.5 volts versus the saturated calomel elec-
trode. Determine the diffusion current of the Test Preparation, $\left(i_{d}\right)_{U}$, as the difference between the residual current and the limiting current. Similarly and concomitantly determine the diffusion current, $\left(i_{d}\right)_{s}$, of the Standard Preparation. Calculate the quantity, in $\mu \mathrm{g}$, of phenylmercuric nitrate $\left(\mathrm{C}_{6} \mathrm{H}_{5} \mathrm{HgNO}_{3}\right)$ in each mL of the specimen taken by the formula:

$$
2.5 C\left[\left(i_{d}\right)_{U} /\left(i_{d}\right)_{S}\right]
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of phenylmercuric nitrate in the Standard Preparation.

## Thimerosal

Standard Preparation-On the day of use, place about 25 mg of thimeroset,

■USP Thimerosal RS, ${ }_{\square 2 S}$ (USP28)
accurately weighed, in a $250-\mathrm{mL}$ volumetric flask, add water to volume, and mix. Protect from light. Pipet 15 mL of this solution into a $25-\mathrm{mL}$ volumetric flask, add 1.5 mL of gelatin solution ( 1 in 1000), then add potassium nitrate solution ( 1 in 100) to volume, and mix.

Test Preparation-Pipet 15 mL of the test specimen into a 25 mL volumetric flask, add 1.5 mL of gelatin solution (1 in 1000), add potassium nitrate solution (1 in 100) to volume, and mix.

Procedure-Transfer a portion of the Test Preparation to a polarographic cell, and deaerate by bubbling nitrogen through the solution for 15 minutes. Insert the dropping mercury electrode of a suitable polarograph (see Polarography $\langle 801\rangle$ ), and record the polarogram from -0.2 to -1.4 volts versus the saturated calomel electrode. Determine the diffusion current, $\left(i_{d}\right)_{U}$, as the difference between the residual current and the limiting current. Similarly and concomitantly determine the diffusion current, $\left(i_{d}\right)_{S}$, of the Standard Preparation. Calculate the quantity, in $\mu \mathrm{g}$, of thimerosal $\left(\mathrm{C}_{6} \mathrm{H}_{9} \mathrm{HgNaO}_{2} \mathrm{~S}\right)$ in each mL of the test specimen taken by the formula:

$$
1.667 C\left[\left(i_{d}\right)_{U} /\left(i_{d}\right)_{S}\right],
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of thimerosal in the Standard Preparation; and the other terms are as defined therein.

## Briefing

〈386〉 Environmentally Sensitive Preparations, page 1143 of PF 29(4) [July-Aug. 2003]. Following the PSD Open Conference held October 12-15, 2003, this chapter was revised to incorporate comments received. The revised version was further discussed with FDA representatives, and based on the comments presented by FDA, additional revisions were made. Listed below are highlights of the revisions made to the chapter:

1. Emphasis on packaging selection.
2. Definition of repackager(s)-contract and wholesale.
3. Deletion of $37^{\circ} \mathrm{C}$, in item 2 b , under Criteria to Determine if a Product is an Environmentally Sensitive Preparation.
4. Deletion of $65 \pm 5 \%$ relative humidity, item 2 c under the same section.
5. Removal of all references to data and replacing it with stability and packaging information.
6. Introduction of icons in appropriate sections of the text.

The PSD Committee believes that these changes address FDA's and manufacturers' concerns, as well as defining, more precisely, information required from the manufacturers.
(PSD: C. Okeke) RTS-40548-7; 40622-1; 40657-1

## Add the following:

## - 386$\rangle$ ENVIRONMENTALLY SENSITIVE PREPARATIONS

## In the interest of enstring the integrity of a pharmaceuti-

eal article as it reaches the patient for acourse of treatment, this chapter foeuses on preparations that may be repackaged or dispensed in other than the market package so that proper storage and shipment instructions can be ineluded with the efficial preparation. It is assumed that, as long as these pack aged preparations are transported aceording to the directions in the packuge insert, the original manufacturer's packages are-sufficient for assuring that these requirements are met.

An individual preparation is an Envirommentally Sensi-
tive Preparation if data indicate the failure of that preparation to conform to a monograph requirement after expesure tone of the following sets of criteria.

## СRझТЕRझА ТО-DETERMझNE IF A PRODUCT IS AN

## ENVHRONMENTALLY SENSHTHVE PREPARATION

NOTE-The desage form may be protected from light dur ing the studies.

1. Use pertinent stability data available on file, or
2. Betermine if a preparation meets the test requirements (a-d) listed below. If a preparation does not meet a menegraph requirement after expestre-to-enditions speciffed for requirement $a$, retest as-directed for $b, c$, or $d$, as apprepriate.
a. For any dosage form: 3-menths at a temperature-of $40 \pm 2^{\circ}$ and $75 \pm 5 \%$ relative humidity in the market container, or $30 \pm 2^{\circ}$ and $60 \pm 5 \%$ relative hemidity for 6 menths.
b. For solutions: 3-months at a temperature of $37^{\circ}$ to $40 \pm 2^{\circ}$ and ambient humidity in the market container.
e. For semisolids and heterogeneous liquids, such as ereams, transdermal systems, gels, emulsions, and-suspensions; and for sterile solids for injection: 6 months at atemperature of $30 \pm 2^{\circ}$ and $60 \pm 5 \%$ relative hemid ity in the market container.
3. For solid oral dosage form: 30 days at a temperature of $25 \pm 2^{\circ}$ and $60 \pm 5 \%$ relative humidity in an open dish (i.e., the container without closure, coil, desiecant, or tusealed blisters).

## Definitions

For the purpose of this chapter, a packager is deffned as ene whe puts a drug product inte a primary container for distribution to patients. A packager may be a repackager, a pharmacist, or a manufacturer.

## Labeling, Storage, and Shipping

Pecisions regarding the labeling of a product as an Envirammentally Sensitive Preparation are the respensibility of the packager and are based on the product's characteristies and stability history.

Where data establish that a preparation is an Enviremment tally-Sensitive Preparation, any of the following labeling and shipping arrangements are employed, as appropriate, teensure menegraph conformity.
a. The artiele is shipped in a manner that (1) ensures that its integrity is maintained, and (2) is based on product int formation, packaging data, and the distribution system theed.
b. The article-is shipped in suitable appropriate protective packaging insulated package that could include feillaminated polyethylene bags, desiceant containers, or packages of sufficient desiceant capacity.
e. The article is shipped with a validated time temperature monitoring device (see Monitoring Devices Tine, Femperature, and Humidity $\langle 1418\rangle$ andether goodstor age and shipping practice documents). The menitoring device is affixed either to the outer shipping package or to the packuging of individual containers (for example, for mixed shipments).
4. Unepened packages shall be moved through the distribution chain with the menitoring device intact.
e. Where-shipping is expected to extend beyond 48 heurs, instructions are included, specifying that the article is not to be used if the menitoring device discloses a ent mulative history of exposure equivalent to mere than-48 hours at or above a temperature of $40^{\circ}$. A manufacturer may make other assurances about packaging and distri bution arrangements based on product data and infor mation.

## Instructions to the Pharmacist or Repackager

Suitable information must be available to identify an Envirommentally Sensitive Preparation to the pharmacist or repackager along with appropriate instructions for handling the preparation. For example, the labeling of a mantafac
farer's maltiple-unit package (or market repackage) of a hut midity sensitive preparation may include one or more of the following statements:
at Be net dispense mere than a 30-day supply of the preseription in one multiple-unit container.
b. Dispense it in a desiccant container of sufficient desiceant capacity.
e. Pispense it in a tight or Class $A$ container (see Con tainers Permeation- 674$\rangle$ ) if it is net dispensed in a market package.
4. "Do net repackage", if the medieation is net to be repackaged.
e. Dispense it in a unit of use container (see Packaging Unit of Use $\langle 1136\rangle$-.
f. Label the patient's-containers to-state "use the contents within 30 days frem the first day that individual eontainer is opened".

## Instructions-to-Institutional-Settings

In an institutional setting, store packages of an Environmentally Sensitive Preparation at controlled room temperature or aceording to labeled requirements in the market package. Packages dispensed for use by a partieular patient should bear a beyond use date of 3 months or 90 days and a statement "Store at $20^{\circ}$ to $25^{\circ}\left(68^{\circ} \mathrm{F}\right.$ to $\left.77^{\circ} \mathrm{F}\right)$ ", unless (1) dat suppert other labeling or (2) other manafacturer's ree emmendations are applieable-

## Instruetions to the Mantafacturer

For an Environnentally Sensitive Preparation for which data-suppert other labeling, beyond-use dates, or expestre equivalents, the manufacturer must inelude labeling and in-
formation suitable for optimal handling by the practitioner Or pharmacist, by the repackager, and by the patient. Product development or stability datacan be used to determine appropriate labeling and shipping statements that will properly inform patients and practitioners.

When repackagers and pharmacists, ineluding hespitat, emergency medical services, mail service, Internet based services, and other practitioners, request information about product behavior upon expesure to various temperature and humidity conditions, pharmaceutieal manufacturers are-encouraged to provide such information if available.

## Exemptions

4. The following preparations are-exempt frem the above eonsiderations: these labeled that they must be stored and transperted refrigerated or frozen; labeled radiopharmaceuticals; and these-shipped and received-in net more than the time period specified on the outer package, provided data are available to show that the stability of the article is not compromised dering that period under the expected conditions of temperature and/or htmidity.
5. For classifying a preparation as an Enviromnentally Sensitive Prepatation, the general chapter Uniformity Of Desage Units $\langle 905\rangle$-does not apply.

In the interest of ensuring that a pharmaceutical article meets monograph requirements when it reaches the patient for a course of treatment, this chapter focuses on preparations that may be repackaged or dispensed in other than the market package so that proper packaging selection, storage, and shipment instructions can be included with the official preparation. Most articles when shipped or stored in the manufacturer's original container-closure system, or that of an appropriate contract repackager (see below), are
not compromised under stressful environmental conditions in the expected distribution system. However, there is uncertainty about the preparation's stability if it has been repackaged into another container. This chapter is intended to focus on these repackaging and distribution processes to ensure that proper communication and requirements are established to protect the preparation until it reaches the patient.

An individual preparation is an Environmentally (Humidity and/or Temperature) Sensitive Preparation if stability information demonstrates the failure of that preparation to conform to a monograph requirement under conditions described in either of the two criteria described below.

## CRITERIA TO DETERMINE IF A PRODUCT IS AN ENVIRONMENTALLY SENSITIVE PREPARATION

NOTE-The dosage form may be protected from light during the studies.

1. Use pertinent stability information available on file, or
2. Determine if a preparation meets the test requirements ( $a-d$ ) listed below. If a preparation does not meet a monograph requirement after exposure to conditions specified for requirement $a$, retest for conformance as directed for $b, c$, or $d$, as appropriate.
a. For any dosage form in the market container: 3 months at a temperature of $40 \pm 2^{\circ}$ and $75 \pm 5 \%$ relative humidity, or 6 months at $30 \pm 2^{\circ}$ and $65 \pm 5 \%$ relative humidity or other appropriate storage condition.
b. For solutions in the market container: 3 months at a temperature of $40 \pm 2^{\circ}$ and ambient humidity.
c. For semisolids and heterogeneous liquids, such as creams, transdermal systems, gels, emulsions, and suspensions; and for sterile solids for injection in the market container: 6 months at a temperature of $30 \pm 2^{\circ}$.
d. For solid oral dosage forms that are not Temperature Sensitive Preparations: 30 days at a temperature of $30 \pm 2^{\circ}$ and $65 \pm 5 \%$ relative humidity in an open dish (or the market container without closure, seal, coil, desiccant; or unsealed blisters).

## DEFINITIONS

For the purpose of this chapter, a packager is defined as one who puts a drug product into a primary container for distribution to patients. A packager may be a repackager, a pharmacist, or a manufacturer.
A repackager is an establishment that removes the preparation from its original container and places it into another suitable container or container closure system, usually of smaller size, and sends it to a second location in anticipation of a need (see Packaging Practice-Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container $\langle 1146\rangle)$. A contract repackager is a repackager that acts on an article owned by the manufacturer. Repackagers are regulated under the FD\&C Act (see 21 CFR 210 and 211).
A pharmacy or pharmacist dispenser or pharmacy repackager is regulated by the various states. A wholesaler repackager is a repackager that acts on a product owned by the wholesaler and is regulated by the various states.

## LABELING, STORAGE, AND SHIPPING

Decisions regarding the labeling, storage, and shipping of an article as an Environmentally Sensitive Preparation are the responsibility of the packager or intermediary (e.g., wholesaler) initiating that phase of distribution and are based on the manufacturer's suggested storage conditions. For an Environmentally Sensitive Preparation, employ any of the following labeling and shipping arrangements, as appropriate, to ensure continued conformity with the monograph.
a. Consider using one or more icons or other symbols on the label to notify all recipients of the environmentally sensitive nature of the preparations (see Figures 1-4 below).
b. Ship the article in a manner that: (1) ensures that its attributes are maintained, and (2) is based on product and packaging information and the distribution system used.
c. Ship the article in suitable protective packaging that could include insulated packaging, foil-laminated polyethylene bags, desiccant containers, or packages of sufficient desiccant capacity for the distribution system used.
d. Ship the article with a Time-temperature monitoring device (see Monitoring Devices-Time, Temperature, and Humidity $\langle 1118\rangle$ and the monograph). The monitoring device is affixed either to the outer shipping package or to the packaging of individual containers,
for example, for mixed shipments. Alternatively, ship it in a suitably monitored vehicle compartment. Unopened packages shall be moved through the distribution chain with the monitoring device intact.
e. A manufacturer may make specific recommendations about packaging and distribution arrangements based on product and packaging information. In absence of such recommendations, where shipping is expected to extend beyond 48 hours, include instructions specifying that the article is not to be used if the monitoring device discloses a cumulative history of exposure equivalent to more than 48 hours at or above a temperature of $40^{\circ}$.
f. The Poison Prevention Packaging Act of 1970 (see the General Notices) requires in certain cases the use of special packaging-child-resistant or senior friendly. The packaging of Environmentally Sensitive Preparations should conform to these regulations.

## INSTRUCTIONS TO THE PHARMACIST OR REPACKAGER

Suitable information must be available to identify an Environmentally Sensitive Preparation to the pharmacist or repackager along with appropriate instructions for handling the preparation. For example, the labeling of a manufacturer's multiple-unit package (or contract repackage) of a Humidity Sensitive Preparation may include one or more of the following statements:
a. Do not dispense more than a 30-day supply of the Preparation in one multiple-unit container. Label the patient's containers to state "use the contents within 30 days from the first day that the individual container is opened."
b．Do not repackage in single－unit containers．
c．Dispense in a desiccant container of sufficient desiccant capacity．
d．Dispense in a tight or Class A container（see Con－ tainers－Permeation $\langle 671\rangle$ ）if it is not dispensed in a market package．
e．Dispense in a unit－of－use container（see Packaging－ Unit of Use 〈1136〉）．
f．Do not repackage if the medication is labeled not to be repackaged．

## INSTRUCTIONS TO INSTITUTIONAL

## PRACTITIONERS

In a pharmacy or an institutional setting，store packages of an Environmentally Sensitive Preparation at controlled room temperature or according to other labeled conditions in the market package．Packages dispensed for use by a par－ ticular patient should bear a discard－after date of 3 months or 90 days and a statement＂Store at $20^{\circ}$ to $25^{\circ}\left(68^{\circ} \mathrm{F}\right.$ to $77^{\circ}$ F）＂，unless（1）stability information supports other labeling， or（2）other recommendations of the manufacturer are applicable．

## INSTRUCTIONS TO THE MANUFACTURER

For an Environmentally Sensitive Preparation for which stability information supports other labeling，discard－after dates，or exposure equivalents，the manufacturer must in－ clude labeling and information suitable to enable optimal handling by the practitioner or pharmacist，by the repack－
ager，and by the patient．Product development or stability information can be used by the manufacturer to determine appropriate labeling and shipping statements，or icons or symbols（see Figures 1－4 below），that will properly inform repackagers，patients，and practitioners．See Instructions to the Pharmacist or Repackager，above．

When repackagers and pharmacists，including hospital， emergency medical services，mail service，Internet－based services，and other practitioners，request information about product behavior upon exposure to various temperature and humidity conditions，pharmaceutical manufacturers are en－ couraged to provide such information，if available．

## EXEMPTIONS

1．The following preparations are exempt from the above considerations：those labeled that they must be stored and transported refrigerated or frozen；and those shipped and received in not more than the time period specified on the outer package，provided stability infor－ mation is available to show that the stability of the ar－ ticle is not compromised during that period under the conditions of temperature and／or humidity expected for the distribution system used．

2．For classifying a preparation as an Environmentally Sensitive Preparation，Uniformity of Dosage Units〈905〉 does not apply．■2S（USP28）


Figure 1.


Avoid Heat


Figure 4.

Figure 2.

# Physical Tests and Determinations 

## BRIEFING

〈621〉Chromatography, USP 27 page 2272, page 3325 of the Second Supplement, and page 1007 of $P F 30$ (3) [May-June 2004]. A reference to TLC plates with a preadsorbent zone is included in the Thin-Layer Chromatography section. The PA2 Expert Committee agreed to include a Quantitation Limit Solution as part of the system suitability test for the Chromatographic purity or Related compounds tests. The objective of this procedure is to ensure that under the test conditions, the system is able to detect impurities in low concentration. A paragraph introduced in the System suitability section suggests that changes in the chromatographic system can produce unexpected changes in the performance of the test. The analyst must ensure that the changes introduced in the chromatographic system do not have a negative impact on the test performance. Changes in the allowable adjustments are also included.
(PA2: H. Pappa) RTS-37798-1; 41430-1; 41284-1; 41572-1

## Change to read:

## INTRODUCTION

This chapter defines the terms and procedures used in chromatography and provides general information. Specific requirements for chromatographic tests and assays of

■procedures for $_{\text {■2S (USP28) }}$
drug substances and dosage forms, including adsorbent and developing solvents, are given in the individual monographs.

Chromatography is defined as a procedure by which solutes are separated by a dynamic differential migration process in a system consisting of two or more phases, one of which moves continuously in a given direction and in which the individual substances exhibit different mobilities by reason of differences in adsorption, partition, solubility, vapor pressure, molecular size, or ionic charge density. The individual substances thus ebtined
$\square_{\text {separated }}{ }_{\text {■2S (USP28) }}$
can be identified or determined by analytical metheds.
■procedures
S. 12 S (USP28)

The general chromatographic technique requires that a solute undergo distribution between two phases, one of them fixed (stationary phase), the other moving (mobile phase). It is the mobile phase that transfers the solute through the medium until it eventually emerges separated from other solutes that are eluted earlier or later. Generally, the solute is transported through the separation medium by means of a flowing stream of a liquid or a gaseous solvent known as the "eluant." The stationary phase may act through adsorption, as in the case of adsorbents such as activated alumina; silien gel, and ion exchange resins,

or it may act by dissolving the solute, thus partitioning the latter between the stationary and mobile phases. In the latter process, a tiquid coating held on an inert support serves as the stationary phase.
-In the latter process, a liquid coated onto an inert support, or chemically bonded onto silica gel, or directly onto the wall of a fused silica capillary, serves as the stationary phase. $\mathbf{m}_{2 S}$ (USP28)
Partitioning is the predominant mechanism of separation in gas-liquid chromatography, paper chromatography, and forms of column chromatography
$\boldsymbol{m}_{\text {and thin-layer chromatography }}^{\mathbf{m}_{2 S} \text { (USP28) }}$
designated as liquid-liquid ehremagraphy.

- $_{\text {separation. }}^{\text {■2S (USP28) }}$

In practice, separations frequently result from a combination of adsorption and partitioning effects.
-Other separation principles include ion exchange, ion pair formation, size exclusion, hydrophobic interaction, and chi-
ral recognition. $\mathbf{m}_{2 S}$ (USP28)
The types of chromatography useful in qualitative and quantitative analysis that are employed in the $U S P$ ests assays

■procedures $_{\text {■2S }}$ (USP28)
are column, gas, paper, thin-layer,

- (including high-performance thin-layer chromatogra-


## phy), ${ }^{2 S}$ (USP28)

and pressurized liquid chromatography (commonly called highpressure or high-performance liquid chromatography). Paper and thin-layer chromatography are ordinarily more useful for purposes of identification, because of their convenience and simplicity. Column chromatography offers a wider choice of stationary phases and is useful for the separation of individual compounds, in quantity, from mixtures. Both ehromatography and pressurized lif rid chromatography require more elaborate apparatus and usually provide high resolution metheds hat will identify and quantitate very small amounts of material.

- Modern high-performance thin-layer chromatography, gas chromatography, and pressurized liquid chromatography require more elaborate apparatus but usually provide high resolution and identify and quantitate very small amounts of material. ${ }^{\text {2S }}$ (USP28)

Use of Reference Substances in Identity Tests-In paper and thin-layer chromatography, the ratio of the distance (this distance being measured to the point of maximum intensity of the spot
$■_{\text {or zone) }}^{\text {■2S (USP28) }}$
traveled on the medium by a given compound to the distance traveled by the front of the mobile phase, from the point of application of the test substance, is designated as the $R_{F}$ value of the compound. The ratio between the distances traveled by a given compound and a reference substance is the $R_{R}$ value. $R_{F}$ values vary with the experimental conditions, and thus identification is best accomplished where an authentic specimen of the compound in question is used as a reference substance on the same chromatogram.

For this purpose, chromatograms are prepared by applying on the thin-layer adsorbent or on the paper in a straight line, parallel to the edge of the chromatographic plate or paper, solutions of the substance to be identified, the authentic specimen, and a mixture of nearly equal amounts of the substance to be identified and the authentic specimen. Each sample application contains approximately the same quantity by weight of material to be chromatographed. If the substance to be identified and the authentic specimen are identical, all chromatograms agree in color and $R_{F}$ value and the mixed chromatogram yields a single spot; i.e., $R_{R}$ is 1.0 .

## Change to read:

## THIN-LAYER CHROMATOGRAPHY

In thin-layer chromatography, the adsorbent is a relatively thin, uniform layer of dry, finely powdered material applied to a glass, plastic, or metal sheet or plate, glass plates being most commonly employed. The coated plate can be considered an "open chromatographic column" and the separations achieved may be based upon adsorption, partition, or a combination of both effects, depending on the particular type of suppert,

its preparation, and its use with different solvents. Thin-layer chromatography on ion-exchange flms

- layers $_{\text {2S (USP28) }}$
can be used for the fractionation of polar compounds. Presumptive identification can be effected by observation of spots
- or zones $_{\mathbf{m 2 S}}$ (USP28)
of identical $R_{F}$ value and about equal magnitude obtained, respectively, with an unknown and a reference sample chromatographed on the same plate. A visual comparison of the size of the spets
- or intensity of the spots or zones $_{\text {m2S (USP28) }}$
may serve for semiquantitative estimation. Quantitative measurements are possible by means of densitometry, fluoresenee, and flurescence quenehing;
-(absorbance or fluorescence measurements), $\mathbf{\square} 2$ (USP28) or the spots may be carefully removed from the plate, followed by elution with a suitable solvent and spectrophotometric measurement. For two-dimensional thin-layer chromatography, the chromatographed plate is turned at a right angle and again chromatographed, usually in another chamber equilibrated with a different solvent system.

Apparatus-Acceptable apparatus and materials for thin-layer chromatography consist of the following.

Flat glass plates of convenient size, typieally $20 \mathrm{~cm} \times 20 \mathrm{~cm} .{ }^{+}$
Analigning tray or a flat surface upen whieh to align and rest the plates during the applieation of the adsorbent.

A storage rack to hold the prepared plate during drying and tramspertation. The rack holding the plates should be kept in a desiccutor or be capable of being sealed in order to protect the plater from the environment after removal from the drying oven. The adsorbent consists of finely divided adsorbent materials, nermally 5 to $-40 \mu \mathrm{~m}$ in diameter, suitable for chrematography. It ean be applied direetly to the glass plate or can be bended to the plate by means of plaster of paris (hydrated calcium sulfate) [at a ratio of $5 \%$ to $15 \%$ ] or with stareh paste or other binders. The for mer will not yield as hard a surface as will the stareh, but it is net
affected by strongly oxidizing spray reagents. The adsorbent may centain fluorescing material to aid in the visualization of spots that absorb ultraviolet light.

A spreader, which, when moved over the glass plate, will apply a uniform layer of adsorbent of desired thickness over the entire sufface of the plate.

A developing ehember that can aceommodate one or more plates and ean be properly elesed and sealed as deseribed under Aseend ing Chromatography. The chamber is fitted with a plate support rack that supports the plates, back to back, with the lid of the chamber in place.

A template (generally made of plastic) to aid in placing the eest spots at definite intervals, to mark distanees as needed, and to aid im tabeling the plates.

A graduated mieropipet eapable of delivering $10 \mu \mathrm{~L}$ volumes. Total volumes of test and standard solutions are specified in the individual menegraph.
Aredgent spratyer that will emit a finespray and will not itself be attacked by the reagent.
An ultraviolet light souree suitable for observations with shert $(254 \mathrm{~nm})$ and long ( 360 nm ) UV wavelengths.

- A TLC or HPTLC plate. The chromatography is generally carried out using precoated plates or sheets (on glass, aluminum, or polyester support) of suitable size. It may be necessary to clean the plates prior to separation. This can be done by migration of, or immersion in, an appropriate solvent. The plates may also be impregnated by procedures such as development, immersion, or spraying. At the time of use, the plates may be activated, if necessary, by heating in an oven at $120^{\circ}$ for 20 minutes. The stationary phase of TLC plates has an average particle size of $10-15 \mu \mathrm{~m}$, and that of HPTLC plates an average particle size of $5 \mu \mathrm{~m}$. Commercial plates with a preadsorbant zone can be used if they are specified in a monograph. Sample applied to the preabsorbant region develops into sharp, narrow bands at the pre-absorbant-sorbent interface. Alternatively, flat glass plates of convenient size, typically $20 \mathrm{~cm} \times 20 \mathrm{~cm}$ can be coated as described under Preparation of Chromatographic Plates.

A suitable manual, semiautomatic, or automatic application device can be used to ensure proper positioning of the plate and proper transfer of the sample, with respect to volume and position, onto the plate. Alternatively, a template can be used to guide in manually placing the test spots at definite intervals, to mark distances as needed, and to aid

[^248]in labeling the plates. For the proper application of the solutions, micropipets, microsyringes, or calibrated disposable capillaries are recommended.

For ascending development, a chromatographic chamber made of inert, transparent material and having the following specifications is used: a flat bottom or twin trough, a tightly fitted lid, and a size suitable for the plates. For horizontal development, the chamber is provided with a reservoir for the mobile phase, and it also contains a device for directing the mobile phase to the stationary phase.

Devices for transfer of reagents onto the plate by spraying, immersion, or exposure to vapor and devices to facilitate any necessary heating for visualization of the separated spots or zones.

A UV light source suitable for observations under short ( 254 nm ) and long ( 365 nm ) wavelength UV light.

A suitable device for documentation of the visualized chromatographic result.

Procedure-Apply the prescribed volume of the test solution and the standard solution in sufficiently small portions to obtain circular spots of 2 to 5 mm in diameter ( 1 to 2 mm on HPTLC plates) or bands of 10 to 20 mm by 1 to 2 mm ( 5 to 10 mm by 0.5 to 1 mm on HPTLC plates) at an appropriate distance from the lower edge-during chromatography the application position must be 3 mm (HPTLC) to 5 mm (TLC) above the level of the developing solvent-and from the sides of the plate. Apply the solutions on a line parallel to the lower edge of the plate with an interval of at least 10 mm ( 5 mm on HPTLC plates) between the centers of spots or 4 mm ( 2 mm on HPTLC plates) between the edges of bands, and allow to dry.

Ascending Development-Line at least one wall of the chromatographic chamber with filter paper. Pour into the chromatographic chamber a quantity of the mobile phase sufficient for the size of the chamber to give, after impreg-
nation of the filter paper, a level of depth appropriate to the dimension of the plate used. For saturation of the chromatographic chamber, close the lid, and allow the system to equilibrate. Unless otherwise indicated, the chromatographic separation is performed in a saturated chamber.

Place the plate in the chamber, ensuring that the plate is as vertical as possible and that the spots or bands are above the surface of the mobile phase, and close the chamber. The stationary phase faces the inside of the chamber. Remove the plate when the mobile phase has moved over the prescribed distance. Dry the plate, and visualize the chromatograms as prescribed. For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

## Horizontal Development-Introduce a sufficient quantity

 of the developing solvent into the reservoir of the chamber using a syringe or pipet. Place the plate horizontally in the chamber, connect the mobile phase direction device according to the manufacturer's instructions, and close the chamber. If prescribed, develop the plate starting simultaneously at both ends. Remove the plate when the mobile phase has moved over the distance prescribed in the monograph. Dry the plate, and visualize the chromatograms as prescribed.For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

Detection-Observe the dry plate first under short-wavelength UV light ( 254 nm ) and then under long-wavelength UV light ( 365 nm ) or as stated in the monograph. If further directed, spray, immerse, or expose the plate to vapors of the specified reagent, heat the plate when required, observe, and compare the test chromatogram with the standard chromatogram. Document the plate after each observation. Measure and record the distance of each spot or zone from the point
of origin, and indicate for each spot or zone the wavelength under which it was observed. Determine the $R_{F}$ values for the principal spots or zones (see Glossary of Symbols).

Quantitative Measurement-Using appropriate instrumentation, substances separated by TLC and responding to ultraviolet-visible (UV-Vis) irradiation prior to or after derivatization can be determined directly on the plate. While moving the plate or the measuring device, the plate is examined by measuring the reflectance of the incident light. Similarly, fluorescence may be measured using an appropriate optical system. Substances containing radionuclides can be quantified in three ways: (1) directly by moving the plate alongside a suitable counter or vice versa; (2) by cutting the plates into strips and measuring the radioactivity on each individual strip using a suitable counter; or (3) by scraping off the stationary phase, dissolving it in a suitable scintillation cocktail, and measuring the radioactivity using a liquid scintillation counter (see Radioactivity $\langle 821\rangle$ ).

The apparatus for direct quantitative measurement on the plate is a densitometer that is composed of a mechanical device to move the plate or the measuring device along the x axis and the $y$-axis, a recorder, a suitable integrator or a computer; and, for substances responding to UV-Vis irradiation, a photometer with a source of light, an optical device capable of generating monochromatic light, and a photo cell of adequate sensitivity, all of which are used for the measurement of reflectance. In the case where fluorescence is measured, a suitable filter is also required to prevent the light used for excitation from reaching the photo cell while permitting the emitted light or specific portions thereof to pass. The linearity range of the counting device must be verified.

For quantitative tests, it is necessary to apply to the plate not fewer than three standard solutions of the substance to be examined, the concentrations of which span the expected
value in the test solution (e.g., $80 \%, 100 \%$, and $120 \%$ ). Derivatize with the prescribed reagent, if necessary, and record the reflectance or fluorescence in the chromatograms obtained. Use the measured results for the calculation of the amount of substance in the test solution.

Preparation of Chromatographic Plates-
Apparatus-
Flat glass plates of convenient size, typically $20 \mathrm{~cm} \times 20$ cm .

An aligning tray or a flat surface upon which to align and rest the plates during the application of the adsorbent.

A storage rack to hold the prepared plates during drying and transportation. The rack holding the plates should be kept in a desiccator or be capable of being sealed in order to protect the plates from the environment after removal from the drying oven.
The adsorbent consists of finely divided adsorbent materials, normally 5 to $40 \mu \mathrm{~m}$ in diameter, suitable for chromatography. It can be applied directly to the glass plate or can be bonded to the plate by means of plaster of Paris (calcium sulfate hemihydrate [at a ratio of $5 \%$ to $15 \%$ ]) or with starch paste or other binders. The plaster of Paris will not yield as hard a surface as will the starch, but it is not affected by strongly oxidizing spray reagents. The adsorbent may contain fluorescing material to aid in the visualization of spots that absorb UV light.

A spreader, which, when moved over the glass plate, will apply a uniform layer of adsorbent of desired thickness over the entire surface of the plate. $\quad$ 2S (USP28)

Procedure-[NOTE-In this procedure, use purified water that is obtained by distillation.] Clean the

- $^{\text {glass }}{ }_{\text {■2S (USP28) }}$
plates scrupulously, as by immersion in chromic acid cleansing mixture,
-using an appropriate cleaning solution (see Cleaning Glass Apparatus $\langle 1051\rangle$ ), ■ $^{2 S}$ (USP28)
rinsing them with copious quantities of water until the water runs off the plates without leaving any visible water or oily spots, then dry. It is important that the plates be completely free from lint and dust when the adsorbent is applied.

Arrange the plate or plates on the aligning tray, place a $5-\times 20-$ cm plate adjacent to the front edge of the first square plate and another $5-\times 20-\mathrm{cm}$ plate adjacent to the rear edge of the last square, and secure all of the plates so that they will not slip during the application of the adsorbent. Position the spreader on the end plate opposite the raised end of the aligning tray. Mix 1 part of adsorbent with 2 parts of water (or in the ratio suggested by the supplier) by shaking vigorously for 30 seconds in a glass-stoppered conical flask, and transfer the slurry to the spreader. Usually 30 g of adsorbent and 60 mL of water are sufficient for five $20-\times 20-\mathrm{cm}$ plates. Complete the application of adsorbents using plaster of Paris binder within 2 minutes of the addition of the water, because thereafter the mixture begins to harden. Draw the spreader smoothly over the plates toward the raised end of the aligning tray, and remove the spreader when it is on the end plate next to the raised end of the aligning tray. (Wash away all traces of adsorbent from the spreader immediately after use.) Allow the plates to remain undisturbed for 5 minutes, then transfer the square plates, layer side up, to the storage rack, and dry at $105^{\circ}$ for 30 minutes. Preferably place the rack at an angle in the drying oven to prevent the condensation of moisture on the back sides of plates in the rack. When the plates are dry, allow them to cool to room temperature, and inspect the uniformity of the distribution and the texture of the adsorbent layer; transmitted light will show uniformity of distribution, and reflected light will show uniformity of texture. Store the satisfactory plates over silica gel in a suitable chamber.

Place fwe filter paper wicks, 18 cm in height and ws wide as the length of the developing chamber, into the chamber, add about 100 mL of the solvent (sufficient to have depth of 5 to 10 mm at the bettom of the chamber), seal the eover to the top of the chamber, and allow the system to equilibrate; it is essential that the wieks become completely wet. Altematively, the chamber may be completely lined with filter paper. In either ease, assure that the fllter paper dips into the solvent at the bettom of the chamber. Where vapor saturation of the chamber by these methods is undesirable, it is so indicated in the individual menegraph.

Apply the test solution and the standard solution, as directed in the individual menegraph, at peints about 1.5 cm apart and about 2 em from the lower edge of the plate (the lower edge is the first part over which the-spreader moved in the applieation of the adsorbent tayer), and allow to dry. Avoid physieal distubanee of the adsor bent during the spoting procedure (by the pipet or other applientor) or when handling the plates. The template will aid in determining the spot points and the 10 to 15 cm distance through which the solvent from should pass.

Place a mark 10 to 15 cm above the spet point. Arrange the plate en the supperting rack (test spets toward the bottom), and introduce the rack into the developing chamber. Allow the solvent in the chamber to reach the lower edge of the adsorbent, but do not allow the spot points to be immersed. Put the cover in place, and maintain the systemuntil the solvent aseends to a peint 10.015 cm above the initial spots, this usually requires about 15 minntes to 1 hour. Remove the plate from the developing chamber, mark the solvent frent, air dry the plates, and observe first mender shert wavelength UV light ( 254 mm ) and then under long wavelength UV light ( 360 nm ). Measure and record the distance of each spot from the peint of origin, and indiente for each spet the wavelength under which it was observed. Determine the $R_{t}$ values for the principat spots (see Glossaty of Symbels). If further directed, spray the spots with the reagent speciffed, observe, and compare the test chromat egram with the standard chrematogram.

## Contintous Development Thin-Layyr Chromatography

In centrast to conventional thin layer chremategraphy, which is earried out in clesed tank, the eontinnous development or continHous flow technigue allows the upper end of the plate to project threugh a slot in the cover of the developing chamber. When the developing solvent reaches the slot, contintrous-vaporation or eurs, producing a steady flow of solvent over the plate. In conventional thin layer ehromatography, spot migration ceases when the solvent reaches the top of the plate, after which the spots simply enlarge by diffusion. In the continueus flow process, spet migration contintes as long as the plate remains in the tank and the developing solvent is not exhatusted.

Development may be continued for several heurs after the sol tent reaches the top of the plate, to provide adequate migration of the spots. Usually spot of a standard solution, a test solution, anda mixture of equal amounts of test and standard solutions, are initial y y applied at a standard distanee frem the base of the plate. Identity of the standard and test substances is confirmed by their migrating equal distances from the origin and by the observation that the two substances applied as mixture-show ne tendeney to-separate.
A major advantage of continuous development thin layer chromatography stems from the greater solvent selectivity for solvents of low solvent strength. Solvent strength refers to the property of a developing solvent that eauses solutes to migrate, and it is strengly influeneed by the polarity of the-solvent. Inereasing the solvent strength by adding a more polar solvent causes the $R_{\text {, value }}$ to in rease. Solvent selectivity refers to the ability of a solvent system to produce different $R_{L}$ values for closely related substances. In eonventional thin layer chromatography, a solvent system giving an $R_{f}$ value in the range of 0.3 to 0.7 , but with adequate selectivity to permit separation of the substances being examined is usually selected. It is muth easier to find solvent systems producing adequate migration than to find these affording adequate-selectivity.

Solvent systems of lower strength generally exhibit higher selec tivity, but are diffieult to employ in conventional thin layer chromatography beeause they result in very little migration before the solvent reaches the top-of the plate. Migration may be increased, however, by repeated drying and redevelopment of the plate-or, more conveniently, by providing means for evaporation of solvent at the top of the plate, which results in continueus development. Two-echniques are used: contintrous development and short bed eontinuous development thin layer chromatography.

An $R_{L}$ value cannot be measured in continurus development thin layer chrematography. Substances may be compared either by their migration distance over a fixed period of time or by comparisen with the migration of a standard- substance applied to the plate.

## GONTINUOUS DEVELOPMENT

Apparatus Aeceptable apparatus and materials for continteres development thin layer chromatography are the same as these de scribed under conventional Thin Layer Chrematography, exeeptas follows.

Adeveloping chamber is used that consists of a rectangular tank, approximately $23 \mathrm{~cm} \times 23 \mathrm{~cm} \times 9 \mathrm{~cm}$, equipped with a glass solvent treugh and a platform about 3.75 cm high to elevate the solvent treugh above the base of the tank. The chamber is fitted with a cover having a $21 \times 6 \mathrm{em}$ slot in the front edge.

Proeedure- Apply the standard solution, the test solution, and a mix of equal amounts of the standard solution and the test solution to a line about 2 cm from the base of the plate. Place the plate in the elevated emply solvent trough with the adsorbent on the underside of the leaning plate. The adsorbent rests against a piece of heary (about 1 mm thick) ${ }^{2}$ filter paper measuring $20 \mathrm{em}-x$

[^249]3 cm , folded lengthwise and placed over the from edge of the tank. Place the developing solvent in the trough; set the cover in place, and seal all openings except where the adsorbent contacts the paper wick. The plate extends about 1 em beyond the top of the tank. After the solvent reaches the top of the plate, allow development to continue for an appropriate time. Then remove and dry the plate, and deteet the spets by suitable means.

## SHORT BED CONTINUOUS DEVELOPMENT

A major advantage of the short bed teehnique derives from the fact that solvent velocity is inversely related to bed length. Since spet migration depends upen the total amount of solvent passing over the plate, the short bed permits usefull migration to be ob fained in a reasonable time with solvent having very low solvent strength. Lower diffusion in solvents of low solvent strength produres smaller and more dense spots, which enhances both detect ability and discernment of small differences in migration distance.

Apparatus Acceptable apparatts and materials for shert bed eontinuous development thin layer chromatography are the same as those described under conventional Thin Layer Chromatograt phy, exeept as follows.

A shallow developing ehamber ${ }^{2}$ approximately $22 \mathrm{~cm} \times-9 \mathrm{~cm}$ $* 3 \mathrm{~cm}$, equipped with a eover plate and tight fitting polytef wings that enable the chamber to be sealed against the plate, is used. The
inside bottom of the chamber contains ridges that suppert the plate and allow it to be inserted at different angles, thereby varying the length of the plate contained within the tank.

Procedure-Apply the standard solution, the test solution, and a mixture of equal parts of the standard solution and the test solut tion to a line about 2 cm from the base of the plate. Place the plate in the developing chamber (adsorbent side up), and add the devel eping solvent to the chamber. No paper wick is employed. After the solvent reaches the top of the plate, allow development to eontime for an appropriate time. Then remove and dry the plate, and detect the spets by suitable means.

- ${ }^{\text {nS }}$ (USP28)


## Change to read:

## INTERPRETATION OF CHROMATOGRAMS

Figure 1 represents a typical chromatographic separation of two substances, 1 and 2 , where $t_{1}$ and $t_{2}$ are the respective retention times; and $h, h / 2$, and $W_{h / 2}$ are the height, the half-height, and the width at half-height, respectively, for peak 1. $W_{1}$ and $W_{2}$ are the respective widths of peaks 1 and 2 at the baseline. Air peaks are a feature of gas chromatograms and correspond to the solvent front in liquid chromatography.


Fig. 1. Chromatographic separation of two substances

Chromatographic retention times are characteristic of the compounds they represent but are not unique. Coincidence of retention times of a test and a reference substance can be used as a feature in construction of an identity profile but is insufficient on its own to establish identity. Absolute retention times of a given compound vary from one chromatogram to the next. Comparisons are normally made in terms of relative retention, $*$,
$\square_{r,}$ ■1S (USP28)
which is calculated by the equation:


$$
r=\frac{t_{2}-t_{a}}{t_{1}-t_{a}},
$$

where $t_{2}$ and $t_{1}$ are the retention times, measured from the point of injection, of the test and reference substances, respectively, determined under identical experimental conditions on the same column, and $t_{a}$ is the retention time of a nonretained substance, such as methane in the case of gas chromatography.

In this and the following expressions, the corresponding retention volumes or linear separations on the chromatogram, both of which are directly proportional to retention time, may be substituted in the equations. Where the value of $t_{a}$ is small, $R_{R_{R}}$
$\boldsymbol{■}_{\mathbf{m}_{1 S}}$ (USP28)
may be estimated from the retention times measured from the point of injection $\left(t_{2} t_{+}\right)$.

- $R_{R}$.■1S (USP28)

[^250]The number of theoretical plates, $N$, is a measure of column efficiency. For Gaussian peaks, it is calculated by the equation:


$$
N=16\left(\frac{t}{W}\right)^{2}, \square_{1 \mathrm{~S}(U S P 28)}
$$

where $t$ is the retention time of the substance and $W$ is the width of the peak at its base, obtained by extrapolating the relatively straight sides of the peak to the baseline. $W_{\text {Hs }}$ is the peak width at half height, obtained direetly by electronic integrators.
-1S (USP28)
The value of $N$ depends upon the substance being chromatographed as well as the operating conditions such as mobile phase or carrier gas flow rates and temperature, the quality of the packing, the uniformity of the packing within the column and, for capillary columns, the thickness of the stationary phase film, and the internal diameter and length of the column.

The separation of two components in a mixture, the resolution, $R$, is determined by the equation:

$$
R=\frac{2\left(t_{2}-t_{1}\right)}{W_{2}+W_{1}}
$$

in which $t_{2}$ and $t_{1}$ are the retention times of the two components, and $W_{2}$ and $W_{1}$ are the corresponding widths at the bases of the peaks obtained by extrapolating the relatively straight sides of the peaks to the baseline.

Where electronic integrators are used, it may be convenient to determine the resolution, $R$, by the equation:

$$
R=\frac{2\left(t_{2}-t_{1}\right)}{1.70\left(W_{1, h} / 2+\mathrm{W}_{2, h / 2}\right)}
$$

and to determine the number of theoretical plates, $N$, by the equation:

$$
N=5.54\left(t / W_{h / 2}\right)^{2}
$$

$\square_{\text {where }} W_{h / 2}$ is the peak width at half-height, obtained directly by electronic integrators.■1S (USP28)
However, in the event of dispute, only equations based on peak width at baseline are to be used.

Peak areas and peak heights are usually proportional to the quantity of compound eluting. These are commonly measured by electronic integrators but may be determined by more classical approaches. Peak areas are generally used but may be less accurate if peak interference occurs. For manual measurements, the chart should be run faster than usual, or a comparator should be used to measure the width at half-height and the width at the base of the peak, to minimize error in these measurements. For accurate quantitative work, the components to be measured should be separated from any interfering components. Peak tailing and fronting and the measurement of peaks on solvent tails are to be avoided.

Chromatographic purity tests for drug raw materials are sometimes based on the determination of peaks due to impurities, expressed as a percentage of the area due to the drug peak. It is preferable, however, to compare impurity peaks with those in the chromatogram of a standard at a similar concentration. The standard may be the drug itself at a level corresponding to, for example, $0.5 \%$ impurity, or in the case of toxic or signal impurities, a standard of the impurity itself.

## Change to read:

## SYSTEM SUITABILITY

System suitability tests are an integral part of gas and liquid chromatographic methods. They are used to verify that the

- detection sensitivity, ${ }^{\text {mS }}$ (USP28)
resolution, and reproducibility of the chromatographic system are adequate for the analysis to be done. The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such.
-The detection sensitivity is a measure used to ensure the suitability of a given chromatographic procedure for the complete detection of the impurities in the Chromatographic purity or Related compounds tests by injecting a volume of a Quantitation Limit Solution equal to that of the Test solution. Unless otherwise specified in the individual monograph, the Quantitation Limit Solution may be prepared by dissolving the drug substance Reference Standard in the same solvent as that used for the Test preparation at a $0.05 \%$ concentration level relative to the amount of drug substance in the Test Preparation for drug substances, and a $0.1 \%$ level relative to the amount of drug substance in the Test Preparation for drug products. The signal-to-noise ratio for the drug substance peak obtained with the Quantitation

Limit Solution should be not less than 10. n2s (USP28)
The resolution, $R$, [NOTE-All terms and symbols are defined in the Glossary of Symbols] is a function of the column efficiency, $N$, and is specified to ensure that closely eluting compounds are resolved from each other, to establish the general resolving power of the system, and to ensure that internal standards are resolved
from the drug. Column efficiency may be specified also as a system suitability requirement, especially if there is only one peak of interest in the chromatogram; however, it is a less reliable means to ensure resolution than direct measurement. Column efficiency is a measure of peak sharpness, which is important for the detection of trace components.

Replicate injections of a Standard preparation used in the assay or other standard solution are compared to ascertain whether requirements for precision are met. Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation, $S_{R}$, if the requirement is $2.0 \%$ or less; data from six replicate injections are used if the relative standard deviation requirement is more than $2.0 \%$.

The tailing factor, $T$, a measure of peak symmetry, is unity for perfectly symmetrical peaks and its value increases as tailing becomes more pronounced (see Fig. 2). In some cases, values less than unity may be observed. As peak asymmetry increases, integration, and hence precision, becomes less reliable.


Fig. 2. Asymmetrical chromatographic peak
These tests are performed by collecting data from replicate injections of standard or other solutions as specified in the individual monograph. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions (see Procedures under Tests and Assays in the General Notices). Adjustments of operating eonditions to meet system suit ability requirements may be neeessary.
-If adjustments of operating conditions to meet system suitability requirements are necessary, each of the following is the maximum specifieatienvariation that can be considered, unless otherwise directed in the monograph. Adjustments are permitted only when Reference Standards suitable standards (including Reference Standards) are available for all amalytes compounds used in the suitability test and are used to show that the adjustments have improved the quality of the chromatography in meeting system suitability requirements. Adjustments to chromatographic systems performed in order to comply with system suitability requirements are not to be made to compensate for column failure or to circumvent replacing a deteriorated column. The changes described below may require additional validation data unless
the user can verify the suitability of the method under the new conditions. This verification consists of assessing the analytical performance characteristics that can be affected by the change (e.g., specificity, linearity, precision, accuracy) to ensure the adequacy of the method. Multiple adjustments that may have a cumulative effect in the performance of the system are to be avoided.
pH of Mobile Phase (HPLC)-The pH of the aqueous buffer used in the preparation of the mobile phase can be adjusted to within 0.2 units of the value or range specified.

Concentration of Salts in Buffer (HPLC)—The concentration of the salts used in the preparation of the aqueous buffer used in the mobile phase can be adjusted to within $\pm 10 \%$, provided the permitted pH variation (see above) is met.

## Ratio of Components in Mobile Phase (HPLC) - The

 amount of the miner The following adjustment limits apply to minor components of the mobile phase (specified at $50 \%$ or less). The amount(s) of these component(s) can be adjusted by $\pm 30 \%$ relative or $\pm 2 \%$ absolute (i.e., in relation to the mobile phase), whichever is latger. However, the change in any component cannot exceed $\pm 10 \%$ absolute (i.e., in relation to the total mobile phase), nor can the final concentration of any component be reduced to zero. Adjustment can be made to one minor component in a ternary mixture. Examples of adjustments for binary and ternary mixtures are given below.
## Binary Mixtures-

SPECIFIED RATIO OF $50: 50$ - Thirty percent of 50 is $15 \%$ absolute, but this exceeds the maximum permitted change of $\pm 10 \%$ absolute in either component. Therefore, the mobile phase ratio may be adjusted only within the range of $40: 60$ to $60: 40$.

SPECIFIED-PATIO-OF-95:5_Thirty percent of 5 is $1.5 \%$ absolute. However, because adjustments up to $\pm 2 \%$ abse lete are allowed, the ratio may be adjusted within the range of $93: 7$ to $97: 3$.

SPECIFIED RATIO OF 2:98-Thirty percent of 2 is $0.6 \%$ absolute. In this ease an absolute adjustment of $\pm 2 \%$ is not at fowe because it would reduce the amount of the first empore. Therefore the maximum allowed adjustment is within the range of $1.4: 98.6$ to $2.6: 97.4$.

## Ternary Mixtures-

SPECIFIED RATIO OF $60: 35: 5$-For the second component, $30 \%$ of 35 is $10.5 \%$ absolute, which exceeds the maximum permitted change of $\pm 10 \%$ absolute in any component. Therefore the second component may be adjusted only within the range of $25 \%$ to $45 \%$ absolute. For the third component, $30 \%$ of 5 is $1.5 \%$ absolute. sinee $\pm 2 \%$ is permit ted and provides more flexibility, the third compenent may be adjusted within the range of $3 \%$ to $7 \%$ absolute. In all cases, a sufficient quantity of the first component is used to give a total of $100 \%$. Therefore, mixture ranges of $50: 45: 5$ to $70: 25: 5$ or $58: 35: 7-62: 35: 3$ $58.5: 35: 6.5$ to $61.5: 35: 3.5$ would meet the requirement.

## Detar Wavelength of UV-Visible Detector

 (HPLC)—Deviations from the wavelengths specified in the method are not permitted. The procedure specified by the detector manufacturer, or another validated procedure, is to be used to verify that error in the detector wavelength is, at most, $\pm 3 \mathrm{~nm}$.Column Length (GC, HPLC): can be adjusted by as much as $70 \%$.

Column Inner Diameter (GC, HPLC): can be adjusted by as much as $\pm 25 \% 50 \%$. $\pm 25 \%$ for HPLC and $\pm$ $50 \%$ for GC.

Film Thickness (Capillary GC): can be adjusted by as much as $-50 \%$ to $100 \%$.

Particle Size (HPLC): can be reduced by as much as 50\%.

Particle Size (GC): going from a larger to a smaller or a smaller to a larger (if it is the same "Range Ratio", which is the diameter of the largest particle divided by the diameter of the smallest particle) particle size GC mesh support is acceptable, provided the chromatography meets the requirements of the system suitability.

Flow Rate (GC, HPLC): can be adjusted by as much as $\pm 50 \%$.

Injection Volume (GC, HPLC): can be reduced as far as is consistent with accepted precision and detection limits.

It may be-inereased to as mueh as wiee the volume-specifled, provided there are ne adverse-effects-on factors sueh as baseline, peak shapes, reselutien, linearity, and retention times.

Column Temperature (HPLC): can be adjusted by as much as $\pm 20^{\circ} . \pm 10^{\circ}$. Column thermostating is recommended to improve control and reproducibility of retention time.

Column Oven Temperature (GC): can be adjusted by as much as $\pm 2 \%$, in terms of $\pm 10 \%$.

Oven Temperature Program (GC)—Adjustment of temperatures is permitted as stated above. For the times specified for the temperature to be maintained or for the temperature to be changed from one value to another, an adjustment of up to $\pm 20 \%$ is permitted.

Gradient Elution-(HPLC) The configuration of the equipment employed may significantly alter the resolution, retention time, and relative retentions deseribed in the meth-

## ed. Should this oceur, it may be due to excess dwell time,

which is the volume between the point at whieh the et
thants meet and the top-of the eolumat.as (USP28)
Unless otherwise directed in the monograph, system suitability parameters are determined from the analyte peak.

To ascertain the effectiveness of the final operating system, it should be subjected to suitability testing. Replicate injections of the standard preparation required to demonstrate adequate system precision may be made before the injection of samples or may be interspersed among sample injections. System suitability must be demonstrated throughout the run by injection of an appropriate control preparation at appropriate intervals.

The control preparation can be a standard preparation or a solution containing a known amount of analyte and any additional materials useful in the control of the analytical system, such as excipients or impurities. Whenever there is a significant change in equipment or in a critical reagent, suitability testing should be performed before the injection of samples. No sample analysis is acceptable unless the requirements of system suitability have been met. Sample analyses obtained while the system fails
$\square_{\text {System suitability }} \mathbf{m}^{2 S}$ (USP28)
requirements are unacceptable.

## Change to read:

## GLOSSARY OF SYMBOLS

To promote uniformity of interpretation, the following symbols and definitions are employed where applicable in presenting formulas in the individual monographs. [NOTE-Where the terms $W$ and $t$ both appear in the same equation they must be expressed in the same units.]

## $*$

relativeretention,

$e_{R}, e_{f}, e_{U}$
eeneentrations of Reference-Standard, inter fal-standard, and analyte-in a partieular solutien.
$\epsilon_{4} \quad$ eencentration ratio-of analyte and internat standard in test solution-or Assay preparation,

$\epsilon_{s} \quad$ eoncentration ratio of Reference Standard and internal standard in Standard solution,

$f^{\square}$ 1S (USP28)
$k^{\prime}$
distance from the peak maximum to the leading edge of the peak, the distance being measured at a point $5 \%$ of the peak height from the baseline.
' capacity factor,

$$
\begin{aligned}
& k^{\prime}=\frac{\text { amount of substance in stationary phase }}{\text { amount of substance in mobile phase }} \\
& k^{\prime}=\frac{\text { time spent by substance in stationary phase }}{\text { time spent by substance in mobile phase }}=\frac{t}{t_{a}}-1 .
\end{aligned}
$$

$$
\mathbf{■}_{N}=16\left(\frac{t}{W}\right)^{2} \text { or } N=5.54\left(\frac{t}{W_{h / 2}}\right)^{2} \mathbf{■}_{1 \mathrm{~s}(U S P 28)}
$$


$Q_{4}$
(2) Standard, internalstandard, and analyte-in a particular selution. equantity ratio of analyte and internal standard in test solution or Assay preparation,


Qs
quantity ratio of Reference-Standard and internal standard in Standard solution,

relative retention

$$
r=\frac{t_{2}-t_{a}}{t_{1}-t_{a}}
$$

peak response of an impurity obtained from a chromatogram peak response of the Internal Standard
obtained from a chromatogram $\mathbf{1 S}_{1 \text { S }}$ (USP28) peak response of the Reference Standard obtained from a chromatogram. peak response of the analyte obtained from a chromatogram.

R
$R_{F} \quad$ chromatographic retardation factor equal to the ratio of the distance from the origin to the center of a zone divided by the distance from the origin to the solvent front.
$R_{p}$

$$
\operatorname{or} R=\frac{2\left(t_{2}-t_{1}\right)}{1.70\left(W_{1, h / 2}+W_{2, h / 2}\right)} \text { ■ } 1 \mathrm{~S}(U S P 28)
$$

relative retention

relative retention time

$$
R_{R}=\frac{t_{2}}{t_{1}}
$$

$S_{R}(\%) \quad$ relative standard deviation in percentage,
$R_{R} 1 \mathrm{~S}$ (USP28)

$$
R_{S}=\frac{r_{s}}{r_{I}}
$$

peak response ratio for Assay preparation containing the analyte and internal standard,

$$
R_{U}=\frac{r_{U}}{r_{I}}
$$

peak response ratio for a Standard preparation containing Reference Standard and internal standard,
ene
?

$$
S_{R}(\%)=\frac{100}{\bar{X}}\left[\frac{\sum_{i=1}^{N}\left(X_{i}-\bar{X}\right)^{2}}{N-1}\right]^{1 / 2},
$$

where $X_{i}$ is an individual measurement in a set of $N$ measurements and $X$ is the arithmetic mean of the set.
tailing factor,

$$
T=\frac{W_{0.05}}{2 f}
$$

retention time measured from time of injec-
tion to time of elution of peak maximum.
retention time measured from time of injec-
tion to time of elution of peak maximum.
$a \quad$ retention time of nonretarded component, air with thermal conductivity detection. width of peak measured by extrapolating the relatively straight sides to the baseline. width of peak at half height. width of peak at $5 \%$ height.
$T$
$t$
$t$
$t_{a}$
$W$
$W_{h / 2}$
$W_{0.05}$ W
$W_{h / 2}$
$W_{0.05}$

## Change to read:

## CHROMATOGRAPHIC REAGENTS

The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer. [NOTE-Particle sizes given in this listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category of packings or phases listed below, there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

## Packings

L1-Octadecyl silane chemically bonded to porous silica or ceramic micro-particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L2-Octadecyl silane chemically bonded to silica gel of a controlled surface porosity that has been bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L3-Porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.
L4-Silica gel of controlled surface porosity bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L5-Alumina of controlled surface porosity bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L6-Strong cation-exchange packing-sulfonated fluorocarbon polymer coated on a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.
L7-Octylsilane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.
L8-An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support,
-3 to $\quad$ IS (USP28)
$10 \mu \mathrm{~m}$ in diameter.
L9- $10-\mu \mathrm{m}$ irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating.

L10-Nitrile groups chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L11-Phenyl groups chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L12-A strong anion-exchange packing made by chemically bonding a quaternary amine to a solid silica spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L13-Trimethylsilane chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L14-Silica gel $10 \mu \mathrm{~m}$ in diameter

- 1 IS (USP28)
having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating,
-5 to $10 \mu \mathrm{~m}$ in diameter. $\quad$ 1s (USP28)
L15-Hexylsilane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.
L16-Dimethylsilane chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L17-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form, 7 to $11 \mu \mathrm{~m}$ in diameter.

L18-Amino and cyano groups chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L19-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the calcium form, about $9 \mu \mathrm{~m}$ in diameter.
L20-Dihydroxypropane groups chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L21-A rigid, spherical styrene-divinylbenzene copolymer, 5 to $10 \mu \mathrm{~m}$ in diameter.

L22-A cation-exchange resin made of porous polystyrene gel with sulfonic acid groups, about $10 \mu \mathrm{~m}$ in size.

L23-An anion-exchange resin made of porous polymethacrylate or polyacrylate gel with quaternary ammonium groups, about $10 \mu \mathrm{~m}$ in size.

L24-A semi-rigid hydrophilic gel consisting of vinyl polymers with numerous hydroxyl groups on the matrix surface, 32 to $63 \mu \mathrm{~m}$ in diameter. ${ }^{5}$

L25-Packing having the capacity to separate compounds with a molecular weight range from 100-5000 (as determined by polyethylene oxide), applied to neutral, anionic, and cationic water-soluble polymers. A polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contained some residual carboxyl functional groups) was found suitable.

L26-Butyl silane chemically bonded to totally porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L27-Porous silica particles, 30 to $50 \mu \mathrm{~m}$ in diameter.
L28-A multifunctional support, which consists of a high purity, $100 \AA$, spherical silica substrate that has been bonded with anionic exchanger, amine functionality in addition to a conventional reversed phase C 8 functionality.

L29-Gamma alumina, reverse-phase, low carbon percentage by weight, alumina-based polybutadiene spherical particles, $5 \mu \mathrm{~m}$ in diameter with a pore volume of $80 \AA$.

L30-Ethyl silane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L31-A strong anion-exchange resin-quaternary amine bonded on latex particles attached to a core of $8.5-\mu \mathrm{m}$ macroporous particles having a pore size of $2000 \AA$ and consisting of ethylvinylbenzene cross-linked with $55 \%$ divinylbenzene.

L32-A chiral ligand-exchange packing-L-proline copper complex covalently bonded to irregularly shaped silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

[^251]L33-Packing having the capacity to separate dextrans by molecular size over a range of 4000 to $500,000 \mathrm{Da}$. It is spherical, silica-based, and processed to provide pH stability. ${ }^{6}$
L34-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the lead form, about $9 \mu \mathrm{~m}$ in diameter.

L35-A zirconium-stabilized spherical silica packing with a hydrophilic (diol-type) molecular monolayer bonded phase having a pore size of $150 \AA$.

L36-A 3,5-dinitrobenzoyl derivative of L-phenylglycine covalently bonded to $5-\mu \mathrm{m}$ aminopropyl silica.

L37-Packing having the capacity to separate proteins by molecular size over a range of 2,000 to $40,000 \mathrm{Da}$. It is a polymethacrylate gel.
L38-A methacrylate-based size-exclusion packing for watersoluble samples.

L39-A hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin.

L40-Cellulose tris-3,5-dimethylphenylcarbamate coated porous silica particles, 5 to $20 \mu \mathrm{~m}$ in diameter.

L41-Immobilized $\alpha_{1}$-acid glycoprotein on spherical silica particles, $5 \mu \mathrm{~m}$ in diameter.

L42-Octylsilane and octadecylsilane groups chemically bonded to porous silica particles, $5 \mu \mathrm{~m}$ in diameter.

L43-Pentafluorophenyl groups chemically bonded to silica particles $\square_{\text {by }}$ a propyl spacer, $\mathbf{m S}_{\text {(USP27) }} 5$ to $10 \mu \mathrm{~m}$ in diameter.
L44-A multifunctional support, which consists of a high purity, $60 \AA$, spherical silica substrate that has been bonded with a cationic exchanger, sulfonic acid functionality in addition to a conventional reversed phase C8 functionality.

L45-Beta cyclodextrin bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L46-Polystyrene/divinylbenzene substrate agglomerated with quaternary amine functionalized latex beads,
-about.IS (USP28)
$10 \mu \mathrm{~m}$ in diameter.
L47-High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, $8 \mu \mathrm{~m}$ in diameter. ${ }^{7}$

L48-Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion-exchange microbeads, $15 \mu \mathrm{~m}$ in diameter.

L49-A reversed-phase packing made by coating a thin layer of polybutadiene onto spherical porous zirconia particles, 3 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{8}$

L50-Multifunction resin with reversed-phase retention and strong anion-exchange functionalities. The resin consists of ethylvinylbenzene, $55 \%$ cross-linked with divinylbenzene copolymer, 3 to $15 \mu \mathrm{~m}$ in diameter, and a surface area not less than $350 \mathrm{~m}^{2}$ per g . Substrate is coated with quaternary ammonium functionalized latex particles consisting of styrene cross-linked with divinylbenzene. ${ }^{9}$

L51-Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{10}$

[^252]L52-A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{11}$

L53-Weak cation-exchange resin consisting of ethylvinylbenzene, $55 \%$ cross-linked with divinylbenzene copolymer, 3 to 15 $\mu \mathrm{m}$ diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than $500 \mu \mathrm{Eq} /$ column. ${ }^{12}$

L54-A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 $\mu \mathrm{m}$ in diameter. ${ }^{13}$
${ }^{\mathbf{\Delta}}$ L55-A strong cation-exchange resin made of porous silica coated with polybutadiene-maleic acid copolymer, about $5 \mu \mathrm{~m}$ in diameter. ${ }^{14} \mathbf{\Delta U S P 2 7}$
${ }^{\mathbf{4}}$ L56-Propyl silane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{15} \mathbf{\Delta}$ USP27
-L57-A chiral-recognition protein, ovomucoid, chemically bonded to silica particles, about $5 \mu \mathrm{~m}$ in diameter, with a pore size of 120 À. $\mathbf{m}^{2 S}$ (USP27)
${ }^{\bullet}$ L58-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, about 7 to $11 \mu \mathrm{~m}$ in diameter. ${ }^{16}$ 2S (USP27)
${ }^{\text {4}}$ L57 \#\# (Nevirapine, Supelcosil ABZ)——Spherical, porous silica gel, 3 or $5 \mu \mathrm{~m}$ in diameter, the surface of which has been covalently modified with palmitamidopropyl groups and endcapped with acetamidopropyl groups to a ligand density of about $6 \mu$ moles per $\mathrm{m}^{2}{ }^{\mathrm{a}} \mathbf{\Delta U S P 2 8}$
${ }^{\text {4 }}$ L58 \#\# (Albumin Human, Antithrombin III Human, TSKgel G3000 SW)_Packing having the capacity to separate proteins by molecular weight over the range of 10 to 500 kDa . It is spherical $(10 \mu \mathrm{~m})$, silica-based, and processed to provide hydrophilic characteristics and pH stability. ${ }^{\mathrm{b}}{ }_{\triangle U S P 28}$

[^253]-L64 \#\# (Lycopene, Lycopene Preparation, YMC 30)C30 silane bonded phase on a fully porous spherical silica, 3 to $15 \mu \mathrm{~m}$ in diameter. ${ }^{1 \mathrm{~S}}$ (USP28)

L\#\# (En@xaparin-Sodium-Injection, IenPac AG11) [Tध

## eome.?

L\#\# (Enoxaparin Sodium Injection, IonPac AS11) [TO
eome.]
E\#\# (Enoxaparin-Sodium, Dowex 1X8) [Tocome.]
E\#\# (Enoxaparin Sodium, Dowex 50WX2) [T0
come.
■L\#\# (Dalteparin Sodium, anion-exchange Dowex
1X8)—[To come.]
L\#\# (Dalteparin Sodium, cation-exchange Dowex
50WX2)-[To come. $]_{\square 2 S ~(U S P 28)}$

## Phases

G1-Dimethylpolysiloxane oil.
G2-Dimethylpolysiloxane gum.
G3-50\% Phenyl-50\% methylpolysiloxane.
G4-Diethylene glycol succinate polyester.
G5-3-Cyanopropylpolysiloxane.
G6-Trifluoropropylmethylpolysiloxane.
G7-50\% 3-Cyanopropyl-50\% phenylmethylsilicone.
G8-80\% Bis(3-cyanopropyl)-20\% 3-cyanopropylphenylpoly-
siloxane (percentages refer to molar substitution).
G9-Methylvinylpolysiloxane.
G10-Polyamide formed by reacting a $\mathrm{C}_{36}$ dicarboxylic acid with 1,3-di-4-piperidylpropane and piperidine in the respective mole ratios of $1.00: 0.90: 0.20$.

G11—Bis(2-ethylhexyl) sebacate polyester.
G12-Phenyldiethanolamine succinate polyester.
G13-Sorbitol.
G14-Polyethylene glycol (av. mol. wt. of 950 to 1050).
G15-Polyethylene glycol (av. mol. wt. of 3000 to 3700 ).
G16-Polyethylene glycol compound (av. mol. wt. about 15,000 ). A high molecular weight compound of polyethylene glycol with a diepoxide linker. Available commercially as Polyethylene Glycol Compound 20M, or as Carbowax 20M, from suppliers of chromatographic reagents.

G17-75\% Phenyl-25\% methylpolysiloxane.
G18-Polyalkylene glycol.
G19-25\% Phenyl-25\% cyanopropyl-50\% methylsilicone.
G20-Polyethylene glycol (av. mol. wt. of 380 to 420).
G21-Neopentyl glycol succinate.
G22-Bis(2-ethylhexyl) phthalate.
G23-Polyethylene glycol adipate.
G24-Diisodecyl phthalate.
G25-Polyethylene glycol compound TPA. A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with terephthalic acid. Available commercially as Carbowax $20 \mathrm{M}-\mathrm{TPA}$ from suppliers of chromatographic reagents.

G26-25\% 2-Cyanoethyl-75\% methylpolysiloxane.

G27-5\% Phenyl-95\% methylpolysiloxane.
G28-25\% Phenyl-75\% methylpolysiloxane.
G29-3,3'-Thiodipropionitrile.
G30-Tetraethylene glycol dimethyl ether.
G31-Nonylphenoxypoly(ethyleneoxy)ethanol (av. ethyleneoxy chain length is 30); Nonoxynol 30 .

G32-20\% Phenylmethyl-80\% dimethylpolysiloxane.
G33-20\% Carborane-80\% methylsilicone.
G34-Diethylene glycol succinate polyester stabilized with phosphoric acid.

G35-A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with nitroterephthalic acid.

G36-1\% Vinyl-5\% phenylmethylpolysiloxane.
G37-Polyimide.
G38-Phase G1 containing a small percentage of a tailing inhibitor. ${ }^{17}$

G39—Polyethylene glycol (av. mol. wt. about 1500).
G40-Ethylene glycol adipate.
G41-Phenylmethyldimethylsilicone ( $10 \%$ phenyl-substituted).
G42-35\% phenyl-65\% dimethylpolysiloxane (percentages refer to molar substitution).

G43-6\% cyanopropylphenyl-94\% dimethylpolysiloxane (percentages refer to molar substitution).

G44-2\% low molecular weight petrolatum hydrocarbon grease and $1 \%$ solution of potassium hydroxide.

G45-Divinylbenzene-ethylene glycol-dimethylacrylate.
G46-14\% Cyanopropylphenyl-86\% methylpolysiloxane.
G47-Polyethylene glycol (av. mol. wt. of about 8000).
G48-Highly polar, partially cross-linked cyanopolysiloxane.
G49 Proprietary derivatized phenyl groups on a polysiloxane backbene. ${ }^{\text {º }}$
-G50 \#\# (Docosahexaenoic Acid)—Polyethylene glycol, cross-linked (av. mol. wt. of more than 20,000). ${ }^{\mathrm{c}_{1 S}}{ }_{\text {(USP28) }}$

## Supports

NOTE-Unless otherwise specified, mesh sizes of 80 to 100 or, alternatively, 100 to 120 are intended.

S1A-Siliceous earth for gas chromatography has been flux-calcined by mixing diatomite with $\mathrm{Na}_{2} \mathrm{CO}_{3}$ flux and calcining above $900^{\circ}$. The siliceous earth is acid-washed, then water-washed until neutral, but not base-washed. The siliceous earth may be silanized by treating with an agent such as dimethyldichlorosilane ${ }^{19}$ to mask surface silanol groups.
S1AB-The siliceous earth as described above is both acid- and base-washed. ${ }^{19}$

S1C-A support prepared from crushed firebrick and calcined or burned with a clay binder above $900^{\circ}$ with subsequent acidwash. It may be silanized.

S1NS-The siliceous earth is untreated.
S2-Styrene-divinylbenzene copolymer having a nominal surface area of less than $50 \mathrm{~m}^{2}$ per g and an average pore diameter of 0.3 to $0.4 \mu \mathrm{~m}$.

[^254]S3-Copolymer of ethylvinylbenzene and divinylbenzene having a nominal surface area of 500 to $600 \mathrm{~m}^{2}$ per $g$ and an average pore diameter of $0.0075 \mu \mathrm{~m}$.

S4-Styrene-divinylbenzene copolymer with aromatic -O and N groups, having a nominal surface area of 400 to $600 \mathrm{~m}^{2}$ per $g$ and an average pore diameter of $0.0076 \mu \mathrm{~m}$.

S5-40- to 60-mesh, high-molecular weight tetrafluorethylene polymer.

S6-Styrene-divinylbenzene copolymer having a nominal surface area of 250 to $350 \mathrm{~m}^{2}$ per g and an average pore diameter of $0.0091 \mu \mathrm{~m}$.

S7-Graphitized carbon having a nominal surface area of $12 \mathrm{~m}^{2}$ per g .

S8-Copolymer of 4-vinyl-pyridine and styrene-divinylbenzene.

S9-A porous polymer based on 2,6-diphenyl-p-phenylene oxide.
S10-A highly polar cross-linked copolymer of acrylonitrite and divinylbenzene.

S11-Graphitized carbon having a nominal surface area of 100 $\mathrm{m}^{2}$ per g modified with small amounts of petrolatum and polyethylene glycol compound. ${ }^{20}$

S12-Graphitized carbon having a nominal surface area of 100 $\mathrm{m}^{2}$ per g .

## BRIEFING

$\langle 643\rangle$ Total Organic Carbon, USP 27 page 2285. This is the third attempt by the Pharmaceutical Waters Expert Committee to revise this general test chapter. This revision incorporates most of the comments received since the publication of proposed revisions in PF 29(6) [Nov.-Dec. 2003], which have been cancelled. This current proposal adds quantitative values to the testing procedure that provide more flexibility in its application. Please address comments to Frank Barletta, liaison to the Pharmaceutical Waters Expert Committee.

$$
\text { (PW: F. Barletta) } \quad \text { RTS }-41409-1
$$

## Change to read:

Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon. Organic molecules are introduced into the water from the source water, from purification and distribution system materials, and from biofilm growing in the system. TOC can also be used as a process control attribute to monitor the performance of unit operations comprising the purification and distribution system.

A number of acceptable methods exist for analyzing TOC. This chapter does not limit or prevent alternative technologies from being used, but provides guidance on how to qualify these analytical technologies for use as well as guidance on how to interpret instrument results for use as a limit test. The Solltan
$\mathbf{- S u c r o s e ~ S o l u t i o n}_{\text {■2S (USP28) }}$

[^255]is a theoretically easy-to-oxidize solution that gives an instrument response at the attribute limit. The analytical technology is qualified by challenging the capability of the instrument using a theoretically difficult to oxidize solution in the system suitability portion of the method.

Analytical technologies utilized to measure TOC share the objective of completely oxidizing the organic molecules in an aliquot of sample water to carbon dioxide $\left(\mathrm{CO}_{2}\right)$, measuring the resultant $\mathrm{CO}_{2}$ tevels,

- concentration, $\boldsymbol{m}_{2 S}$ (USP28)
and expressing this response as carbon concentration. All technologies must discriminate between the inorganic carbon, which may be present in the water from sources such as dissolved $\mathrm{CO}_{2}$ and bicarbonate, and the $\mathrm{CO}_{2}$ generated from the oxidation of organic molecules in the sample.

Two general approaches are used to measure TOC. One approach determines TOC by subtracting the measured inorganic carbon (IC) from the measured total carbon (TC), which is the sum of organic carbon and inorganic carbon:

$$
\mathrm{TOC}=\mathrm{TC}-\mathrm{IC}
$$

The other approach first purges the IC from the sample before any carbon measurement is performed. However, this IC purging step also purges some of the organic molecules, which can be retrapped, oxidized to $\mathrm{CO}_{2}$, and quantitated as purgeable organic carbon (POC). The remaining organic matter in the sample is also oxidized to $\mathrm{CO}_{2}$ and quantitated as nonpurgeable organic carbon (NPOC). In this approach, TOC is the sum of POC and NPOC:

$$
\mathrm{TOC}=\mathrm{POC}+\mathrm{NPOC}
$$

In pharmaceutical waters, the amount of POC is negligible and can be discounted. Therefore, for the purpose of this methodology, NPOC is equivalent to TOC.

## Change to read:

Reagent Water-Use water having a TOC level of not more than 0.10 mg per L. [NOTE-A conductivity requirement may be neeessary to enstre methed reliability.
$\mathbf{\square}_{\text {specified }}$ by the equipment manufacturer. $]_{\text {²S }}$ (USP28)

## Change to read:

Glassware Preparation-Organic contamination of glassware $\mathbf{m}_{\text {containers }}{ }^{\text {2S (USP28) }}$
results in higher TOC values. Therefore, use glassware and sample containers that have been scrupulously cleaned of organic residues. Any method that is effective in removing organic matter can be used (see Cleaning Glass Apparatus $\langle 1051\rangle$ ). Use Reagent Water for the final rinse.

## Change to read:

## Standard-Solution

## ■Sucrose Solution-m2S (USP28)

Unless otherwise directed in the individual monograph, dissolve in the Reagent Water an accurately weighed quantity of USP Sucrose RS, to obtain a solution having a concentration of about 1.2 mg of sucrose per $\mathrm{L}(0.50 \mathrm{mg}$ of carbon per L$)$.

## Change to read:

Test Solution-[NOTE-Use extreme caution when obtaining samples for TOC analysis. Water samples can be easily contaminated during the process of sampling and transportation to a testing facility.] Collect the Test Solution in a ightentainer with minimat head-space, and test in a timely manner to minimize
$\boldsymbol{m}_{\text {Such }}$ a manner that minimizes ${ }_{\square 2 S}$ (USP28)
the impact of organic contamination from the closure and container.

## Change to read:

System Suitability Solution-Dissolve

- Unless otherwise directed in the monograph, dis-


## solve ${ }_{\text {as }}$ (USP28)

in Reagent Water an accurately weighed quantity of USP 1,4-Benzoquinone RS to obtain a solution having a concentration of 0.75 mg per $\mathrm{L}(0.50 \mathrm{mg}$ of carbon per L$)$.

## Change to read:

Reagent Water Control-Use a suitable quantity of Reagent Water obtained at the same time as that used in the preparation of the Stand Solution

■Sucrose Solution $_{\mathbf{m}_{2 S} \text { (USP28) }}$ and the System Suitability Solution.

## Change to read:

Other Control Solutions-Prepare appropriate reagent blank solutions or other specified solutions needed for establishing the apparatus baseline or for calibration adjustments following the manufacturer's instructions, and run the appropriate blanks to zero the instrument,
$\boldsymbol{m}_{\text {if }}$ necessary.■2S (USP28)

## Change to read:

System Suitability-Test the Reagent Water Control in the apparatus, and record the respense, $r_{w}$. Repent the test using the Stanatad Soldtion, and record the respense, rs. Caleulate the correeted Standted Solution respense, which is also the limit respense, by subtracting the Reagent Water Control respense from the respense of the Standetrd Solution. The theoretical limit of 0.50 mg of carben per liter is equal to the corrected Standard Solution response, + s${ }_{\mathrm{F}}^{\mathrm{w}}$-Test the Syistem Stuitability Solution in the apparatus, and record the response, $r$. Caleulate the corrected System Suitability Solution respense by subtrating the Reagent Water Control respense frem

-TOC value, $r_{w}$. Repeat the test using the Sucrose Solution, and record the TOC value in ppm , $r_{s}$. Calculate the response efficiency of the Sucrose Solution by the formula:

$$
100\left[\left(r_{s}-r_{w}\right) / C_{s}\right],
$$

in which $C_{S}$ is the concentration of the Sucrose Solution, in mg of carbon per L (ppm). Test the System Suitability Solution in the apparatus, and record the TOC value in ppm,
$r_{\text {SS. }}$ W2S (USP28)
Calculate the response efficiency for the System Suitability Solution by the formula:

$$
\begin{aligned}
& 100\left[\left(r_{m}-r_{\#}\right) /\left(r_{s}-r_{\#}\right)\right] \\
& \bullet 100\left[\left(r_{S S}-r_{W}\right) / C_{S S}\right]
\end{aligned}
$$

in which $C_{s s}$ is the concentration of the System Suitability
Solution, in mg of carbon per L (ppm). $\mathbf{w}^{2 S}$ (USP28)
The system is suitable if the response efficiency

- of both the Sucrose Solution and the System Suitability So-
lution ${ }_{\text {2S }}$ (USP28)
is not less than $85 \%$ and not more than $115 \%$ of the theoretical response.


## Change to read:

Procedure-Perform the test on the Test Solution, and record the respense, $r_{4}$. The Test Solution meets the requirements if $\Psi_{\Perp}$ is not more than the limit response, $+r_{s}=$
-the TOC value: it contains not more than 0.5 mg of carbon

## per L (ppm). ${ }^{2 S}$ (USP28)

This method also can be performed alternatively using on-line instrumentation that has been appropriately calibrated, standardized, and has demonstrated acceptable system suitability. The acceptability of such on-line instrumentation for quality attribute testing is dependent on its location(s) in the water system. These instrument location(s) and responses must reflect the quality of the water used.

## BRIEFING

〈785〉 Osmolality and Osmolarity, USP 27 page 2335 and page 3331 of the Second Supplement. On the basis of comments received, it is proposed to revise the Measurement of Osmolality section to clarify that vapor pressure osmometers may be used for osmolality determinations. Although used less frequently than osmometers that measure freezing point depression, vapor pressure osmometers require a smaller volume of specimen and provide comparable results.
(PA4: H. Pappa) RTS-41268-1

## Change to read:

## MEASUREMENT OF OSMOLALITY

The osmolality of a solution is commonly determined by the measurement of the freezing point depression of the solution.
Apparatus-The apparatus, an osmometer for freezing point depression measurement, consists of the following: a means of cooling the container used for the measurement; a resistor sensitive to temperature (thermistor), with an appropriate current- or poten-tial-difference measurement device that may be graduated in temperature change or in osmolality; and a means of mixing the sample.
-Osmometers that measure the vapor pressures of solutions are less frequently employed. They require a smaller volume of specimen (generally about $5 \mu \mathrm{~L}$ ), but the accuracy and precision of the resulting osmolality determination are comparable to those obtained by the use of osmometers that depend upon the observed freezing points of solutions.■2S (USP28)

Standard Solutions-Prepare Standard Solutions as specified in Table 1, as necessary.

Table 1. Standard Solutions for Osmometer Calibration ${ }^{2}$

| Standard Solutions <br> (Weight in g of sodium chloride <br> per kg of water) | Osmolality <br> $(\mathrm{mOsmol} / \mathrm{kg})$ <br> $\left(\xi_{m}\right)$ | Molal Osmotic <br> Coefficient <br> $\left(\Phi_{m, \mathrm{NaCl}}\right)$ | Freezing Point <br> Depression $\left({ }^{\circ}\right)$ |
| :---: | :---: | :---: | :---: |
| 3.087 | 100 | 0.9463 | $\Delta T_{f}$ |

[^256]Test Solution-For a solid for injection, constitute with the appropriate diluent as specified in the instructions on the labeling. For solutions, use the sample as is. [NOTE-A solution can be diluted to bring it within the range of measurement of the osmometer, if necessary, but the results must be expressed as that of the diluted solution and must NOT be multiplied by a dilution factor to calculate the osmolality of the original solution. The molal osmotic coefficient is a function of concentration. Therefore, it changes with dilution.]

Procedure-Set the zero of the apparatus using water. To calibrate the apparatus, choose at least two solutions from Table 1 such that the osmolalities of the Standard Solutions span the expected range of osmolality of the Test Solution. Introduce an appropriate volume of each Standard Solution into the measurement cell as per the manufacturer's instructions, and start the cooling system. Usually, the mixing device is programmed to operate at a temperature below the lowest temperature expected from the freezing point depression. The apparatus indicates when the equilibrium is attained. Calibrate the osmometer using an appropriate adjustment device such that the reading corresponds to either the osmolality or freezing point depression value of the Standard Solution shown in Table 1. [NOTE-Some instruments indicate osmolality and some others show freezing point depression.] Before each measurement, rinse the measurement cell at least twice with the solution to be tested. Repeat the procedure with each Test Solution. Read the osmolality of the Test Solution directly, or calculate it from the measured freezing point depression.

Assuming that the value of the osmotic coefficient is essentially the same whether the concentration is expressed in molality or molarity, the experimentally determined osmolality of a solution can be converted to osmolarity in the same manner in which the concentration of a solution is converted from molality to molarity. Unless a solution is very concentrated, the osmolarity of a solution $\left(\xi_{c}\right)$ can be calculated from its experimentally determined osmolality $\left(\xi_{m}\right)$ :

$$
\xi_{c}=1000 \xi_{m} /\left(1000 / \rho+\Sigma w_{i} \nu_{i}\right)
$$

where $w_{i}$ is the weight in g ; and $\nu_{i}$ is the partial specific volume, in mL per g , of the $i^{\text {th }}$ solute. The partial specific volume of a solute is the change in volume of a solution when an additional 1 g of solute is dissolved in the solution. This volume can be determined by the measurement of densities of the solution before and after the addition of the solute. The partial specific volumes of salts are generally very small, around 0.1 mL per g . However, those of other solutes are generally higher. For example, the partial specific volumes of amino acids are in the range of $0.6-0.9 \mathrm{~mL}$ per $g$.

BriEfing
<851 $\rangle$ Spectrophotometry and Light-Scattering, USP 27 page 2387 and page 3139 of the First Supplement. On the basis of comments received, revisions are proposed to update the recommended reference materials for calibration.
(PA4: H. Pappa) RTS-41336-1

## Change to read:

## PROCEDURE

## Absorption Spectrophotometry

Detailed instructions for operating spectrophotometers are supplied by the manufacturers. To achieve significant and valid results, the operator of a spectrophotometer should be aware of its limitations and of potential sources of error and variation. The instruction manual should be followed closely on such matters as care, cleaning, and calibration of the instrument, and techniques of handling absorption cells, as well as instructions for operation. The following points require special emphasis.

Check the instrument for accuracy of calibration. Where a continuous source of radiant energy is used, attention should be paid to both the wavelength and photometric scales; where a spectral line source is used, only the photometric scale need be checked. A number of sources of radiant energy have spectral lines of suitable intensity, adequately spaced throughout the spectral range selected. The best single source of UV and visible calibration spectra is the quartz-mercury arc, of which the lines at $253.7,302.25,313.16$, $334.15,365.48,404.66$, and 435.83 nm may be used. The glassmercury arc is equally useful above 300 nm . The $486.13-\mathrm{nm}$ and $656.28-\mathrm{nm}$ lines of a hydrogen discharge lamp may be used also. The wavelength scale may be calibrated also by means of suitable glass filters, which have useful absorption bands through the visible and UV regions. Standard glasses containing didymium (a mixture of praseodymium and neodymium) have been used widely, although glasses containing holmium were found to be superior. More recently, standard
${ }^{-}$Standard ${ }_{\text {ne2 }}$ (USP28)
holmium oxide solution has superseded the use of holmium glass. ${ }^{1}$ The wavelength scales of near-IR and IR spectrophotometers are readily checked by the use of absorption bands provided by polystyrene films, carbon dioxide, water vapor, or ammonia gas.

For checking the photometric scale, a number of standard inorganic glass filters as well as standard solutions of known transmittances such as orsium chremate or
-n2S (USP28)
potassium dichromate are available. ${ }^{2}$
Quantitative absorbance measurements usually are made on solutions of the substance in liquid-holding cells. Since both the solvent and the cell window absorb light, compensation must be made
${ }^{1}$ Gertified helmium oxide-selution, SPM H2034, (wavelength-standard frem 240 to 650 nm ) may be obtained frem the
■ ■2S (USP28)
National Institute of Standards and Technology (NIST), Gaithersburg, MD 20899: "Spectral Transmittance Characteristics of Holmium Oxide in Perchloric Acid," J. Res. Natl. Bur. Stds. 90, No. 2, 115 (1985). mitm-oxide glasses are nolonger available. Helmium oxide filters, witheut eertifieation, are available from-Kopp-Glass Ine., Pittsburgh, PA 15218.
■ ■2S (USP28)
The performance of an uncertified filter should be checked against a certified standard
2 For further detail regarding checks on beth the wavelength and

- ${ }^{-2 S}$ (USP28)
photometric scales of a spectrophotometer, reference may be made to the following NIST publications: SRM \#93le "Liquid Absorbance Standard for UV and Vis Spectrophotometry," J. Res. Natl. Bur. Stds. 76A, 405 and 469 (1972); SRM \#930e "Glass Filters for Spectrophotometry-for verification of the transmittance and absorbance scales of spectrophotometry in the visible spectral domain ( $10 \%$ T, 20\%T, 30\%T)," NIST Spec. Publ. 260-116 (1994).
for their contribution to the measured absorbance. Matched cells are available commercially for UV and visible spectrophotometry for which no cell correction is necessary. In IR spectrophotometry, however, corrections for cell differences usually must be made. In such cases, pairs of cells are filled with the selected solvent and the difference in their absorbances at the chosen wavelength is determined. The cell exhibiting the greater absorbance is used for the solution of the test specimen and the measured absorbance is corrected by subtraction of the cell difference.

With the use of a computerized Fourier transform IR system, this correction need not be made, since the same cell can be used for both the solvent blank and the test solution. However, it must be ascertained that the transmission properties of the cell are constant.

Comparisons of a test specimen with a Reference Standard are best made at a peak of spectral absorption for the compound concerned. Assays prescribing spectrophotometry give the commonly accepted wavelength for peak spectral absorption of the substance in question. It is known that different spectrophotometers may show minor variation in the apparent wavelength of this peak. Good practice demands that comparisons be made at the wavelength at which peak absorption occurs. Should this differ by more than $\pm 1 \mathrm{~nm}$ from the wavelength specified in the individual monograph, recalibration of the instrument may be indicated.

## TEST PREPARATION

For determinations utilizing UV or visible spectrophotometry, the specimen generally is dissolved in a solvent. Unless otherwise directed in the monograph, determinations are made at room temperature using a path length of 1 cm . Many solvents are suitable for these ranges, including water, alcohols, chloroform, lower hydrocarbons, ethers, and dilute solutions of strong acids and alkalies. Precautions should be taken to utilize solvents free from contaminants absorbing in the spectral region being used. It is usually advisable to use water-free methanol or alcohol, or alcohol denatured by the addition of methanol but not containing benzene or other interfering impurities, as the solvent. Solvents of special spectrophotometric quality, guaranteed to be free from contaminants, are available commercially from several sources. Some other analytical reagent-grade organic solvents may contain traces of impurities that absorb strongly in the UV region. New lots of these solvents should be checked for their transparency, and care should be taken to use the same lot of solvent for preparation of the test solution and the standard solution and for the blank.

No solvent in appreciable thickness is completely transparent throughout the near-IR and IR spectrum. Carbon tetrachloride (up to 5 mm in thickness) is practically transparent to $6 \mu \mathrm{~m}$ ( $1666 \mathrm{~cm}^{-1}$ ). Carbon disulfide ( 1 mm in thickness) is suitable as a solvent to $40 \mu \mathrm{~m}\left(250 \mathrm{~cm}^{-1}\right)$ with the exception of the $4.2-\mu \mathrm{m}$ to $5.0-\mu \mathrm{m}\left(2381-\mathrm{cm}^{-1}\right.$ to $\left.2000-\mathrm{cm}^{-1}\right)$ and the $5.5-\mu \mathrm{m}$ to $7.5-\mu \mathrm{m}$ $\left(1819-\mathrm{cm}^{-1}\right.$ to $\left.1333-\mathrm{cm}^{-1}\right)$ regions, where it has strong absorption. Other solvents have relatively narrow regions of transparency. For IR spectrophotometry, an additional qualification for a suitable solvent is that it must not affect the material, usually sodium chloride, of which the cell is made. The test specimen may also be prepared by dispersing the finely ground solid specimen in mineral oil or by mixing it intimately with previously dried alkali halide salt (usually potassium bromide). Mixtures with alkali halide salts may be examined directly or as transparent disks or pellets obtained by pressing the mixture in a die. Typical drying conditions for potassium
bromide are $105^{\circ}$ in vacuum for 12 hours, although grades are commercially available that require no drying. ${ }^{\mathbf{m}}$ Infrared microscopy or $\mathrm{a}_{\mathbf{1}_{1 S}(U S P 27)}$ mineral oil dispersion is preferable where disproportionation between the alkali halide and the test specimen is encountered. For suitable materials the test specimen may be $\square_{\text {prepared neat as a thin sample for IR microscopy or }}^{1 S}$ (USP27) Suspended neat as a thin film ${ }^{\mathbf{-}}$ for mineral oil dispersion. 1 (USP27) For Raman spectrometry, most common solvents are suitable, and ordinary (nonfluorescing) glass specimen cells can be used. The IR region of the electromagnetic spectrum extends from 0.8 to 400 $\mu \mathrm{m}$. From 800 to $2500 \mathrm{~nm}(0.8$ to $2.5 \mu \mathrm{~m})$ is generally considered to be the near-IR (NIR) region; from 2.5 to $25 \mu \mathrm{~m}(4000$ to $400 \mathrm{~cm}^{-1}$ ) is generally considered to be the mid-range (mid-IR) region; and from 25 to $400 \mu \mathrm{~m}$ is generally considered to be the farIR (FIR) region. Unless otherwise specified in the individual monograph, the region from 3800 to $650 \mathrm{~cm}^{-1}$ ( 2.6 to $15 \mu \mathrm{~m}$ ) should be used to ascertain compliance with monograph specifications for IR absorption.

Where values for IR line spectra are given in an individual monograph, the letters $s, m$, and $w$ signify strong, medium, and weak absorption, respectively; $s h$ signifies a shoulder, $b d$ signifies a band, and $v$ means very. The values may vary as much as $0.1 \mu \mathrm{~m}$ or $10 \mathrm{~cm}^{-1}$, depending upon the particular instrument used. Polymorphism gives rise to variations in the IR spectra of many compounds in the solid state. Therefore, when conducting IR absorption tests, if a difference appears in the IR spectra of the analyte and the standard, dissolve equal portions of the test substance and the standard in equal volumes of a suitable solvent, evaporate the solutions to dryness in similar containers under identical conditions, and repeat the test on the residues.

In NIR spectroscopy much of the current interest centers around the ease of analysis. Samples can be analyzed in powder form or by means of reflectance techniques, with little or no preparation. Compliance with in-house specifications can be determined by computerized comparison of spectra with spectra previously obtained from reference materials. Many pharmaceutical materials exhibit low absorptivity in this spectral region, which allows incident nearIR radiation to penetrate samples more deeply than UV, visible, or IR radiation. NIR spectrophotometry may be used to observe matrix modifications and, with proper calibration, may be used in quantitative analysis.

In atomic absorption spectrophotometry, the nature of the solvent and the concentration of solids must be given special consideration. An ideal solvent is one that interferes to a minimal extent in the absorption or emission processes and one that produces neutral atoms in the flame. If there is a significant difference between the surface tension or viscosity of the test solution and standard solution, the solutions are aspirated or atomized at a different rate, causing significant differences in the signals generated. The acid concentration of the solutions also affects the absorption processes. Thus, the solvents used in preparing the test specimen and the standard should be the same or as much alike in these respects as possible, and should yield solutions that are easily aspirated via the specimen tube of the burner-aspirator. Since undissolved solids present in the solutions may give rise to matrix or bulk interferences, the total undissolved solids content in all solutions should be kept below $2 \%$ wherever possible.

## CALCULATIONS

The application of absorption spectrophotometry in an assay or a test generally requires the use of a Reference Standard. Where such a measurement is specified in an assay, a formula is provided in order to permit calculation of the desired result. A numerical constant is frequently included in the formula. The following derivation is provided to introduce a logical approach to the deduction of the constants appearing in formulas in the assays in many monographs.

The Beer's law relationship is valid for the solutions of both the Reference Standard ( $S$ ) and the test specimen ( $U$ ): in which $A_{S}$ is the absorbance of the Standard solution of concentration $C_{S}$; and $A_{U}$ is the absorbance of the test specimen solution of concentration $C_{U}$. If $C_{S}$ and $C_{U}$ are expressed in the same units and the absorbances of both solutions are measured in matching cells having the same dimensions, the absorptivity, $a$, and the cell thickness, $b$, are the same; consequently, the two equations may be combined and rewritten to solve for $C_{U}$ :
(3)

$$
C_{U}=C_{S}\left(A_{U} / A_{S}\right)
$$

Quantities of solid test specimens to be taken for analysis are generally specified in mg. Instructions for dilution are given in the assay and, since dilute solutions are used for absorbance measurements, concentrations are usually expressed for convenience in units of $\mu \mathrm{g}$ per mL . Taking a quantity, in mg , of a test specimen of a drug substance or solid dosage form for analysis, it therefore follows that a volume $\left(V_{U}\right)$, in L , of solution of concentration $C_{U}$ may be prepared from the amount of test specimen that contains a quantity $W_{U}$, in mg, of the drug substance [NOTE- $C_{U}$ is numerically the same whether expressed as $\mu \mathrm{g}$ per mL or mg per L], such that:
(4) $W_{U}=V_{U} C_{U}$.

The form in which the formula appears in the assay in a monograph for a solid article may be derived by substituting $C_{U}$ of equation (3) into equation (4). In summary, the use of equation (4), with due consideration for any unit conversions necessary to achieve equality in equation (5), permits the calculation of the constant factor $\left(V_{U}\right)$ occurring in the final formula:
(5) $\quad W_{U}=V_{U} C_{S}\left(A_{U} / A_{S}\right)$.

The same derivation is applicable to formulas that appear in monographs for liquid articles that are assayed by absorption spectrophotometry. For liquid dosage forms, results of calculations are generally expressed in terms of the quantity, in mg , of drug substance in each mL of the article. Thus it is necessary to include in the denominator an additional term, the volume $(V)$, in mL , of the test preparation taken.

Assays in the visible region usually call for comparing concomitantly the absorbance produced by the Assay preparation with that produced by a Standard preparation containing approximately an equal quantity of a USP Reference Standard. In some situations, it is permissible to omit the use of a Reference Standard. This is true where spectrophotometric assays are made with routine frequency, and where a suitable standard curve is available, prepared with the respective USP Reference Standard, and where the substance assayed conforms to Beer's law within the range of about $75 \%$ to $125 \%$ of the final concentration used in the assay. Under these circumstances, the absorbance found in the assay may be interpolated on the standard curve, and the assay result calculated therefrom.

Such standard curves should be confirmed frequently, and always when a new spectrophotometer or new lots of reagents are put into use.

In spectrophotometric assays that direct the preparation and use of a standard curve, it is permissible and preferable, when the assay is employed infrequently, not to use the standard curve but to make the comparison directly against a quantity of the Reference Standard approximately equal to that taken of the specimen, and similarly treated.

## Fluorescence Spectrophotometry

The measurement of fluorescence is a useful analytical tech nique. Fluorescence is light emitted from a substance in an excited state that has been reached by the absorption of radiant energy. A substance is said to be fluorescent if it can be made to fluoresce. Many compounds can be assayed by procedures utilizing either their inherent fluorescence or the fluorescence of suitable derivatives.

Test specimens prepared for fluorescence spectrophotometry are usually one-tenth to one-hundredth as concentrated as those used in absorption spectrophotometry, for the following reason. In analytical applications, it is preferable that the fluorescence signal be linearly related to the concentration; but if a test specimen is too concentrated, a significant part of the incoming light is absorbed by the specimen near the cell surface, and the light reaching the center is reduced. That is, the specimen itself acts as an "inner filter." However, fluorescence spectrophotometry is inherently a highly sensitive technique, and concentrations of $10^{-5} \mathrm{M}$ to $10^{-7}$ M frequently are used. It is necessary in any analytical procedure to make a working curve of fluorescence intensity versus concentration in order to establish a linear relationship. All readings should be corrected for a solvent blank.

Fluorescence measurements are sensitive to the presence of dust and other solid particles in the test specimen. Such impurities may reduce the intensity of the exciting beam or give misleading high readings because of multiple reflections in the specimen cell. It is, therefore, wise to eliminate solid particles by centrifugation; filtration also may be used, but some filter papers contain fluorescent impurities.

Temperature regulation is often important in fluorescence spectrophotometry. For some substances, fluorescence efficiency may be reduced by as much as $1 \%$ to $2 \%$ per degree of temperature rise. In such cases, if maximum precision is desired, temperature-controlled specimen cells are useful. For routine analysis, it may be sufficient to make measurements rapidly enough so that the specimen does not heat up appreciably from exposure to the intense light source. Many fluorescent compounds are light-sensitive. Exposed in a fluorometer, they may be photo-degraded into more or less fluorescent products. Such effects may be detected by observing the detector response in relationship to time, and may be reduced by attenuating the light source with filters or screens.

Change of solvent may markedly affect the intensity and spectral distribution of fluorescence. It is inadvisable, therefore, to alter the solvent specified in established methods without careful preliminary investigation. Many compounds are fluorescent in organic solvents but virtually nonfluorescent in water; thus, a number of solvents should be tried before it is decided whether or not a compound is fluorescent. In many organic solvents, the intensity of fluorescence is increased by elimination of dissolved oxygen, which has a strong quenching effect. Oxygen may be removed by bubbling an inert gas such as nitrogen or helium through the test specimen.

A semiquantitative measure of the strength of fluorescence is given by the ratio of the fluorescence intensity of a test specimen and that of a standard obtained with the same instrumental settings. Frequently, a solution of stated concentration of quinine in 0.1 N sulfuric acid or fluorescein in 0.1 N sodium hydroxide is used as a reference standard.

## Light-Scattering

Turbidity can be measured with a standard photoelectric filter photometer or spectrophotometer, preferably with illumination in the blue portion of the spectrum. Nephelometric measurements require an instrument with a photocell placed so as to receive scattered rather than transmitted light; this geometry applies also to fluorometers, so that, in general, fluorometers can be used as nephelometers, by proper selection of filters. A ratio turbidimeter combines the technology of $90^{\circ}$ nephelometry and turbidimetry: it contains photocells that receive and measure scattered light at a $90^{\circ}$ angle from the sample as well as receiving and measuring the forward scatter in front of the sample; it also measures light transmitted directly through the sample. Linearity is attained by calculating the ratio of the $90^{\circ}$ angle scattered light measurement to the sum of the forward scattered light measurement and the transmitted light measurement. The benefit of using a ratio turbidimetry system is that the measurement of stray light becomes negligible.

In practice, it is advisable to ensure that settling of the particles being measured is negligible. This is usually accomplished by including a protective colloid in the liquid suspending medium. It is important that results be interpreted by comparison of readings with those representing known concentrations of suspended matter, produced under precisely the same conditions.

Turbidimetry or nephelometry may be useful for the measurement of precipitates formed by the interaction of highly dilute solutions of reagents, or other particulate matter, such as suspensions of bacterial cells. In order that consistent results may be achieved, all variables must be carefully controlled. Where such control is possible, extremely dilute suspensions may be measured.

The specimen solute is dissolved in the solvent at several different accurately known concentrations, the choice of concentrations being dependent on the molecular weight of the solute and ranging from $1 \%$ for $M_{w}=10,000$ to $0.01 \%$ for $M_{w}=1,000,000$. Each solution must be very carefully cleaned before measurement by repeated filtration through fine filters. A dust particle in the solution vitiates the intensity of the scattered light measured. A criterion for a clear solution is that the dissymmetry, $45^{\circ} / 135^{\circ}$ scattered intensity ratio, has attained a minimum.

The turbidity and refractive index of the solutions are measured. From the general $90^{\circ}$ light-scattering equation, a plot of $H C / \tau$ versus $C$ is made and extrapolated to infinite dilution, and the weightaverage molecular weight, $M$, is calculated from the intercept, 1/ $M$.

## Visual Comparison

Where a color or a turbidity comparison is directed, color-comparison tubes that are matched as closely as possible in internal diameter and in all other respects should be used. For color comparison, the tubes should be viewed downward, against a white background, with the aid of a light source directed from beneath the bottoms of the tubes, while for turbidity comparison the tubes should be viewed horizontally, against a dark background, with the aid of a light source directed from the sides of the tubes.

In conducting limit tests that involve a comparison of colors in two like containers (e.g., matched color-comparison tubes), a suit able instrument, rather than the unaided eye, may be used.

# GENERAL CHAPTERS 

## General Information

## Briefing

$\langle\mathbf{1 0 7 0}\rangle$ Emergency Medical Services Vehicles and Ambu-lances-Storage of Preparations. Following the PSD Open Conference in October 2003, the PSD Expert Committee determined that the treatment of the handling and storage of medications in emergency medical services vehicles had to be on a separate, faster track from the rest of the content of the proposed general chapter Good Storage and Shipping Practices $\langle 1079\rangle$ (see page 1612 of PF 29(5) [Sept.-Oct. 2003]. As a result of the considerable discussion of this topic at the Open Conference, the text is revised extensively from that which appeared in the conference workbook. It is proposed here as an informational chapter. This proposed general chapter includes a list of the most commonly used articles in EMS vehicles. Readers are invited to submit any available stability data that will allow assignment of reasonable storage and handling limits for these preparations. Alternatively, typical residence time stability studies at elevated and reduced temperature conditions for the limited drugs in this list are invited. Because space is limited in an EMS vehicle, identification of just those preparations having more stringent storage requirements would have practical benefit. In preparing this text for public comment, the Expert Committee has drawn on input from several notable experts in this area.
(PSD: C. Okeke) RTS-41624-1

Add the following:
> - \{1070〉 EMERGENCY MEDICAL SERVICES VEHICLES AND AMBULANCES-STORAGE OF PREPARATIONS

The storage and handling of pharmaceuticals in emergency vehicles and ambulances should be done so that the attributes of the official articles are preserved. For examples, see the list below for typical articles. There are a number of
practices that need consideration when an effective plan is formulated, evaluated, put in place, and periodically re-evaluated. Those practices are listed here.

Monitoring devices should be in place to record weekly temperatures, and allow calculation of mean kinetic temperature for conformance to controlled room temperature storage for those vehicles utilized continuously. Measurement should also be made during a typical challenging 24-hour period, and the derived temperature should be used for calculation of MKT and storage temperature of the sample.

## PHARMACEUTICAL STORAGE CABINET MONITORING; LOCATION OF PARKED <br> VEHICLES

Ambulances and other emergency medical response vehicles that routinely carry Pharmacopeial articles should be monitored to verify that temperature profiles and on-board pharmaceutical storage cabinets or cold chests are within established limits. Suitable monitoring devices are to be placed in the pharmaceutical cabinet of each vehicle that records highest and lowest temperatures, at the least, of each hot summer and cold winter day. Ambulance personnel should consider parking in the shade or in air-conditioned garages in the summer or in heated garages in the winter to avoid temperature extremes.

## STOCK ROTATION

A program of regular stock rotation should be in place for articles with low rates of turnover. Rotation is understood as transfer of the articles with suitable marking of stock items to an appropriate climate controlled facility or storage cab-
inet such as in an ambulance bay. Off-vehicle storage of each article is subject to the storage requirement in the approved labeling or the pertinent USP monograph.

## PORTABLE CARRYING CASE STORAGE AND MONITORING

The portable bag or carrying case in which drugs are kept is to be insulated, and when not in use, should be kept in a pharmaceutical storage cabinet or at controlled room temperature within facilities. Storage in portable bags or cases only rather than in on-board cabinets should be considered to facilitate stock rotation where that is indicated. The use of time-temperature indicators is recommended to monitor cumulative insult to the contents of all compartments.

## ADDITIONAL REQUIREMENTS FOR SOME <br> ARTICLES

All articles are to be protected from excessive heat, $40^{\circ}$. If the article requires storage in a cold or dry place or at controlled room temperature, then suitable measures are to be taken to maintain it within the defined limits, see General Notices-Preservation, Packaging, Storage, and Labeling. Articles that have the most stringent storage requirements determine the storage of mixed loads.

## STORAGE AND HANDLING OF SENSITIVE PREPARATIONS

Environmentally Sensitive Preparations (see $\langle 386\rangle$ ) are not to be stored in emergency response vehicles unless the on-board cabinet in which the medications is stored is climate controlled or a time-temperature indicator is attached to each package. If Environmentally Sensitive Preparations
must be kept in the EMS vehicle, then medications supply should be rotated with reserve stock on a schedule based on local climate, but not longer than every 3 days.

## USE OF TIME-TEMPERATURE INDICATORS

Attach time-temperature indicators to individual Thermally Sensitive Preparations where time outside of the on-board cabinet can exceed 4 days total. On-board cabinets must be insulated and should use active heating/cooling devices in accord with the local climate and as specified for the preparations while medications are inside.

## COMPOSITE INVENTORY OF TYPICAL AMBULANCE SERVICE MEDICATIONS

NOTE-Each vehicle may carry only a portion of the articles herein, or others.

Adenosine Injection
Afrin
Albuterol Sulfate Injection
Amiodarone
Amyl Nitrite Inhalant
Aspirin Tablets
Atropine Sulfate Injection
Atropine and 2-PAM Antidote [Mark 1 Kits]
Atrovent
Bretylium Tosylate Injection
Calcium Chloride Injection
Calcium Gluconate Injection

## Activated Charcoal

Dextrose 50\%, Dextrose 25\% Injection
Diazepam Gel
Diazepam Injection
Diltiazem
Diphenhydramine Injection
Dopamine Injection
Epinephrine $1: 10000$, Epinephrine $1: 1000$ Injection Furosemide Injection
Glucagon for Injection
Lidocaine Hydrochloride Injection, Lidocaine 1\% Gel
Magnesium Sulfate
Methylprednisone
Metoprolol
Midazolam
Morphine Sulfate Injection
Nalbuphine
Naloxone Hydrochloride Injection
Nitroglycerin Spray, Nitroglycerin Tablets,
Nitroglycerin Ointment
Oxytocin Injection
Promethazine
Sodium Bicarbonate Injection
Sodium Nitrite Injection
Sodium Thiosulfate Injection
Terbutaline Injection
Tetracaine Ophthalmic Solution, Ointment
Thiamine Hydrochloride Injection
Toradol Injection $\mathbf{Q 2 S}^{\text {(USP28) }}$

## BRIEFING

$\langle\mathbf{1 1 1 2}\rangle$ Microbiological Attributes of Nonsterile Pharmaceutical Products-Application of Water Activity Determination, page 2009 of $P F 28(6)$ [Nov.-Dec. 2002]. This new chapter, which previously appeared in Pharmacopeial Previews, is now moved to In-Process Revision with the following changes on the basis of comments received:
(1) The title of the chapter has changed.
(2) The importance of container-closure integrity in maintaining the water activity level during the product shelf life is emphasized.
(3) Reduced microbial limits testing must be justified through risk assessment and not solely on water activity determinations.
(4) The ability of more resistant microorganisms to persist in drug products of low water activity is acknowledged.
(AMB: D. Porter) RTS-41476-1

## Add the following:

## 〈1112〉 MICROBIOLOGICAL ATTRIBUTES OF NONSTERIEE PHARMACEUTICAL PRODUCTSAPPLICATION OF WATER ACTIVITY DETERMINATION APPLICATION OF WATER ACTIVITY DETERMINATION TO NONSTERILE PHARMACEUTICAL PRODUCTS

The determination of the water activity of nonsterile pharmaceutical dosage forms aids in the decisions relating to the following:
(a) optimizing product formulations to improve antimicrobial effectiveness of preservative systems,
(b) reducing the degradation of active pharmaceutical ingredients within product formulations susceptible to chemical hydrolysis,
(c) reducing the susceptibility of formulations (especially liquids, ointments, lotions, and creams) to microbial contamination, and
(d) providing a tool for the rationale for reducing the frequency of microbial limit testing and screening for objectionable microorganisms for product release and stability testing using methods contained in the general test chapter Microbial Limit Tests $\langle 61\rangle$.

Reduced water activity ( $a_{W}$ ) will greatly assist in the prevention of microbial proliferation in pharmaceutical products; and the formulation, manufacturing steps, and testing of nonsterile dosage forms should reflect this parameter.

Low water activity has traditionally been used to control microbial deterioration of foodstuffs. Examples where the available moisture is reduced are dried fruit, syrups, and pickled meats and vegetables. Low water activities make these materials self-preserved. Low water activity will also prevent microbial growth within pharmaceutical drug products. Other product attributes, for example, low or high pH , absence of nutrients, presence of surfactants, and addition of antimicrobial agents, as well as low water activity, help to prevent microbial growth. However, it should be noted that more resistant microorganisms, including spore-forming

Clostridium spp., Bacillus spp., Salmonella spp. and filamentous fungi, although they may not proliferate in a drug product with a low water activity, may persist within the product.

When formulating an aqueous oral or topical dosage form, candidate formulations should be evaluated for water activity so that the drug product may be self-preserving, if possible. For example, small changes in the concentration of sodium chloride, sucrose, alcohol, propylene glycol, or glycerin in a formulation may result in the creation of a drug product with a lower water activity that can discourage the proliferation of microorganisms in the product. This is particularly valuable with a multiple-use product that may be contaminated by the user. Packaging studies should be conducted to test product stability and to determine that the con-tainer-closure system protects the product from moisture gains that would increase the water activity during storage.
Reduced microbial limits testing may be justified through risk assessment. This reduction in testing, when justified, may entail forgoing full microbial limits testing, implementing skip-lot testing, or eliminating routine testing.

Nonaqueous liquids or dry solid dosage forms will not support spore germination or microbial growth due to their low water activity. The frequency of their microbial monitoring can be determined by a review of the historic testing database of the product and the demonstrated effectiveness of microbial contamination control of the raw materials, ingredient water, and the manufacturing proess manufacturing process, formulation, and packaging system. The testing history would include microbial monitoring during product development, scale-up, process validation, and routine testing of sufficient marketed product lots (e.g., up to 20 lots) to ensure that the product has little or no potential for microbial contamination. Because the water activity requirements for different Gram-reactive bacteria, bacterial spores, yeasts, and molds are well described in the literature, ${ }^{1}$ the appropriate microbial limit testing program for products of differing water activities can be established. For example, Gram-negative bacteria including the specific objectionable microorganisms, Pseudomonas aeruginosa, Escherichia coli, and Salmonella species will not proliferate or survive in preserved products with water activities below 0.91 , while Gram-positive bacteria such as Staphylococcus aureus will not proliferate below 0.86, and Aspergillus niger will not proliferate below 0.77 . Furthermore, even the most osmophilic yeast and xerophilic fungi will not proliferate below 0.60 , and they cannot be isolated on compendial microbiological media. ${ }^{1}$ The water activity requirements measured at $25^{\circ}$ for the growth of a range of representative microorganisms are presented in Table 1.

[^257]Table 1. Water Activities $\left(a_{W}\right)$ Required to Support the Growth of Representative Microorganisms

| Bacteria | Water Activity $\left(a_{w}\right)$ | Molds and Yeast | Water Activity $\left(a_{w}\right)$ |
| :--- | :---: | :---: | :---: |
| Pseudomonas aeruginosa | 0.97 | Rhyzopus nigricans | 0.93 |
| Bacillus cereus | 0.95 | Mucor plumbeus | 0.92 |
| Clostridium botulinum, | 0.95 | Rhodotorula mucilaginosa | 0.92 |
| Type A |  |  |  |
| Escherichia coli | 0.95 | Saccharomyces cerevisiae | 0.90 |
| Clostridium perfringens | 0.95 | Paecilomyces variotti | 0.84 |
| Lactobacillus viridescens | 0.95 | Penicillium chrysogenum | 0.83 |
| Salmonella spp. | 0.95 | Aspergillus fumigatus | 0.82 |
| Enterobacter aerogenes | 0.94 | Penicillium glabrum | 0.81 |
| Bacillus subtilis | 0.90 | Aspergillus flavus | 0.78 |
| Micrococcus lysodekticus | 0.93 | Zygosachharomyces rouxii | 0.77 |
| Staphylococcus aureus | 0.86 | (osmophilic yeast) | 0.62 |
|  |  | Xeromyces bisporus |  |
| Halobacterium halobium | (xerophilic fungi) | 0.61 |  |
| (halophilic bacterium) |  |  |  |

Pharmaceutical drug products with water activities well below 0.75 (e.g., direct compression tablets, powder and liquid-filled capsules, nonaqueous liquid products, ointments, rectal suppositories, etc.) would be excellent candidates for reduced microbial limit testing for product release and stability evaluation. This is especially true when pharmaceutical products are made from ingredients of good microbial quality, when manufacturing environments do not foster microbial contamination, when there are processes that inherently reduce the microbial content, when the formulation of the drug product has antimicrobial activity, and when manufacturing sites have an established testing history of low bioburden associated with their products. Table 2 contains suggested microbial limit testing strategies
for typical pharmaceutical and over-the-counter (OTC) drug products based on water activity. Other considerations, as listed above, would be applied when setting up the microbial limits testing program for individual drug products because water activity measurements cannot solely be used to justify the elimination of microbial content testing for product release.

Similar arguments could be made for the microbial limits testing of pharmaceutical ingredients. However, this would require pharmaceutical manufacturers to have a comprehensive knowledge of the pharmaceutical ingredient manufacturer's manufacturing processes, quality programs, and testing record. This could be obtained through a supplier audit program.

Table 2. Microbial Limit Testing Strategy for Typieal Representative Pharmaceutical and OTC Drug Products Based on Water Activity

| Products | Water Activity $\left(a_{W}\right)$ | Greatest Potential <br> Contaminants | Testing Recommended |
| :---: | :---: | :---: | :---: |
| Nasal inhalant | 0.99 | Gram-negative bacteria | TAMC, ${ }^{*}$ TCYMC, absence of $S$. aureus and $P$. aeruginosa |
| Hair shampoo | 0.99 | Gram-negative bacteria | TAMC, TCYMC, absence of $S$. aureus and $P$. aeruginosa |
| Antacid | 0.99 | Gram-negative bacteria | TAMC, TCYMC, absence of $E$. coli and Salmonella spp. |
| Topical cream | 0.97 | Gram-positive bacteria | TAMC, TCYMC, absence of $S$. aureus and $P$. aeruginosa |
| Oral liquid | 0.90 | Gram-positive bacteria and fungi | TAMC and TCYMC |
| Oral suspension | 0.87 | Fungi | TAMC and TCYMC |
| Topical ointment | 0.55 | None | TCYMG Reduced testing |
| Lip balm | 0.36 | None | None Reduced testing |
| Vaginal and rectal suppositories | 0.30 | None | None Reduced testing |
| Compressed tablets | 0.36 | None | None Reduced testing |
| Liquid-filled capsule | 0.30 | None | None Reduced testing |

* TAMC $=$ Total aerobic microbial count; TCYMC $=$ Total combined yeast and mold count.
note-The water activities cited in Table 2 for the different dosage forms are representative, and companies are urged to test their individual products before developing a testing strategy.

Water activity, $a_{H}$, is the ratio of vapor pressure of $\mathrm{H}_{2} \mathrm{O}$ in product $(P)$ to vapor pressure of pure $\mathrm{H}_{2} \mathrm{O}(P o)$ at the same temperature. It is numerically equal to $1 / 100$ of the relative humidity ( RH ) generated by the product in a closed system. RH can be calculated from direct measurements of partial vapor pressure or dew point or indirect measurement by sensors whose physical or electric characteristics are altered by the RH to which they are exposed.

The relationship between $a_{W}$ and equilibrium relative humidity (ERH) are represented by the following equations:

$$
a_{W}=P / P o \text { and } \operatorname{ERH}(\%)=a_{W} \times 100
$$

The $a_{W}$ measurement may be conducted using the dew point/ chilled mirror method. ${ }^{2}$ A polished, chilled mirror is used as the condensing surface. The cooling system is electronically linked to a photoelectric cell into which light is reflected from the condensing mirror. An air stream, in equilibrium with the test sample, is directed at the mirror which cools until condensation occurs on the mirror. The temperature at which this condensation begins is the dew point from which the ERH is determined. Sample preparation should be considered as it may affect the water activity level of the material tested. Commercially available instruments using the dew point/chilled mirror method or other technologies need to be evaluated for suitability, validated, and calibrated when used to make water activity determinations. These instruments are typically calibrated using saturated salt solutions at $25^{\circ}$ as listed in Table 3.

Table 3. Standard Saturated Salt Solutions Used to Calibrate Water Activity Determination Instruments

| Saturated Salt Solutions | ERH (\%) | $a_{W}$ |
| :--- | :---: | :---: |
| Potassium sulfate $\left(\mathrm{K}_{2} \mathrm{SO}_{4}\right)$ | 97.3 | 0.973 |
| Barium chloride $\left(\mathrm{BaCl}_{2}\right)$ | 90.2 | 0.902 |
| Sodium chloride $(\mathrm{NaCl})$ | 75.3 | 0.753 |
| Magnesium nitrate $\left(\mathrm{Mg}\left(\mathrm{NO}_{3}\right)_{2}\right)$ | 52.9 | 0.529 |
| Magnesium chloride $\left(\mathrm{MgCl}_{2}\right)$ | 32.8 | 0.328 |

## BRIEFING

〈1117〉 Microbiological Best Laboratory Practices, page 842 of PF 29(3) [May-June 2003]. This proposed general information chapter, which previously appeared in Pharmacopeial Previews, has been revised in response to comments received and is now forwarded to In-Process Revision. Along with numerous editorial

[^258]changes, the sections on Media Preparation and Quality Control, Maintenance of Microbiological Cultures, and Interpretation of Laboratory Results underwent substantial revision.
(AMB: D. Porter)
RTS-41617-1

## Add the following:

## - 1117$\rangle$ MICROBIOLOGICAL GOOD BEST LABORATORY PRACTICES

## INTRODUCTION

Good laboratory practices in a microbiology laboratory consist of activities that depend on several principles: aseptic technique, control of media, control of test strains, control of equipment, diligent recording and evaluation of data, and training of the laboratory staff. Because of the known variability in microbiology data, reliability and reproducibility are dependent on the use of accepted methods and adherence to good laboratory practices.

## MEDIA PREPARATION AND QUALITY CONTROL

## Media Preparation

Culture media are the basis for most microbiological tests. While growth media can be prepared in a laboratory from individual components, many laboratories, for their easeef use, use dehydrated media or purchase commereially prepared media in plates of glass entainers. Manufacturers of media attempt to standardize raw materiats frem biologieat sourees, but must constantly deal with unavoidable differ ences in raw materials obtained from natural sources and with lot to lot variability of media. The performanee of media prepared in a laboratory or by a manufacturer is highly dependent on preparation. Improper media preparation can eatuse unsatisfactory conditions for microbial growth or re-
eovery and unreliable results. Safeguarding the quality of this media is therefore critical to the success of the microbiology laboratory. Media preparation, proper storage, and quality control testing can assure a consistent supply of high quality media.

It is important to choose the correct media or components in making media based on the use of accepted sources or references for formulas. The manufacturer's formula and instructions for preparation routinely accompany dehydrated media and ready-made media. Because different media types may have different preparation requirements (e.g., heating, additives, pH adjustment, etc.), it is important to follow these instructions to ensure preparation of acceptable media quality. A certificate of analysis describing expiry dating and recommended storage conditions accompanies ready-made media, as well as the quality control organisms used in growth-promotion and selectivity testing of that media.

Water is the universal diluent for microbiological media. Purified Water is most often used for media preparation, but in certain cases the use of deionized or distilled water may be appropriate. The volume of the water used should be recorded.
Consistent preparation of media requires accurate weighing of dehydrated media or media constituents. A calibrated balance with the appropriate weight range for the ingredients should be used, andelean. Clean weighing containers and tools (such as spatulas) should be used to prevent foreign substances that may alter the composition of the finished media from entering the formulation. The weight of the components should be recorded.

Dehydrated media should be thoroughly dissolved in water prior to dispensing and sterilization. If heating is necessary to help dissolve media, care should be taken not to overheat media as all culture media, to a greater or lesser
extent, are heat-sensitive. The of hot plate with mag netic stirrer is recemmended for consistent mixing and heat ing. Equipment used in the preparation of media should be appropriate to allow for controlled heating and constant agitation and mixing of the media. Darkening of media (Mail-lard-type reaction or nonenzymatic browning) is a general indication of overheating. When adding required supplements to media, adequate mixing of the medium after adding the supplement should be performed.

Preparation of media in phelean or undedicated poorly cleaned glassware can allow inhibitory substances to enter the media. Inhibitory substances can come from detergent residue after cleaning glassware or from prior materials used in the glassware. Be sure that the cleaning process removes debris and foreign matter, and that the detergent is thoroughly rinsed out with high Purified Water. See Cleaning Glass Apparatus $\langle 1051\rangle$ for additional guidance.
Sterilization of media should be performed within the parameters provided by the manufacturer or validated by the user. Commercially prepared media should provide documentation of the sterilization method that was used. Forex temperaneously prepared media, follow the manufacturer's instrutions for heating or sterilization. Ideally the manufacturer should provide the sterility assurance level (SAL) of the media against a recognized biological indicator. Autoclaving by moist heat is the preferred sterilization technique, except in instances when the manufacturer speifies the use ef boiling is required in order to avoid deterioration of heatlabile components of the media. Sterilization by filtration may also be appropriate for some formulations.

The effects of timperature the sterilization method and conditions on the media should be validated by sterility and growth-promotion testing of the media. In addition, if sterilized by moist heat, the autoclave cycle should be validated to ensure proper heat distribution for se-
lected loads and volumes. Typically, manufacturers recommend using an autoclave cycle of $121^{\circ}$ for 15 minutes using a validated autoclave cycle. These conditions apply to time at temperature of the media. As the load configuration of the autoclave will influence the rate of heating, longer cycles may be required for larger loads. However, the sterilization time will be dependent on the media volume and autoclave load. Sterilization cycles in which the autoclave is slow to come up to temperature may result in overheating of the media. In such eases it may be preferable to the attoclave to deliver a $F_{9}$ of 15 minutes to include the heating up and eooling down part of the cycle. The overkill validation up proach used in many production operations results in -ex treme sterilization conditions and may destroy the growthprometing qualities of most bacterial or myeologieal growth madia. Therefore, care must be taken to validate a sterilization cycle to deliver the minimum SAL required, balancing the need for a sterile media against the tendency of the media to degrade under excessive heating. Storage of the media in the autoclave after the liquid cycle is completed is not recommended after cooling, as it may damage the media. Improper heating or sterilizing conditions-for commercially prepared or internally prepared media-may result in a difference in color change, loss of clarity, altered gel strength, or pH drift from the manufacturer's recommended range.

Check the pH of each batch of medimm The pH of each batch of medium should be confirmed after it has cooled to room temperature $\left(25^{\circ}\right)$ by aseptically withdrawing a sample for testing. A flat pH probe is recommended for agar surfaces, and for liquids an immersion probe is recommended. The pH of media should be in a range of $\pm 0.2$ of the value indicated by the manufacturer, unless a wider range is acceptable by the validated method.

Prepared media should be checked by $100 \%$ inspection of
plates and tubes for the following: cracked containers, un equal filling of containers, dehydration resulting in cracks or dimpled surfaces on solid medium, hemolysis, crystal formation from possible freezing, excessive number of bub-

## bles, and mierebial contamination.

Prepared media should be checked by appropriate inspection of plates and tubes for:

- Cracked containers or lids
- Unequal filling of containers
- Dehydration resulting in cracks or dimpled surfaces on solid medium
- Hemolysis
- Excessive darkening or color change
- Crystal formation from possible freezing
- Excessive number of bubbles
- Microbial contamination
- Status of redox indicators (if appropriate)
- Lot number and expiry date checked and recorded
- Sterility of the media


## Media Storage

It is prudent to consider how the manufacturer or supplier transports and stores media prior to distribution to the end user. Manufacturers of media should use transport and storage conditions that minimize the loss of moisture, control the temperature, and provide mechanical protection to the prepared media.

Media should be labeled properly with batch or lot numbers, preparation and expiration dates, and media identification. Media should be stored according to manufacturer's instructions. Media prepared in-house should be stored under entrolled refrigeration in a seled container. validated conditions. Do not store agar at or below $0^{\circ}$ this eould destroy as freezing could damage the gel structure.

Protect stored media from exposure to light and excessive temperature. Before prolonged storage, agar plates should be placed into a sealed package or container to retard moisture loss.

Remelting of an original container of solid media should be performed only once to avoid media whose quality is compromised by overheating or potential contamination. It is recommended that remelting be performed in a heated water bath or by using free-flowing steam. The use of microwave ovens and heating plates is common, but result in overheating of the media as well as exposing the laboratory stantial care should be take to avoid damaging media by overheating, and to avoid the potential injury to laboratory personnel danger from glass breakage and burns. The molten agar medium should be held in a monitored water bath at a temperature of $45^{\circ}$ to $50^{\circ}$ for not more than 8 hours. Caution should be taken when pouring the media from a container immersed in a water bath to prevent water from the bath comingling with the poured sterile media. Wiping the exterior of the container dry prior to pouring may be advisable.

Disposal of used cultured media (as well as expired media) should follow local biological hazard safety procedures.

## Quality Control Testing

It is important to confim the quality of the media. While growth media can be prepared in a laboratory from individual components, many laboratories, for their ease-of-use, use dehydrated media or purchase commercially prepared media in plates or glass containers. Manufacturers of media attempt to standardize raw materials from biological sources, but must constantly deal with unavoidable differences in raw materials obtained from natural sources and therefore lot-to-lot variability of media must be considered. The performance of media prepared in a laboratory or by a
manufacturer is highly dependent on preparation. Improper media preparation can cause unsatisfactory conditions for microbial growth or recovery and unreliable results.

Quality control tests should be performed on all prepared media. Tests routinely performed on inhouse prepared media are pH , growth promotion, and periodic stability checks to confirm the expiry dating.

When ical media is properly prepared and sterilized using a validated method, then the growth-promotion testing may be limited to each incoming lot of dehydrated media unless otherwise instructed by the relevant compendial method. If the media preparation was not validated, then every batch of media would be subjected to growth-promotion testing. Test organisms may be selected from the appropriate compendial test chapter, based on the manufacturer's recommendation for a particular medium or may include representative environmental isolates.

Expiration dates on media should have supporting growth-promotion testing to indicate that the performance of the media still meets acceptance criteria up to and including the expiration date. All media may be used, i.e., ineet tate the the length of shelf life of a batch of media will depend on the stability of the ingredients and formulation under specified conditions, as well as the type of container and closure.
When a tet batch of media does not meet the requirements of growth-promotion testing, an investigation should be initiated to identify the cause of themeng let. This investigation should include a corrective action plan to prevent the recurrence of the problem. Any nonconforming lot should not be used if an assignable cause or corrective resolution relative to nongrowth support is undetermined.

Some reagents are used for diagnostic purposes to help support identification of microbial organisms, e.g., Gram stain, oxidase test reagents, etc. These may have attributes that can be quality control tested similar to microbiological media. Select the correct quality control standard microorganisms, following the manufacturer's instructions, and perform the testing prior to unknown sample diagnostic testing.

Special care should be taken with media that is used in environmental monitoring studies. It is practice to pre-ineubate prepared paekaged envirenmental monitoring media the relevant test temperature(s) in sealed containers Or plastic sleeves and to-imspect them for any nomsterile units. This will prevent extraneous contamination from be ing earrie int controlled environments and will prevent false pesitive results. Media used for environmental monitoring of critical areas should preferably be double-wrapped and terminally sterilized. If terminal sterilization is not performed, media should be subjected to pre-incubation and $100 \%$ inspection prior to use within a critical area. This will prevent extraneous contamination from being carried into controlled environments and will prevent false-positive results. A raised agar level for surface contact plates should be verified.

## MAINTENANCE OF MICROBIOLOGICAL CULTURES

Biological specimens can be the most delicate standards to handle because their viability and characteristics are dependent on adequate handling and storage. Refereneent fures from national eulture eollections sueh as the Ameriean Type Culture Collection (ATCC) should be han dled and stored with eare. Standardizing the handling and storage of cultures by the user laboratory should be done in a way that will minimize the opportunity for contamination or alteration of growth characteristics. Them-
tures are routinely used for quality control of media and for microbiologieal assays, in both industrial and clinieal mierobiology laboratories, and thus require consistent, aeet rate, and reproducible handling practices. The careful and consistent treatment of stock cultures is critically important to the consistency of microbiological test results. Cultures for use in compendial tests should be acquired from a national culture collection. They Gultures can be acquired frozen, freeze-dried, on slants, or in ready-to-use forms. Confirmation of the identity of standard eulture collection should be performed prior to using the culture in quality entrol testing. Confirmation of the purity of the culture and the identity of the culture should be performed prior to its use in quality control testing. Ready-to-use cultures may require confirmation of purity, identity, and inoculum size. This confirmation of identity for commonly used laboratory strains should ideally be done at the level of genotypic analysis (i.e., DNA fingerprinting, 16 S rRNA gene sequencing or PCR analysis using suitably validated probes).

Preparation and resuscitation of cultures should follow the instructions of the stepplier. The supplier may have to be contacted to determine how it performs quantitation and identifieation, so that the user laboratory can follow the predtres. supplier or a validated, established method. The "Seed-Lot" technique is recommended for storage of stock cultures.

Stock cultures can be matle by transferring a suspension of the original or reference eultures to cryoprotective medium in vials and freezing unted suspensions The original sample from the national culture collection is resuscitated and grown in an appropriate medium. Aliquots of this stock culture (the first transfer or passage) are suspended in cryoprotective medium, transferred to vials and frozen at $-30^{\circ}$ or below, until use. If stored at $-70^{\circ}$, or in lyophilized form,
strains may be kept indefinitely. These frozen stocks can then be used to inoculate monthly or weekly working cultures. Đe Once opened, do not refreeze unused cell suspensions after culturing a working suspension becuse there is an inered risk flos viability suspension. The unused portion should be discarded to minimize the risk of loss of viability and contamination of the stock.

The number of transfers of working control cultures should be tracked to prevent excessive subculturing that increases the risk of phenotypic alteration. The of establishing "Seed Cultures" is recommended, which should be ne mere than five passages from the original stock obtained from the oulture ollection. One passage is defined as the transfer of organisms from a viable culture to fresh medium with growth of the microorganisms. Any form of subculturing is considered to be a transfer/passage.

## MAINTENANCE OF LABORATORY EQUIPMENT

Most equipment (incubators, water baths, autoclaves, etc.) is subject to standard validation practices of incoming qualification, operational qualification, and performance qualification. Additionally, periodic calibration (generally annually) is commonly required. New equipment, critical to the operation of the laboratory, should be qualified according to a protocol approved by the quality assurance unit (QAU).

Equipment Instruments ( pH meters, spectrophotometers, etc.) used in a microbiology laboratory should be calibrated on a regular schedule and tested to verify performance on a routine basis. The frequency of calibration and performance verification will vary based on the type of equipment instrument and the importance of that equipment to the generation of data in the laboratory.

## LABORATORY LAYOUT AND OPERATIONS

Laboratory layout and design should carefully consider the requirements of good microbiological practices and laboratory safety. It is essential that cross-contamination of microbial cultures be minimized to the greatest extent possible, and it is also important that microbiological samples be handled in an environment that makes contamination highly unlikely. The reliability of mierebial laberatery oper-ations-an be enhanced by proper layout; and good separaもion of activities can enhance the reliability of mierobiologieal laboratory operations.

In general, a laboratory should be divided into clean or aseptic areas and live culture areas. These sections of the laboratory should be separated and sheuld have separate ens. Areas in which environmental or sterile product samples are handled and incubated should be maintained completely free of live cultures, if possible. If complete separation of live and clean culture zones cannot be accomplished, then other eountermeasures barriers and aseptic practices should be employed to reduce the likelihood of accidental contamination. These ers include protective clothing, sanitization and disinfection procedures, and biological safety cabinets designated for clean or aseptic operations only. Procedures for handling spills or mishaps with live cultures should be in place and all relevant technical personnel should be trained regarding these methods.

Some samples will demonstrate microbial growth and require further laboratory works the nature of analysis to identify the contaminants. When growth is detected, the sample should be taken from the clean section of the laboratory to the live culture section without undue delay. Subculturing, staining, microbial identification, or other investigational operations should be undertaken in the live culture section of the laboratory. If possible, any
sample found to contain growing colonies should not be opened in the clean zone of the laboratory. Careful segregation of contaminated samples and materials will reduce false-positive results.

Staff engaged in sampling activities should not enter or work in the live culture handling section of a laboratory unless special precautions are taken including protective clothing, gloves, and careful sanitization of hands upon exiting. Ideally, staff assigned to sampling activities, particularly those in support of aseptic processing, should not work in the vicinity of live culture laboratory operations. Also, all microbiological samples should be taken using aseptic techniques including those taken in support of nonsterile products. If possible, all microbiological samples should be taken under full aseptic conditions in specialized sampling areas.

It is important to consider that microbial contamination of samples, which lead to false-positive results, is always possible unless careful aseptic precautions are taken. Facilities should be designed so that raw material and excipient sampling can be done under controlled conditions, including proper gowning and sterilized sampling equipment. It may not always be possible to sample utility systems, such as water systems, under full aseptic conditions; however, it should be noted that when samples are not taken aseptically, their reliability is inevitably compromised.

Environmental sampling methods should require minimal aseptic handling in loading and unloading sampling instruments. Whenever possible, sampling equipment should be loaded with its microbiological recovery media in the environment that is to be sampled.

All testing in laboratories used for critical testing procedures, such as sterility testing of final dosage forms, bulk product, seed cultures for biological production, or cell cul-
tures used in biological production should be performed under fullape controlled conditions. Isolator technology is also appropriate for critical, sterile microbiological testing. Isolators have been shown to have lower levels of environmental contamination than manned clean rooms, and therefore, are generally less likely to produce false-positive results. The general information chapter, Sterility Test ing Validation fisolator Sistems- $\langle 1208$ ), provides gener al guidane on the validation of isolators for sterility testing. Proper validation of isolators is critical both to ensure environmental integrity and to prevent the possibility of falsenegative results as a result of chemical disinfection of materials brought into or used within isolators (see Sterility Testing—Validation of Isolator Systems $\langle 1208\rangle$ ).

## TRAINING OF PERSONNEL

Each person engaged in all phases of pharmaceutical manufacture should have the education, training, and experience to do their job. Mierobiologists in the pharmaceutical taboratory should have sufficient academic training in mi erobiology or allied life seience and should be adequately trained in laberatory procedures and testing doeumentation eonducted in the mierobiology laboratory. The demands of microbiological testing require that the core educational background of the staff, supervisors, and managers be in microbiology or a closely related biological science. They should be assigned responsibilities in keeping with their level of skill and experience.

A coherent system of operating procedures is necessary to run the microbiology laboratory. These procedures serve two purposes in a training program. Firstly, these SOPs describe the methodology that the microbiologist will follow to obtain accurate and reproducible results and so serve as the basis for training. Secondly, by tracking the procedures in which a particular microbiologist has demonstrated pro-
ficiency, the procedure number or title also serves to identify what training the microbiologist has received specific to his or her job function.

Training curricula should be established for each laboratory staff member specific for their job function. They should not independently conduct a microbial test until they are qualified to run the test. Training records should be current, documenting the microbiologist's training in the proper revision to the particular SOP.

Periodic performance assessment is a wise investment in data quality. This performance testing should provide evidence of competency in core activities of the microbiology laboratory such as hygiene, plating, aseptic technique, documentation, and others as suggested by the microbiologist's job function.

Microbiologists with supervisory or managerial responsibilities should have appropriate education and inhouse training in supervisory skills, laboratory safety, scheduling, laberatory investigations, technical report writing, phamaceutical products, and in mantifacturing relevant SOPs and other critical aspects of the company's processes as suggested in their role of directing a laboratory function.

The demands of mierobiologieal testing require that the evre educational background of the-staff, supervisors, and managers be in mierobiolegy or a clesely related biologicat seience.

## DOCUMENTATION

Documentation should be sufficient to demonstrate that the testing was performed in a laboratory and by methods that were under control. This includes but is not limited to documentation of the following:

- Microbiologist training and verification of proficiency
- Equipment validation, calibration, and maintenance
- Equipment performance during test (e.g., 24-hour /7day chart recorders)
- Media preparation, sterility checks, and growth-promotion eapability and selectivity capabilities
- Media inventory and control testing
- Critical components of test conducted as specified by a procedure
- Data and calculations verified
- Reports reviewed by QAU or a qualified responsible manager
- Investigation of of specification results data deviations (if needed).


## MAINTENANCE OF LABORATORY RECORDS

Proper recording of data and studies is critical to the success of the microbiology laboratory. The over-riding principle is that the test should be performed as written in the SOP, the SOP should be written to reflect how the test is actually performed, and the laboratory notebook should provide a record of all critical details needed to confirm the integrity of the data. At a minimum, the laboratory write-up should include the following:

- Date
- Material tested
- Microbiologist's name
- Procedure number
- Document test results
- Deviations (if any)
- Documented parameters (equipment used, microbial stock cultures used, media lots used)
- Management/Second review signature

Every critical piece of equipment should be noted in the write-up, and all should be on a calibration schedule documented by SOP and maintenance records. Where appropriate, logbooks or forms should be available and supportive of
the laboratory notebook records. Equipment temperatures (waterbaths, incubators, autoclaves) should be recorded and traceable.

Training currieula should be established for each labora fory staff member specific for their job fanction. They should not independently conduet a mierobial test until they are qualified to rum the test. Training records should be current, doeumenting the mierobiologist's training in the proper revision to the partieular SOP. This The governing SOP and revision should be clearly noted in the write-up. Changes in the data should be crossed off with a single line and initialed. Original data should not be erased or covered over.

Test results should include the original plate counts, allowing a reviewer to recreate the calculations used to derive the final test results. Methods for data analysis should be detailed in cited SOPs.

All laboratory records should be archived and protected against catastrophic loss. A formal record retention and retrieval program should be in place.

## INTERPRETATION OF ASSAY RESULTS

Analytical microbiological assay results can be difficult to interpret for several important reasons: (1) Microorganisms are both ubiquitous in nature and common environmental contaminants; particularly organisms associated with humans predominate in many types of microbiological analysis; (2) The analyst has the potential to introduce contaminating organisms during sample handling or processing in the laboratory; (3) Microorganisms may not be homogeneously distributed within a sample or an environment; and
(4) Growth and reeovery based mierobiologieat Microbiological assays are subject to considerable variability of out-
come. as ypieal variability may be on the order of $\pm 0.5$ togit. Therefore, minor differences from an expected outcome may not be significant.

Because of these characteristics of microbiological analysis, laboratory studies should be conducted with the utmost care to avoid exogenous contamination as previously discussed in this chapter. Equally important, results must be interpreted from a broad microbiological perspective considering not only the nature of the putative contaminant, but the likelihood of that organism(s) surviving in the pharmaceutical ingredient, excipient, or environment under test. In addition, the growth characteristics of the microorganism should be considered (especially in questions of the growth of filimentous fungi in liquid media).

When results are observed that do not conform to a compendium monograph or another established quantitative target, an investigation into the finding is required. There are generally two distinct reasons for the observation of microbial contamination that does not comply with a target or requirement: There may be either a laboratory error or laboratory environmental conditions that produced an invalid result, or the product contains a level of contamination or specific types of contaminants outside established levels or limits. In either case, laboratory management and, in most cases, general management should be notified immediately.

A full and comprehensive evaluation of the situation surrounding the result should be undertaken. All microbiological conditions or factors that could bring about the observed condition should be fully considered, including the magnitude of the excursion compared to established limits or levels. It is critical to know if the finding is statistically significant in light of assay variability.

The laboratory environment, the protective conditions in place for sampling, historical findings concerning the material under test, and the nature of the material particularly with regard to microbial survival or proliferation in contact with the material should be considered in the investigation.
Eaboratories should as a standard practice retain preparafions, difutions, and any other assay related materials or artieles that might be usefuliminvestigating a test outeome. In addition, interviews with the laboratory analyst(s) may provide information regarding the actual conduct of the assay that can be valuable in determining the reliability of the result and in determining an appropriate course of action. If laboratory operations are identified as the cause of the nonconforming test outcome, then a corrective action plan should be developed to address the problem(s). Following the approval and implementation of the corrective action plan, the situation should be carefully monitored and the adequacy of the corrective action determined.

If assay results are invalidated based upon the discovery of an attributable error, this action must be documented. Laboratories also should have approved procedures for confirmatory testing (retesting), and if necessary, resampling where specific regulatory or compendial guidance do not govern the conduct of an assay investigation. Mieraby taberatery investigations frequently do not reveal the sotree of contamination because miereorganisms are ubiquiteus. Pharmacopeial and regulatory ageney guidelines present instructions for handling mierobiological result failures for some tests, particularly for sterility and bacterial endotoxin testing (see Sterility Tests $\langle 77$ ) and Bueterial Endetoxin Fests (85) ). These instructions should be followed in addition to the laboratory investigation.u2S (USP28)

## Briefing

〈1136〉 Packaging—Unit of Use, page 1215 of $P F$ 29(4) [JulyAug. 2003]. This proposed general information chapter, which previously appeared in the In-Process Revision section, has been modified based on comments received at the PSD Open Conference held October 12-15, 2003, in Washington, DC. Changes were made to the definitions to make the chapter consistent with the definitions in the General Notices. Other changes were made to clarify the intent of the chapter.
(PSD: C. Okeke) RTS-40548-6; 40704-1; 41220-1

## Add the following:

## ■ $\langle 1136\rangle$ PACKAGING—UNIT OF USE

## INTROPUCTION

This chapter is intended to provide guidance in the applieation of unit of use packaging. Unit-of use packaging, when provided by the manufacturer, offers some of the following attractive advantages. (1) The ability to dispense a desage form to a patient in the manufacturer's original container ensures that the-suitability of the container has been established based on the manufacturer's stability studies. (2) Gounting and repackaging of dosage units in the pharmacy is eliminated, thereby reducing the pessibility of human erfor. (3) The pharmacist is able to affix the label for the patient onto the unit-of use package and is free to use the manufacturer's expiration date as the beyond use date (provided that the date is equivalent to one year or less, and that other factors were-considered that might cause a-different beyond use date to be necessary). (4) The number of dosage units in a single unit of use package may be determined on a ease by case basis.

## DEFINHTHA

GONTAINER CLOSURE SYSTEM-is equivalent to a packas ing system. It is the sum of the packaging components that, together, contain and protect the dosage form. UNTI OF USE PACKAGE-is a container elosure-system that is designed to hold a specifie quantity of a drug product for a specific use and that is to be dispensed to a patient without any modification exeept for the addition of apprepriate la beling (see General Notices and Requirements). The pack aging of a unit of use system may be a multiple unit eontainer or a unit dose single-unit container. A unit of use may be a drug product in either a liquid or solid dosage form (see also the FDA Guidance for Industry on Containex Closure Systems for Packaging Human Drags and Biolog ies). [NOTE-The terms unit-of use package and a unit-ofuse container may be used interchangeably.] PEBLISTERING is the process of removing medication from a blister type container.

MMMEDHATE CONTAINER-is acontainer that is in direct contact with the article or preparation.

MATERIALSOF CONSTRUCTION-include substances used to manufacture-or package components-such as glass, plasties Fincluding high-density polyethylene-(HDPE), low density polyethylene (LDPE), and polypropylene (PP)], resins, and other materials as listed in the general test chapter Con tainers $(664$ ) and in the FDA Guidance for Industry on Comainer Closure Syistems for Packaging Haman Drugs and Biologics.

## TYPE OF-CONTAHNER FOR UNHT OF-USE

## Single-Unit Container

A single-mit container is a minit doseor asingle-doseconminer intended for either oral or parenteral use. See-Generat Notices and Requirements.

## UNHT DOSE CONTAINER

A single unit container or a single dose container, unit dose container, intended for oral use, is a container that has been packaged in the desage regime for the-course-of the therapy appropriate for the drug that is to be adminis tered.

## SINGLE-DOSE CONTAINER

A single-dose container, intended for parenteral use, is a eontainer that has been packaged in the dosage regime for the course of the therapy appropriate-for the drug that is to be administered.

## Multiple-Unit Container

A multiple unit or a multiple dose container is prepack aged in bettles or containers for injections of the drug in appropriate quantities. A multiple-dose container is a multipleunit container for articles intended for parenteral administra-tien-only.

## MATERLALS-OF-CONSTRUCTHON

## Unit-of-Use-Container

The Peisen Prevention Packaging Act (PPPA) of 1970 att therizes the use of special packaging child-resistant and senior friendly packaging. Child resistant packaging protects children frem serious injury or illness from ingesting or handling hazardous household products ineluding drugs. Unit of use containers are required to be child resistant. Unit of use containers in child resistant single unit containers include-supported blisters, sueh as-separate, peet,
push, and tear noteh; and enelosed or in-card blisters, sueh as pull tabs, slide packs, ete. Unit-of use containers in mat tiple unit containers include glass and plastic containers.

## GLASS

The packaging material equivalent to the immediatecentainer that is glass meets the glass test requirements Any glass packaging material used in the immediate container should meet the glass test requirements for Limits for Glass Fypes and Chemical Resistance Glass-Comtainers: Pow dered Glass, Weter Attack at 121, and Arsenic under the general test chapter Containers- $\langle 664$ )=

## PLASTIE

The packaging material equivalent to the immediatecen tainer that is plastic meets the test requirements Any plastic packaging material used in the immediate container should meet the plastic test requirements for Plasties in the generat test chapters-Containers $\langle 664$ ) and Containeris Permeafien $\langle 674\rangle$. Depending on the type of plastic packaging mat terial used, the packaging material meets the requirements for Biologieal Tests Plasties and Other Polymers, Physierehemical Tests Plasties, Polyethylene Containers, Poly ethylene Terephthalate/Polyethylene Terephthatate $G$, and Polypropylene Containers.

The test for meisture vaper transmission may be carried out as described in the general test chapter Containers-Permeation-(674) for multiple unit and unit dose containers.

## PACKAGING-CLOSURE TYPES

Reclosables and nonreclosables may be used for both sol id and liquid dosage forms. Both must be packaged in compliance with the 16 CFR 1700.15-standards.

## Reclosables

Reclesables are containers with suitable clesures that may incorperate tamper evidence and child resistance capabilities. Reclosables may be used for glass or plastic containers.


#### Abstract

\section*{Nonreclosables}

Nenreclosables are containers with clesures that are nen-reclosable-such as blisters, sachets, strips, and other singleunit containers. Nenreclosables may include packs such as celd formed feil blisters, feil strip packs, and PVC/Aclar eembining multilayer materiats that are therme-formed or eold-formed foil blisters (see Packaging Practie Re packaging a Single Solid Oral Drag Product Into a Unit Pose Container $\langle 1446$ ). Nenreclesables may be child resis ant depending on the intended use and place of use. Heuseheld nenreelesables are subject to the PPPA as definedin-16 ERF 1700.14. However, because of some unit dose designs, not all unit dose packages comply with the PPPA.

\section*{士ABELING}

The unit of use entainers are labeled as such to include manufacturer's lot numbers, aceuracy or bar codes, andex piration dates expiration dates, and in some instances, the manufacturer's lot numbers and bar codes as provided in the Labeling section of the-General Notices and Require ments under Preservation, Packaging, Storage, and Label ing. Some of the advantages of having bar codes on the label include reduced medieationerrors, improved inventery con-


frol, and improved aceess to medieation identity. The labeling covers information placed in the pack by the manufac turer and the label added at the dispensing stage by the pharmacist. container by the manufacturer (see General Nofices and Requirenents). Acceptable labeling can range from the full labeling for multiple-unit containers to an abbreviated labeling when the container is too small to include all the text. Full labeling may atso be provided on the carton if it is net present on the immediate container.

## REPACKAGING AND-REPROCESSING

Unit-of use containers are reprocessed or repackaged as instructed by the manufacturer or as directed in the generat test chapter Containers $\langle 664$ ) or in the general information ehapter Packaging Practice Repackaging a Single Solid Oral Drug Product Into a Unit Dose Container- $\langle 1146\rangle$.-A unit of use package may not be reprocessed by a pharmacist ence it has been deblistered from a unit dose container (see General Notices and Requirements for application of the appropriate beyond use date for a multiple unit or unit dose eontainer). However, under eurrent Good Manufacturing Practices (eGMPs) and tight quality controls, the manufactarer or contract repackager may repackage and reprocess unit of use containers.

## RESPӨNS円ВЩНY OF THE DЏSPENSER

The unit of use packageshall contain such label informat tion as the following:

## Eabeling

The labeling on a unit of use container also ineludes a lat beladed at the dispensing stage by the pharmacist. Prior to dispensing the unit of use package, the-dispenser shall add tabel(s) that provide the following information:
(1) the name of the patient;
(2) the name and strength, the directions for use as preseribed by a doctor or health care provider, and the name of the preseriber, ant
(3) any storage instruction, appropriate package insert, length of days of use, beyond use date, and other infor mation as deemed appropriate by federal and state laws. In the pharmacy setting, pharmacists are encouraged to use bar codes, in conjunction with computerized prescription orders, to conflrm that the right drug is being dispensed to the right patient. Bar coding would minimize errors and ereate-opportanity for medieation fraceability and accountability.

## Information-to-Patient

Patients must be given information that applies to the speeifie brand of prodtret being dispensed.

## INFORMATION FROM MANUFACTURERS

The manufacturer should provide appropriate product de velopment or stability data information that can be used to determine appropriate labeling, storage, and shipping statements that will properly inform patients and practitioners. The manufacturer may make other assurances based on product information and data on packaging and distribution arfangements. In the event that a product is not to be repackaged, the manufacturer may state so-in the labeling. The manufacturer also includes labeling and information suitable for optimal handling by the practitioner and the patient. The labeling and information should be bar coded to eliminate medication errer and promete medieation tracenbility.

## QUАЦНТ CONTROL OF PACKAGHNG SYSTEM

The packaging system shall meet the general considera-
tions for system suitability, pretection, safety, and perfor
manee characteristies as deseribed in the FDA Guidtace
for Industry on Container Closure Systems for Packaging
Human Drugs and Biologies, in the general test chapter
Containers- $\langle 664$, and in the general information chapter
Packaging Practice Repackaging a Single Solid Orat
Prug Product Into a Unit Dose Container-(1146):

## INTRODUCTION

This chapter provides guidance in the use and application of unit-of-use packaging and is intended for use by drug manufacturers, repackagers, and pharmacists. Suppliers of packages and packaging components may find the information useful, as well.

The General Notices defines a unit-of-use container as one that contains a specific quantity of a drug product that is intended to be dispensed as such without further modification except for the addition of appropriate labeling.

Unit-of-use packaging, when provided by the manufacturer, offers some of the following attractive advantages. (1) The ability to dispense a dosage form to a patient in the manufacturer's original container, a practice that recognizes that the suitability of the container has been established on the basis of the manufacturer's stability studies. (2) The counting and repackaging of dosage units in the pharmacy is eliminated, thereby reducing the possibility of human error. (3) The pharmacist is able to affix the label for the patient onto the unit-of-use package and is free to use the manufacturer's expiration date as the beyond-use date. (4) The number of dosage units in a single unit-of-use package may be determined on a case-by-case basis. (5) Patient com-
pliance is improved. (6) The unit-of use package can protect against countertfeiting because traceability of product is ensured through bar coding techniques and NDC numbers.

Unit-of-use packaging, when provided by repackagers, offers the same attractive advantages as those offered by manufacturer. However, unit-of-use repackagers should conform to all requirements as presented in Good Repackaging Practices $\langle 1178\rangle$. There are a number of reasons as to why repackagers produce unit-of-use packaging; for example, (1) requests from institutions, (2) better inventory control, (3) reduced dispensing times, and (4) variations in some drug therapies.

The packaging of a unit-of-use system may be a multiple container or a single-unit container. A unit-of-use system may contain a drug product in a liquid, semi-solid, or solid dosage form (see also the FDA Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics). [NOTE-The terms unit-of-use package and unit-of-use container may be used interchangeably.]

The Poison Prevention Packaging Act (PPPA) of 1970 requires in certain cases the use of special packaging-child-resistant and senior-friendly. Child-resistant packaging protects children from serious injury or illness resulting from ingesting or handling hazardous products including drugs.

Since drugs packaged in unit-of-use packaging are intended to be dispensed to the consumer without repackaging by the pharmacist, the manufacturer or repackager is responsible for the special packaging of PPPA-regulated substances in unit-of-use containers (16 CFR 1701.1).

## TYPES OF CONTAINERS FOR UNIT-OF-USE

Unit-of-use containers are required to be child-resistant if they are intended to be dispensed directly to the patient pursuant to a prescription. Unit-of-use packaging intended for
institutional or hospital use may or may not be required to be child-resistant. Unit-of-use containers that are child-resistant single-unit containers include supported blisters, such as separate, peel, push, and tear notch and enclosed or incard blisters, such as pull tabs and slide packs. Blister packaging is discussed in the general chapter Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container $\langle 1146\rangle$. Unit-of-use containers that are multiple-unit containers include glass and plastic containers.

## Single-Unit Container

A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single-dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show any evidence of tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity, and/or strength, name of the manufacturer, lot number, and expiration date of the article.

## Unit-Dose Container

A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, directly from the container.

## Single-Dose Container

A single-dose container is a single-unit container for articles intended for parenteral administration only. It is labeled as such.

## Multiple-Unit Container

A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

## PACKAGING FABRICATION MATERIALS

Packaging fabrication materials include substances used to manufacture packaging containers such as glass, plastics (including high-density polyethylene (HDPE), low-density polyethylene (LDPE), polyethylene terephthalate, polyethylene terephthalate G and polypropylene (PP), other resins, and other materials as listed in the general test chapter Containers $\langle 661\rangle$ and in the FDA Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics.

## Glass

Any glass packaging material used in the immediate container should meet the glass test requirements for Limits for Glass Types and Chemical Resistance-Glass Containers: Powdered Glass, Water Attack at $121^{\circ}$, and Arsenic under the general test chapter Containers $\langle 661\rangle$.

## Plastic

Any plastic packaging material used in the immediate container should meet the plastic test requirements for Plastics in the general test chapters Containers $\langle 661\rangle$ and Con-tainers-Permeation $\langle 671\rangle$. Depending on the type of plastic packaging material used, the packaging material meets the requirements for Biological Tests-Plastics and Other Polymers, Physicochemical Tests-Plastics, Polyethylene Containers, Polyethylene Terephthalate/Polyethylene Terephthalate G, and Polypropylene Containers.

The test for moisture vapor transmission may be carried out as described in the general test chapter ContainersPermeation $\langle 671\rangle$ for multiple-unit and unit-dose containers.

## PACKAGING CLOSURE TYPES

Reclosables and nonreclosables may be used for solid, semi-solid, and liquid dosage forms. Both must be packaged in compliance with the 16 CFR 1700.15 standards.

## Reclosables

Reclosables are containers with suitable closures that may incorporate tamper evidence and child-resistance capabilities. Reclosables may be used for glass or plastic containers.

## Nonreclosables

Nonreclosables are containers with closures that are nonreclosable such as blisters, sachets, strips, and other singleunit containers. Nonreclosables may include packs such as cold-formed foil blisters, foil strip packs, and PVC/Aclar combining multilayer materials that are thermo-formed or cold-formed foil blisters (see Packaging Practice-Repackaging a Single Solid Oral Drug Product Into a UnitDose Container $\langle 1146\rangle$ ). Nonreclosables may be child resistant depending on the intended use and place of use. Household nonreclosables are subject to the PPPA as defined in 16 CFR 1700.14. However, because of some unit-dose designs, not all unit-dose packages comply with the PPPA.

## LABELING

The unit-of-use containers are labeled to include expiration dates, the manufacturer's lot number, the NDC designation, and bar codes as provided in the Labeling section of the General Notices and Requirements under Preservation, Packaging, Storage, and Labeling and in Good Repackaging Practices $\langle 1178\rangle$. Some of the advantages of having bar codes on the label include reduced medication errors, improved inventory control, and improved access to medication identity. The labeling covers information placed in the container by the manufacturer (see General Notices and Requirements). Acceptable labeling can range from the full labeling as for multiple-unit containers to an abbreviated labeling when the container is too small to include all the text. Full labeling may also be provided on the carton if it is not present on the immediate container.

## REPACKAGING AND REPROCESSING

Unit-of-use containers are reprocessed or repackaged as instructed by the manufacturer or as directed in the general test chapter Containers $\langle 661\rangle$ or in the general information chapter Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container $\langle 1146\rangle$. A unit-of-use package that is a blister package may not be reprocessed by a pharmacist once it has been deblistered from a unit-dose container (see General Notices and Requirements for application of the appropriate beyond-use date for a multiple-unit or unit-dose container). Deblistering is the process of removing medication from a blister-type container. However, under current Good Manufacturing Practices (cGMPs) and tight quality controls, the manufacturer or contract repackager may repackage and reprocess unit-of-use containers.

## INFORMATION FROM MANUFACTURERS

The manufacturer should provide appropriate stability information that can be used to determine appropriate labeling, storage, and shipping statements that will properly inform patients and practitioners. The manufacturer may make other assurances based on product information on packaging and distribution arrangements. In the event that a product is not to be repackaged, the manufacturer may state so in the labeling. The manufacturer also includes labeling and information suitable for optimal handling by the practitioner and the patient. The labeling and information should be bar coded to eliminate medication error and promote medication traceability.

## RESPONSIBILITY OF THE DISPENSER

## Labeling

The labeling on a unit-of-use container also includes a label added at the dispensing stage by the pharmacist. Prior to dispensing the unit-of-use package, the dispenser shall add label(s) that provide the following information:
(1) the name of the patient;
(2) the name and strength, the directions for use as prescribed by a doctor or health-care provider, and the name of the prescriber; and
(3) any storage instruction, beyond-use date, and other information as deemed appropriate by federal and state laws.
In the pharmacy setting, pharmacists are encouraged to use bar codes, in conjunction with computerized prescription orders, to confirm that the right drug is being dispensed to the right patient. Bar coding would minimize errors and create opportunity for medication traceability and accountability.

## Information to Patient

Patients must be given information that applies to the specific prescription being dispensed.

## QUALITY CONTROL OF PACKAGING SYSTEM

The packaging system shall meet the general considerations for system suitability, protection, safety, and performance characteristics as described in the FDA Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics, in the general test chapters Containers $\langle 661\rangle$ and Containers-Permeation $\langle 671\rangle$, and in the general information chapter Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container $\langle 1146\rangle \cdot$.2S (USP28)

## Briefing

<1211〉Sterilization and Sterility Assurance of Compendial Articles, USP 27 page 2616. This proposed revision provides numerous updates to the chapter. Lethality value $\left(F_{0}\right)$ is discussed. New taxonomic terms for biological indicator species are used. Differences between biological indicator usage for moist-heat versus gas sterilization are discussed. The sections covering various modes of sterilization have been revised and updated. A section on vapor phase hydrogen peroxide sterilization has been added. The previous discussion pertaining to Stage 2 of sterilization testing has been deleted to reflect the currently official chapter Sterility Tests $\langle 71\rangle$.
(AMB: D. Porter) RTS-41616-1

## Change to read:

This informational chapter provides a general description of the concepts and principles involved in the quality control of articles that must be sterile. Any modifications or variations in sterility test procedures from those described under Sterility Tests $\langle 71\rangle$ should be validated in the context of the entire sterility assurance program and are not intended to be alternative methods to those described in that chapter.

Within the strictest definition of sterility, a specimen would be deemed sterile only when there is complete absence of viable mieroorgenisms from it.
-if it could be demonstrated that it was completely free of
viable microbial contamination. ${ }^{2 S}$ (USP28)
However, this absolute definition cannot currently be applied to an entire lot of finished
-aseptically produced 2S (USP28)
compendial articles because of limitations in testing. Absolute sterility cannot be practically demonstrated tion of erery finished article.

- in any sterility test because of the destructive nature of the test and the limited sensitivity of current methods. ${ }^{2 S}$ (USP28) The sterility of a lot purported to be sterile is therefore defined in probabilistic terms, where the likeliherninn artiele is neeptably remote.
-and provided the likelihood of contamination is sufficiently remote, the product is considered microbiologically safe. ${ }^{\text {m2S (USP28) }}$
Such a state of sterility assurance can be established only through the use of adequate sterilization cycles and subsequent aseptic proeescing, if any, under appropriate current goed manufacturing prac tice, and not by reliance solely on sterility testing.
- for final dosage forms or sterilization of components followed by aseptic processing, if any, under appropriate current good manufacturing practice, and not by reliance solely on sterility testing. ${ }^{\text {2S }}$ (USP28)
The basic principles for validation and certification of a sterilizing process are enumerated as follows:
(1) Establish that the preeess equipment has eapability of operat ing within the required parameters.
-Establish that the process equipment was properly installed, supplied with appropriate utilities, and has the capability of operating within the required parameters (Installation Qualification)..n2S (USP28)
(2) Demonstrate that the critical control equipment and instrumentation are capable of operating within the prescribed parameters for the process equipment
-(Operation Qualification). $\boldsymbol{\bullet}^{2 S}$ (USP28)
(3) Perform replicate cycles representing the required operational range of the equipment and employing actual or simulated product. Demonstrate that the processes have been carried out within the prescribed protocol limits and finally that the probability of microbial survival in the replicate processes completed is not greater than the prescribed limits
-(Performance Qualification). $\mathbf{\bullet 2 S}^{\text {(USP28) }}$
(4) Monitor the validated process during routine operation. Periodically as needed, requalify and recertify the equipment.
(5) Complete the protocols, and document steps (1) through (4) above.

The principles and implementation of a program to validate an aseptic processing procedure are simitar to the validation of a ster ilization process. In aseptic processing, the compenents of the finat dosage form are sterilized separately and the finished article is as sembled in an aseptic manner.
-parallel in some respects to the validation of a sterilization process. In aseptic processing, the components of the final dosage form (e.g., ampuls, vials, stoppers, and syringes) are sterilized separately and the finished article is assembled in an aseptic manner in an appropriately controlled environment.■2S (USP28)

Proper validation of the sterilization process or the aseptic process requires a high level of knowledge of the field of sterilization, andeleanroom technology.
-clean room design and operation, and aseptic manufacturing practice and technology. ${ }^{2 S}$ (USP28)
In order to comply with currently acceptable and achievable limits in sterilization parameters, it is necessary to employ appropriate instrumentation and equipment to control the critical parameters such as temperature, and time, humidity, and sterilizing sas eoneentration, or absorbed radiation.
-pressure and time (moist-heat sterilization), relative humidity, temperature and sterilizing gas concentration (gaseous sterilization), or absorbed radiation (irradiation sterilization). $\quad$ 2S (USP28)
An important aspect of the validation program in many sterilization procedures involves the mployment
$\mathbf{- s e l e c t i o n ~}$ and use ${ }_{\text {2S }}$ (USP28)
of biological indicators (see Biological Indicators for Sterilization $\langle 1035\rangle$ ). The validated and certified
$■_{\text {sterilization }}{ }_{\text {2S (USP28) }}$
process should be revalidated periodieally; however, the revalidat tion program need not neeessarily be as extensive as the originat program.

- evaluated annually to ensure that it is performing as validated; however, this so-called revalidation program need not be as extensive as the original program. ${ }^{2 S}$ (USP28)
A typical validation program, as outlined below, is one designed for the steam autoclave, but the principles are applicable to the other sterilization procedures discussed in this informational chapter. The program comprises several stages:
The Installation Qualification stag is in that eontrols and other instrumentan are properly designed and ealibrated.
-(IQ) stage is intended to establish that the equipment is correctly installed and serviced by appropriate utilities and controls and that other instrumentation are properly designed and calibrated. ${ }^{2 S}$ (USP28)
Documentation should be on file demonstrating the quality of the required utilities such as steam,
$\boldsymbol{■}_{\text {Vacuum, }}$ п2S (USP28)
water, and air. The Operational Qualification


## 

stage is intended to confirm that the empty chamber functions within the parameters of temperature at all of the key chamber locations prescribed in the protocol. It is usually appropriate to develop heat profile records, i.e., simultaneous temperatures in the chamber employing multiple temperature-sensing devices. A typical acceptable range of temperature in the empty chamber is $\pm 1^{\circ}$ when the cham ber temperattre is not less than $121^{\circ}$.

■at a temperature target appropriate to the process. ■2S (USP28) The Confirmatory stage of the validation program,

- or Performance Qualification (PQ) stage, $\mathbf{m}_{2}$ (USP28) is the actual sterilization of materials or articles

■using loading patterns to be employed.■2S (USP28) This determination requires the employment of temperature-sensing

■ and recording $_{\square 2 S}$ (USP28)
devices inserted into samples of the articles as ell as either samples of the articles to which appropriate concentrations of suitable test miervorganisms have been added, or separate biologieal indieators in operationally fully loaded autoclave ennfigurations. The effectiveness of he delivery or penetration into the actual articles and the time of the expesture are the wo main factors that deter mine the lethality of the sterilization process. The final stage of the validation program requires the documentation of the suppert ing data developed-in evecuting the program.
-to assess temperature penetration. The process parameters including heat-up and cool-down data can be used to select an appropriate exposure time for the required process lethality.

Once sterilization parameters of temperature and time are established, the physically measured lethality is assessed with biological indicators. The user should have a scientific rationale for the selection of a biological indicator organism.
The biological indicator system may consist of spores inoculated directly into or onto an article or a packaged biological indicator acquired from a vendor. A variety of strategies can be employed for sterilization cycle evaluation including bioburden based or overkill approaches (see Biological Indicators for Sterilization $\langle 1035\rangle$ and PDA Technical Monograph \#1 for a more detailed treatment of this subject). $\begin{aligned} & \text { 2S (USP28) }\end{aligned}$

It is generally accepted that terminally sterilized injectable articles or critical devices purporting to be sterile, when processed in the autoclave, attain a $10^{-6}$ microbial survivor probability, i.e., assurance of less than one chance in one million that viable microorganisms are present in the sterilized article or dosage form. With
heat-stable articles, the approach often is to considerably exceed the critieal time necessary to achieve the $10^{-4}$ mierobial surviver probability (overkill).
-an overkill approach is frequently chosen. (Overkill is defined in moist-heat sterilization as a process that delivers a
lethality value or $F_{0}$ of $\geq 12$ minutes.) $\mathbf{m}_{\text {2S }}$ (USP28)
However, with an article where extensive heat exposure may have a damaging effect
(i.e., loss of potency, physical attributes, or packaging integrity), $\mathbf{m}_{2 S}$ (USP28)
it may not be feasible to employ this overkill approach. In this latter instance, the development of the sterilization cycle depends heavily on knowledge of the microbial burden of the product based on examination, over a suitable time period, of a substantial number of lots of the presterilized product.
-Particular attention should be given to the number and resistance to moist heat of spore-forming bacteria within the
presterilization bioburden. п2S (USP28)
The D value is the time (in minutes) required to reduce the microbial population by $90 \%$ or $1 \log$ cycle (i.e., to a surviving fraction of $1 / 10$ ), at a specific temperature. Therefore, where the D value of a biological indicator preparation of, for example, Billus stear hermophilus

## -Geobacillus stearothermophilus (formally Bacillus stearo-

thermophilus) ATCC 7953.2S (USP28)
spores is 1.5 minutes under

- defined $_{\text {■2S (USP28) }}$
process parameters (e.g., at $121^{\circ}$, if it is treated for 12 minutes under the same conditions), it can be stated that the lethality input is 8
$\square_{\text {should }}$ result in a spore $\log$ reduction value (SLR) of

8. 12 S (USP28)

The effect of applying this input to the product would depend on the initial microbial burden. Assuming that its resistance to sterilization is equivalent to that of the biological indicator, if the microbial burden of the product in question is $10^{2}$ microorganisms, a lethality input of 2D yields a microbial burden of $1\left(10^{\circ}\right.$ theoretical) and a further 6D yields a calculated microbial survivor probability of $10^{-6}$. (Under the same conditions, a lethality imput of 12 D may be used in a ypieal "overkill"' approach.)
-n2S (USP28)
Generally, the survivor probability achieved for the article under the validated sterilization cycle is not completely correlated with what may occur with the biological indicator. For valid use, therefore, it is essential that the resistance of the biological indicator be greater than that of the natural microbial burden of the article sterilized. It is then apprepriate to make a worst ease assumption and treat the microbial burden as though its heat resistance were equiv alent to that of the biolegieal indieator, although it is not likely that the most resistan of a yypieal mierobial burden isolates will dem enstrate a heat resistance of the magnitude shown by this species, frequently employed as a biolegienl indientor for steam steriliza tion. In the above example, a 12 minute cyele-is considered ade quate for sterilization if the product had a mierobial burden of $10^{-3}$ mieroorganisms. However, if the indieator originally had $10^{6} \mathrm{mi}$ eroorganisms content, actully a-10-3 probability of survival could beexpect; i.e., 1 in 100 biologieal indientors may yield pesitive
results. This type of situation may be avoided by selection of the appropriate biological indieator. Altematively, high content indien tors may be used on the basis of a predetermined acceptable count reduction.
-The widely recognized biological indicators used to evaluate a sterilization process are generally more resistant than the mean resistance of process bioburden. The difference in resistance between moist-heat biological indicators and that of the bioflora can be enormous, although the difference in magnitude is much smaller for gas sterilization. Generally some margin of safety is built into the development and validation of sterilization processes. In moist heat the high resistance of the biological indicator may in and of itself result in worst-case conditions. $\quad$ 2S (USP28)

The D value for the Baeillus stearethemmphilus preparation- determined or verified for these conditions-should be reestablished when a specifie program of validation is changed. Determination ef survival eurves (see Biologieal Indieators-(1035)) -or what has been called the fractional cyele approach may be employed to determine the $D$ value of the biological indicator preferred for the specific sterilization procedure. The fractional cyele approach may also be used to waluate the resistance of the mierobial burden. Fractional cyeles are studied either for mierobial count reduction er for fraction negative achievement. These numbers may be used to determine the lethality of the process under production conditions. The data can be used in qualified production equipment to establish appropriate sterilization cyeles. A suitable biologieal in dientor such as the Bacillus stearothermophilus preparation may be employed also during routine sterilization. Any mierobial burden method for sterility assuranee requires adequate surveillanee of the mierobial resistance of the artiele to detect any changes, in addition to periodic surveillanee of other attributes.
-However, this is unlikely to be true in gas sterilization processes. When allowing for worst-case conditions to ensure safety, it is important to recognize that sterilization processes are always a trade off between microbiological safety and materials resistance to the sterilization process. Processes that deliver far more lethality than is necessary to achieve microbiological safety may damage product or components and actually reduce microbiological safety of the product by affecting container or package integrity.
The D value for the Geobacillus stearothermophilus preparation determined or verified for these conditions should be re-established when a specific program of validation is changed. Criteria for the selection and testing of biological
indicators are also given in ISO 14161 Sterilization of Health Care Products. $\quad$ 2S (USP28)

## Change to read:

## METHODS OF STERILIZATION

In this informational chapter, five methods of terminal sterilization, including removal of microorganisms by filtration, and guidelines for aseptic processing are described. Modern technological developments, however, have led to the use of additional procedures. These include blow-molding (at high temperatures), forms of moist heat other than saturated steam and UV irradiation, as well as on-line continuous filling in aseptic processing. The choice of the appropriate process for a given dosage form or component requires a high level of knowledge of sterilization techniques and information concerning any effects of the process on the material being sterilized. ${ }^{1}$

## Steam

## -Moist-Heat ${ }_{\text {2S }}^{\text {(USP28) }}$

 SterilizationThe process of thermal sterilization employing
$\boldsymbol{■}_{\text {moist }}$ heat $_{\text {n2S }}$ (USP28)
under pressure is carried out in a chamber called an autoclave,
$\square_{\text {or }}$ in process pipe work, or directly in a product container
using microwave, for example, as a heat source.m2S (USP28 It is probably the most widely employed sterilization process. ${ }^{2}$ The basic principle of operation is that the air in the sterilizing chamber is displaced by the saturated steam, achieved by employing vents or traps. In order to displace air more effectively from the chamber and from within artieles, the sterilization cyele may inelude air and steam-vaeution stages. The design or choiee of a cyele for given

[^259]products or compenents depends on a number of factors, including the heat lability of the material, knowledge of heat penetration inte the articles, and other factors described under the validation program (see abeve). Apat frem that description of sterilization cyele parameters, using a temperature of 121 , the $\mathrm{F}_{4}$ concept may be appropriate. The $\mathrm{F}_{4}$, at a particular temperature other than $121^{\circ}$, is the time (in minutes) required to provide the lethality equivalent to that provided at $121^{\circ}$ for a stated time. Modern attoclaves gen erally operate with a control system that is significantly more respensive than the steam reduction valve of older units that have been in serviee for many years. In order for these older whits to achieve the precision and level of enntrol of the eyele-diseussed in this chapter, it may be neeessay to upgrade or modify the con frol equipment and instrumentation on these units. This modifieation is warrantedonly if the chamber and steam jacket are intact for eontinned safe use and if depesits that interfere with heat distribu tion can be removed.
-In moist-heat sterilization employing steam in an autoclave chamber, the air within the chamber can be removed by either gravity or vacuum. In autoclaves, which rely on steam acting directly on articles, the removal of air and penetration of steam into materials may be critical when porous loads are being sterilized. The effectiveness of air removal and steam penetration can best be assessed using biological indicators. Ideally, there should be a relatively close match between physically measured lethality and biological lethality. Air removal is not critical in processes where the steam is used to heat the contents of a container; such loads are often called nonporous. Air and steam mixtures, or hot water under pressure, can also achieve moist-heat sterilization of product in containers. In this case the contents of containers (generally aqueous solutions) are heated in a manner that protects the container-closure system by attempting to equalize pressure on the inside and outside of the container. This type of process is applied only to nonporous loads, and, in this case, air removal is irrelevant. In line moist-heat sterilization on product containers can be accomplished using microwave to heat the contents of a sealed container that holds within it an aqueous solution.■2S (USP28)

## Dry-Heat Sterilization

The process of thermal sterilization of Pharmacopeial articles by dry heat is usually carried out by a batch process in an oven designed expressly for that purpose. A modern oven is supplied with heated, filtered air, distributed uniformly throughout the chamber
by convection or radiation and employing a blower system with devices for sensing, monitoring, and controlling the critical parameters.

- A modern oven is supplied with heated, HEPA-filtered air, distributed uniformly throughout the chamber by convection or radiation and employing a blower system with devices for sensing, monitoring, and controlling the critical
parameters of time and temperature. ${ }^{2 S}$ (USP28)
The validation of a dry-heat sterilization facility is carried out in a manner similar to that for a steam sterilizer described earlier. Where the unit is employed for sterilizing components such as containers intended for intravenous solutions, care should be taken to avoid accumulation of particulate matter in the chamber. A typical acceptable range in temperature in the empty chamber is $\pm 15^{\circ}$ when the unit is operating at not less than $250^{\circ}$.
-The dry-heat sterilization cycle should be not less than 30
minutes at $250^{\circ}$. ${ }^{\text {2S (USP28) }}$
In addition to the batch process described above, a continuous process
-(i.e., a dry-heat sterilization and depyrogenation tun-
nel), $\quad$ 2S (USP28)
is frequently employed to sterilize and depyrogenate glassware as part of an integrated continuous aseptic filling and sealing system. Heat distribution may be by convection or by direct transfer of heat from
$\square_{\text {a heating element }} \mathrm{or}_{\text {2S (USP28) }}$
an open flame. The continuous system usually requires a much higher temperature than cited above for the batch process because of a much shorter dwell time
-(e.g., $350^{\circ}$ for 5 minutes, although temperatures in the
range of $280^{\circ}$ for 3 minutes are adequate). $\quad$. 2 S (USP28)
However, the total temperature input during the passage of the product should be equivalent to that achieved during the chamber process. The continuous process also usually necessitates a rapid cooling stage prior to the aseptic filling operation. In the qualification and validation program, in view of the short dwell time, parameters for uniformity of the temperature, and particularly the dwell time, should be established.

A mierobial survival probability of $10^{-12}$ is considered achiev able for heat stable articles or compenents. An example of a bio logieal indicator for validating and menitoring dry heat sterilization is a preparation of Bacillus subtilis spores. Since dry heat is frequently employed to render glassware or containers free from pyrogens as well as viable mierobes, a pyrogen challenge, where neeessary, should be an integral part of the validation program, e.g., by ineculating one or more of the articles to be treated with 1000 or more USP Units of bacterial endotoxim. The test with timulus lysate could be used to demonstrate that the endotoxie substanee has been inactivated to not more than $1 / 1000$ of the oris inal amount ( 3 log cyele reduction). For the test to be valid, both the original ameunt and, after aceeptable inactivation, the remaining amount of endotoxin should be measured. For additional infor mation on the endotoxin assay, see Bacterial Endotoxins Test $\langle 85\rangle$ :

- An example of a biological indicator suitable for validating and monitoring dry-heat sterilization is a preparation of $B a$ cillus atrophaeus (formally Bacillus subtilis var. niger)

ATCC 9372 spores. Validation of dry-heat processes using biological indicators is necessary only when depyrogenation is not required. Because dry heat is frequently employed to render glassware or containers free from pyrogens as well as viable microbes, a pyrogen inactivation study is necessary. A common target value for pyrogen inactivation is a $3-\log$ reduction. This study is conducted by inoculating test articles with a concentration of endotoxin suitable to demonstrate a 3-log or greater reduction. The resistance of bacterial endotoxins is quite high; therefore, a process that results in a 3-log endotoxin reduction will also result in material that is sterile. See Bacterial Endotoxins Test $\langle 85\rangle$ for the details of the test method. $\quad$ 2S (USP28)

## Gas

## - Ethylene Oxide ${ }_{\text {n2S }}$ (USP28) Sterilization

The choice of gas sterilization as an alternative to heat is frequently made when the material,

- especially the packaging components, $\quad$ 2S (USP28)
to be sterilized cannot withstand the high temperatures obtained in the steam sterilization or dry-heat sterilization processes.
- Under these circumstances irradiation may be a suitable


## sterilization process. 2 2S (USP28)

The active agent generally employed in gaseous sterilization is ethylene oxide of acceptable sterilizing quality. Among the disadvantages of this sterilizing agent are its highly flammable nature unless mixed with suitable inert gases, its mutagenic properties, and the possibility of toxic residues in treated materials, particularly those containing chloride ions.
-It is also possible that direct contact between the gas and microbial cells does not occur if the organisms are occluded
in crystals or within proteineous material. $\mathbf{W 2 S}^{25}$.(USP28)
The sterilization process is generally carried out in a pressurized chamber designed similarly to a steam autoclave but with the additional features (see below) unique to sterilizers employing this gas. Facilities employing this sterilizing agent should be designed to provide adequate

- presterilization humidification and ${ }_{\mathbf{L S}}$ (USP28)
poststerilization degassing, to enable microbial survivor monitoring, and to minimize exposure of operators to the potentially harmful gas. ${ }^{3}$
-This method should only be used when no other method is
practicable. ${ }^{2 S}$ (USP28)
Qualification of a sterilizing process employing ethylene oxide gas is accomplished along the lines discussed earlier. However, the program is more comprehensive than for the other sterilization procedures, because in addition to temperature, the humidity, vacuum or positive pressure, and ethylene oxide concentration also require rigid control. An important determination is to demonstrate that all critical process parameters in the chamber are adequate during the entire cycle. Because the sterilization parameters applied to the articles to be sterilized are critical variables, it is frequently advisable to precondition the load to achieve the required moisture content in order to minimize the time of holding at the required temperature, prior to placement of the load in the ethylene oxide chamber. The validation process is generally made employing product inoculated with appropriate biological indicators such as spore preparations of Beillhusuthilis.


## - Bacillus atrophaeus (formally Bacillus subtilis var. niger)

ATCC 9372. ${ }^{2 S}$ (USP28)
For validation they may be used in full chamber loads of product, or simulated product. The monitoring of moisture and gas concentration requires the use of sophisticated instrumentation that only knowledgeable and experienced individuals can calibrate, operate, and maintain. The biological indicators may be employed also in monitoring routine runs.
As is indicated elsewhere in this chapter, the biological indicator may be employed in a fraction negative mode to establish the ultimate microbiological survivor probability in designing an ethylene oxide sterilization cycle using inoculated product or inoculated simulated product.
One of the principal limitations of the ethylene oxide sterilization process is the limited ability of the gas to diffuse to the innermost product areas that require sterilization. Package design and chamber loading patterns therefore must be determined so that there is minimal resistance to gas diffusion
-during the sterilization process and degassing. 2S $^{2 S}$ (USP28)

## Sterilization by Ionizing Radiation

The rapid proliferation of medical devices unable to withstand heat sterilization and the concerns about the safety of ethylene oxide have resulted in increasing applications of radiation sterilization. It is, however, applicable also to drug substances and final dosage forms. The advantages of sterilization by irradiation include low chemical reactivity, low measurable residues, and the fact that there are fewer variables to control. In fact, radiation sterilization is unique in that the basis of control is essentially that of the absorbed radiation dose, which can be precisely measured.
-This measurement may be readily used for parametric release of the irradiated articles.■2S (USP28)

[^260]Because of this characteristic, new procedures have been developed to determine the sterilizing dose. These, however, are still under review and appraisal, particularly with regard to the need, or otherwise, for additional controls and safety measures. Irradiation causes only a minimal temperature rise, but can affect certain grades and types of plastics and glass.

The two types of ionizing radiation in use are radioisotope decay (gamma radiation) and electron-beam radiation. In either case the radiation dose to yield the required degree of sterility assurance should be established such that within the range of minimum and maximum doses set, the properties of the article being sterilized are acceptable.

For gamma irradiation, the validation of a procedure includes the establishment of article materials compatibility, establishment of product loading pattern and completion of dose mapping in the sterilization container (including identification of the minimum and maximum dose zones), establishment of a timer setting, and demonstration of the delivery of the required sterilization dose. For electron-beam irradiation, in addition, the on-line control of voltage, current, conveyor speed, and electron beam scan dimension must be validated.

For gamma radiation sterilization, an effective sterilizing dose, which is tolerated without damaging effect, should be selected. Although
-25 kilo Gray unit (kGy) or ${ }^{\text {2S }}$ (USP28)
2.5 megarads (Mrad) of absorbed radiation was historically selected, it is desirable and acceptable in some cases to employ lower doses for devices, drug substances, and finished dosage forms. In other cases, however, higher doses are essential. In order to validate the efficacy particularly of the lower exposure levels, it is necessary to determine the magnitude (number and degree) of the natural radiation resistance of the microbial population of the product. Specific product loading patterns
-and product densities $_{\text {mS }_{\text {(USP28) }}}$
must be established and absorbed minimum and maximum dosage distribution must be determined by use of chemical dosimeters. (These dosimeters are usually dyed plastic cylinders, slides, or squares that show color intensification based directly on the amount of absorbed radiation energy, ; they require carefulealibra tion
$\square_{\text {which }}$ require careful calibration by an outside calibration

## laboratory.) $\mathbf{m 2 S}_{\text {(USP28) }}$

The setting of the preferred absorbed dose has been carried out on the basis of pure cultures of resistant microorganisms and employing inoculated product, e.g., with spores of Bacillus pumilus as biological indicators. A fractional experimental cycle approach provides the data to be utilized to determine the $\mathrm{D}_{10}$ value of the biological indicator. This information is then applied in extrapolating the amount of absorbed radiation to establish an appropriate microbial survivor probability. The most recent procedures for gamma radiation sterilization base the dose upon the radiation resistance of the natural heterogeneous microbial burden contained on the product to be sterilized. Such procedures are currently being refined but may provide a more representative assessment of radiation resistance, especially where significant numbers of radiationresistant organisms are present. ${ }^{4}$ These range from inoculation with standard resistant organisms such as Bacillus pumilus to subprocess (sublethal) dose exposure of finished product samples taken from production lines. Certain hypotheses are common to all of these methods. While the total microbial population present on an article generally consists of a mixture of microorganisms of differing sensitivity to radiation, the step of subjecting the article to a

[^261]less than totally lethal sterilization dose eliminates the less resistant microbial fraction. This results in a residual relatively homogeneous population with respect to radiation resistance, and yields consistent and reproducible results of determinations with the residual population. The amount of laboratory manipulation required is dependent upon the particular procedure used.

One such procedure requires the enumeration of the microbial population on representative samples of independently manufactured lots of the article. The resistance of the microbial population is not determined and dose setting is based on a standard arbitrary radiation resistance assigned to the microbial population, derived from data obtained from manufacturers and from the literature. The assumption is made that the distribution of resistances chosen represents a more severe challenge than the natural microbial population on the product to be sterilized. This assumption, however, is verified by experiment. After verification, the appropriate radiation sterilization dose is read from a table.

Another, more elaborate, method does not require the enumeration of the microbial population but uses a series of incremental dose exposures to allow a dose to be established such that approximately 1 out of 100 samples irradiated at that dose will be nonsterile. This is not the ultimate sterilization dose, but provides the basis to determine the sterilization dose by extrapolation from the dose yielding 1 out of 100 nonsterile samples, using an appropriate resistance factor that characterizes the remaining microorganism-resistant population. A periodic audit is conducted to check that the findings continue to be operative.

More elaborate procedures, requiring more experimentation and including the isolation of microbial cultures, include one where, after determining the substerilization dose (yielding 1 out of 100 nonsterile samples), the resistance of the surviving microorganisms is used to determine the sterilizing dose. Another is based on different determinations, starting with a substerilization incremental dose that results in not more than $50 \%$ of the samples being nonsterile. After irradiation of sufficient samples at this dose, a number of microbial isolates are obtained. The radiation resistance of each of these is determined. The sterilization dose is then calculated using the resistance determinations and the $50 \%$ sterilizing dose initially determined. Audit procedures are required for these methods as for the others described.

Where the required minimum radiation dose has been determined and delivery of that dose has been confirmed (by chemical or physical dosimeters), release of the article being sterilized could be effected within the overall validation of sterility assurance (which may include such confirmation of applied dosage, the use of biological indicators, and other means).

## ■Vapor-Phase Hydrogen Peroxide Sterilization

Hydrogen peroxide may be applied as liquid, vapor, or an aerosol to act as a surface sterilant that breaks down to water and oxygen so that it does not leave toxic residues. It is widely used in aseptic packaging operations in the food, pharmaceutical, and medical device industries. In the pharmaceutical industry it has more recently found application for the decontamination of aseptic processing equipment,
such as isolators and freeze driers. Users should verify the suitability of their process materials for exposure to hydrogen peroxide vapors.

The factors influencing its antimicrobial activity are concentration, dew point, temperature, and contact time. A typical vapor-phase hydrogen peroxide cycle for a freeze-drier would be the evacuation of the air, with its continuous replacement with hydrogen peroxide vapor at concentrations below $10 \mathrm{mg} / \mathrm{L}$ maintained at $50^{\circ}$ for up to 90 min utes. 2SS $^{\text {(USP28) }}$

## Sterilization by Filtration

Filtration through microbial retentive materials is frequently employed for the sterilization of heat-labile solutions by physical removal of the contained microorganisms. A filter assembly generally consists of a porous matrix
$\boldsymbol{m}_{\text {in }}$ the form of a cartridge $\boldsymbol{m}_{2 S}$ (USP28)
sealed or clamped into an impermeable housing. The effectiveness of a filter medium or substrate depends upon the pore size of the porous material and may depend upon adsorption of bacteria on or in the filter matrix or upon a sieving mechanism. There is some evidence to indicate that sieving is the more important component of the mechanism. Fiber-shedding filters, particularly those containing asbestos, are to be avoided unless no alternative filtration procedures are possible. Where a fiber-shedding filter is required, it is obligatory that the process include a nonfiber-shedding filter introduced downstream or subsequent to the initial filtration step.

Filter Rating - Rating the pore size of filter membranes is by a neminal rating that refleets the capability of the filter membrane to retain mierorgenisms of size represented by specified strains, het by determination of an average pore size and statement of distribut tion of sizes.
-The pore size of filter membranes is a nominal rating that reflects the capability of the filter membrane to retain microorganisms of a size represented by specified strains. Poresize rating is not a determination of an average pore size
nor does it address the distribution of sizes. nes $^{2 S}$ (USP28) Sterilizing filter membranes (those which are used for removing a majority of contaminating microorganisms) are membranes capable of retaining $100 \%$ of a culture of $10^{7}$ microorganisms of a strain of Psematander

- Burkholderia diminuta ${ }_{\text {■2S }}$ (USP28)
(ATCC 19146) per square centimeter of membrane surface under a pressure of not less than 30 psi ( 2.0 bar ). Such filter membranes are nominally rated $0.22 \mu \mathrm{~m}$ or $0.2 \mu \mathrm{~m}$, depending on the manufacturer's practice. ${ }^{5}$ This rating of filter membranes is also specified for reagents or media that have to be sterilized by filtration (see treatment of isopropyl myristate under Oils and Oily Solutions or

[^262]Ointments and Creams in the chapter Sterility Tests $\langle 71\rangle$ ). Bacterial filter membranes (also known as analytical filter membranes), which are capable of retaining only larger microorganisms, are labeled with a nominal rating of $0.45 \mu \mathrm{~m}$. No single authoritative method for rating $0.45-\mu \mathrm{m}$ filters has been specified, and this rating depends on conventional practice among manufacturers; $0.45-\mu \mathrm{m}$ filters are capable of retaining particular cultures of Serratia marcescens (ATCC 14756) or Ps. diminter

- Burkholderia diminuta (ATCC 19146)

Test pressures used vary from low ( $5 \mathrm{psi}, \theta .33$
$\mathbf{n 0 . 3 4}_{\text {n2S (USP28) }}$
bar for Serratia, or $0.5 \mathrm{psi}, 0.34$
$\mathrm{m}_{0.034}{ }_{\text {2S (USP28) }}$
bar for Ps. diminimut

- Burkholderia diminuta) $\boldsymbol{m}_{\text {2S (USP28) }}$
to high ( $50 \mathrm{psi}, 3.4 \mathrm{bar}$ ). They are specified for sterility testing (see Membrane Filtration in the section Test for Sterility of the Product to be Examined under Sterility Tests $\langle 71\rangle$ ), where less exhaustive microbial retention is required. There is a small probability of testing specimens contaminated solely with small microorganisms. Filter membranes with a very low nominal rating may be tested with a culture of Acholeplasma laidlawii or other strain of Mycoplasma, at a pressure of $7 \mathrm{psi}(0.7 \mathrm{bar})$
$\mathbf{\bullet}_{(0.48}$ bar) $\mathbf{m}_{2 S}$ (USP28)
and be nominally rated $0.1 \mu \mathrm{~m}$. The nominal ratings, based on microbial retention properties, differ when rating is done by other means (e.g., by retention of latex spheres of various diameters). It is the user's responsibility to select a filter of correct rating for the particular purpose, depending on the nature of the product to be filtered. It is generally not feasible to repeat the tests of filtration capacity in the user's establishment. Microbial challenge tests are preferably performed under a manufacturer's conditions on each lot of manufactured filter membranes.

The user must determine whether filtration parameters employed in manufacturing will significantly influence microbial retention efficiency. Some of the other important concerns in the validation of the filtration process include product compatibility, sorption of drug, preservatives or other additives, and initial effluent endotoxin content.

Because the effectiveness of the filtration process is also influenced by the microbial burden of the solution to be filtered, the determination of the microbiological quality of solutions prior to filtration is an important aspect of the validation of the filtration process in addition to establishment of the other parameters of the filtration procedure, such as pressures, flow rates, and filter unit characteristics. Hence, another method of describing filter-retaining capability is by the log reduction value (LRV). For instance, a $0.2-\mu \mathrm{m}$ filter that can retain $10^{7}$ microorganisms of a specified strain will have an LRV of not less than 7, under the stated conditions.

The process of sterilization of solutions by filtration has recently achieved new levels of proficiency, largely as a result of the development and proliferation of membrane filter technology. This class of filter media lends itself to more effective standardization and quality control and also gives the user greater opportunity to confirm the characteristics or properties of the filter assembly before and after use. The fact that membrane filters are thin polymeric films offers many advantages but also some disadvantages when compared to depth filters such as porcelain or sintered material. Because much of the membrane surface is a void or open space, the properly assembled and sterilized filter offers the advantage of a high flow rate. A disadvantage is that because the membrane is usually fragile, it is essential to determine that the assembly was properly made and that the membrane was not ruptured during assembly, sterilization, or use. The housings and filter assemblies that are chosen should first be validated for compatibility and in-
tegrity by the user. While it may be possible to mix assemblies and filter membranes produced by different manufacturers, the compatibility of these hybrid assemblies should first be validated. Additionally, there are other tests that are made by the manufacturer of the membrane filter that are not usually repeated by the user. These include microbiological challenge tests. Results of these tests on each lot of manufactured filter membranes should be obtained from the manufacturer by the user for his records.

Filtration for sterilization purposes is usually carried out with assemblies having membranes of nominal pore size rating of 0.2 $\mu \mathrm{m}$ or less, based on the validated challenge of not less than $10^{7}$ Psetedomonas dimintute
$\mathbf{- B u r k h o l d e r i a ~ d i m i n u t a ~}_{\mathbf{\square} 2 \mathrm{~S}}$ (USP28)
(ATCC No. 19146) suspension per square centimeter of filter surface area. Membrane filter media that are now available include cellulose acetate, cellulose nitrate, fluorocarbonate, acrylic polymers, polycarbonate, polyester, polyvinyl chloride, vinyl, nylon, polytef, and even metal membranes, and they may be reinforced or supported by an internal fabric. A membrane filter assembly should be tested for initial integrity prior to use, provided that such test does not impair the validity of the system, and should be tested after the filtration process is completed to demonstrate that the filter assembly maintained its integrity throughout the entire filtration procedure. Typical use tests are the bubble point test, the diffusive airflow test, the pressure hold test, and the forward flow test. These tests should be correlated with microorganism retention.
-The test limits may be established for the filters wetted with Water for Injection (prior to use) or product (post use).■2S (USP28)

## Aseptic Processing

While there is general agreement that sterilization of the final filled container as a dosage form or final packaged device is the preferred process for ensuring the minimal risk of microbial contamination in a lot, there is a substantial class of products that are not terminally sterilized but are prepared by a series of aseptic steps. These are designed to prevent the introduction of viable mi eroorganisms into compenents, where-sterile, or once an intermediate proeess has rendered the bulk product or its eompenents free frem viable miereorganisms.
-Advances in aseptic processing have resulted in manufacturing operations that produce a product that is extremely safe and has a very low probability of microbial contamination. Aseptic processes are designed to prevent the introduction of viable microorganisms into components, where sterile, or once an intermediate process has rendered the bulk product or its components free from viable microorga-

## nisms.n2S (USP28)

This section provides a review of the principles involved in producing aseptically processed products with a minimal risk of microbial contamination in the finished lot of final dosage forms.

A product defined as aseptically processed is likely to consist of components that have been sterilized by one of the processes described earlier in this chapter. For example, the bulk product, if a filterable liquid, may have been sterilized by filtration. The final
empty container components would probably be sterilized by heat, dry heat being employed for glass vials and an autoclave being employed for rubber closures. The areas of critical concern are the immediate microbial environment where these presterilized components are exposed during assembly to produce the finished dosage form and the aseptic filling operation.
The requirements for a properly designed, validated and maintained filling or other aseptic processing facility are mainly directed to (i) an air environment free from viable microorganisms, of a proper design to permit effective maintenance of air supply units and (ii) the provision of trained operating personnel who are adequately equipped and gowned.
-Studies done on aseptic processing environments have consistently reported that the human operator is the only significant source of microbial contamination in the manufacturing process. Therefore, operator training and the consistent use of proper gowning and aseptic handling tech-
niques are vital to achieving asepsis. ${ }^{2 S}$ (USP28)
The desired environment may be achieved through the high level of air filtration technology now available, which contributes to the delivery of air of the requisite microbiological quality. ${ }^{6}$ The facilities include both primary (in the vicinity of the exposed article) and secondary (where the aseptic processing is carried out) barrier systems.
For a properly designed aseptic processing facility or aseptic filling area, consideration should be given to such features as nonporous and smooth surfaces, including walls and ceilings that can be sanitized frequently; gowning rooms with adequate space for personnel and storage of sterile garments; adequate separation of preparatory rooms for personnel from final aseptic processing rooms, with the availability where necessary of such devices as airlocks or air showers; proper pressure differentials between rooms, the most positive pressure being in the aseptic processing rooms or areas; the employment of laminar (unidirectional) airflow in the immediate vicinity of exposed product or components, and filtered air exposure thereto, with adequate air change frequency; appropriate humidity and temperature environmental controls; and a documented sanitization program. Proper training of personnelin hygienic and gowning techniques should be undertaken so that, for example, gowns, gloves, and other body eoverings substantially eover expesed skin surfaces.

■2S (USP28)

[^263]Certification and validation of the aseptic process and facility are achieved by establishing the efficiency of the filtration systems, by employing microbiological environmental monitoring procedures, and by processing of sterile culture medium as simulated product.
-The efficiency of the air filters should be checked on a routine basis, typically at least annually.m2S (USP28)

Monitoring of the aseptic facility should include periodic environmental filter examination as well as routine particulate and microbiological environmental monitoring, and may include periodic sterile culture medium processing.
-See Microbiological Evaluation of Clean Rooms and other
Controlled Environments $\langle 1116\rangle \cdot$.n2S (USP28)

## Change to read:

## STERILITY TESTING OF LOTS

It should be recognized that the referee sterility test might not detect microbial contamination if present in only a small percentage of the finished articles in the lot because the specified number of units to be taken imposes a significant statistical limitation on the utility of the test results. This inherent limitation, however, has
-It should also be noted that the sensitivity of the sterility test may not be sufficient in all cases to recover very small numbers of viable organisms. These inherent limitations,

## however, have $\mathbf{m}^{2 S}$ (USP28)

to be accepted because current knowledge offers no nondestructive alternatives for ascertaining the microbiological quality of every finished article in the lot, and it is not a feasible option to increase the number of specimens significantly.

The primary means of supporting the claim that a lot of finished articles purporting to be sterile meets the specifications consist of the documentation of the actual production and sterilization record of the lot and of the additional validation records that the sterilization process possesses the capability of totally inactivating the established product microbial burden or a more resistant challenge. Further, it should be demonstrated that any processing steps involving exposed product following the sterilization procedure are performed in an aseptic manner, to prevent contamination. If data derived from the manufacturing process sterility assurance validation studies and from in-process controls are judged to provide greater assurance that the lot meets the required low probability of containing a contaminated unit (compared to sterility testing results from finished units drawn from that lot), any sterility test procedures adopted may be minimal, or dispensed with on a routine basis. However, assuming that all of the above production criteria have been met, it may still be desirable to perform sterility testing on samples of the lot of finished articles. Such sterility testing is usually carried out directly after the lot is manufactured as a final product quality control test. ${ }^{7}$ Sterility tests employed in this way in manufacturing control should not be confused with those described under Sterility Tests $\langle 71\rangle$. The procedural details may be the same

[^264]with regard to media, inocula, and handling of specimens, but the number of units and incubation time(s) selected for testing may differ. The number should be chosen relative to the purpose to be served (i.e., according to whether greater or lesser reliance is placed on sterility testing in the context of all the measures for sterility assurance in manufacture). Also, longer times of incubation would make the test more sensitive to slow-growing microorganisms. In the growth promotion tests for media, such slow growers, particularly if isolated from the product microbial burden, should be included with the other test stains. Negative or satisfactory sterility test results serve only as further support of the existing evidence concerning the quality of the lot if all of the pertinent production records of the lot are in order and the sterilizing or aseptic process is known to be effective. Unsatisfactory test results, however, in manufacturing quality control indicate a need for further action (see Performance, Observation, and Interpretation).

## Definition of a Lot and Selection of Specimens for Sterility Test Purposes

Articles may be terminally sterilized either in a chamber or by a continuous process. In the chamber process, a number of articles are sterilized simultaneously under controlled conditions, for example, in a steam autoclave, so that for the purpose of sterility testing, the lot is considered to be the contents of a single chamber. In the continuous process, the articles are sterilized individually and consecutively, for example, by exposure to electron-beam radiation, so that the lot is considered to be not larger than the total number of similar items subjected to uniform sterilization for a period of not more than 24 hours.

For aseptic fills, the term "filling operation" describes a group of final containers, identical in all respects, that have been aseptically filled with the same product from the same bulk within a period of time not longer than 24 consecutive hours without an interruption or change that would affect the integrity of the filling assembly. The items tested should be representative of each filling assembly and should be selected at appropriate intervals throughout the entire filling operation. If more than three filling machines, each with either single or multiple filling stations, are used for filling a single lot, a minimum of 20 filled containers (not less than 10 per medium) should be tested for each filling machine, but the total number generally need not exceed 100 containers.

For small lots, in the case of either aseptic filling or terminal sterilization, if the number of final containers in the lot is between 20 and 200 , about $10 \%$ of the containers should usually be tested. If the number of final containers in the lot is 20 or less, not fewer than 2 final containers should be tested.

## Change to read:

## PERFORMANCE, OBSERVATION, AND INTERPRETATION

## -PERFORMANCE AND OBSERVATION ${ }_{\text {■2S }}$ (USP28)

The facility for sterility testing should be such as to offer no greater a microbial challenge to the articles being tested than that of an aseptic processing production facility. The sterility testing procedure should be performed by individuals having a high level of aseptic technique proficiency. The test performance records of these individuals should be documented.

The extensive aseptic manipulations required to perform sterility testing may result in a probability of nonproduct-related contamination of the order of $10^{-3}$, a level similar to the overall efficiency
of an aseptic operation and comparable to the microbial survivor probability of aseptically processed articles. This level of probability is significantly greater than that usually attributed to a terminal sterilization process, namely, one in one million or $10^{-6}$ microbial survivor probability. Appropriate, known-to-be-sterile, finished articles should be employed periodically as negative controls as a check on the reliability of the test procedure. Preferably, the technicians performing the test should be unaware that they are testing negative controls. Of these tests, a false positive frequency not exceeding $2 \%$
$\mathbf{m}_{0} 0.1 \%$ (USP28)
is desirable.
For aseptically processed articles, these facts support the routine use of the test set forth under Sterility Tests $\langle 71\rangle$ or a more elaborate one. The production and validation documentation should be acceptable and complete. For effectively terminally sterilized products, however, the lower microbial survivor probability may direct the use of a less extensive test than the compendial procedure specified under Sterility Tests $\langle 71\rangle$, or even preclude the necessity altogether for performing one

■and using parametric release to evaluate the sterility assurance of the products (see Terminally Sterilized Pharmaceu-
tical Products--Parametric Release <1222〉). [2S (USP28)
This added reliability of sterility assurance of terminal sterilization depends upon a properly validated and documented sterilization process. Sterility testing alone is no substitute.

## Interpretation of Quality Control Tests

The overall responsibility for the operation of the test unit and the interpretation of test results in relation to acceptance or rejection of a lot should be in the hands of those who have appropriate formal training in microbiology and have knowledge of industrial sterilization, aseptic processing, and the statistical concepts involved in sampling. These individuals should be knowledgeable also concerning the environmental control program in the test facility to assure that the microbiological quality of the air and critical work surfaces are consistently acceptable.

Quality control sterility tests (either according to the official referee test or modified tests) may be earied out in separate stag es in order to rule out false positive results. First Stage. Regardless of the sampling plan used, if no evidence of mierobial growth is found, the results of the test may be taken as indicative of absence of intrinsic contamination of the lot.

If mierobial growth is foumd, proeed to the Second Stage (ma less the First Stege test can be invalidated). Evidence for invalidat ing a First Stage test in order to repent it as a First Stage test may be obtained frem a review of the testing envirenment and the relerant records thereto. Finding of mierobial growth in negative con frols need not be considered the sole-grounds for invalidating a First Stage test. When proeeding to the Seend Stage, partieularly where depending on the results of the test for lot release, coneur rently, initiate and document a complete review of all applicable production and control records. In this review, consideration should be paid to the following: (1) a check on monitoring records of the validated sterilization eycle applieable to the product; (2) sterility test history relating to the particular product for both fimished and in process samples, as wellas sterilization records of support ing equipment, containers/elosures, and sterile compenents, if any; and (3) environmental control data, ineluding those obtained from
media fills, expesure plates, filtering records, any sanitization re eords and microbial monitoring records of operators, gowns, gloves, and garbing practices.

Failing any lead from the above review, the eurrent mierebiat profile of the product should be checked against the known histor ieal profile for possible change. Records should be checked con eomitantly for any changes in souree of product eompenents and/or in processing procedures that might be contributory. Depending on the findings, and in extreme cases, consideration may have to be given to revalidation of the total manufacturing process. For the Second Stage, it is not pessible to specify a particular num ber of specimens to be taken for testing. It is usual to select double the number speciffed for the Finst Stege under Sterility Tests $\langle 74\rangle$; of other reasonable number. The minimum volumes tested frem each specimen, the media, and the incubation periods are the same as these indieated for the First Stege.

If no mierobial growth is found in the Second Stage, and the documented roview of appropriate records and the indieated product investigation does not suppert the possibility of intrinsic eontamination, the lot may meet the requirements of a test for sterility. If growth is found, the lot fails to mee the requirements of the test. As was indien for the Finst Stage test, the Second Stage test may similarly be invalidated with appropriate vidence, and, if so done, repeated as a Second Stage test.
-Given the low probability of detecting nonsterile units in a sterility test, repeat sterility testing is not recommended. Repeat testing should only be undertaken when a laboratory investigation supplies evidence that the test was invalid during test sample integrity, media or diluents contamination, or gross loss of environmental controls in the sterility testing area.
If microbial growth is found, a complete review of all applicable production and control records should be initiated and documented. In this review consideration should be paid to the following: (1) a check on monitoring records of the validated sterilization cycle applicable to the product; (2) sterility test history relating to the particular product for both finished and in-process samples, as well as sterilization records of supporting equipment, containers-closures, and sterile components, if any; (3) environmental control data, including those obtained from media fills, exposure plates, filtering records, any sanitization records and microbial monitoring records of operators, gowns, gloves, and garbing practices.п2S (USP28)

## BRIEFING

$\langle\mathbf{1 2 1 6}\rangle$ Tablet Friability, USP 27 page 2621 and page 891 of PF 28(3) [May-June 2002]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the specifications provided in this general information chapter. The Stage 5B Consensus harmonization draft for this chapter has been signed off by the Pharmacopeial Discussion Group members. The regional ADOPTION STAGE 6A text presented herein is being published in the In-Process Revision section in this issue of $P F$ for information only, not for public comment. This text is scheduled for publication in the Second Supplement to USP 28-NF 23, with a scheduled implementation date of 1 August 2005.

Major differences between the current text and that of the Stage 4 Official Inquiry harmonization draft, as published in the $P F$ 28(3) reference previously cited, are listed below.
(1) Paragraph 4-The maximum weight loss percentage value is revised to reflect the intended upper limit restriction of $1.04 \%$. The text is also revised to clarify that, when it is necessary to perform the test two additional times, the mean weight loss from the three samples tested is taken as the test result. Deletion of the last sentence is proposed because it is not considered necessary to distinguish "new formulations" from others.
(2) Paragraph 6-Deletion of the text regarding special packaging for effervescent tablets and chewable tablets is proposed because this packaging statement is considered to be irrelevant to the current context. The proposed deletion of the text specifying a relative humidity less than $40 \%$ for testing of hygroscopic tablets is intended to allow for the use of any appropriate relative humidity based on the individual dosage form under test. Effervescent tablets, for example, may require a relative humidity of $20 \%$ rather than simply "less than $40 \%$."
(3) Paragraph 7-The revised text is intended to broaden the types of apparatuses permitted for use in this test.
(PDF: W.L. Paul) RTS-41362-1

## Change to read:

## 〈1216〉 TABLET FRIABILITY

This chapter provides guidelines for the friability determination of compressed, uncoated tablets. The test procedure presented in this chapter is generally applicable to most compressed tablets. Measurement of tablet friability supplements other physical strength measurements, such as tablet crushing strength.

Use a drum,* with an internal diameter between 283 and 291 mm and a depth between 36 and 40 mm , of transparent synthetic polymer with polished internal surfaces, and not subject to static buildup (see figure for a typical apparatus). One side of the drum is removable. The tablets are tumbled at each turn of the drum by a curved projection with an inside radius between 75.5 and 85.5 mm that extends from the middle of the drum to the outer wall. The drum is attached to the horizontal axis of a device that rotates at $25 \pm 1 \mathrm{rpm}$. Thus, at each turn the tablets roll or slide and fall onto the drum wall or onto each other.

[^265]

## Tablet Friability Apparatus

For tablets with a unit mass equal to or less than 650 mg , take a sample of whole tablets corresponding to 6.5 g . For tablets with a unit mass of more than 650 mg , take a sample of 10 whole tablets. The tablets should be carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh.

Generally, the test is run once. If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If the results are doubtful or if the weight loss is greater than the targeted value, the test should be repeated twice and the mean of the three tests determined. A maximum

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■mean_\2S (USP28)
weight loss
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${ }^{-}$from the three samples $\boldsymbol{m}_{2 S}$ (USP28) of not more than $1 \%$ of the weight of the tablets being tested
${ }^{-1.0 \%}{ }^{\text {m }}$ 2S (USP28)
is considered acceptable for most products. In the ease of new for mulations, an initial weight loss of $0.8 \%$ would be permitted untit suffieient packaging data are-obtained to extend the limit to a tar geted value of $1 \%$.

## ■2S (USP28)

If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about $10^{\circ}$ with the bench top and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

Effervescent tablets and chewable tablets may have different specifications as far as friability is concerned, and these
nermally require-special packaging.

- ${ }^{\text {2S }}$ (USP28)

In the case of hygroscopic tablets, a
$\square_{\text {an }}$ appropriate $\mathbf{n}_{2 S}$ (USP28)
humidity-controlled environment (relative hunidity less than-40\%)

- ${ }^{-2 S}$ (USP28)
is required for testing.
Adrum with duat seooping supperts for the rumning of two sam ples at one time is also permitted.
-Drums with dual scooping projections, or an apparatus with more than one drum, for the running of multiple samples at one time, are also permitted.■2S (USP28)

BRIEFING
$\langle\mathbf{1 2 2 2}\rangle$ Terminally Sterilized Pharmaceutical ProductsParametric Release, page 3144 of the First Supplement. It is proposed to clarify the use of the sterility asurance level (SAL) with aseptic processing. It is also proposed to revise the discussion of the number of spores required for the evaluation of a sterilization process and to change the exponent referring to SAL in the section Radiation Sterilization from positive to negative. In addition, a number of editorial changes are also proposed.
(AMB: D. Porter) RTS-41618-1

## Change to read:

## INTRODUCTION

Parametric release is defined as the release of terminally sterilized batches or lots of sterile products based upon the compliance with the defined critical parameters of sterilization without having to perform the requirements under Sterility Tests $\langle 71\rangle$. Parametric release is a possibility when the mode of sterilization is very well understood, the physical parameters of processing are well defined, predictable, and measurable, and the lethality of the cycle has been microbiologically validated through the use of appropriate biological indicators or, in the case of ionizing radiation, the appropriate microbiological and dosimetric tests. The use of parametric release for sterilization processes requires prior FDA approval. It should be expected that the regulatory agencies evaluating submissions including the use of parametric product release would insist upon a well supported scientific rationale for the sterilization process and well documented validation data. The agencies would need assurance that any marketed sample of product will be sterile and would pass the requirements for sterility as found in the general chapter Sterility Tests $\langle 71\rangle$.

It is important to consider the limitations of the Sterility Tests $\langle 71\rangle$ in the evaluation of terminally sterilized products. The sterility test described in general chapter $\langle 71\rangle$ is limited in its sensitivity and is statistically ill-suited to the evaluation of terminally sterilized products given the exceedingly low probability of contaminated units. Therefore, once a sterilization process is fully validated and operates consistently, a combination of physical sterilization data such as accumulated lethality or dosimetry in combination with other methods, such as biological indicators or physicochemical integrators, can provide more accurate information than the sterility test regarding the release of terminally sterilized product to the marketplace.

There are four modes of sterilization that theoretically and practically could qualify for parametric release: moist heat, dry heat, ethylene oxide, and ionizing radiation sterilization. This information chapter first will cover the general issues related to parametric
release, regardless of the modes of sterilization, and then discuss some specific modes of sterilization. The chapter will not address the parametric release of terminally sterilized medical devices.

Terminally sterilized products represent the lowest risk category of sterile pharmaceutical products. Unlike products aseptically manufactured in a microbiologically controlled environment, terminally sterilized products are in a mierobially lethal preeess. The processes used to render terminally sterilized products free of microbial contamination are known to provide a greater degree of sterilization assurance than produets produced only by a septic proeessing.
$\square_{\text {subjected to }}$ a sterilization process the microbiological lethality of which can be quantified. Because aseptic processing relies on exclusion of microbiological contamination and is not based upon lethality imparted on the product in its sealed container, it is not possible to establish a quantitative estimate of the sterility assurance level, or SAL. Although the term SAL is often used to describe the process capability of aseptic processes, it is important to note that in the case of aseptic processing, SAL can only be estimated from media fill contamination rates or other forms of risk assessment. In the case of terminal sterilization, it is possible to calculate a minimum SAL or Probability of Nonsterility (PNS) quite accurately. Therefore, the term SAL has different contextual meanings when used to describe aseptic rather than terminal processes and it is important that this difference is fully understood by scientists and engineers working in the field of sterile product manufacturing and control. The terms PNS and SAL are often used interchangeeably.m2S (USP28)

Terminally sterilized products must have a probability of nonsterility (PNS) of not more than one in a million units produced. This is often stated as a PNS
$\square_{\text {Or SAL }}^{\text {(12S (USP28) }}$
of $10^{-6}$, or the probability of product bioburden surviving the sterilization process in any single unit of product is less than one in one million. The proof that a terminally sterilized product complies with the $10^{-6}$ PNS can be accomplished by several different sterilization cycle development approaches. The proper application of these methods requires extensive scientific knowledge regarding the sterilization method selected for use with a specific product.

The general methods used for
$\boldsymbol{m}_{\text {strategies used to }}$ validate $\mathrm{a}_{\mathbf{\square} 2 \text { (USP28) }}$
terminal sterilization process development fall into three categories:

1. Bioburden-based process.
2. Biological indicator/bioburden combined process.
3. Overkill process.

The bioburden-based process is not frequently used, and
2S (USP28)
requires extensive knowledge of product bioburden. It should be noted that several radiation dose-setting procedures involve establishing radiation processes on the basis of bioburden count and radiation resistance. This method requires that at least a $10^{-6} \mathrm{PNS}$ be attained for bioburden by the sterilization process. This means that if the product bioburden action level is 10 microorganisms or one logarithm, at least seven logarithms of bioburden must be inactivated to assure a $10^{-6}$ PNS. The bioburden-based method requires the user to develop suitable critical control points within the process to control the bioburden titer. Products that readily permit bioburden survival require more controlled manufacturing environments and more precise in-process control. This process is better suited for cycle development for clean or ultra-clean products containing fewer than 10 mierobes per unit
-a consistently low level of colony forming units (CFU) per
product unit ${ }_{\text {2S }}$ (USP28)
with a low frequency of spore-forming microorganisms. Also, this process may be necessary to permit terminal sterilization of a product that may potentially lose key qualities or attributes as a result of a more rigorous sterilization process.

Certain bioburden processes may include products that may be inherently antimicrobial or that can withstand more lethal sterilization processes. Products in this category will require correspondingly less rigorous control of the manufacturing process and less restrictive in-process control points. The microbiologist may find that formal hazard analysis procedures, such as Hazard Analysis Critical Control Point (HACCP), are useful in establishing appropriate manufacturing control conditions and in-process control parameters.

The biological indicator/bioburden combined process is generally used when the manufacturer desires a sterilization process that demonstrates the inactivation of high numbers of biological indicator microorganisms known to be resistant to the process. While the manufacturer may have preferred utilizing an overkill process, potential loss of some product attributes may occur in an overkill process thereby necessitating the use of a biological indicator/bioburden combined process. This process requires knowledge of the bioburden load on and in the product, and a database relative to the sterilization resistance of the bioburden. The relative resistance of the selected biological indicator to that of the bioburden must be established on or in the product. Frequently, biological indicator counts of approximately $10^{6}$ spores per indicator are used in the development of such processes. Fractional exposure cycles are generally conducted to determine the relative sterilization resistance (or D value) between product inoculated with the biological indicator microorganism(s) and frequently encountered bioburden. This process is frequently used for sterilization cycle development by manufacturers of terminally sterilized parenteral products and for ethylene oxide sterilization of medical devices.

The overkill process is frequently used when the article being sterilized is completely inert to the sterilizing agent and sterilization cycle conditions without any concern for loss of product attributes or quality. When using this process, some bioburden knowledge should be available especially
-to ensure that the materials are not adulterated before ster-
ilization. These data may include ${ }_{\square 2 S}{ }^{\text {(USP28) }}$
product bioburden count data and knowledge concerning the prevalence of spore formers. The database for this process need not be as extensive as bioburden data required for the bioburden process or the biological indicator/bioburden process. Generally, process resistant biological indicators containing approximately $10^{6}$ spores are used to establish the endpoint of the sterilization process. This process is then doubled to provide a $10^{\text {² }}$ SAL for the biolegient indienter. The premise is that this proeess will exeeed the requirements neessay to inactivate bioburden to a $10^{-6}$ PNS. This pro-
eess is frequently used to sterilize certain fabricated metal emponents, tools, and equipment sterilized prior to use in an aseptic processing area.
-However, a spore population of $N_{0}$ can be chosen to provide an appropriate challenge to evaluate the process. Overkill is generally defined as a process that would produce a minimum of $F_{0}$ of 12 minutes (see Critical Operating Parameters below) and is demonstrated biologically based upon the spore log reduction of calibrated biological indicators. D2S $^{\text {(USP28) }}$

## Change to read:

## GENERAL REVIEW

## Validation of Sterilization Process

Parametric release first requires that the chosen sterilization process be designed and validated to achieve a $10^{-6} \mathrm{PNS}$ relative to the inactivation of bioburden. Validation of most sterilization processes includes the validation of physical parameters of the process and of its microbiological effectiveness through the use of biological indicators. The use of biological indicators for establishing or periodically validating gamma radiation sterilization processes is not required. Widely recognized biological indicator organisms are used in the validation of moist heat process

## ${ }^{\square}$ processes $_{\text {■2S }}$ (USP28)

because they provide a means of comparing physically measured lethality data with biological lethality. There should be a reasonable correlation between physically measured lethality data $\left(F_{0}\right)^{1}$ and biological lethality as determined by the evaluation of the process with biological indicators.
Because the predictability of effectiveness of bioburden based temminal sterilization is associated with the number and resistance of mieroorganisms on or in a product, one of the compenents of parametric release is an active-sterilization mierobiology eontrol program to menitor the count and sterilization resistance of product bioburden.
-The predictable effectiveness of bioburden-based terminal sterilization is based on the number and resistance of microorganisms on or in a product. For this reason, one component of parametric release is an active microbiology control program to monitor the count and sterilization resistance of product bioburden. 2 2S (USP28)
Bioburden control and enumeration is of far less significance when the overkill process design is used. In many cases, overkill processes do not require extensive ongoing assessment of bioburden and require less in-process control of the manufacturing environment.

[^266]
## Sterilization Microbiology Control Program

The purpose of this control program is to ensure that the microbiological status of the product, prior to being terminally sterilized, has not significantly deviated from the established microbiological control level used for validation of the sterilization process. The microbiology control program includes the monitoring of the bioburden on or in the product and the monitoring of the microbiological status of any necessary containers, closures, or packaging materials. Also included is a program to evaluate the microbiological status of the environment where the product is processed. The control program is particularly important in cases where the terminal sterilization is not based on overkill, but rather on the bioburden or combined bioburden/biological indicator cycle development approach. In many cases, bioburden control and manufacturing environmental monitoring will not be required for overkill process designs, where the $F_{0}$ of the process is at least 12 minutes. In other cases, even when overkill processes are employed, some limited monitoring will be needed. Monitoring of overkill processes for bioburden is generally required only in cases where the product is supportive of microbial growth, and, therefore, biological amplification of any bioburden is likely. Of particular concern in this case is the potential for the product to be contaminated with microbial toxins or to be degraded by microorganisms.

The frequency of monitoring will depend on the variations of bioburden from potential sources. The number of microorganisms, their identification, as well as their resistance to the specified sterilization mode should be considered when parametric release of terminally sterilized product is established. Resistance to a specified sterilization mode by different species can influence sterilization effectiveness and the determination of sterilization process conditions when using the bioburden or combined bioburden/biological indicator method of cycle development. In the bioburden approach to process development, indicator organisms more resistant than typical bioburden may be used, although extreme differentials in resistance are not required. Information on the performance of biological indicators may be found in the general chapter Biological Indicators-Resistance Performance Tests $\langle 55\rangle$.

## Change Control System

Changes introduced to the sterilization processing equipment could result in a significant departure of the initially validated parametric release process. It is, therefore, essential that a change control system be instituted. A change control system is a formal system with appropriate standard operating procedures, which would include approval of changes in the sterilization processing equipment. This system would assess all the changes in relation to the critical parameters included in parametric release. The change control system also includes technical and management review and "go-no go" hurdles. If a change would significantly affect any critical parameter, each parameter would have to be revalidated in terms of sterility assurance of the pharmaceutical product to a minimum $10^{-6} \mathrm{PNS}$. Appropriate regulatory notification would also be part of the revalidation process.

## Release Procedures

A quality assurance program should be established that describes in detail the batch or lot release steps for parametric release of sterilized products and the required documentation. Although the assessment of the sterility assurance of products is primarily based on measurement of physical process parameters, a number of areas should be reviewed, documented, and approved for the parametric release of these products. These areas can include the following: a review of bateh records; a review of the ongoing mi
erobiologieal environmental contrel program results; a review of any process physicochemical or bioburden indicators or integra ters; a review of the maintenance status of processing equipment, ehange orders, and deviation control reeords; produet bioburden data and any revalidation data; and the-status-ofequipment calibration.
-These areas may include the following: a review of batch records; a review of the ongoing microbiological environmental control program results and presterilization bioburden; and a review of records of thermographic data and results of indicators that may have been used to demonstrate process control. It is also important to ensure that the sterilizer is current relative to calibration, maintenance, and revalidation.■2S (USP28)
The implementation and practice of parametric release is not an intermittent program. Once such a program is implemented, release of the sterilized product is made in accordance with the requirements of the regulatory approved program. Product release by other means is not acceptable if the predefined critical operational parameters are not achieved.

## Change to read:

## MODES OF STERILIZATION

## Moist Heat Sterilization

Moist heat sterilization of pharmaceutical products includes several types of sterilizing environments and sterilizing media. Saturated steam, hot water spray, and submerged hot water processes are all considered as moist heat sterilizing environments. Different processes may be used to sterilize products by moist heat, and they include batch-type sterilizers and continuous-type sterilizers.

## CRITICAL OPERATING PARAMETERS

A defined list of key process parameters and their respective operating limits are defined and established in the sterilization process specifications. Critical operating parameters are those that are absolutely essential to ensure product sterilization to a $10^{-6} \mathrm{PNS}$. Examples of critical operating parameters may include, but are not limited to, minimum and maximum limits for process peak dwell temperature, average peak dwell temperature, and the results of the batch or lot release test that satisfies the requirements of CFR, Part 211. $F_{0}$ is not listed as a critical parameter because a specific $F_{0}$ range can be achieved by variable temperature and time relationships. The target $F_{0}$ range, however, could be listed as a secondary (noncritical) parameter provided the specific time at temperature range was specified to achieve the target $F_{0}$ range. Other measured parameters may be considered secondary (or noncritical) parameters and may include maximum and minimum time to peak dwell, chamber pressure, and if applicable, chamber water level, sterilizing water time above defined temperature limits, and recirculating water pump pressure differential.

## Ethylene Oxide Sterilization

The application of parametric release of pharmaceutical products sterilized by ethylene oxide is more difficult than parametric release of products sterilized by moist heat processes. Sterilization by ethylene oxide (ETO) has more critical parameters than moist heat sterilization that are interrelated and that determine whether, at a minimum, a $10^{-6} \mathrm{PNS}$ is obtained when these parameters are within the specified limits of a validated cycle.

## CRITICAL OPERATING PARAMETERS

These eritieal parameters include the following: temperature, a meunt of relative humidity present, ethylene-oxide coneentration, everall expesure time, produet and lead density, and gas permeability factors.
-Critical parameters may include the following: temperature, amount of relative humidity present, ethylene oxide concentration, overall exposure time, product and load density, and gas permeability factors. ${ }^{2 S}$ (USP28)

Parametric release of pharmaceutical products can be achieved if an automated measurement system for the critical parameters is employed and sterilization loads are closely defined and validated relative to product types, densities, packaging materials, and overall load configurations. An example of the measurement of critical factors that may be considered for parametric release would be the use of calibrated ETO pressure recordings to provide an estimate of ETO concentration during the process hold time or the use of direct measurement of ETO concentration by IR or gas chromatography. Because of variances that might occur in the key parameters during sterilization, parametric release is not widely used for products sterilized by ETO.
However, to ensure parametric release, in addition to the attainment of critical parameters of the ethylene oxide sterilization process, biological indicators (and their sterility testing after sterilization processing) or the use of physicochemical integrators for the ethylene oxide sterilization can be used in each sterilized load.

## Radiation Sterilization

Two radiation sterilizing processes have been used: gamma and electron beam sterilization (i.e., ionizing radiation). Some pharmaceutical products, either in bulk or in their finished formats, have been sterilized by radiation. In discussing the critical parameters of radiation sterilization necessary for parametric release, it is customary to refer to parametric release as dosimetric release. Dosimetric release is provided by the use of a chemical dosimeter that measures the delivery of a minimum specified radiation dosage, which has been shown to provide sterilization of the product to a minimum $10^{-6} \mathrm{PNS}$.

The use of a dosimeter in ionizing radiation sterilization measures delivery of a minimum absorbed radiation dose to a pre-established low dose zone in the irradiated product carrier. This will require mapping of the profile of absorbed ionizing radiation across the density ranges processed in the product carrier. The lowest specified radiation dosage for the process is correlated to predictable bioburden reduction levels by any one of the three documented methods. ${ }^{2}$ An alternative method may be considered whereby extensive product bioburden count and radiation resistance data are available. Dose verification studies would be conducted to en-
${ }^{2}$ ANSI/AAMI/ISO 11137-1996, Sterilization of Health Care ProductsRequirements for Validation and Routine Control-Radiation Sterilization, July 11, 1994.
sure that the worst case bioburden load, relative to resistance and numbers, can be inactivated at the lowest dose zone in the carrier system to provide at least a $10^{6}$

## ${ }^{-10^{-6}}$ 2S (USP28)

SAL. This method would of course require an ongoing program of bioburden assessment. The target for the radiation cycle is a minimum $10^{-6}$ PNS relative to the product bioburden. Because the radiation cycle is calculated on the basis of the bioburden, dosimetric release should include a batch evaluation of the bioburden number and of its radiation resistance.

Dosimetric release of a radiation-sterilized product depends on the delivery of at least a minimum dosage; thus, the critical operational parameters that govern the delivery of that dosage must be within specified limits. These operational critical parameters may include the following: a stacking configuration within the radiation carrier, bulk density of the product, speed of the conveyor or carrier system, distance to the radiation source, duration of product exposure, and appropriate defined adjustments for a decaying radiation source. Demonstration of consistency in the absorbed radiation dosage at areas of minimum and maximum zones of radiation absorption within the fully loaded carriers on a batch-to-batch basis is a necessary condition for dosimetric release of radiation-sterilized pharmaceutical products.

## Change to read:

## SUMMARY

The conversion to parametric release in lieu of product sterility testing as described in general chapter Sterility Tests $\langle 71\rangle$ requires prior FDA approval. Parametric release is advantageous for terminally sterilized products. The extensiveness of data required to establish parametric release,
-compared to the general chapter $\langle 71\rangle$ procedures, which lack sensitivity to very low levels of microbial contamina-
tion, $\mathbf{m}_{2 S}$ (USP28)
can result in a more accurate and reliable assessment of the probability of nonsterility of product lots. than the procedures as defined in chapter $\langle 74\rangle$ because these lack sensitivity to very low levels of mierebial contamination.

■ $\mathbf{m}^{\text {S }}$ (USP28)

## BRIEFING

〈1231 > Water for Pharmaceutical Purposes, USP 27 page 2628 and page 1641 of PF 29(5) [Sept.-Oct. 2003]. The Pharmaceutical Waters Expert Committee received numerous letters commenting on the proposed revision of this general information chapter, which is indicative of the importance placed on the information in this chapter by users of pharmaceutical waters. The Expert Committee met on March 4, 2004 to address all of these concerns and have revised many parts of the chapter. The Expert Committee believes that this revised document covers most aspects of pharmaceutical waters. With further enhancements, the Expert Committee believes that this chapter could serve as a guidance document for regulatory purposes, but recommended that this concept be re-evaluated during the next Convention cycle (2005-
2010) when a new Expert Committee will be on board. Please direct comments to Frank Barletta, liaison to the Pharmaceutical Waters Expert Committee.
(PW: F. Barletta) RTS-41393-1

## Change to read:

## 〈1231〉 WATER FOR PHARMACEUTICAL PURPOSES

Water is the mest widely used substanee, raw material, or ingredient in the production, processing, and formutation of compendial artieles. Control of the mierobiologieal quality of these waters is impertant beeause proliferation of mierorgenaisms ubiquitous to water may oceur during the purifieation, storage, and distribution of this substane. If water is used in the final product, these miereerganisms or their metabolic produets may eventtally catuse ad verse consequences.

Water that is used in the early stages of the production of drug substanees and that is the semree or feed water for the preparation of the various typer of purified waters must meet the requirements of the National Primary Drinking Water Regulations. (NPDWR) (40-CFR 141) isstred by the Environmental Protection Ageney (EPA). Comparable regulations for drinking water of the Etropean Union or Japan are acceptable. These requirements ensure the $a b-$ sence of coliferms, which, if determined to be of fecal origin, may pertend or indiente the presence of other microorganisms of feed origin, including viruses that may be pathogenic for humams. On the other hand, meeting these National Drinking Water Regulations would not rule out the presence of other mieroorganisms, whieh, while not considered a major public health concern, could, if present, constitute a hazarder be considered undesirable in a drug substance or formulated product. For this reason, there are many dif ferent grades of pharmaceutieal waters.

## TYPES-OF-WATER

Prinking Water Drinking Water is not eovered by a compendial menegraph but must cemply with the quality attributes of the EPA NPDWN or comparable regulations of the Emropean Union-or Japan. It may be derived from variety of sourees ineluding a publie water utility, a private water supply (e.g., a well), or a combi nation of mere than one of these sotrees. Drimking Water may be used in the early stages of chemieal synthesis and in the early stay es of the cleaning of pharmaceutical manufacturing equipment. It is the preseribed serree feed water for the production of phatmaceut tieal waters. As seasenal variations in the quality attributes of the drinking water supply ean ecur, processing steps in the produetion ef pharmaceutieal waters must be designed for this characteristic.

Purified-Water Purified Water (see USP menegraph) is used as an exeipient in the production of official preparations; in phar maceutieal applientions, such as cleaning of certain equipment; and in the preparation of some bulk pharmaceutical chemieals. Purified Water mast meet the requirements for ionic and organic chemieal purity and must be protecte from mierobial proliferation. It is prepared using Drinking Water as a feed water and is purified using thit operations that melude deionzation, distillation, ion ex ehange, revers osmesis, filtration, or other suitable procedures. Purified Water systems must be validated.

Purified Water systems that produce, store, and cireulate water under ambient conditions are susceptible to the establishment of tenacious biofilms of mieroorgonisms, which can be the source of undesirable levels of viable mieroorganisms or endotoxins in the effluent water. These systems require frequent sanitization and mierobiologieal monitoring to ensure water of appropriate mi erobiologieal quality at the points of use.
Sterile Purified-Water Sterile-Puriffed-Water [USP mene graph to come] is Purified Water that is packaged and rendered sterile. It is used in the preparation of nomparenteral compendial dosage forms where a sterile form of Purified Water is required.

Water for Injection Water for Injection (see USP menograph) is an excipient in the production of injections and for use in phar maceuticalapplications, suchas cleaning of certain equipment, and in the preparation of some bulk pharmaceutieal-chemieals. The source or feed water for this article is Drinking Water, which may have been preliminarily purified but which is finally subjected to distillation or reverse osmesis. It must meet all of the chemical requirements for Purified Water and in addition the requirements
 from mierobial contamination. The system used to produee, store, and distribute Water for Injection must be designed to prevent mi erobial contamination and the formation of mierobial endorins, and it must be validated.

Sterile-Water for Injection_Sterile-Water for Injection (see USP monegraph) is Water for Injection that is packaged and ren dered sterile. Sterile-Water for Injection is intended for extempera neous preseription compounding and is distributed in sterile units. It is used as a diltuent for parenteral products. It is packaged in sim gle dose containers not larger than 1 liter in size.
Bacteriostatic-Water for Injection-Bacteriostatic Water for thjection (see USP monograph) is sterile- Water for Injection to which has been added one or more suitable antimicrobial preserva tives. It is intended to be used as a diluent in the preparation of parenteral products. It may be packaged in single dose or multiple dose containers not larger than 30 mb .
Sterile-Water for Irrigation-Sterile-Water for Irrigntion (see USP monograph) is Water for Injection, packaged in-single dose en andiners of larger than 1 liter in size, that is intended to be deliv ered rapidly and is rendered sterile. It need not meet the requirement under small volume injections in the chapter Particulate Matter $\langle 788$ ) -
Sterile-Water for Inhalation-Sterile Water for Inhalation (see USP menegraph) is Water for Injection that is packaged and ren dered sterile and is intended for use in imhalators and in the preparation of inhalation solutions.

## VALDAFION AND-QUAЦIFICATION-OF WATER PURIFICATION, STORAGE, AND DISTRHBUTION SYSTEMS

Establishing the dependability of pharmaceutienl water purifien tion, storage, and distribution systems requires an appropriate period of menitoring and observation. Ordinarily, few problems are encountered in maintaining the chemieal purity of Purified Water and-Water for Injection. However, it is more diffieult to meet established mierobiologieal quality criteria consistently. A typieat program involves intensive daily sampling and testing of major proeess points for at least one month after operational criteria have been established for each sampling peint.
Validation is the procedure whereby substantiation to a high ler el of assurne that a specific proeess will consistently produce a product eonforming to an established set of quality attributes is at quired and doeumented. The validation defines the critieal process parameters and their operating ranges. A validation program qual iffes the design, installation, operation, and performanee of equip-
ment. It begins when the system is defined and moves through sev eral stages: qualification of the installation (M), operational quat iffation ( $(Q)$ ), and performance qualification (PQ). A graphical
representation of a typieal water system validation life cycle is shown in Figurre 1. A validation plan for a water system ypieally includes the following steps:
(1) Establishing standards for quality attributes andoperating parameters.

(2) Defining systems and subsystems suitable to produce the desired quality attributes frem the available source water. (3) Selecting equipment, controls, and menitoring teehnolegies.
(4) Develeping an IQ stage consisting of instrument calibra tiens, inspections to verify that the drawings aceurately depiet the as built configuration of the water system and, where nee essary, special tests to verify that the installation meets the design requirements.
(5) Developing an OQ stagensisting of tests and inspec tions to verify that the equipment, system alerts, and controls are operating reliably and that appropriate Alert and Action Levels are established. This phase of qualification may over tap with aspects of the next step.
(6) Developing a prospective PQ stage to confirm the appropriateness of critical process parameter operating ranges. $A$ eeneurrent or retrespective PQ - is performed to demenstrate system reproducibility over an appropriate time period. During this phase of validation, Alert and Action Levels for key equality attributes and operating parameters are veriffed. (7) Supplementing a validation maintenance program (alse ealle continuous validation life eyele) that includes a mechanism to control changes to water system and establishes and carries out seheduled preventive maintenance including recalibration of instruments. In addition, validation maintenance includes a monitoring program for critical process pa rameters and a corrective action program.
(8) Instituting a schedule for periodic review of the system performance and requalification.
$(\vartheta)$ Completing protocols and doemmenting Steps 18.

## PHARMACEUTICAL WATER SYSTEMS

The quality attributes of water for a partieular applieation are dietated by the requirements of its usage. Sequential processing steps that are used for treating water for different pharmaeeutieat
purposes are shown in Figutre 2. A typical evaluation process to select an appropriate water quality for a particular pharmaceutieal purpese is shown in the decision tree in Figure 3. These diagrams may be used to assist in defining requirements for specific water uses and in the selection of unit operations.


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Fig. 3. Selection-of water for pharmareutienl purposes.

## PURIFID-WATER AND-WATER FOR INJECTHN SYSTEMS

The design, installation, and operation of systems to produce Purifed Hater and Hater for Injection inelude similariompenents, eentrol techniques, and procedures. The quality attributes of both waters differ only in the presence of a bacterial endotoxin requirement for Water for Injection and in their methods of preparation, at least at the last stage of preparation. The similarities in the quality attributes provide considerable commen ground in the design of water systems to mee either requirement. The-critical difference is the degree of eontrolof the system and the final purifieation steps needed to enstre bacterial and bacterial endotoxin removal.

Production of pharmaceutical water employs sequential unit operations (processing steps) that address specific water quality attri butes and protee the peration of subsequent treatment steps. The
fanal unit operations used to produce Water for Injection have been limited to distillation and reverse osmesis. Distillation has a long history of reliable performance and can be validated as a unit operation for the production of Water for Injection. Other technologies such as ultrafltration may be suitable in the production of Hater for Injection, but at this time experience with this proeess is not widespread.
The validation plan should be designe to establish the suitabil ity of the system and to provide a therough understanding of the purification mechanism, range of operating conditions, required pretreatment, and the most likely mode of failure. It is also neeessary to demenstrate the effectiveness of the monitering seheme and to establish the requirements for validation maintenance.

Trials conducted in a pilot installation can be valuable in defining the operating parameters and the expected water quality and in identifying failure modes. However, qualification of the specific unit operation can only be performed as part of the validation of the installed operational-system.

The selection of specific unit operations and design-characteris ties for a water system should take into consideration the quality of the feed water, the technology chesen for subsequent processing steps, the extent and complexity of the water distribution system, and the appropriat compendial requirements. For example, in the design of a system for Water for Injection, the final process (distil fation or reverse osmesis) must have effective bacterial endotoxin reduction capability and must be validated.

The following is a brief description of selected unit operations and the operation and validation concerms associated with them. This review is not comprehensive in that not all unit operations are discussed, ner are all potential problems addressed. The pur pose is to highlight issues that foeus on the design, installation, op eration, maintenanee, and monitoring parameters that facilitate water system validation.

Filtration tee hmology plays an impertant role in water systems, and filtration units are available in a wide range of designs and for various applientions. Removalefficiencies differ signifienntly from eoarse filters, such as gramular anthracite, quartz, or sand for larger water systems and depth cartridges for smaller water systems, to membrane filters for very small particle control. Unit and system ennfigurations wary widely in type of filtering media and loeation in the process. (Use of membrane filters is diseussed in a later paragraph.)

Gramlar or eartridge filters are used for prefiltration. They remove solid contaminants frem the water supply and protect downstream system compenents from contamination that can inhibit equipment performance and shorten their effective life. Design and operational issues that may impact performane of depth filters include channeling of the filtering media, blockage from silt, mi erobial growth, and filtering media loss. Control measures inelude pressure and flow monitoring, backwashing, samitizing, andreplac ing filtering media. An impertant design concern is sizing of the filter to prevent channeling or media loss resulting from inapprepriate water flow rates.

Aetivated earbon-beds adsorb low molecular weight organie material and oxidizing additives, such as chlorine compounds, and remove them frem the water. They are used to achieve certain quality attributes and to protect against reaction with downstream stainless steel surfaces, resins, and membranes. The chief operating eoneerns regarding activated earbon beds inelude the propensity to suppert bacteria growth, the petential for hydraulic chammeling, the inability to be regenerated in situ, and the shedding of bacteria, en dotoxins, orgenic chemicals, and fine carbon paritieles. Control meastres include appropriate high water flow rates, samitization with hot water or steam, backwashing, testing for adserption capacity, and frequent replacement of the earben bed. Alternative teeh nologies sueh as chemieal additives and regenerable organie sear enging deviees can be used in place of activated carben beds.

Chemieal additives are used in water systems to control miere orgunisms by use of chlorine compounds and ozone, to enhance the removal of suspended solids by use of floceulating agents, to remove chlorine compernds, to adjust pH , and to remeve carbenate eompounds. Subsequent processing steps are required to remove the added chemienls. Control of additives and subsequent menitor ing to enstre remoral of additive and of any of their reaction prod uets should be designed into the system and ineluded in the menitering pregram.

Organie seavenging deviees use macroreticular anion en ehange resins eapable of removing organie material and endotox ins from the water. They can be regenerated with appropriate biocidal caustic solutions. Operating eoneerns are associated with seavenging eapacity and shedding of resin fragments. Control mea sures include testing of effluent, monitoring performance, and using downstream filters to remove resin fines.

Water softeners remove cations such as calcium and magnesium that interfere with the performance of downstream processing equipment such as reverse osmosis membranes, deionization col umms, and distillation units. Water seftener resin beds are regenerated with sodium chloride solution (brine). Coneerns inelude mierorgenism proliferation, channeling due to inappropriate wa ter flow rates, orgenic fouling of resin, fracture of the resin beads, and contamination frem the brine-solution used for regeneration. Control measures include recireulation of water during periods of low water use, periodic sanitization of the resin and brine-sys tem, use of mierobial control deviees (e.g., UV and ehlorine), appropriate regeneration frequeney, eflluent monitoring (hardness), and downstream filtration to remove resin fines.

Peionization( P ), eleetrodeionization(EDI) and Eleetrodialysis (EPR) are effective methods of improving the chemieal qual ity attributes of water by removing cations and anions.

DI systems have charged resins that require periodic regenera tion with an acid and base. Typically, cationic resins are regenerat ed with either hydrechloric or sulfuric acid, which replace the eaptured positive ions with hydrogen ions. Anionic resins are regenerated with sodium or petassimm hydroxide, which replace tured negative ions with hydroxide ions. Both regenerant ehemicals are biocidal and offer a meastre of mierobial control. The system can be designed so that the cation and anion resins are separated or that they form a mixed bed. Rechargeable resim eanisters can also be used for this purpose.

The EDI system use a combination of mixed resin, selectively permeable membranes, and an electrie eharge to provide contint ous flow (product and waste concentrate) and contintrous regeneration. Water enters beth the resin section and the waste (eencentrate) section. As it passes through the resin, it is deionized to become product water. The resin acts as aconductor enabling the electrical potential to drive the captrred cations and anions through the resin and appropriate membranes for concentration and remor al in the waste water stream. The electrieal potential also separates the water in the resin (product) section into hydrogen and hydrox ide ions. This permits continueus regeneration of the resin witheut the need for regenerant additives.

Electrodialysis (EDR) is similar proess that uses only electric ity and selectively permeable membranes to separate, concentrate, and flush the removedions from the water stream. It, however, is less efficient than EDI beeause it contains no resin to enhanee ion removal and eurrent flow. Also, EDR units require periodic polar ity reversal and flushing to maintain-operating performance.

Goncerns for all forms of deionization units inelude mierobiat and-endotoxin control, chemieal additive impact on resins and membranes, and loss, degradation, and fouling of resin. Issues of eoncern specifie to DI units include regeneration frequeney, chan neling, complete resin separation for mixed bed regeneration, and mixing air contamination (mixed beds). Control measures vary but fypieally inelude recireulation loops, mierobial eontrol by UV light, conductivity monitoring, resin testing, mieropereus filtration of mixing air, mierobial menitoring, frequent regeneration to min imize and control mieroorganism growth, sizing the equipment for suitable water flow, and use of elevated temperatures. Regeneration piping for mixed bed units should be configured to ensure that regeneration chemieals contact all internal-surfaces and resins. Reehargeable canisters can be the-source of contamination and should be carefully monitored. Full knowledge of previous resin use, minimum strage time between regeneration and use, and appropriate sanitizing procedures are critical factors ensuring proper performance.

Reverse osmosis ( $\mathrm{R} 日$ ) units employ a semipermeable membrane and a substantial prescure differential to drive water threugh the membrane to achieve chemied, mierebial, and endotoxin quality improvement. The proeess streams eonsist of supply water, product water (permeate), and waste water (reject). Pretreat ment and system configuration variations may be necessary de pending on souree water to achieve desired performance and reliability. Concerns associated with the design and operation of

RO units include membrane material sensitivity to bacteria and sanitizing agents, membrane fouling, membrane integrity, seal in tegrity, and the volume of waste water. Failure of membrane or seat integrity will result in produet water contamination. Methods of eontrol consist of suitable pretreatment of the water stream, appropriate membrane-material selection, integrity challenges, membran design such as spiral wound to promete flushing action, periodic sanitization, menitoring of differential pressures, conductivity, microbial levels, and total organic carben. The configuration of the RO unit effers controloppertunities by expanding the singlepass seheme to parallel staged, reject staged, two pass, andeombination designs. An example would be the use of a pass design to improve reliability, quality, and efficieney. RO units ean be used alone or in combination with DI and EDI units for operational and quality enhaneements.

Ultrafiltration is another technology that uses a permeable membrane, but unlike $R O$ it works by mechanieal separation rather than-osmesis. Due to the filtration ability of the membrane, mac remolecular and mierobial impurities, such as endotoxins, are redured. This technelogy may be appropriate as an intermediate or final purification step. Similar to PO , suecessfulperformane is dependent upen other system unit operations and system configurn tion.

Isstes of concern include compatibility of membrane material with sanitizing agents, membrane integrity, fouling by particles and mieroorgmisms, eartridge contaninant retention, and senl in tegrity. Control measures include sanitization, designs capable of flushing the membrane curface, integrity challenges, regular ear tridge changes, elevated feed whter temperature, and monitoring talorganie earben and differential pressure. Additional flexibility in operation is possible based on the way units are arranged such as in a parallel or series configuration. Care should be taken to avoid stagnant water conditions that could promote mieroorganism growth in back up or standby units.

Mierobial retentive filters (membrane flters) prevent the passage of mieroorganisms and very small particles. They are used in tank air and inert gas vents and for filtration of compressed air gases used in the regeneration of mixed bed deionization units. Areas of concern are blockage of tank vents by condensed water vapor, which ean eatse mechaniend damage to the tank, andeoncentration of mierergenisms on the surface of the membrane filter, creating the potential for contamination of the tank or deionizer contents. Control measures include the use of hydrophebic filters and heat fracing vent flter housings to prevent vaper condensation. Sterili zation of the unit prior to initial use and periodieally thereafter or regular filter changes are also recommended control methods. Mierobial retentive filters are sometimes incorporated into purifica tion systems or in water distribution piping. This appliention should be carefully controlled beeause as noted above, these units ean become a souree for mierobial contamination. The petentiat exists for the release of mieroorganisms should the membrane filter fupture or as a result of mierobial grow through. Other means of eontrolling mieroorganisms and fine partieles can be employed in place of membrane filters in the purification and distribution see tion of water systems. Filters that are intended to be mieroretentive should be sanitized and integrity tested prior to initial use and at appropriate intervals thereafter.

Positively charged filter media reduce endotoxin levels by electrostatic attraction and adsorption. Applieation may be mit operation or distribution systemrelated depending upen the mierobiat entrol requirements. Filter media that are mierobial retentive require the same coneems and controls as indiented in the provious paragraph. Concerms include flow rate, membrane and seal integ rity, and retention capacity, which can be affected by the develop ment of a finite charge potential on the filter. Control measures inelude menitoring differential pressure and endotoxin levels, proper sizing, testing membrane-integrity, and configuring units in series to centrol break through.

Distillation units provide chemical and microbial purification via thermal vaporization, mist elimination, and condensing. A variety of designs are wailable including single effect, multiple of fect, and vaper compression. The latter two configurations are normally used in larger systems beeause of their generating ea pacity andefficieney. Distilled water systems may require less ris orous control of feed water quality than do membrane systems. Ar eas of concern include carry over of impurities, evaporator flooding, stagnant water, pump and compressor seal design, and eonductivity (quality) variations during start up and operation. Methods of control consist of reliable mist elimination, vistal of automated high water level indieation, use of sanitary pumps and eompressors, proper drainage, blow down control, and use of on line conduetivity sensing with automated diversion of unaceept able quality water to the waste stream.

Storage tanks are included in water distribution systems to optimize processing equipment capacity. Storage also allous for rou tine maintenance while maintaining continuous supply to meet manufacturing needs. Design and operation considerations are needed to prevent the development of biefllm, to minimize corro sion, to aid in the use of chemieal sanitization of the tanks, and to safeguard mechanical integrity. These considerations may inelude using elosed tanks with smooth interiors and the ability to spray the tank head space. This minimizes corrosion and biofilm development and dids in sanitizing thermally or chemically.
Storage tanks require venting to compensate for the dymamies of ehanging water levels. This ean be aceomplished with a hydrephebie mierobial retentive membrane filter fitted ento an atmospherie vent. Alternatively, an attomatic membrane filtered compressed gas pressurization and venting system may be used. Rupture disks equipped with a rapture alarm deviee serve as a farther safeguare for the mechanieal integrity of the tank.

Distribution configuration should allow for the continuous flow of water in the piping by means of recireulation or should provide for the periodic flushing of the system. Experienee has shown that eontintrously recireulated systems are easier to maintain.

Pumps should be designed to deliver fully turbulent flow eonditions to retard the development of biofilms. Compenents and dis tribution lines should be sloped and fitted with drain peints so that the system can be completely drained. In distribution systems, where the water is cireulated at a high temperature, dead legs and low flow conditions should be avoided, and valved tie in peints should have length to diameter ratios of 6 or less. In ambi ent emperature distribution systems, partieular care-should beexereised to avoid poeket areas and provide for complete drainage. Water exiting from a loop should not be returned to the system. Distribution design should include the placement of sampling valves in the storage tank and at other locations such as in the refan line of the reeireulating water system. The primary sampling site for water should be the valves that deliver water to the peint of use. Direct connections to processes or auxiliary equipment should be designed to prevent reverse flow into the controlled water sys tem. The distribution system should permit sanitization for mieroerganism contrel. The system may be contintously operated at sanitizing conditions or sanitized periodienlly.

## INSTAぬLATION AND MATERHALS OF GONSTRUCTHO AND-COMPONENT SELECTHON

Installation techniques are important beeause they can affect the mechanieal, corresive, and sanitary integrity of the system. Valve installation attitude-should promete-gravity drainage. Pipe supports should provide appropriate slopes for drainage and should be designed to support the piping adequately under worst ease thermalconditions. Methods of connecting system compenents in eluding units of operation, tanks, and distribution piping require eareful attention to preclude potential problems.

Stainless steel welds should provide reliable joints that are inter nally smooth and corrosion free. Low carbon stainless-steel, com patible wire filler, where necessary, inert gas, automatic welding machines, and regular inspection and doeumentation help to ensure acceptable weld quality. Follow ap cleaning and passivation are important for removing contamination and corrosion products and to reestablish the passive comrosion resistant surface. Plastic materials can be fused (welded) in seme cases and also require smooth, uniform internal surfaces. Adhesives should be avoided due to the potential for voids and chemieal reactions. Mechanieal methods of joining, such as flange fittings, require care to avoid the ereation of offsets, sepps, penetrations, and voids. Control meastres inelude go alignment, properly sized gaskets, appropriate spae ing, uniform sealing foree, and the avoidanee of threaded fittings.

Materials of eonstruetion-should be selected to be compatible with control measures such as sanitizing, cleaning, and passivating. Femperature rating is a critical factor in choosing appropriate materials because surfaces may be required to handle elevated oper ating and sanitization temperatures. Should chemieals or additives be used to clean, control, or sanitize the system, materials resistant t these chemieals or additives must be utilized.

Materials should be capable of handling turbulent flow andele wated velocities without wear on the corrosive barrier impact, such as the passivation related chromium oxide surface of stainless steel. The finish on metallic materials such as stainless steel, whether it be a refined mill finish, polished to a specific grit, or an electropelished treatment, should complement system design and provide-satis factory corrosion and mierobial activity resis tance. Auxiliary equipment and fittings that require-seals, sackets, diaphragms, filter media, and membranes shouldexelude materials that permit the possibility of extactables, shedding, and mierobiat activity.

Insulating materials exposed to stainless steel surface should be free of ehlerides to avoid the phenemenen of stress corresion eracking that can lead to system contamination and the destruction of tanks and critienl system components.

Specifications are impertant to ensure proper selection of materials and to serve as areference for system qualification and main tenance. Information such as mill reports for stainless steel and reperts of compesition, ratings, and material handling capabilities for nonmetallic substances should be reviewed for suitability and retained for reference.

Component (atuxiliary equipment) selection should be made with assuranee that it doe not creat a souree for contamination intusion. Heat exchangers should be double tube sheet or coneen trie tube desigh. They should inelude differential pressure menitor ing or utilize heat transfer medium of equal or better quality to avoid problems should leaks develop. Pumps should be of sanitary design with seals that prevent contamination of the water. Valves should have smoeth internal surface with the seat andelesing deviee expesed to the flushing action of water, such as oceurs in diaphragm valves. Valves with poeket areas or clesing devices (e.g., ball, plug, gate, globe) that move into and out of a flow area should be avoided.

## SANHTHZATHON

Mierobial control in water systems is achieved primarily through sanitization practices. Systems can be sanitized using either ther mal or chemieal means. In line UV light at a wavelength of 254 nm ean also be used "s "snitize" water in the system contint eusly.

Thermal appreaches to system sanitization include periodic or eentinurusly eireulating het water and the use of steam. These feehniques are limited to systems that are compatible with the high er temperatures needed to achieve sanitization, such as stainless steel and some polymer formulations. Although thermal methods eontrol biofflm development, they are net effective in removing es ablished biofflms.

Chemical methods, where compatible, can be used on a wider variety of construction materials. These methods typieally employ oxidizing agents such as halogenated compounds, hydrogen perox ide, ozone, or peracetic acid. Halogenated eompounds are effective sanitizers but are diffieult to flush from the system and tend to leave biofllms intact. Compounds such as hydrogen peroxide, ozone, and peracetic acid oxidize bacteria and biofilms by forming reactive peroxides and free radieals (notably hydroxyl radieals). The shori half life of these compounds, particularly ozone, may require that it be added eontintrously during the sanitization process. Hydrogen peroxide andozone rapidly degrade to water andoxygen; peracetie acid degrades to acetic acid in the presence of UV light.

UV light impacts on the development of biofilms by reduring the rate of new mierobial colenization in the system; however, it is only partially effective against planktonic mieroorganisms. Alone, UV light is not an effective tool beenuse it does not elimi nate existing biofilm. However, when coupled with conventional thermal or chemieal sanitization technologies, it is most effective and ean prolong the interval be ween system sanitizations. The use of UV light also facilitates the degradation of hydregen peroxide and ozone.
Sanitization steps require validation to demenstrate the capabil ity of reducing and holding mierobial contamination at aceeptable levels. Validation of thermal methods should inelude a heat distri bution study to demenstrate that sanitization temperatures are a ehieved throughout the system. Validation of chemieal methods require a demenstration of adequate chemieal-concentrations throughout the system. In addition, when the sanitization proeess is completed, effective removal of chemieal residues must be dem enstrated.
The frequency of sanitization is generally dictated by the results of system menitering. Conclusions derived from the trend analysis of the mierobiologieal dat should be used as the alert mechanism for maintenance. The frequency of sanitization should be estabtished such that the system operates in a state of mierobiologieal control and doe not exeeed Alert Levels.

## OPERATION, MAINTENANCE, AND CONTROL

A preventive maintenanee program should be established to en stre that the water system remains in a state of control. The program should include (1) procedures for operating the system, (2) monitoring programs for critieal quality attributes and operating eonditions ineluding calibration of eritieal instruments, (3) sehed the for periodic sanitization, (4) preventive maintenance of compo nents, and (5) centrol of ehanges to the meehanienl system and to eperating conditions.

Operating Proeedures. Procedures for operating the water system and performing routine maintenance and corrective action should be written, and they should also-define the point when at tion is required. The procedures should be well documented, detail the function of each job, assign whe is respensible for performing the work, and describe how the job is to be conducted.
Monitoring Program- Gritieal quality attributes andoperating parameters should be documented and monitored. The program may inelude a combination of in line sensors or recorders (e.g., a eondtretivity meter and recorder), manual documentation of oper ational parameters (such as carbon filter pressure drop) and labor atory tests (e.g., total microbial counts). The frequency of sampling, the requirement for evaluating test results, and the neeessity for initiating corrective action should be ineluded.
Sanitization- Depending on system design and the selected units of operation, routine periodic sanitization may be necessary to maintain the system in a state of mierobial control. Technolegies for sanitization are deseribed above.

Preventive Maintenance A preventive maintenance program should be in effeet. The program should establish what preventive maintenance is to be performed, the frequency of maintenance work, and how the work should be documented.

Change-Contrel. The mechanical eonfiguration andoperating eonditions must be controlled. Propesed changes should be valuated for their impact on the whole system. The need to requalify the system after changes are made should be determined. Following a decision to modify a water system, the affeeted drawings, manmals, and procedures should be revised.

## SAMPLING CONSIPERATHONS

Water systems should be monitered at a frequeney that is suffit eient to ensure that the system is in contrel and contintes to produee water of aceptable quality. Samples should be taken from representative locations within the processing and distribution system. Established sampling frequeneies should be based on system validation data and should cover critieal areas. Unit operation sites might be sampled less frequently than peint of use sites. The sampling plan should take into consideration the desired attributes of the water being sampled. For example, systems for Water for Injec tion, beeause of their mere-critieal mierobiologieal requirements, may require a more rigoreus sampling frequeney.

When sampling water systems, special care should be taken to ensure that the sample is representative. Sampling perts should be sanitized and thoreughly flushed before a sample is taken. Samples eontaining chemical sanitizing agents require neutralization prior to mierobiologieal analysis. Samples for mierobiologieal analysis should be tested immediately or suritably protected to preserve the sample until analysis ean begin.

Samples of flowing water are only indieative of the concentrat tion of planktonic (free floating) mieroerganisms present in the system. Benthic (attached) mieroorganisms present as biofilms are generally present in greater numbers and are the source of the planktonic population. Mieroorganisms in biofilms represent a continuous soure of contamination and are diffieult to sample and quantify. Consequently, the planktonic pepulation is used as an indieator of system contamination levels and is the basis for sys tem Alert Levels. The censistent appearance of elevated planktenic levels is usually an indiention of advaneed biofilm development in need of remedial control. System control and sanitization arekey in eontrolling biofilm formation and the consequent planktonic population.

## MICROBHAL CONSIPERATHONS

The major exogenous souree of mierobial contamination is seuree or feed water. Feed water quality must, at a minimum, meet the quality attributes of drinking water for which the level of coli forms are regulated. A wide varie of other mieroorganisms, chief ly Gram negative bacteria, may be present. These mierereganisms may compromise subsequent purification steps.
Examples of other potential exogenous sources of microbial eontamination inelude umprotected vents, faulty air filters, back flow from contaminated outlets, drain air breaks, and replacement activat carben and deionizer resins. Sufficient eare should be given to system design and maintenance in order to min imize mierobial contamination from these sources.

Unit operations can be a major source of endogenous microbiat eontamination. Mieroorganisms present in feed water may udsorb to carben beds, deionizer resins, filter membranes, and other unit eperation surfaces and initiate the formation of a biofilm. Bioflmis an adaptive respense by certain mieroorganisms to survive in a fow nutrient envirenment. Mierorgenisms in a biofilm are protected from the action of many biocides. Downstream colenization ean oceur when mieroorganisms are sloughed off and earried in other areas of the water system. Mieroorganisms may also attach
to suspended particles such as carben bed fines and serve as a source of contamination to subsequent purification equipment and-distribution systems.
Anether souree of endegeneus mierobial contamination is the distribution system. Mieroorganisms can colonize pipe-strafaces, walves, and other areas. There they proliferate, forming a biofllm, which then provides a continterns souree of mierobial contamination.

Endotoxins are lipopolysaceharides from the cell envelope that is external to the cell wall of Gram negative bacteria. Gram negative bacteria readily form biofilms that can beeome a source of en dotoxins. Endotoxins may either be associated with living mieroorganisms or fragments of dead mieroorganisms, or they may be free molecules. The free form of endotexims may be reteased fromeell surface or biofilms that colenize the water system, or they may enter the water system via the feed water. Endotoxim levels may be minimized by controlling the introduction of mieroerganisms and mierobial proliferation in the system. This may be aceomplished through the nommal exelusion or removal action af forded by various unit operations within the treatment system as well as threugh system sanitization. Other control methods inelude the use of ultrafliters or charge modified filters, either in line or at the point of use. The presence of endotoxins may be monitored as described in the chapter Bacterial Endoxins Test (85):

## МЕТНӨВӨЦӨGICAL CONSHERATIONS*

The objective of a water system mierobiolegieal menitoring program is to provide sufffient information to control the mierobio logieal quality of the water produced. Product quality requirements should dictate water quality needs. An appropriate level of control may be maintained by using dat trending techniques and limiting specific antraindieated miereorganisms. Consequently, it may net be necessary to detect all of the mieroorganisms present. The monitoring program and methodology should indicate adverse trends and detect mieroorganisms that are potentially harmful to the fin ished product or consumer.

Final selection of method variables should be based on the individual requirements of the system being menitored. It should be recognized that there is no single methed that is capable of detect ing all of the potential mierobial contaminants of a water system. Methods selected should be capable of isolating the numbers and typer of organisms that have been deemed significent relative to system eontrol and product impact for each individual system.

Several criteria should be considered when selecting a methodte menitor the mierobial content of a pharmaceutienl water system. These include method sensitivity, range of organisms recovered, sample throughput, incubation period, cost, and teehnieal complexity. An additional consideration is the use of the classieal "eut ture" approaches vs. a sophisticated instrument approach.

## THE CLASSICAL CULTURE APPROACH

Classical culture appreaches for mierobial testing of water in elude but are not limited to pour plates, spread plates, membrane filtration, and mest prebable number (MPN) tests. These metheds are-generally easy to perform, are less expensive, and provide ex eellent sample precessing throughput. Method sensitivity ean be increased via the use of larger sample sizes. This strategy is used in the membrane filtration method.

Culture approaches are further defined by the type of medium used in combination with the ineubation temperature and duration. This combination should be selected aceording to the monitoring

[^268]needs presented by a specific water system as well as its ability to recover mieroorganisms that could have a detrimental effect on the product or process.

There are basic forms of media available for traditional mierebielegieal analysis. "high" mutrient and "'low" nutrient. Hight futrient media are intended as seneral media for the-isolation and enumeration of heterotrophic bacteria. Low nutrient media are benefficial for isolating slow growing bacteria and bacteria that have been injured by previous exposure to disinfectants and sanitizers sueh as chlorine. Low nutrient media may be compared to high mutrient media, especially during the validation of a water system, in order to determine-if any additional mambers or ypes of bacteria are present so that their impact on the end use may be assessed. Additionally, the effleaey of system eontrols and sanitization on these slower growing or impaired bacteria can alse be assessed.

Duration and temperature of incubation are also critieal aspeets of a mierebiolegieal test method. Classieal methodelegies usimes high nutrient media have required ineubation at $30^{\circ} \mathrm{C}$ to $35^{\circ} \mathrm{C}$ for 48 to 72 hours. In certain water systems ineubation at lower temperatures (e.s., $20^{\circ} \mathrm{C}$ to $25^{\circ} \mathrm{C}$ ) and lenger periods (e.5., 5-10.7 days) ean produce higher counts when compared to lassieal metheds. Whether or not a partieular system needs to be menitered using lower incubation temperatures or longer incubation times sheuld be determined during system validation.

The decision to use longer ineubation periods should be made after considering the need for timely information and the ype-of eerrective actions required when an Alert or Action Level is ex ceeded. The advantages gained by ineubating for longer times, namely recovery of injured miereorganisms, slow growers, or more fastidious mieroerganisms, should be balanced against the need to have a timely investigation and to take corrective aetion, as well as the ability of these mieroergenisms to detrimentally af feet products or processes.

## "INSTRUMENT" APPROACH

Examples of imstrument approaches include mieroscopic direet eounting teehniques (e.g., epifluoreseenee and immanofluoreseence), radiemetric, impedemetric, and biechemieally based methedelegies. These metheds all persess a variety of advantages and disadvantages.

One advantage is their precision and aceuracy. In general, instru ment appreaches often have a-shorter lead time-for obtainimes results, which facilitates timely system control. This advantage, however, is often counterbalaneed by limited sample proeessing throughput due to laber intensive sample processing or other in strument limitations. In addition, instrumental approaches are de structive in that further iselate manipulation for characterization purpeses are precluded. Generally, some form of mierobial isolate eharacterization may be arequired element of water system menitoring. Consequently, eulturing approaches have traditionally been preferred over imstrumental approaches beeatse they offer a balance-of desirable test attributes and pest test eapabilities.

## RECOMAMNDED-METHЮDӨЦӨGIES

The following general methods obtained from Standard Meth ods for the Examination of Water and Wastewater, 18 th Edition, American Public Health Association, Washingten, DC 20005, are considered appropriate for establishing trends in the number of celony forming units observed in the routine mierebiolegieat menitering of ingredient water. It is recegnized, hewever, that othercombinations of media, time, and temperature of ineubation may eceasienally or even consistently result in higher numbers of coleny forming units being observed. The-extended-ineubation periods that are usually required by some of the alternative methods available offer disadvantages that may outweigh the hight
er counts obtained. The somewhat higher baseline counts would not necessarily have greater utility in detecting an exeursion-or a trend.

Methodelegies that ean be recemmended as-generally satisfacfory for menitoring pharmaceutical water systems are as follows:-

| Prinking Water: | POUR PLATE METHЮР |
| :---: | :---: |
|  | Minimmam sample 1.0 mE |
|  | Plate-count agar |
|  | Plateceumt agar |
|  | 42 to 72 heurs ineubation at $30^{\circ} \mathrm{C}$ ${ }^{5}-35^{\circ} \mathrm{C}$ |
| Purified Water: | POUR PLATE METHЮР |
|  | Minimman-sample 1.0 mL |
|  | Platecount agar |
|  | $48+72$ hems ineubation at $30^{\circ} \mathrm{C}$ ${ }_{-}-35^{\circ} \mathrm{C}$ |
| Weter for Injection: | MEMBRANE FILTRATION METЮЮР Minimum-sample 100 mL |
|  | Plate count agar |
|  | 48 to 72 heurs ineubation at |
|  | $30^{\circ} \mathrm{C}-35^{\circ} \mathrm{C}$ |

## Identifieation of Mieroorganisms

Identifying the isolates recovered from water monitoring meth ods may be impertant in instances where-specific waterborne mi eroorganisms may be detrimental to the product or processes in which the water is used. Mieroorganism information such as this may alse be usefut when identifying the seuree of mierobial cen tamination in a product or process.

Often a limited group of mieroorganisms are continuously reeovered from a water system. After repented characterization, an experienced mierobiologist may beeome proficient at their identifieation basedenenly a few traits sueh as colonial merphology and staining characteristies. This level of characterization is adequate for mest situations.

## Alert and Action Levels

The individual menegraphs for Purfifed Water and Water for In jection do not inelude-specific mierobial limits. These were pur pesefully omitted since most current microbiological techniques available require at least 48 hours to obtain definitive results. By that time, the water from which the sample was ataken has already been employed in the production proeess. Failure to meet a com pendial specification would require rejecting the product lot in volved, and this is not the intent of an alert or action guideline. The establishment of quantitative mierobiologieal gridelines for water for pharmaceutical purposes is in order because such guidelines will establish procedures that are to be implemented in the event that signifieant exeursions beyend these limits oceur:

Water systems should be mierobiologieally monitored to confrm that they continue operate within their design specifientions and produre water of aceeptable quality. Menitering data may be empared to established process parameters or product speciffen tions. A refinement to the use of process parameters and product specifications is the establishment of Alert and Action Levels, which signal a shift in process performance. Alert and Action Lev els are distinet from proeess parameters and product specifieations in that they are used for monitoring and control rather than aceept or reject decisions.

Alert Levels are levels or ranges that, when eveeded, indieate that a process may have drifted frem its normal operating condition. Alert Levels constitute a warning and do not necessarily require a corrective action.

Action Levels are levels or ranges that, when exceeded, indicate that a process has drifted from its normal operating range. Exceed ing an Action Level indicates that corrective action should be aken to bring the preeess back inte its nermal operating range.

Alert and Action Levels are established within process and prod Het specifieation tolerances and are basedonacombination of teeh nieal and product related considerations. Consequently, eweeding an Alert or Action Level doe not imply that product quality has been compromised.

Technieal censiderations used to establish Alert and Action Ler els should inelude a review of equipment design specifieations to ensure that the purification equipment is capable of achieving the required level of purity. In addition, samples should be collected and analyzed over a period of time to develop data reflecting nor mal water quality trends. Historieal or statistically based levels ean be established using the above data. Levels astablished in this way measure process performance and are independent of product eoneerns.

Product related Alert and Action Levels-should represent both product quality coneerns and the ability to effectively manage the purifieation proeess. These levels are ypieally based on a review of proeess data and an assessment of product sensitivity to ehemical and mierobiologieal contamination. The assessment of product susceptibility might include preservative efficacy, water activity, pH , ete. The levels should be set such that, when exeed ed, produret quality is not compromised.

Monitering data should be analyzed on an ongoing basis to en sure that the proeess eontintes to perform within aceeptable limits. An analysis of data trends is often used to a mance. This information ean be used to prediet depatures from established operating parameters, thereby signaling the need for appropriate preventative maintenance.

It should be reeognized that the mierobial Alert and Action Lev els established for any pharmaceutical water system are necessarily linked to the monitoring method chosen. Using the recommended methodologies, generally considered appropriate Aetion Levels are 500 coleny forming units (efu) per mL for Drinking Water, 100 eft per mL for Purified Whter and 10 efuper 100 mL for Heter for Iniection.

It should be emphasized that the above action guidelines are net intended to be totally inelusive for every situation where ingredient waters are employed. For example, Gram negative miereorganisms are not excluded from ingredient waters, nor is the presence of Gram negative mieroorganisms prohibited in Drinking Weter in the Federal Regulations. The reason for this is that these miereor ganisms are ubiquiteus to the aqueus enviromment and theirex elusion would likely require a sterilization process that would not be appropriate or feasible in many manufacturing seenarios. How ever, there are situations where they might not be tolerated: in top ieal products and in some oral dosage forms. It is, therefore, incumbent upen the manufacturer to supplement the general action gridelines to fit each partieular manufacturing sittation.

## -INTRODUCTION

Water is widely used as a raw material, ingredient, and solvent in the processing, formulation, and manufacture of pharmaceutical substances and compendial articles. Its breaduse makes it an impertant substance whese quality requires careftuly established specifieations to render it suit able for the majority of its uses. Because these varied uses
each require failored specifieations, a number ofeompendiat menegraphs havebeencreated products, active pharmaceutical ingredients (APIs) and intermediates, compendial articles, and analytical reagents. This general information chapter provides additional information about water, its quality attributes that are not included within a water monograph, processing techniques that can be used to improve water quality, and a description of minimum water quality standards that should be considered when selecting a water source.

This information chapter is not intended to replace existing regulations or guides that already exist to cover USA and International (ICH or WHO) GMP issues, engineering guides, or other regulatory (FDA, EPA, or WHO) guidances for water. The contents will help users to better understand pharmaceutical water issues and some of the microbiological and chemical concerns unique to water. This chapter is not an all-inclusive writing on pharmaceutical waters. It contains points that are basic information to be considered, when appropriate, for the processing, holding, and use of water. It is the user's responsibility to assure that pharmaceutical water and its production meet applicable governmental regulations, guidances, and the compendial specifications for the types of water used in compendial articles.

Control of the chemical purity of these waters is important and is the main purpose of the monographs in this compendium. Unlike other official articles, the bulk water monographs (Purified Water and Water for Injection) also limit how the article can be produced because of the belief that the nature and robustness of the purification process is directly related to the resulting purity. The chemical attributes listed in these monographs should be considered as a set of minimum specifications. More stringent specifications may be needed for some applications to ensure suitability for par-
ticular uses. Basic guidance on the appropriate applications of these waters is found in the monographs and is further explained in this chapter.

Control of the microbiological quality of water is important for many of its uses. All packaged forms of water are requiredtebe-sterile-either beeatise their uses require this attribute or beeause potential contaminating miereorganisms, if not removed or killed prier to packaging, eould contintue to grow tnehecked to extremely high levets after packaging, rendering the water potentially unsuitable for many of its other nonsterile uses. that have monograph standards are required to be sterile because some of their intended uses require this attribute for health and safety reasons. USP has determined that a microbial specification for the bulk monographed waters is inappropriate seral and has not been included within the monographs for these waters. These waters can be used in a variety of applications, some requiring extreme microbiological control and others requiring none. Unlike for packed waters, the The needed microbial specification for a given bulk water depends upon its use. A single specification for this dif-ficult-to-control attribute would unnecessarily burden some water users with irrelevant specifications and testing. However, ther some applications may require even more careful microbial control to avoid the proliferation of microorganisms ubiquitous to water during the purification, storage, and distribution of this substance. Anether rean steh a A microbial specification would be inapprepriate is also be inappropriate when related to the "utility" or continuous supply nature of this raw material. A microbial specifications are typically assessed by test methods that take at least 48 to 72 hours to generate results. Because pharmaceutical waters are generally produced by continuous processes and used in products and manufacturing processes soon after generation, the water is likely to have been used well before
definitive test results are available. Failure to meet a compendial specification whether relevant to that particular He or not, would require rejecting would require investigating the impact and making a pass/fail decision on all product lots between the previous sampling's acceptable test result and a subsequent sampling's acceptable test result. How ever, the establishment of quantitative microbiological guidelines for specific phamaceutical water uses is not to tally inappropriate for especially critieal uses. In these sitt ations, manufacturing at risk (using the water in a entinuous mode prior to availability of test results) may be contraindieated. Instead, action and alert levels should be used as in process controls to keep the mierobial quality of the water within levels that reflect a state of control of the Water system with mierobial counts well under any speciff eation established for a specific eritieal use. The technical and logistical problems created by a delay in the result of such an analysis does not eliminate the user's need for microbial specifications. Therefore, such water systems need to be operated and maintained in a controlled environment that requires that the system be validated to provide assurance of operational stability and that its microbial attributes be quantitatively monitored against established alert and action levels that would provide an early indication of system control. The issues of water system validation and alert/action levels and specifications are included in this chapter.

## SOURCE OR FEED WATER CONSIDERATIONS

To ensure adherence to certain minimal chemical and microbiological quality standards, water used in the production of drug substances or as source or feed water for the preparation of the various types of purified waters must meet the requirements of the National Primary Drinking Water Regulations (NPDWR) (40 CFR 141) issued by the U.S. Environmental Protection Agency (EPA) or
regulations for drinking water of the European Union or Jathe drinking water regulations of the European Union or Japan, or the WHO drinking water guidelines. Limits on the types and quantities of certain organic and inorganic contaminants ensure that the water will contain only small, safe quantities of potentially objectionable chemical species. Therefore, water pretreatment systems will only be challenged to remove small quantities of these potentially difficult-to-remove chemicals. Also, control of objectionable chemical contaminants at the source-water stage eliminates the need to specifically test for some of them (e.g., trihalomethanes and heavy metals) after the water has been further purified.
Microbiological requirements of drinking water ensure the absence of coliforms, which, if determined to be of fecal origin, may indicate the potential presence of other potentially pathogenic microorganisms and viruses of fecal origin. Meeting these microbiological requirements does not rule out the presence of other microorganisms, which could be considered undesirable if found in a drug substance or formulated product.

On the other hand, meeting these regulations does not rule out the presence of other mieroorganisms, which, while net eonsidered a major public health concern could, if present, eonstitute a hazard or be considered undesirable in a druty substance or formulated product.
To accomplish microbial control, Municipal Water Authorities add drinking water, among other things, disindisinfectants to drinking water. Chlorinecontaining and other oxidizing substances have been used for many decades for this purpose and have generally been
considered to be relatively innocuous to humans. However, these oxidants can interact with naturally occurring organic matter to produce disinfection by-products (DBPs), such as trihalomethanes (THMs, including chloroform, bromodichloromethane, and dibromochloromethane) and haloacetic acids (HAAs, including dichloroacetic acid and trichloroacetic acid). The levels of DBPs produced vary with the level and type of disinfectant used and the levels and types of organic materials found in the water, which can vary seasonally. of herrly.

Because high levels of DBPs are considered a health hazard so control of their levels is mandated by Drinking Water Regulations intended to redure exposure to these substanees to nomhazardous levels. in drinking water, Drinking Water Regulations mandate their control to generally accepted nonhazardous levels. However, depending on the unit operations used for further water purification, a small fraction of the DBPs in the starting water may carry over to the finished water. Therefore, the importance of having minimal levels of DBPs in the starting water, while achieving effective disinfection, is important.

DBP levels in drinking water can be minimized by using disinfectants such as ozone, chloramines, or chlorine dioxide. Like chlorine, their oxidative properties are sufficient to damage some pretreatment unit operations and must be removed early in the pretreatment process. The complete removal of some of these disinfectants can be ehallenging. problematic. For example, chloramines may degrade during the disinfection process or during pretreatment removal, thereby releasing ammonia, which in turn can carry over to the finished water. Pretreatment unit operations must be
designed and operated to adequately remove the disinfectant, drinking water DBPs, and objectionable disinfectant degradants. A serious problem can occur if unit operations designed to remove chlorine were, without warning, challenged with chloramine-containing drinking water from a municipality that had been mandated to cease use of chlorine disinfection to comply with ever tightening EPA Drinking Water THM specifications. The dechlorination process might incompletely remove the chloramine, which could irreparably damage downstream unit operations, but also the release of ammonia during this process might carry through pretreatment and prevent the finished water from passing compendial conductivity specifications. The purification process must be reassessed if the drinking water disinfectant is changed, emphasizing the need for a good working relationship between the pharmaceutical water manufacturer and the drinking water provider.

## TYPES OF WATER

There are many different grades of water used for pharmaceutical purposes. Several of the are described in USP monographs that specify uses, acceptable methods of preparation, and quality attributes. These waters can be divided into two general types: bulk waters, which are typically produced on site where they are used; and
packaged waters, which are produced, packaged, and sterilized to preserve microbial quality throughout their packaged shelf life. There are several specialized types of packaged waters, differing in their designated applications, packaging limitations, and other quality attributes.

There are also other types of water for which there are no monographs. These are all bulk waters, with names given for descriptive purposes only. Most of these waters are used in specific analytical methods. The associated text may not specify or imply certain quality attributes or modes of preparation. These nonmonographed waters may not necessarily adhere strictly to the stated or implied modes of preparation or attributes. Waters produced by other means or controlled by other test attributes may equally satisfy the intended uses for these waters. It is the user's responsibility to ensure that such waters, even if produced and controlled exactly as stated, be suitable for their intended use. Wherever the term "water" is used within this compendia without other descriptive adjectives or clauses, the intent is that water of no less purity than Purified Water be used.
What follows is a brief description of the various types of pharmaceutical waters and their significant uses or attributes. Figure 1 may also be helpful in understanding some of the various types of waters.


Fig. 1. Water for phamacentieal purpeses.


Fig. 1. Water for pharmaceutical purposes.

Bulk Monographed Waters and Steam
The following waters are typically produced in large volume by a multiple-unit operation water system and distributed by a piping system for use at the same site. These particular pharmaceutical waters must meet the quality attributes as specified in the related monographs., but the for lowing disenssion gives further insight as to their uses and requirements.

Purified Water—Purified Water (see USP monograph) is used as an excipient in the production of nonparenteral preparations and in other pharmaceutical applications, such as cleaning of certain equipment and nonparenteral productcontact components. Unless otherwise specified, Purified Water is also to be used for all tests and assays for which water is indicated (see General Notices and Requirements). Purified Water is also referenced throughout the $U S P-N F$. Regardless of the font and letter case used in its spelling, water complying with the Purified Water monograph is intended. Purified Water must meet the requirements for ionic
and organic chemical purity and must be protected from microbial contamination. The minimal quality of source or feed water for the production of Purified Water is Drinking Water. This source water may be purified using unit operations that include deionization, distillation, ion exchange, reverse osmosis, filtration, or other suitable purification procedures. Purified water systems must be validated to reliably and consistently produce and distribute water of acceptable chemical and microbiological quality. Purified water systems that function under ambient conditions are particularly susceptible to the establishment of tenacious biofilms of microorganisms, which can be the source of undesirable levels of viable microorganisms or endotoxins in the effluent water. These systems require frequent sanitization and microbiological monitoring to ensure water of appropriate microbiological quality at the points of use.

The Purified Water monograph also allows bulk packaging for commercial use elsewhere. When this is done, the required specifications are those of the packaged water Sterile Purified Water, except for Sterility and Labeling. There is a potential for microbial contamination and other quality changes of this bulk packaged non-sterile water to occur. Therefore, this form of Purified Water should be prepared and stored in such a fashion that limits microbial growth and/or simply used in a timely fashion before microbial proliferation renders it unsuitable for its intended use. Also depending on the material used for packaging, there will be extractable compounds leaching into the water from the packaging. Though this article may meet its required chemical attributes, such extractables may render the water an inappropriate choice for some applications. It is the user's responsibilitiy to assure fitness for use of this packaged article when used in manufacturing, clinical, or analytical applications where the pure bulk form of the water is indicated.

Water for Injection—Water for Injection (see USP monograph) is used as an excipient in the production of parenteral and other preparations where product endotoxin content must be controlled, and in other pharmaceutical applications, such as cleaning of certain equipment and parenteral product-contact components. The minimum quality of source or feed water for the generation of Water for Injection is Drinking Water as defined by the U.S. EPA, EU, Japan, or the WHO. This source water may be preliminarily purified pre-treated to render it suitable for subsequent distillation (or whatever other validated process is used according to the monograph). The resulting finished water must meet all of the chemical requirements for Purified Water as well as an additional bacterial endotoxin specification. Since endotoxins are produced by the kinds of microorganisms that are prone to inhabit water, the equipment and procedures used by the system to purify, store, and distribute Water for Injection must be designed to minimize or prevent microbial contamination as well as remove incoming endotoxin from the starting water. Water for Injection systems must be validated to reliably and consistently produce and distribute this quality of water.

The Water for Injection monograph also allows it to be packed in bulk for commercial use. Required specifications include the test for Bacterial endotoxins, and those of the packaged water Sterile Purified Water, except for Labeling. Bulk packaged Water for Injection is required to be sterile, thus eliminating microbial contamination quality changes. However, packaging extractables may render this water an inappropriate choice for some applications. It is the user's responsibility to ensure fitness for use of this packaged article when used in manufacturing, clinical, or analytical applications where the purer bulk form of the water is indicated.

Water for Hemodialysis—Water for Hemodialysis (see USP monograph) is used for hemodialysis applications, primarily the dilution of hemodialysis concentrate solutions. It is produced and used on-site and is made from EPA Drinking Water which has been further purified to reduce chemical and microbiological components. It may be packaged and stored in unreactive containers that preclude bacterial entry. The term "unreactive containers" implies that the container, especially its water contact surfaces, are not changed in any way by the water, such as by leaching of container-related compounds into the water or by any chemical reaction or corrosion caused by the water. The water contains no added antimicrobials and is not intended for injection. Its attributes include specifications for Water conductivity, Total organic carbon (or oxidizable substances), Microbial limits, and Bacterial endotoxins. The water conductivity and total organic carbon attributes are identical to those established for Purified Water and Water for Injection; however, instead of total organic carbon, the organic content may alternatively be measured by the test for Oxidizable substances. The Microbial limits attribute for this water is unique among the "bulk" water monographs, but is justified on the basis of this water's specific application that has microbial content requirements related to its safe use. The Bacterial endotoxins attribute is likewise established at a level related to its safe use.

Pure Steam—Pure Steam (USP monograph to come) is intended for use in steam sterilizing porous loads and equipment and in other processes such as cleaning where condensate would directly contact official articles, containers for these articles, process surfaces that would in turn contact these articles, or materials which are used in analyzing such articles. Pure Steam is also intended to be used for air humidification in controlled manufacturing areas where official articles or article-contact surfaces are exposed to the
resulting conditioned air. The primary intent of using this quality of steam is to ensure that official articles or articlecontact surfaces exposed to it are not contaminated by residues within the steam. Pure Steam is prepared from suitably pretreated source water, analogous to the pretreatment used for Purified Water or Water for Injection, vaporized with a suitable mist elimination, and distributed under pressure. The sources of undesirable contaminants within Pure Steam could be derived from entrained source water droplets, anticorrosion steam additives, or particulate matter from the steam production and distribution system itself; therefore, the attributes in the monograph should preclude most of the contaminants that could arise from these sources.

These purity attributes are measured on the condensate of the article, rather than the article itself. This, of course, imparts great importance to the cleanliness of the Pure Steam condensate generation and collection process because it must not adversely impact the quality of the resulting condensed fluid.

Other steam attributes not detailed in the monograph, in particular, the presence of even small quantities of noncondenseable gases or the existence of a superheated or dry state, may also be important for applications such as sterilization. The large release of energy (latent heat of condensation) as water changes from the gaseous to the liquid state is the key to steam's sterilization efficacy and its efficiency, in general, as a heat transfer agent. If this phase change (condensation) is not allowed to happen because the steam is extremely hot and in a persistent super heated, dry state, then its usefulness could be seriously compromised. Noncondensable gases in steam tend to stratify or collect in certain areas of a steam sterilization chamber or its load. These surfaces would thereby be at least partially insulated from the steam condensation phenomenon, preventing them from experiencing the full energy of the sterilizing conditions.

Therefore, control of these kinds of steam attributes, in addition to its chemical purity, may also be important for certain Pure Steam applications. However, because these additional attributes are use-specific, they are not mentioned in the Pure Steam monograph.

Note that less pure plant steam may be used for steam sterilization of nonporous loads, general cleaning and sterilization of nonproduct contact equipment and analytical materials, humidification of air in nonmanufacturing areas, where used as a nonproduct contact heat exchange medium, and in all compatible applications involved in bulk pharmaceutical chemical and API manufacture.

## Packaged Monographed Waters

The following monographed waters are packaged forms of either bulk Purified Water or bulk Water for Injection that have been sterilized to preserve their microbiological properties. These waters may have specific intended uses as indicated by their names and may also have restrictions on packaging configurations related to those uses. In general, these packaged waters may be used in lieu of the bulk form of water from which they were derived. However, the user should take into consideration that the packaging and sterilization processes used for the articles may leach materials from the packaging material into the water over its shelf life, rendering it less pure than the original water placed into the package. The chemical attributes of these waters are still defined primarily by the wet chemistry methods and specifications similar to those formerly used for the bulk pharmaceutical waters prior to their replacement with water conductivity and total organic carbon (TOC). It is the user's responsibility to ensure fitness for use of this article when used in manufacturing, clinical, or analytical applications where the purer bulk form of the water is indicated.

Sterile Purified Water-Sterile Purified Water (see USP monograph) is Purified Water, packaged and rendered sterile. It is used in the preparation of nonparenteral compendial dosage forms or in analytical applications requiring Purified Water where access to a validated Purified Water system is not practical, where only a relatively small quantity is needed, where sterile Purified Water is required, or where bulk packaged Purified Water is not suitably microbiologically controlled. of sterile Purifit Water is required.

Sterile Water for Injection—Sterile Water for Injection (see USP monograph) is Water for Injection packaged and rendered sterile. It is used for extemporaneous prescription compounding and as a sterile diluent for parenteral products. It may also be used for other applications where bulk Water for Injection or Purified Water is indicated but where assess to a validated water system is either not practical or where only a relatively small quantity is needed. Sterile Water for Injection is packaged in single-dose containers not larger than 1 L in size.

Bacteriostatic Water for Injection-Bacteriostatic Water for Injection (see USP monograph) is sterile Water for Injection to which has been added one or more suitable antimicrobial preservatives. It is intended to be used as a diluent in the preparation of parenteral products, most typically for multi-dose products that require repeated content withdrawals. It may be packaged in single-dose or multiple-dose containers not larger than 30 mL .

Sterile Water for Irrigation-Sterile Water for Irrigation (see USP monograph) is Water for Injection packaged and sterilized in single-dose containers of larger than 1 L in size that allows rapid delivery of its contents. It need not meet the requirement under small-volume injections in the general test chapter Particulate Matter in Injections $\langle 788\rangle$. It may also be used in other applications, which do not have particulate matter specifications, where bulk Water for In-
jection or Purified Water is indicated but where access to a validated water system is not practical or where somewhat larger quantities than are provided as Sterile Water for Injection are needed.

Sterile Water for Inhalation—Sterile Water for Inhalation (see USP monograph) is Water for Injection that is packaged and rendered sterile and is intended for use in inhalators and in the preparation of inhalation solutions. It carries a less stringent specification for bacterial endotoxins than Sterile Water for Injection, and therefore, is not suitable for parenteral applications.

## Sterile-Water for Hemodialysis Sterile Water for He

 modialysis [USP monograph tocome] is Water for Injection which has additional attributes for certain ehemieals whieh have been shown to be problematic during hemodialysis. It is used for the dilution of hemodialysis concentrate and oth er hemodialysis applieations.
## Nonmonographed Waters and Steam Manufacturing Waters <br> PharmaeentiealWater Cited in this chapter, this is a

 broad term referring to any water used in the preparation of active pharmaceutical ingredients, exeipients, and fint ished produets as well as any related proeess such as pharmaceutical equipment cleaning or product testing. The term eovers a bread range of water purities, starting with the least pure allowed in any process for USP substances, Drinking Water, and extending to the highest purity reasonably aehievable. The water's purity must be suitable for its intend ed use, but no less pure than the USP andeGMP requirements.Prinking Water Citedin General Notiees and Requirements, the general test chapters, and the dietary supple ment chapters, this water must comply with the quality attributes of the U.S. Environmental Protection Ageney's

National Primaty Drinking Water Regulations (NPDWR) Or comparable regulations of the European Union or Japan. It may be derived from a varie of sourees including a public water utility, a private water supply (e.g., a well), or a eombination of more than one of these sources. Drinking Water may be used in the early stages of eleaning pharmaceutical manufacturing equipment and product-contact eomponents. Drinking Water is also the minimum quality of water which should be used for the preparation of official substances and other bulk pharmaceutical ingredients. Where required by the processing of the materiats to achieve their required fanal purity, higher qualities of water may be needed, perhaps even as pure as-Water for Injection-or Pur rified Water Such higher purity waters might, however, reeeive only selected attributes to be of higher purity than Prinking Water (see-Water for Special Phatmacutical Purpores and Endetoxin and Mierorrganism-Controlled Water below). Drinking Water is the preseribed source feed water for the production of pharmaceutical waters. As seasenal variations in the quality attributes of the Drinking Water supply ean oceur, due consideration to its synthetic and eleaning uses must be given. In addition, the processing steps in the production of pharmaceutieal waters must be designed to aceommodate this variability.

Potable-Water Cited-in the-General Notices and Requirements, the general test chapters, and the dietary supplement chapters, this is an older synonym for Drinking Water (derived from the French adjective potable, meaning drink able).

NPDWR Water Cited in this chapter, this water must eomply with the U.S. Envirenmental Pretection Ageney's National Primary Drinking Water Regulations, the drinking water mandated for use in the United States. The-specifiea-
tions for this water, found in-40 CFP Part 141, inelude max imum contaminant levels for a large number of inorganic, erganic, mierebiolegieal, and radioactive contaminants.

## Water for Special-Pharmaceutical-Purposes-Gited in

 this chapter, this bread term is used to deseribe any type-of water that does not have a menegraph but has special purity requirements stited for its intended purposes.Endotoxin-and-Mieroorganism-Controlled-WaterGited in this chapter, this ype of water has been-subjected foconditions that contrel its mierobial and endotoxin coneentrations at a level suitable for its intended use. It may alse have undergone some level of chemical purification.

LAL Reagent Water Cited in the USP menographs as well as the general chapters, this is a water, usually Water for Injection which may have been sterilized and is free frem a level of endotoxin that would yield any detectable reaction or interference with the Limulus Ameboeyte Lysate reagent used in the Bacterial Endetoxins Test $\langle 85\rangle=$

Endotoxin-Free Water Cited in one USP monograph, this water is a symonymous with LAL Reagent Water.

Carbon-Dioxide-Free-Water Cited in nmmerous-USP monegraphs, general test chapters, and NF menographs, this is Putrified Water or Water for Injection that has been prepared to remove dissolved carben dioxide and biearbenate during its purification and then either protected from earben dioxide reabsorption during its preparation and storage er treated to drive off the dissolved earben dioxide just prior to use, such as by sparging with an inert gas or by boiling. The Reagents section of USP deseribes its preparation as Purified Water that has been boiled for 5 minutes, cooled, and protected from atmospheric carben-dioxide adsorption. Practically speaking, it is extremely diffieult to remove all earben dioxide frem the water by beiling or sparging, and if exposed to air at all, sueh as during cooling or when transferring aquantity of water to a working eontainer for use in a
test, readsorption is inevitable. Deionization by a mixed bed deionizer is an effective initial carben dioxide removal approach. Distillation and reverse osmosis are less effective. Reintrusion of carbon dioxide is pessible if the water is not properly protected after production. The usual uses-of this ype of water are for analyses requiring highly puriffed water or where the test is related to pH , acidity, or alkalinity and the concern is that the carbon dioxide in the water could affeet the test result. The effieacy of the carben dioxide lim itation proeess should be valuated for its impact on the tests in which the water is used. Nermally, the small amount absorbed during reasonably rapid, open to the air handling of truly earben-dioxide-free-water will not affect the testing where Carben Dioxide-Free Water is indicated.

Ammonia-Free-Water Cited in only one USP meno graph, this is Purified-Water or Water for Injection that has been produced in such a way as to prevent the carryover Of ammenia from the source water. Ammenia-is typieally enly a problem in regiens where chloramines are used as the Drinking Water disinfectant. Deionization by a mixed bed deionizer is very effective at removing ammenia, but distillation and reverse osmosis are less effective. In order for distillation and reverse osmosis to produce Ammonia Free-Water in chloramine-using regions, the ammenia must beremoved by earlier unit operations prior to entering the distillation or reverse osmesis units. The use of this water is for a test related to pH and the concern, like with carbon diexide, is that the pH of the water may affect the test result. In most laboratery settings, there is insuffieient atmospheric ammenia to create a need for ammonia reintrusion protec tion, unlike the malogous protection that would be needed for Carbon Dioxide-Free Water:

High Purity Water Cited in one USP monograph and ene-general chapter, this water is well characterized in the general test chapter Containerss $\langle 664\rangle$. In essence, it is water
that is prepared by several sequential steps, an- interim one of which is distillation, that renders it extremely pure rela tive to on line conductivity, particulates, and copper content. This water is used for many of the reagents and tests fer containers int $\langle 664$ ) where less pure-waters would net perform aceeptably, as well as for the reagents employed where cited for the USP monograph tests.

Pistilled-Water Cited in several USP monegraphs and general test chapters, this water is, as the name-suggests, produced by waporizing liquid water and condensing it in a purer state. This water is used primarily for reagent preparation in the USP menegraphs where pure water is needed and in the general test chapter primarily for cleaning purpeses where the leaving of no water impurity residuals is impertant. It is also-cited as the starting water used for making

## High Parity Water.

Freshly Distilled Water Citedin only one USP monegraph, this water is prepared in a similar fashion to Distilled Water, though as the name suggests, immediately before use. It is used for preparing standards and control selations for injection into test animats. Because of this use and the term "freshly", the implied attributes are its chemieal purity as well as its low endetoxin and bioburden (though no ref erence to these mierobial attributes-or specific protection from recontamination is mentioned). Due to the nattre of the testing, Water for Injection could be a reasenable substifate, though as for any test, the suitability of the water must be verifted for this use.

Deionized Water Cited in ntmerous USP menegraphs, general test chapters, and dietary supplement monographs, this water is produeed by an ion exchange process in which the contaminating ions are replaced with either $\mathrm{H}^{+}$-or $\mathrm{OH}^{-}$ iens. In the USP monographs and general test chapters, this water is indieated for cleaning and reagent preparation purpeses. In one general test chapter, it is listed as a suitable
substitute for Purified Water In the dietary supplement men egraphs, it is listed as the water to be used wherever "water" is mentioned, which ineludes reagent and artiele preparations as well as for cleaning. Due to the nature of the testing, Purified Water could be a reasomable-substitute, though as for any test, the suitability of the water must be verified for these uses.

Freshly Deionized-Water Cited in-only two related USP menegraphs, this water is prepared in similar fashien to Deimized Water, theugh as the name-suggests, immediately before it is to be used. This implies the need to avoid any adventitious contamination from the air or container leachables, which in turn implies a reasenably high degree of purity. This water is indieated for use wherever "water" is mentioned, which includes reagent and article preparations as well as for cleaning. Due to the nature of the testing, Putrified Weter could be a reasenable-substitute for mest of the applieations mentioned, though as for any test, the suit ability of the water must be verified for these uses, particu larly for its indicated use in preparing mobile phase solutions where highly deionized water is needed.

Deionized-Distilled-Water Citedin only two USP menegraphs, this water is produced by deionizing (see De imized Water above) Pistilled Water (also-see above). This water is used as a reagent in a chrematography test that requires a high purity. Because of the impertance of this high purity, water that barely meets the requirements for Purified Water would not be acceptable.

Beacrated-Water Cited in USP menographs and wo general infermation chapters, this water is Purifed Water that has been treated to reduce the content of dissolved air by any suitable means stuch as by reducing the headspace air pressure-in a closed container, beiling for at least five minttes, or senication. The Reagents section of USP alse describes its preparation. Deatated Water is primarily indi-
eated for use-in dissolution testing where the presence-of high levels of dissolved gases could outgas during the test and interfere with the test results or aceurate voltametric withdrawals.

Clean Steam Clean Steam (also commonly known as Pure-Steam or Additive-Free Steam) is not specifieally cited in USP, but is commenly used threughout the pharmaceutieal industry. Its quality is sometimes confusingly identified in various references by either the quality of the water from which it is produced or by the quality of the condensate formed from it, both of which make reference to a-USP monegraphed bulk water. Theugh these various preparation and end quality definitions may serve their respective purpeses in isolation, their inconsistently assigned descriptive names create confusion when taken out of context. Therefore, the purpose of this diseussion is to clarify the term "Clean Steam," its production, uses, and quality. Clean Steam may be prepared analogeusly to either Purfified Water or Water for Injection but vaperized and distributed in such a fashion as to render its condensate equivalent in quality to that of Water for Injection It is used where-its condensate directly contacts product or product contact surfaces sueh as during cleaning or sterilization of products, product compenents, and other product contact surfaces and where there is ne subsequent precessing-step to remove any codeposited impurity residtues. The primary intent of using this quatity of steam is to ensure that articles-or product contact surfaces expesed to it are net contaminated by residues that may be deposited by the steam. The souree of this contamination could originate from-entrained source-water, steam additives, or the stemm production and distribution system itself. Depending on its use in sterilization, such as for perous att toclave loads and SIP systems, the presence of even-small quantities of nencondensable gases or an unsaturated or
dry state, such as would exist in a-superheated condition, eould compromise the-steam's sterilizing properties. Therefore, control of these attributes may also be necessary.
In addition to the bulk monographed waters described above, nonmonographed waters can also be used in pharmaceutical processing steps such as cleaning, synthetic steps or as a starting material for further purification. The following is a description of several of these nonmonographed waters as cited in various locations within this compendia.

Drinking Water-This type of water can be referred to as Potable Water (meaning drinkable or fit to drink), National Primary Drinking Water, Primary Drinking Water, or National Drinking Water. Except where a singular drinking water specification is stated (such as the NPDWR [U.S. Environmental Protection Agency's National Primary Drinking Water Regulations as cited in 40 CFR Part 141]), this water must comply with the quality attributes of either the NPDWR, or the drinking water regulations of the European Union or Japan, or the WHO Drinking Water Guidelines. It may be derived from a variety of sources including a public water utility, a private water supply (e.g., a well), or a combination of these sources. Drinking Water may be used in the early stages of cleaning pharmaceutical manufacturing equipment and product-contact components. Drinking Wa$t e r$ is also the minimum quality of water that should be used for the preparation of official substances and other bulk pharmaceutical ingredients. Where compatible with the processes, the allowed contaminant levels in Drinking Water are generally considered safe for use, at least in early synthetic stages, for official substances and other drug substances. Where required by the processing of the materials to achieve their required final purity, higher qualities of water may be needed for these manufacturing steps, perhaps even as pure as Water for Injection or Purified Water. Such higher purity waters, however, might require only selected
attributes to be of higher purity than Drinking Water (see Figure 2 below). Drinking Water is the prescribed source or feed water for the production of bulk monographed pharmaceutical waters. The use of Drinking Water specifications establishes a reasonable set of maximum allowable levels of chemical and microbiological contaminants with which a
water purification system will be challenged. As seasonal variations in the quality attributes of the Drinking Water supply can occur, due consideration to its synthetic and cleaning uses must be given. The processing steps in the production of pharmaceutical waters must be designed to accommodate this variability.


＊Drinking Uiate ris water complying with US $⿴ 囗 十 A N C O U R$ or drinking wate r regulations of EU or dapan or WiHO drinking water guidelines．
＊x Water for sterile API＇s or dosage forms must first be rendered sterile ifthere is not a subsequent sterilization step in the process where used．
＊xx See guidance in this chapter where waters other than Purified Uoater are required by some USP tests and assays．
Note：All water systems should be validated with whatever microbial control is needed to suit the intended purposes of the water．

Fig．2．Selection of water for pharmaceutical purposes．

Hot Purified Water－This water is used in the prepara－ tion instructions for $U S P-N F$ articles and is clearly intended to be Purified Water that has been heated to an unspecified temperature in order to enhance solubilization of other in－
gredients．There is no upper temperature limit for the water （other than being less than $100^{\circ}$ ），but for each monograph there is an implied lower limit below which the desired solubilization effect would not occur．

## Nonmonographed Analytical Waters

Both General Notices and Requirements and the introductory section to Reagents, Indicators, and Solutions clearly state that where the term "water," without qualification or other specification, is indicated for use in analyses, the quality of water shall be Purified Water. However, numerous such qualifications do exist. Some of these qualifications involve methods of preparation, ranging from specifying the primary purification step to specifying additional purification. Other qualifications call for specific attributes to be met that might otherwise interfere with analytical processes. In most of these latter cases, the required attribute is not specifically tested. Rather, a further "purification process" is specified that ostensibly allows the water to adequately meet this required attribute.

However, preparation instructions for many reagents were carried forward from the innovator's laboratories to the originally introduced monograph for a particular $U S P-N F$ article or general test chapter. The quality of the reagent water described in these tests may reflect the water quality designation of the innovator's laboratory. These specific water designations may have originated without the innovator's awareness of the requirement for Purified Water in USP$N F$ tests. Regardless of the original reason for the creation of these numerous special analytical waters, it is possible that the attributes of these special waters could now be met by the basic preparation steps and current specifications of Purified Water. In some cases, however, some of the cited post-processing steps are still necessary to reliably achieve the required attributes.

Users are not obligated to employ specific and perhaps archaically generated forms of analytical water where alternatives with equal or better quality, availability, or analytical performance may exist. The consistency and reliability for producing these alternative analytical waters should be ver-
ified as producing the desired attributes. In addition, any alternative analytical water must be evaluated on an application-by-application basis by the user to ensure its suitability. Following is a summary of the various types of nonmonographed analytical waters that are cited varions tonendian within this $U S P-N F$.

Distilled Water-This water is produced by vaporizing liquid water and condensing it in a purer state. It is used primarily as a solvent for reagent preparation, but it is also specified in the execution of other aspects of tests, such as for rinsing an analyte, transferring a test material as a slurry, as a calibration standard or analytical blank, and for test apparatus cleaning. It is also cited as the starting water to be used for making High Purity Water. Because none of the cited uses of this water imply a need for a particular purity attribute that can only be derived by distillation, water meeting the requirements for Purified Water derived by other means of purification could be equally suitable where Distilled Water is specified.

Freshly Distilled Water—Also called "recently distilled water", it is produced in a similar fashion to Distilled Water and should be used shortly after its generation. This implies the need to avoid endotoxin contamination as well as any other adventitious forms of contamination from the air or containers that could arise with prolonged storage. It is used for preparing solutions for subcutaneous test animal injections as well as for a reagent solvent in tests for which there appears to be no particularly high water purity needed that could be ascribable to being "freshly distilled". In the "testanimal" use, the term "freshly distilled" and its testing use imply a chemical, endotoxin, and microbiological purity that could be equally satisfied by Water for Injection (though no reference is made to these chemical, endotoxin, or microbial attributes or specific protection from recontamination). For nonanimal uses, water meeting the require-
ments for Purified Water derived by other means of purification and/or storage periods could be equally suitable where "recently distilled water" or Freshly Distilled Water is specified.

Deionized Water-This water is produced by an ion-exchange process in which the contaminating ions are replaced with either $\mathrm{H}^{+}$or $\mathrm{OH}^{-}$ions. Similarly to Distilled Water, Deionized Water is used primarily as a solvent for reagent preparation, but it is also specified in the execution of other aspects of tests, such as for transferring an analyte within a test procedure, as a calibration standard or analytical blank, and for test apparatus cleaning. Also, none of the cited uses of this water imply any needed purity attribute that can only be achieved by deionization. Therefore, water meeting the requirements for Purified Water that is derived by other means of purification could be equally suitable where Deionized Water is specified.

Freshly Deionized Water-This water is prepared in a similar fashion to Deionized Water, though as the name suggests, it is to be used shortly after its production. This implies the need to avoid any adventitious contamination that could occur upon storage. This water is indicated for use as a reagent solvent as well as for cleaning. Due to the nature of the testing, Purified Water could be a reasonable alternative for these applications.

Deionized Distilled Water-This water is produced by deionizing (see Deionized Water ) Distilled Water. This water is used as a reagent in a liquid chromatography test that requires a high purity. Because of the importance of this high purity, water that barely meets the requirements for Pu rified Water may not be acceptable. High Purity Water (see below) could be a reasonable alternative for this water.

Filtered Distilled or Deionized Water-This water is essentially Purified Water produced by distillation or deionization that has been filtered through a $1.2-\mu \mathrm{m}$ rated
membrane. This water is used in particulate matter testing where the presence of particles in the water could bias the test results (see Particulate Matter in Injections $\langle 788\rangle$ ). Because the chemical water purity needed for this test could also be afforded by water purification processes other than distillation or deionization, filtered water meeting the requirements for Purified Water, but produced by means other than distillation or deionization could be equally suitable.

Filtered Water-This water is Purified Water that has been filtered to remove particles that could interfere with the analysis where the water is used. Where used for preparing samples for particulate matter testing (see Particulate Matter in Injections $\langle 788\rangle$ ), though unspecified in monographs, water filtration should be through a $1.2-\mu \mathrm{m}$ filter to be consistent with the general test chapter. Where used as a chromatography reagent, monograph-specified filter ratings range from $0.5 \mu \mathrm{~m}$ to unspecified.

High Purity Water-The preparation of this water is defined in Containers $\langle 661\rangle$. It is water that is prepared by deionizing previously distilled water, and then filtering it through a $0.45-\mu \mathrm{m}$ rated membrane. This water must have an in-line conductivity of not greater than $0.15 \mu \mathrm{~S} / \mathrm{cm}$ (6.67 Megohm-cm) at $25^{\circ}$. For the sake of purity comparison, the analogous Stage 1 and 2 conductivity requirements for Purified Water at the same temperature are $1.3 \mu \mathrm{~S} / \mathrm{cm}$ and $2.1 \mu \mathrm{~S} / \mathrm{cm}$, respectively. The preparation specified in Containers $\langle 661\rangle$ uses materials that are highly efficient deionizers and that do not contribute copper ions or organics to the water, assuring a very high quality water. If the water of this purity contacts the atmosphere even briefly as it is being used or drawn from its purification system, its conductivity will immediately degrade, by as much as about $1.0 \mu \mathrm{~S} / \mathrm{cm}$, as atmospheric carbon dioxide dissolves in the water and equilibrates to bicarbonate ions. Therefore, if the analytical use requires that water purity remains as high
as possible, its use should be protected from atmospheric exposure. This water is used as a reagent, as a solvent for reagent preparation, and for test apparatus cleaning where less pure waters would not perform acceptably. However, if a user's routinely available purified water is filtered and meets or exceeds the conductivity specifications of High Purity Water, it could be used in lieu of High Purity Water.

Ammonia-Free Water-Functionally, this water must have a negligible ammonia concentration to avoid interference in tests sensitive to ammonia. It has been equated with High Purity Water that has a significantly tighter Stage 1 conductivity specification than Purified Water because of the latter's allowance for a minimal level of ammonium among other ions. However, if the user's Purified Water were filtered and met or exceeded the conductivity specifications of High Purity Water, it would contain negligible ammonia or other ions and could be used in lieu of High Purity Water.

Carbon Dioxide-Free Water-The introductory portion of the Reagents, Indicators, and Solutions section defines this water as Purified Water that has been vigorously boiled for at least 5 minutes, then cooled and protected from absorption of atmospheric carbon dioxide. Because the absorption of carbon dioxide tends to drive down the water pH , most of the uses of Carbon Dioxide-Free Water are either associated as a solvent in pH -related or pH -sensitive determinations or as a solvent in carbonate-sensitive reagents or determinations. Another use of this water is for certain optical rotation and color and clarity of solution tests. Though it is possible that this water is indicated for these tests simply because of its purity, it is also possible that the pH effects of carbon dioxide containing water could interfere with the results of these tests. A third plausible reason that this water is indicated is that outgassing air bubbles might interfere with these photometric-type tests. The
boiled water preparation approach will also greatly reduced the concentrations of many other dissolved gases along with carbon dioxide. Therefore, in some of the applications for Carbon Dioxide-Free Water, it could be the inadvertent deaeration effect that actually renders this water suitable. In addition to boiling, deionization is perhaps an even more efficient process for removing dissolved carbon dioxide (by drawing the dissolved gas equilibrium toward the ionized state with subsequent removal by the ion-exchange resins). If the starting Purified Water is prepared by an efficient deionization process and protected after deionization from exposure to atmospheric air, water that is carbon dioxidefree can be effectively made without the application of heat. However this deionization process does not deaerate the water, so if Purified Water prepared by deionization is considered as a substitute water in a test requiring Carbon DioxideFree Water, the user must verify that it is not actually water akin to Deaerated Water (discussed below) that is needed for the test. As indicated in the High Purity Water, even brief contact with the atmosphere can allow small amounts of carbon dioxide to dissolve, ionize, and significantly degrade the conductivity and lower the pH . If the analytical use requires the water to remain as pH -neutral and as carbon dioxide-free as possible, even the analysis should be protected from atmospheric exposure. However, in most applications, atmospheric exposure during testing does not significantly affect its suitability in the test.

Ammonia- and Carbon Dioxide-Free Water-As implied by the name, this water should be prepared by approaches compatible with those mentioned for both Ammonia-Free Water and Carbon Dioxide-Free Water. Because the carbon dioxide-free attribute requires post-production protection from the atmosphere, it is appropriate to first render the water ammonia-free using the High Purity Water process followed by the boiling and carbon dioxide-pro-
tected cooling process. The High Purity Water deionization process for creating Ammonia-Free Water will also remove the ions generated from dissolved carbon dioxide and ultimately, by forced equilibration to the ionized state, all the dissolved carbon dioxide. Therefore, depending on its use, an acceptable procedure for making Ammonia- and Carbon Dioxide-Free Water could be to transfer and collect High Purity Water in a carbon dioxide intrusion-protected container.

Deaerated Water-This water is Purified Water that has been treated to reduce the content of dissolved air by "suitable means". In the Reagents section, approaches for boiling, cooling (similar to Carbon Dioxide-Free Water but without the atmospheric carbon dioxide protection), and sonication are given as applicable for test uses other than dissolution and drug release testing. Though Deaerated Water is not mentioned by name in Dissolution $\langle 711\rangle$, suggested methods for deaerating dissolution media (which may be water) include warming to $41^{\circ}$, vacuum filtering through a $0.45-\mu \mathrm{m}$ rated membrane, and vigorously stirring the filtrate while maintaining the vacuum. This chapter specifically mentions indicates that other validated approaches may be used. In other monographs that also do not mention Deaerated Water by name, degassing of water and other reagents is accomplished by sparging with helium. Deaerated Water is used in both dissolution testing as well as liquid chromatography applications where outgassing could either interfere with the analysis itself or cause erroneous results due to inaccurate volumetric withdrawals. Applications where ambient temperature water is used for reagent preparation, but the tests are performed at elevated temperatures, are candidates for outgassing effects. If outgassing could interfere with test performance, including, chromatographic flow, colorimetric, or photometric measurements, or volumetric accuracy, then Deaerated Water should probably be used,
whether called for in the analysis or not. The above deaeration approaches might not render the water "gas-free". At best, they reduce the dissolved gas concentrations so that outgassing caused by temperature changes is not likely.

Recently Boiled Water-This water may include recently or freshly boiled water (with no mention of cooling in the title), but cooling prior to use is clearly intended. Occasionally it is necessary to use when hot. Recently Boiled Water is specified because it is used in a pH -related test or carbonatesensitive reagent, in an oxygen-sensitive test or reagent, or in a test where outgassing could interfere with the analysis, such as specific gravity or an appearance test.

Oxygen-Free Water-The preparation of this water is not specifically described in the compendia. Neither is there an oxygen specification or analysis mentioned. However, all uses involve analyses of materials that could be sensitive to oxidation by atmospheric oxygen. Procedures for the removal of dissolved oxygen from solvents, though not necessarily water, are mentioned in Polarography $\langle 801\rangle$ and Spectrophotometry and Light-Scattering $\langle 851\rangle$. These procedures involve simple sparging of the liquid with an inert gas such as nitrogen or helium followed by inert gas blanketing to prevent oxygen reabsorption. The sparging times cited range from 5 to 15 minutes to an unspecified period. Some Purified Water and Water for Injection systems produce water that is maintained in a hot state and that is inert gas blanketed during its preparation and storage and distribution. Though oxygen is poorly soluble in hot water, such water may not be oxygen-free. Whatever procedure used for removing oxygen should be verified as reliably producing water that is fit for use.

LAL Reagent Water-This water is also referred to as endotoxin-free water. This is usually Water for Injection, which may have been sterilized. It is free from a level of
endotoxin that would yield any detectable reaction or interference with the Limulus amebocyte lysate reagent used in the Bacterial Endotoxins Test $\langle 85\rangle$.

Organic-Free Water-This water is defined by Organic Volatile Impurities $\langle 467\rangle$ as producing no significantly interfering gas chromatography peaks. Referenced monographs specify using this water as the solvent for standard and test solution preparation for the Organic volatile impurities test.

Lead-Free Water-This water is used as a transferring diluent for an analyte in a Lead $\langle 251\rangle$ test. Though no specific instructions are given for its preparation, it must not contain any detectable lead. Purified Water should be a suitable substitute for this water.

Chloride-Free Water-This water is specified as the solvent for use in an assay that contains a reactant that precipitates in the presence of chloride. Though no specific preparation instructions are given for this water, its rather obvious attribute is having a very low chloride level in order to be unreactive with this chloride sensitive reactant. Purified Water could be used for this water but should be tested to assure it is unreactive.

Hot Water-The uses of this water include solvents for achieving or enhancing reagent solubilization, restoring the original volume of boiled or hot solutions, rinsing insoluble analytes free of hot water soluble impurities, solvents for reagent recrystallization, apparatus cleaning, and as a solubility attribute for various $U S P-N F$ articles. In only one monograph is the temperature of "hot" water specified; so in all the other cases, the water temperature is less important, but should be high enough to achieve the desirable effect. In all cases, the chemical quality of the water is implied to be that of Purified Water.

## VALIDATION AND QUALIFICATION OF WATER PURIFICATION, STORAGE, AND DISTRIBUTION SYSTEMS

Establishing the dependability of pharmaceutical water purification, storage, and distribution systems requires an appropriate period of monitoring and observation. Ordinarily, few problems are encountered in maintaining the chemical purity of Purified Water and Water for Injection Nevertheless, the advent of using conductivity and TOC to define chemical purity has allowed the user to more quantitatively assess the water's chemical purity and its variability as a function of routine pretreatment system maintenance, regeneration, etc. Even the presence of such unit operations as heat exchangers and use point hoses can compromise the chemical quality im of water within and delivered from an otherwise well-controlled water system. Therefore, an assessment of the consistency of the water's chemical purity over time must be part of the validation program. However, even with the most well controlled chemical quality, it is often more difficult to consistently meet established microbiological quality criteria owing to phenomena occurring during and after chemical purification. A typical program involves intensive daily sampling and testing of major process points for at least one month after operational criteria have been established for each unit operation, point of use, and sampling point.

An overlooked aspect of water system validation is the delivery of the water to its actual location of use. If this transfer process from the distribution system outlets to the water use locations (usually with hoses) is defined as outside the water system, then this transfer process still needs to be validated to not adversely affect the quality of the water to the extent it becomes unfit for use. Because routine microbial monitoring is performed for the same transfer process
and components (e.g., hoses and heat exchangers) as that of routine water use (see Sampling Considerations), there is some logic to include this water transfer process within the distribution system validation.

Validation is the process whereby substantiation to a high level of assurance that a specific process will consistently produce a product conforming to an established set of quality attributes is acquired and documented. Prior to and during the very early stages of validation, the critical process
parameters and their operating ranges are established. A validation program qualifies and documents the design, installation, operation, and performance of equipment. It begins when the system is defined and moves through several stages: installation qualification (IQ), operational qualification ( OQ ), and performance qualification (PQ). A graphical representation of a typical water system validation life cycle is shown in Figure 3.


Fig. 3. Water system validation life cycle.

A validation plan for a water system typically includes the following steps: (1) establishing standards for quality attributes andererating parameters; of the finished water and the source water; (2) defining systems and stitable subsystems to produce the desired suitable unit operations and their operating parameters for achieving the desired finished water quality attributes from the available source water; (3) selecting piping, equipment, controls, and monitoring technologies; (4) developing an IQ stage consisting of instrument calibrations, inspections to verify that the drawings accurately depict the frillt final configuration of the water system and, where necessary, special tests to verify that the installation meets the design requirements; (5) developing an OQ stage consisting of tests and inspections to verify that the equipment, system alerts, and controls are operating reliably and that appropriate alert and action levels are established (This phase of qualification may overlap with aspects of the next step.); and (6) developing a prospective PQ stage to confirm the appropriateness of critical process parameter operating ranges (During this phase of validation, alert and action levels for key quality attributes and operating parameters are verified.); (7) supplementing a validation maintenance program (also called continuous validation life eycle) that imeludes a mechanism to-contrel-changes to the water system and establishes and carries out seheduled preventive maintenance-ineluding reealibration of instruments (In addition, validation maintenamee includes a menitoring program for eritical process parameters and acorrective action program.); (8) instituting aschedule for periodie review Of the-system perfermance and requaliffeation; and(9)eempleting protecols and deeumenting Steps 1 through 8. (7) assuring the adequacy of ongoing control procedures, e.g., sanitization frequency; (8) supplementing a validation maintenance program (also called continuous validation life cycle) that includes a mechanism to control changes to the
water system and establishes and carries out scheduled preventive maintenance including recalibration of instruments (In addition, validation maintenance includes a monitoring program for critical process parameters and a corrective action program.); (9) instituting a schedule for periodic review of the system performance and requalification, and (10) completing protocols and documenting Steps 1 through 9.

## PURIFIED WATER AND WATER FOR INJECTION SYSTEMS

The design, installation, and operation of systems to produce Purified Water and Water for Injection include similar components, control techniques, and procedures. The quality attributes of both waters differ only in the presence of a bacterial endotoxin requirement for Water for Injection and in their methods of preparation, at least at the last stage of preparation. The similarities in the quality attributes provide considerable common ground in the design of water systems to meet either requirement. The critical difference is the degree of control of the system and the final purification steps needed to ensure bacterial and bacterial endotoxin removal.

Production of pharmaceutical water employs sequential unit operations (processing steps) that address specific water quality attributes and protect the operation of subsequent treatment steps. in Figure 3. A typical evaluation process to select an appropriate water quality for a particular pharmaceutical purpose is shown in the decision tree in Figure 2. These diagrams This diagram may be used to assist in defining requirements for specific water uses and in the selection of unit operations. The final unit operations used to produce Water for Injection are limited to distillation and superior to distillation in the removal of chemical impurities as well as microorganisms and their components. Distillation has a long history of reliable performance and can be
validated as a unit operation for the production of Water for Injection, but other technologies or combinations of technologies can be validated as being equivalently effective. Other technologies, such as ultrafiltration following other chemical purification process, may be suitable in the production of Water for Injection but this time experience with this process is not widespread. if they can be shown through validation to be as effective and reliable as distillation. The advent of new materials for older technologies, such as reverse osmosis and ultrafiltration, that allow intermittent or continuous operation at elevated, microbial temperatures, show promise for a valid use in producing Water for Injection.

The validation plan should be designed to establish the suitability of the system and to provide a thorough understanding of the purification mechanism, range of operating conditions, required pretreatment, and the most likely modes of failure. It is also necessary to demonstrate the effectiveness of the monitoring scheme and to establish the documentation and qualification requirements for the system's validation maintenance. Trials conducted in a pilot installation can be valuable in defining the operating parameters and the expected water quality and in identifying failure modes. However, qualification of the specific unit operation can only be performed as part of the validation of the installed operational system. The selection of specific unit operations and design characteristics for a water system should take into account the quality of the feed water, the technology chosen for subsequent processing steps, the extent and complexity of the water distribution system, and the appropriate compendial requirements. For example, in the design of a system for Water for Injection, the final process (distillation or reverse osmesis) (distillation or whatever
other validated process is used according to the monograph) must have effective bacterial endotoxin reduction capability and must be validated.

## UNIT OPERATIONS CONCERNS

The following is a brief description of selected unit operations and the operation and validation concerns associated with them. Not all unit operations are discussed, nor are all potential problems addressed. The purpose is to highlight issues that focus on the design, installation, operation, maintenance, and monitoring parameters that facilitate water system validation.

## Prefiltration

Filtration eechnolegy plays an impertant role in water systems, and filtration units are available-in awiderange-of designs and for varieus applications. Removal efficiencies differ signiffeantly from cearse fiters, such as mattimedia Or sand for larger water systems and depth cartridges for smaller water systems, to membrane flters for very smalt particlecontrol. Unit and system configurations vary widely in type-of flttering media and lecation in the process. (The tse-of membrane-flters is diseussed in a later paragraph.) Gramular or cartridge filters are used for prefltration and are-often situated at or near the head of the water pretreatment system prior to thit operations designedtoremove the setree water disimfectants. This lecation, however, dees net prectude the need for periedic mierobial contrel since bieflm eanstill proliferate-in the presence-of setree-water disinfectants, albeit slewer than in their absence. These preflters remove-solid contaminants-dewn to a-size-of 7 te 10 رum from the water supply and protect downstream-sys tem compenents from partieulates that can inhibit equipment perfermance and sherten their effective-life. Designt
and operational isstes that may impact performance-of depth filters include channeling of the filtering media, blockage frem-silt, mierebial growth, and filtering media loss during improper backwashing. Control measures in elude pressure and flow monitoring during use and backwashing, sanitizing, and replacing fltering media. An important design concern is sizing of the filter to prevent ehanneling or media loss resulting from inappropriate water flow rates as well as proper sizing to minimize exeessive frequent or infrequent backwashing or cartridge filter replace-

## ment.

The purpose of prefiltration-also referred to as initial, coarse, or depth filtration-is to remove solid contaminants down to a size of 7 to $10 \mu \mathrm{~m}$ from the incoming source water supply and protect downstream system components from particulates that can inhibit equipment performance and shorten their effective life. This coarse filtration technology utilizes primarily sieving effects for particle capture and a depth of filtration medium that has a high "dirt load" capacity. Such filtration units are available in a wide range of designs and for various applications. Removal efficiencies and capacities differ significantly, from granular bed filters such as multimedia or sand for larger water systems, to depth cartridges for smaller water systems. Unit and system configurations vary widely in type of filtering media and location in the process. Granular or cartridge prefilters are often situated at or near the head of the water pretreatment system bfore prior to unit operations designed to remove the source water disinfectants. This location, however, does not preclude the need for periodic microbial control because biofilm can still proliferate, although at a slower rate in the presence of source water disinfectants. Design and operational issues that may impact performance of depth filters include channeling of the filtering media, blockage from silt, microbial growth, and filtering-media loss during improper
backwashing. Control measures involve pressure and flow monitoring during use and backwashing, sanitizing, and replacing filtering media. An important design concern is sizing of the filter to prevent channeling or media loss resulting from inappropriate water flow rates as well as proper sizing to minimize excessively frequent or infrequent backwashing or cartridge filter replacement.

## Activated Carbon

Activated carben beds adserb-low molecular weight organic material and oxidizing additives, such as chlorine and chloramine eompounds, removing them from the water. They are used to achieve certain quality attributes and to pretect against reaction with downstream stainless steelsurfaces, resins, and membranes. The chief operating concerns regarding activated carbon beds include the propensity to stppert bacteria growth, the petential for hydratlic channeling, the inability to be regenerated in sitt, and the-shed ding of bacteria, endotoxins, organic chemicals, and fine earbon particles. Control measures inelude appropriate high water flow rates, sanitization with hot water or steam, back washing, testing for adsorption eapacity, and frequent replacement of the carbon bed. It is impertant to note that the use of steam for carben bed sanitization is often incompletely effective due to channeling rather than even permeation through the bed. This phenemenen can ustally be avoided by using het water sanitization. Alternative technolegiesto aetivated carben beds can be used in order to avoid their mierobial problems, sueh as disinfectant neutralizing chemieat additives and regenerable organic seavenging devices. However, these alternatives do not function by the same mechanisms as activated carben, may not be as-effective at removing some-organies, and have a different set of operating concerns and control measures that may be nearly as troubleseme as activated carben beds. Granular activated
carbon beds adsorb low molecular weight organic material and oxidizing additives, such as chlorine and chloramine compounds, removing them from the water. They are used to achieve certain quality attributes and to protect against reaction with downstream stainless steel surfaces, resins, and membranes. The chief operating concerns regarding activated carbon beds include the propensity to support bacteria growth, the potential for hydraulic channeling, the organic adsorption capacity, appropriate water flow rates and contact time, the inability to be regenerated in situ, and the shedding of bacteria, endotoxins, organic chemicals, and fine carbon particles. Control measures may involve monitoring water flow rates and differential pressures, sanitizing with hot water or steam, backwashing, testing for adsorption capacity, and frequent replacement of the carbon bed. If the activated carbon bed is intended for organic reduction, it may also be appropriate to monitor influent and effluent TOC. It is important to note that the use of steam for carbon bed sanitization is often incompletely effective due to steam channeling rather than even permeation through the bed. This phenomenon can usually be avoided by using hot water sanitization. It is also important to note that microbial biofilm development on the surface of the granular carbon particles (as well as on other particles such as found in deionizer beds and even multimedia beds) can cause adjacent bed granules to "stick" together. When large masses of granules are agglomerated in this fashion, normal backwashing and bed fluidization flow parameters may not be sufficient to disperse them, leading to ineffective removal of trapped debris, loose biofilm, and penetration of microbial controlling conditions (as well as regenerant chemicals as in the case of agglomerated deionizer resins). Alternative technologies to activated carbon beds can be used in order to avoid their microbial problems, such as disinfectant-neutralizing chemical additives and regenerable organic scav-
enging devices. However, these alternatives do not function by the same mechanisms as activated carbon, may not be as effective at removing disinfectants and some organics, and have a different set of operating concerns and control measures that may be nearly as troublesome as activated carbon beds.

## Additives

Chemical additives are used in water systems (a) to control microorganisms by use of sanitants such as chlorine compounds and ozone, (b) to enhance the removal of suspended solids by use of flocculating agents, (c) to remove chlorine compounds, (d) to avoid scaling on reverse osmosis membranes, and (e) to adjust pH for more effective removal of carbonate and ammonia compounds by reverse osmosis. These additives do not constitute "added substances" as long as they are either removed by subsequent processing steps or they nattrally and completely attodegrade or equilibrate to ions and molecules native to the water such as hy drogen and hydroxide ions, oxygen, or water itself. are otherwise absent from the finished water. Control of additives to ensure a continuously effective concentration and subsequent monitoring to ensure their removal as well as their nen native reation/degradation products should be designed into the system and included in the monitoring program.

## Organic Scavengers

Organic scavenging devices use macroreticular weakly basic anion-exchange resins capable of removing organic material and endotoxins from the water. They can be regenerated with appropriate biocidal caustic brine solutions. Operating concerns are associated with organic scavenging capacity, particulate, chemical and microbiological fouling
of the reactive resin surface, flow rate, regeneration frequency , and shedding of resin fragments. Control measures include TOC testing of influent and effluent, backwashing, monitoring hydraulic performance, and using downstream filters to remove resin fines.

## Softeners

Water softeners may be located either upstream or downstream of disinfectant removal units. They utilize sodiumbased cation-exchange resins to remove water-hardness ions, such as calcium and magnesium, that could foul or interfere with the performance of downstream processing equipment such as reverse osmosis membranes, deionization devices, and distillation units. Water softeners can also be used to remove other lower affinity cations, such as the ammonium ion, that may be released from chloramine disinfectants commonly used in drinking water and which might otherwise carryover through other downstream unit operations. If ammonium removal is one of its purposes, the softener must be located downstream of the disinfectant removal operation, which itself may liberate ammonium from neutralized chloramine disinfectants. Water softener resin beds are regenerated with concentrated sodium chloride solution (brine). Concerns include microorganism proliferation, channeling caused by biofilm agglomeration of resin particles, appropriate water flow rates and contact time, ion-exchange capacity, organic and particulate resin fouling, organic leaching from new resins, fracture of the resin beads, resin degradation by excessively chlorinated water, and contamination from the brine solution used for regeneration. Control measures involve recirculation of water during periods of low water use, periodic sanitization of the resin and brine system, use of microbial control devices (e.g., UV light and chlorine), locating the unit upstream of the disinfectant removal step (if used only
for softening), appropriate regeneration frequency, effluent chemical monitoring (e.g., hardness ions and possibly ammonium), and downstream filtration to remove resin fines. If a softener is used for ammonium removal from chloraminecontaining source water, then capacity, contact time, resin surface fouling, pH , and regeneration frequency are very important.

## Deionization

Deionization (DI), electronizan(EDI), and continuous deionizan (CDI) electrodeionization (CEDI) are effective methods of improving the chemical quality attributes of water by removing cations and anions. DI systems have charged resins that require periodic regeneration with an acid and base. Typically, cationic resins are regenerated with either hydrochloric or sulfuric acid, which replace the captured positive ions with hydrogen ions. Anionic resins are regenerated with sodium or potassium hydroxide, which replace captured negative ions with hydroxide ions. Because free endotoxin is negatively charged, there is some removal of endotoxin achieved by the anionic resin. Both regenerant chemicals are biocidal and offer a measure of microbial control. The system can be designed so that the cation and anion resins are in separate or "twin" beds or they can be mixed together to form a mixed bed. Twin beds are easily regenerated but deionize water less efficiently than mixed beds, which have a considerably more complex regeneration process. Rechargeable resin canisters can also be used for this purpose.
The EDI CDI CDI CEDI system uses a combination of mixed resin, selectively permeable membranes, and an electric charge, providing continuous flow (product and waste concentrate) and continuous regeneration. Water enters both the resin section and the waste (concentrate) section. As it passes through the resin, it is deionized to become
product water. The resin acts as a conductor enabling the electrical potential to drive the captured cations and anions through the resin and appropriate membranes for concentration and removal in the waste water stream. The electrical potential also separates the water in the resin (product) section into hydrogen and hydroxide ions. This permits continuous regeneration of the resin without the need for regenerant additives. However, unlike conventional deionization, EDI and-CDI units mest staft with water that is already pretreat to be fairly pure beeatre they cannot handle the heavier ion load of mpurified source water. CEDI units must start with water that is already partially purified because they generally cannot produce Purified Water quality when starting with the heavier ion load of unpurified source water.

Concerns for all forms of deionization units include microbial and endotoxin control, chemical additive impact on resins and membranes, and loss, degradation, and fouling of resin. Issues of concern specific to DI units include regeneration frequency and completeness, channeling, caused by biofilm agglomeration of resin particles, organic leaching from new resins, complete resin separation for mixed bed regeneration, and mixing air contamination (mixed beds). Control measures vary but typically include recirculation loops, effluent microbial control by UV light, conductivity monitoring, resin testing, microporous filtration of mixing air, microbial monitoring, frequent regeneration to minimize and control microorganism growth, sizing the equipment for suitable water flow and contact time, and use of elevated temperatures. Internal distributor and regeneration piping for mixed bed units should be configured to ensure that regeneration chemicals contact all internal bed and piping surfaces and resins. Rechargeable canisters can be the source of contamination and should be carefully monitored. Full
knowledge of previous resin use, minimum storage time between regeneration and use, and appropriate sanitizing procedures are critical factors ensuring proper performance.

## Reverse Osmosis

Reverse osmosic ( RO ) units employ a semipermeable membrane and a-substantial pressure-differential to-drive water threugh the membrane to achieve chemical, mierobial, andendetoxin quality improvement. The process streams eomsist of stpply water, product water (permeate), and wastewater (rejeet). Pretreatment and system eonfiguration variations and chemieat additives may be necessary depending on-source-water to achieve-desired performance and retiability. Concerns asseciated with the design and operation of RO units include membrane materials that are extremely semsitive to-sanitizing agents; to partieulate, chemical, and mierobiatmembrane-fouling; to membrane and sealintegrity; te the passage of dissolved gases, such as earben dioxide and ammenia; and to the volume of wastewater. Failure-of membrane or sealimtegrity will result in prodtet water con tamination. Methods of eentrel consist of suitable pretreat ment of the water stream, appropriate-membrane-materiat selection, integrity challenges, membrane design and heat telerance, periodic sanitization, and menitering of differential pressures, conductivity, mierobial levels, and total organic carbon. The eonfiguration of the $R \Theta$ unit offers eontrol-eppertunities by expanding the single pass scheme to parallelstaged, reject staged, two pass, and combination designs. An example would be the use-of atwo pass designt to improve reliability, quality, andeffeieney. The-development of RO units that can tolerate sanitizing water temper attres as well as-operate-effeiently at elevated temperatures has added greatly to their mierebialcentreland te the aveid
ance of biofouling. RO units can be used alone or in com bination with DI and EDI units for operational and quality

## enhancements.

Reverse osmosis (RO) units employ semipermeable membranes. The "pores" of RO membranes are actually intersegmental spaces among the polymer molecules. They are big enough for permeation of water molecules, but too small to permit passage of hydrated chemical ions. However, many factors including pH , temperature, and differential pressure across the membrane affect the selectivity of this permeation. With the proper controls, RO membranes can achieve chemical, microbial, and endotoxin quality improvement. The process streams consist of supply water, product water (permeate), and wastewater (reject). Depending on source water, pretreatment and system configuration variations and chemical additives may be necessary to achieve desired performance and reliability.

A major factor affecting RO performance is the permeate recovery rate, that is, the amount of the water passing through the membrane compared to the amount rejected. This is influenced by the several factors, but most significantly by the pump pressure. Recoveries of $75 \%$ are typical, and can accomplish a 1 to $2 \log$ purification of most impurities. For most feed waters, this is usually not enough to meet Purified Water conductivity specifications. A second pass of this permeate water through another RO stage usually achieves the necessary permeate purity if other factors such as pH and temperature have been appropriately adjusted and the ammonia from chloraminated source water has been previously removed. Increasing recoveries with higher pressures in order to reduce the volume of reject water will lead to reduced permeate purity. If increased pressures are needed over time to achieve the same permeate flow, this
is an indication of partial membrane blockage that needs to be corrected before it becomes irreversibly fouled, and expensive membrane replacement is the only option.

Other concerns associated with the design and operation of RO units include membrane materials that are extremely sensitive to sanitizing agents and to particulate, chemical, and microbial membrane fouling; membrane and seal integrity; the passage of dissolved gases, such as carbon dioxide and ammonia; and the volume of wastewater, particularly where water discharge is tightly regulated by local authorities. Failure of membrane or seal integrity will result in product water contamination. Methods of control involve suitable pretreatment of the influent water stream, appropriate membrane material selection, integrity challenges, membrane design and heat tolerance, periodic sanitization, and monitoring of differential pressures, conductivity, microbial levels, and TOC.
The development of RO units that can tolerate sanitizing water temperatures as well as operate efficiently and continuously at elevated temperatures has added greatly to their microbial control and to the avoidance of biofouling. RO units can be used alone or in combination with DI and CEDI units as well as ultrafiltration for operational and quality enhancements.

## Ultrafiltration

Ulraflitration is another teehnology that uses a permeable membrane, but unlike RO , it works by mechanieal separafien rather than osmesis. Due to the ability of the membrane to sieve out macromolecules (typically greater tham about 20 K daltons) depending on pere size and other factors, macromolecular and mierobial impurities, steh as endetoxins, ean be retained by these membranes, effectively removing them frem the effluent. This technology may be apprepriate as an intermediate or final purifieation step. Similar to RO , sue
eessful performance is dependent upen pretreatment of the water by upstream unit operations. Issues of concern inelude eompatibility of membrane material with heat and sanitizing
agents, membrane integrity, fouling by partieles and mieroorganisms, and seal integrity. Control measures inelude fit tration medium selection, sanitization, tangential flow designs capable of flushing the membrane surface, integrity ehallenges, regular eartridge changes, elevated feed water temperature, and monitoring totalorganic carbon and differential pressure. Additional flexibility in operation is pessible based on the way units are arranged such as in a parallel or series configuration. Care should be taken to avoid stagnant water conditions that could promete miereorgenism growth in back up or standby units.

Ultrafiltration is a technology most often employed in pharmaceutical water systems for removing endotoxins from a water stream. It can also use semi-permeable membranes, but unlike RO, these typically use polysulfone membranes whose intersegmental "pores" have been purposefully exaggerated during their manufacture by preventing the polymer molecules from reaching their smaller equilibrium proximities to each other. Depending on the level of equilibrium control during their fabrication, membranes with differing molecular weight "cutoffs" can be created such that molecules with molecular weights above these cutoffs ratings are rejected and cannot penetrate the filtration matrix.

Ceramic ultrafilters are another molecular sieving technology. They are cakes of ultra-fine silicate particles, the size of which ultimately determines the molecular porosity, that have been partially sintered together at high temperatures. Ceramic ultrafilters are self supporting and extremely durable, backwashable, chemically cleanable, and steam sterilizable. However, they generally require higher operating pressures than membrane type ultrafilters.

All ultrafiltration devices work primarily by a molecular sieving principle. Ultrafilters with molecular weight cutoff ratings in the range of 10,000 to $20,000 \mathrm{Da}$ are typically used in water systems for removing endotoxins. This technology may be appropriate as an intermediate or final purification step. Similar to RO, successful performance is dependent upon pretreatment of the water by upstream unit operations.
Issues of concern for ultrafilters include compatibility of membrane material with heat and sanitizing agents, membrane integrity, fouling by particles and microorganisms, and seal integrity. Control measures involve filtration medium selection, sanitization, flow design (dead end vs. tangential), integrity challenges, regular cartridge changes, elevated feed water temperature, and monitoring TOC and differential pressure. Additional flexibility in operation is possible based on the way ultrafiltration units are arranged such as in a parallel or series configurations. Care should be taken to avoid stagnant water conditions that could promote microorganism growth in back-up or standby units.

## Charge-Modified Filtration

Charge-modified filters are usually microbially retentive filters that are treated during their manufacture to have a positive charge on their surfaces. Microbial retentive filtration will be disescribed in a subsequent section, but the significant feature of these membranes is their electrostatic surface charge. Such charged filters can reduce endotoxin levels in the fluids passing through them by their adsorption (owing to endotoxin's negative charge) onto the membrane surfaces. Though ultrafilters are more often employed as a unit operation for endotoxin removal in water systems, charge-modified filters may also have a place in endotoxin removal particularly where available upstream pressures are not sufficient for ultrafiltration and for a single,
relatively short term use. Charge-modified filters may be difficult to validate for long-term or large-volume endotoxin retention. Even though their purified standard endotoxin retention can be well characterized, their retention capacity for "natural" endotoxins is difficult to gauge. Nevertheless, utility could be demonstrated and validated as short-term, single-use filters at points of use in water systems that are not designed for endotoxin control or where only an endotoxin "polishing" (removal of only slight or occasional endotoxin levels) is needed. Control and validation concerns include volume and duration of use, flow rate, water conductivity and purity, and constancy and concentration of endotoxin levels being removed. All of these factors may have to be evaluated and challenged prior to using this approach, making this a difficult-to-validate application. Even so, there may still be a possible need for additional backup endotoxin testing both upstream and downstream of the filter.


#### Abstract

Mieroporoust Microbial-Retentive Filtration

Microbial-retentive membrame filters have a larger effec tive pere-size than ultrafiters and are-used to prevent the passage of miereorganisms and similarly sized particles. Fil ters are rated by their manufacturer for the theoretiealsmallest size of bacterial cell they are eapable of retaining. The generally aceepted rating considered to retain all bacteria from a gas stream is 0.2 or 0.22 Hm (absolute, net nominal rating). When used on air or gas vents for tanks and other thit operations, as well as for compressed air gases used in the regeneration of mixed bed deionization units, the membrane surface is typieally hydrophobic (nenwettable by water). Areas of concern are-bleckage-of tank vents by eendensed water vaper or trapped partieutate matter, whieh eancause mechaniealdamage to the tank, andeoncentration of miereorganisms on the surface of the membrane filter,


ereating the petential for contamination of the tank or deionizer contents. Control meastres include heat tracing and proper orientation of vent filter housings to prevent aceumtt lation of vaper condensate. Sterilization of the unit prier to initial use, and periedically thereafter, as well as regular flt ter changes are recemmended control methods.

Mierobial retentive filters are also sometimes used for water filtration in the purification systems or in distribution piping. Though mierobial retentive filters, treated to be hydrophilic and having an absolute filter rating of 0.2 or $0.22 \mu \mathrm{~m}$, are considered to be sterilizing filters for process streams and product formulations, their use in water systems should either be avoided or very careftlly controlled beeause these units can become a source for microbial contamination. The potential exists for the release of microrganisms should the membrane filter rupture or as a result of mierobial grow threugh. There is also evidence that the kinds of micreorganisms that proliferate in ambient wa ter systems are of a size and possess cell strface properties that could allow their passage through these filters. Filters of smaller retention ratings (e.g., $0.1 \mu \mathrm{~m}$ ) may be necessary to more definitively retain these aquatic mierourganisms.

Filters that are intended to be microretentive should be sanitized and integrity tested prior to initialuse and at appropriate intervals thereafter. It may also be neeessary to frequently replace these filters to avoid grow through as well as release of endetoxin from the aecummated bioburdenen the upstream side of the filters. As an added meastre of protection, in line ultraviolet lamps, apprepriately sized for the flow rate, may be used just upstream of mieroretentive filters to inactivate mieroorganisms prior to their capture by the fit ter to woid or greatly delay filter grow hrough.
Mieroretentive filters may be use downstream of unitoperations that tend to release mieroerganisms or upstream of thit operations that are sensitive to microorganisms. Miero-
retentive filters may also be used to filter water feeding the distribution system. Concerns include flow rate, membrane and seal integrity, retention capacity, and service-duration. Gentrol measures include monitoring differential pressure and endetoxin levels, proper sizing, membrane integrity testing, placing ultraviolet lamps immediately upstream, and configuring units in series to control break through.

These hydrophilic filters can also be treated to have a positive charge on the surface of the filter media. Such eharged filters can additionally be used to reduce endotoxin levels in the fluids passing through them by electrostatic attraction and adsorption. However, such applications are diffieult to validate for endotoxin retention beeatse their endotoxin retention capacity for "natural" endotoxim is difficult to gatege from purified endotoxin retention and because the amount of endotoxin in the water, or pyreburden, can be quite variable. These factors make usage duration diffieut to validate.

Microbial-retentive membrane filters have experienced an evolution of understanding in the past decade that has caused previously held theoretical retention mechanisms to be reconsidered. These filters have a larger effective "pore size" than ultrafilters and are intended to prevent the passage of microorganisms and similarly sized particles without unduly restricting flow. This type of filtration is widely employed within water systems for filtering the bacteria out of both water and compressed gases as well as for vent filters on tanks and stills and other unit operations. However, the properties of the water system microorganisms seem to challenge a filter's microbial retention from water with phenomena absent from other aseptic filtration applications, such as filter sterilizing of pharmaceutical formulations prior to packaging. In the latter application, sterilizing grade filters are generally considered to have an assigned rating of 0.2 or $0.22 \mu \mathrm{~m}$. This rather arbitrary rat-
ing is associated with filters that have the ability to retain a high level challenge of a specially prepared inoculum of Brevundimonas (formerly Pseudomonas) diminuta. This is a small microorganism originally isolated decades ago from a product that had been "filter sterilized" using a $0.45-\mu \mathrm{m}$ rated filter. Further study revealed that a percentage of cells of this microorganism could reproducibly penetrate the $0.45-\mu \mathrm{m}$ sterilizing filters. Through the suessful use in product solution filter sterilization, retention filters assigned the historic correlation of B. diminuta retaining tighter filters, thought to be twice as good as $0.45-\mu \mathrm{m}$ filter, assigned ratings of 0.2 or $0.22 \mu \mathrm{~m}$ with their successful use in product solution filter sterilization, both this filter rating and the associated high level B. diminuta challenge have become the current benchmarks for sterilizing filtration. New evidence now suggests that for microbial-retentive filters used for pharmaceutical water, B. diminuta may not be the best model microorganism.

An archaic understanding of microbial retentive filtration would lead one to equate a filter's rating with the false impression of a simple sieve or screen that absolutely retains particles sized at or above the filter's rating. A current understanding of the mechanisms involved in microbial retention and the variables that can affect those mechanisms has yielded a far more complex interaction of phenomena than previously understood. A combination of simple sieve retention and surface adsorption are now known to contribute to microbial retention.

The following all interact to create some unusual and surprising retention phenomena for water system microorganisms: the variability in the range and average pore sizes created by the various membrane fabrication processes, the variability of the surface chemistry and three-dimensional structure related to the different polymers used in these filter matrices, and the size and surface properties of the mi-
croorganism intended to be retained by the filters. B. diminuta may not the best challenge microorganisms for demonstrating bacterial retention for $0.2-$ to $0.22-\mu \mathrm{m}$ rated filters for use in water systems because it appears to be more easily retained by these filters than some water system flora. The well-documented appearance of water system microorganisms on the downstream sides of some 0.2 - to $0.22-\mu \mathrm{m}$ rated filters after a relatively short period of use seems to support that some penetration phenomena are at work. Unknown for certain is if this downstream appearance is caused by a "blow-through" or some other pass-through phenomenon as a result of tiny cells or less cell "stickiness", or by a "growth through" phenomenon as a result of cells hypothetically replicating their way through the pores to the downstream side. Whatever is the penetration mechanism, 0.2 - to $0.22-\mu \mathrm{m}$ rated membranes may not be the best choice for some water system uses.

Microbial retention success in water systems has been reported with the use of some manufacturers' filters arbitrarily rated as $0.1 \mu \mathrm{~m}$. There is general agreement that for a given manufacturer, their $0.1-\mu \mathrm{m}$ rated filters are tighter than their 0.2 - to $0.22-\mu \mathrm{m}$ rated filters. However, comparably rated filters from different manufacturers in water filtration applications may not perform equivalently owing to the different filter fabrication processes and the nonstandardized microbial retention challenge processes currently used for defining the $0.1-\mu \mathrm{m}$ filter rating. It should be noted that use of $0.1-\mu \mathrm{m}$ rated membranes generally results in a sacrifice in flow rate compared to 0.2 - to $0.22-\mu \mathrm{m}$ membranes, so whatever membranes are chosen for a water system application, the user must verify that the membranes are suitable for their intended application, use period, and use process, including flow rate.

For microbial retentive gas filtrations, the same sieving and adsorptive retention phenomena are at work as in liquid filtration, but the adsorptive phenomenon is enhanced by additional electrostatic interactions between particles and filter matrix. These electrostatic interactions are so strong that particle retention for a given filter rating is significantly more efficient in gas filtration than in water or product solution filtrations. These additional adsorptive interactions render filters rated at 0.2 to $0.22 \mu \mathrm{~m}$ unquestionably suitable for microbial retentive gas filtrations. When microbially retentive filters are used in these applications, the membrane surface is typically hydrophobic (non-wettable by water). A significant area of concern for gas filtration is blockage of tank vents by condensed water vapor, which can cause mechanical damage to the tank. Control measures include electrical or steam tracing and a self-draining orientation of vent filter housings to prevent accumulation of vapor condensate. However, a continuously high filter temperature will take an oxidative toll on polypropylene components of the filter, so sterilization of the unit prior to initial use, and periodically thereafter, as well as regular visual inspections, integrity tests, and changes are recommended control methods.

In water applications, microbial retentive filters may be used downstream of unit operations that tend to release microorganisms or upstream of unit operations that are sensitive to microorganisms. Microbial retentive filters may also be used to filter water feeding the distribution system. It should be noted that regulatory authorities allow the use of microbial retentive filters within distribution systems or even at use points if they have been properly validated and are appropriately maintained. A point-of-use filter should only be intended to "polish" the microbial quality of an otherwise well-maintained system and not to serve as the primary microbial control device. The efficacy of system microbial control measures can only be assessed by
sampling the water upstream of the filters. As an added measure of protection, in-line UV lamps, appropriately sized for the flow rate (see Sanitization), may be used just upstream of microbial retentive filters to inactivate microorganisms prior to their capture by the filter. This tandem approach tends to greatly delay potential microbial penetration phenomena and can substantially extend filter service life.

## Ultraviolet Light

The use of UV light for mierobial contrel is diseussed under the Sanitization, but its applications to chemical purift eation are also emerging. At wavelengths of 185 nm, UV light has demenstrated utility in the destruction of the chlerine containing disinfectants used in sotree water as well as for interim stages of water pretreatment. This wavelength of UV light has also been used to reduee TOC levels in recir eulating distribution systems. Areas of concem inelude ad equate UV intensity and residence time, unforeseen hyperchlorination of the source water overwhelming the pho degradation capability, release of ammonia from the photodegradation of chloramines, and mapparent UV bulb failure. The use of low-pressure UV lights that emit a 254nm wavelength for microbial control is discussed under Sanitization, but the application of UV light in chemical purification is also emerging. This $254-\mathrm{nm}$ wavelength is also useful in the destruction of ozone. With intense emissions at wavelengths around 185 nm (as well as at 254 nm ), medium pressure UV lights have demonstrated utility in the destruction of the chlorine containing disinfectants used in source water as well as for interim stages of water pretreatment. High intensities of this wavelength alone or in combination with other oxidizing sanitants, such as hydrogen peroxide, have been used to lower TOC levels in recirculating distribution systems. The organics are typically converted to carbon dioxide, which equilibrates to bicarbonate, and
incompletely oxidized carboxylic acids, both of which can easily be removed by polishing ion-exchange resins. Areas of concern include adequate UV intensity and residence time, gradual loss of UV emissivity with bulb age, gradual formation of UV-absorbing film at the water contact surface, incomplete photodegradation during unforeseen source water hyperchlorination, release of ammonia from chloramine photodegradation, unapparent UV bulb failure, and conductivity degradation in distribution systems using $185-\mathrm{nm}$ UV lights. Control measures include regular inspection or emissivity alarms to detect bulb failures or film occlusions, regular UV bulb sleeve cleaning and wiping, downstream chlorine detectors, downstream polishing deionizers, and regular (approximately yearly) bulb replacement.

## Distillation

Distillation units provide chemical and microbial purification via thermal vaporization, mist elimination, and water vapor condensation. A variety of designs is available including single effect, multiple effect, and vapor compression. The latter two configurations are normally used in larger systems because of their generating capacity and efficiency. Distilled water systems may require less rigorous control of feed water quality than do membrane systems. Areas ofeoneern include carry over of gaseous impurities such as ammonia and carbon dioxide, faulty mist elimination, evaporator flooding, inadequate blowdown, stagnant water in condensers and raporators, pump and compressor seat design, pinhole evaporater and condenser leaks, andeonductivity (quality) variations during stant up and operation. require different feed water controls than required by membrane systems. For distillation, due consideration must be given to prior removal of hardness and silica impurities that may foul or corrode the heat transfer surfaces as well as prior removal of those impurities that could volatize and
condense along with the water vapor. In spite of general perceptions, even the best distillation process cannot afford absolute removal of contaminating ions and endotoxin. Most stills are recognized as being able to accomplish at least a 3 to $4 \log$ reduction in these impurity concentrations. Areas of concern include carry-over of volatile organic impurities such as trihalomethanes (see Source and Feed Water Considerations) and gaseous impurities such as ammonia and carbon dioxide, faulty mist elimination, evaporator flooding, inadequate blowdown, stagnant water in condensers and evaporators, pump and compressor seal design, pinhole evaporator and condenser leaks, and conductivity (quality) variations during start-up and operation.

Methods of control consist of preliminary decarbenation steps, reliable mist elimination, visual or autemated hight water level indication, use of sanitary pumps and eompressers, proper drainage during inactive periods, blow down eontrel, on line conductivity sensing with autemated diver sion of unacceptable quality water to the waste stream, and periodic integrity testing for pinhole leaks. Methods of control may involve preliminary decarbonation steps to remove both dissolved carbon dioxide and other volatile or noncondensable impurities; reliable mist elimination to minimize feedwater droplet entrainment; visual or automated high water level indication to detect boiler flooding and boil over; use of sanitary pumps and compressors to minimize microbial and lubricant contamination of feedwater and condensate; proper drainage during inactive periods to minimize microbial growth and accumulation of associated endotoxin in boiler water; blow down control to limit the impurity concentration effect in the boiler to manageable levels; on-line conductivity sensing with automated diversion to waste to prevent unacceptable water upon still startup or still malfunction from getting into the finished water distribute sys-
tem; and periodic integrity testing for pinhole leaks to routinely assure condensate is not compromised by nonvolatized source water contaminants.

## Storage Tanks

Storage tanks are included in water distribution systems to optimize processing equipment capacity. Storage also allows for routine maintenance within the pretreatment train while maintaining continuous supply to meet manufacturing needs. Design and operation considerations are needed to prevent or minimize the development of biofilm, to minimize corrosion, to aid in the use of chemical sanitization of the tanks, and to safeguard mechanical integrity. These considerations may include using closed tanks with smooth interiors, the ability to spray the tank headspace using sprayballs on recirculating loop returns, and the use of heated, jacketed/insulated tanks. This minimizes corrosion and biofilm development and aids in thermal and chemical sanitization. Storage tanks require venting to compensate for the dynamics of changing water levels. This can be accomplished with a hydrophobic mierobial retentive membrane filter fitt with a properly oriented and heat-traced filter housing fitted with a hydrophobic microbial retentive membrane filter affixed to an atmospheric vent. Alternatively, an automatic membrane-filtered compressed gas pressurization and venting blanketing system may be used. In both cases, rupture disks equipped with a rupture alarm device should be used as a further safeguard for the mechanical integrity of the tank. Areas of concern include microbial growth or corrosion due to irregular or incomplete sanitization and microbial contamination from unalarmed rupture disk failures that are caused by condensate eclusion of hydrephebie occluded vent filters.

## Distribution Systems

Distribution system configuration should allow for either the continuous flow of water in the piping by means of recirculation. or should provide for the periodic flushing of momrecireulating, deadend, or one way systems. Use of nonrecirculating, dead-end, or one-way systems or system segments should be avoided whenever possible. If not possible, these systems should be periodically flushed and more closely monitored. Experience has shown that continuously recirculated systems are easier to maintain. Pumps should be designed to deliver fully turbulent flow conditions to facilitate thorough heat distribution (for hot water sanitized systems) as well as thorough chemical sanitant distribution. Pumps Turbulent flow also appear to either retard the development of biofilms or foree its development be less eeptible to shearing int the or reduce the tendency of those biofilms to shed bacteria into the water. If redundant pumps are used, they should be configured and used to avoid microbial contamination of the system.

Components and distribution lines should be sloped and fitted with drain points so that the system can be completely drained. In stainless steel distribution systems where the water is circulated at a high temperature, dead legs and lowflow conditions should be avoided, and valved tie-in points should have length-to-diameter ratios of six or less. If constructed of heat tolerant plastic, this ratio should be even less to avoid cool points where biofilm development could occur. In ambient temperature distribution systems, particular care should be exercised to avoid or minimize dead leg of any length ratios of any size and provide for complete drainage. If the system is intended to be steam sanitized, careful sloping and low-point drainage is crucial to eess. If system drainage is intended as a mierobial controt strategy, it should also be configured to be dried by passage of dry compressed air or nitrogen throughout the system be-
eatse drained meist piping will also-suppert mierebial preliferation. Water exiting from the distribution system should net be rettrned to the system. condensate removal and sanitization success. If drainage of components or distribution lines is intended as a microbial control strategy, they should also be configured to be completely dried using dry compressed air (or nitrogen if appropriate employee safety measures are used). Drained but still moist surfaces will still support microbial proliferation. Water exiting from the distribution system should not be returned to the system without first passing through all or a portion of the purification train.

The distribution design should include the placement of sampling valves in the storage tank and at other locations, such as in the return line of the recirculating water system. Where feasible, the primary sampling sites for water should be the valves that deliver water to the points of use. Direct connections to processes or auxiliary equipment should be designed to prevent reverse flow into the controlled water system. Hoses and heat exchangers that are attached to points of use in order to deliver water for a particular use must not chemically or microbiologically degrade the water quality. The distribution system should permit sanitization for microorganism control. The system may be continuously operated at sanitizing conditions or sanitized periodically.

## INSTALLATION, MATERIALS OF

## CONSTRUCTION, AND COMPONENT SELECTION

Installation techniques are important because they can affect the mechanical, corrosive, and sanitary integrity of the system. Valve installation attitude should promote gravity drainage. Pipe supports should provide appropriate slopes for drainage and should be designed to support the piping adequately under worst-case thermal and flow conditions. The methods of connecting system components including
units of operation, tanks, and distribution piping require careful attention to preclude potential problems. Stainless steel welds should provide reliable joints that are internally smooth and corrosion-free. Low-carbon stainless steel, compatible wire filler, where necessary, inert gas, automatic welding machines, and regular inspection and documentation help to ensure acceptable weld quality. Follow-up cleaning and passivation are important for removing contamination and corrosion products and to re-establish the passive corrosion resistant surface. Plastic materials can be fused (welded) in some cases and also require smooth, uniform internal surfaces. Adhesive glues and solvents should be avoided due to the potential for voids and ehemieal reactions. extractables. Mechanical methods of joining, such as flange fittings, require care to avoid the creation of offsets, gaps, penetrations, and voids. Control measures include good alignment, properly sized gaskets, appropriate spacing, uniform sealing force, and the avoidance of threaded fittings.

Materials of construction should be selected to be compatible with control measures such as sanitizing, cleaning, and passivating. Temperature rating is a critical factor in choosing appropriate materials because surfaces may be required to handle elevated operating and sanitization temperatures. Should chemicals or additives be used to clean, control, or sanitize the system, materials resistant to these chemicals or additives must be utilized. Materials should be capable of handling turbulent flow and elevated velocities without wear of the corrosion-resistant film such as the passive chromium oxide surface of stainless steel. The finish on metallic materials such as stainless steel, whether it is a refined mill finish, polished to a specific grit, or an electropolished treatment, should complement system design and provide satisfactory corrosion and microbial activity resistance as well as chemical sanitizability. Auxiliary equipment and fittings
that require seals, gaskets, diaphragms, filter media, and membranes should exclude materials that permit the possibility of extractables, shedding, and microbial activity. Insulating materials exposed to stainless steel surfaces should be free of chlorides to avoid the phenomenon of stress corrosion cracking that can lead to system contamination and the destruction of tanks and critical system components.

Specifications are important to ensure proper selection of materials and to serve as a reference for system qualification and maintenance. Information such as mill reports for stainless steel and reports of composition, ratings, and material handling capabilities for nonmetallic substances should be reviewed for suitability and retained for reference. Component (auxiliary equipment) selection should be made with assurance that it does not create a source of contamination intrusion. Heat exchangers should be double shee or eoneentric tube design. They should inelude differential pressure monitoring or utilize heat transfer medium of equal or better quality to aveid problems should leaks develop. constructed to prevent leakage of heat transfer medium to the pharmaceutical water and, for heat exchanger designs where prevention may fail, there should be a means to detect leakage. Pumps should be of sanitary design with seals that prevent contamination of the water. Valves should have smooth internal surfaces with the seat and closing device exposed to the flushing action of water, such as occurs in diaphragm valves. Valves with pocket areas or closing devices (e.g., ball, plug, gate, globe) that move into and out of the flow area should be avoided.

## SANITIZATION

Microbial control in water systems is achieved primarily through sanitization practices. Systems can be sanitized using either thermal or chemical means. Thermal approaches to system sanitization include periodic or continuously cir-
culating hot water and the use of steam. Temperatures of at least $80^{\circ}$ are most commonly used for this purpose, but continuously recirculating water of at least $65^{\circ}$ has also been used effectively in insulated stainless steel distribution systems when attention is paid to uniformity and distribution of such self-sanitizing temperatures. These techniques are limited to systems that are compatible with the higher temperatures needed to achieve sanitization., such as stainless steel and some polymer formulations. Although thermal methods control biofilm development by either continuously inhibiting their growth or, in intermittent applications, by killing the microorganisms within biofilms, they are not effective in removing established biofilms. that beeme antri ent source for rapid biofilm regrowth after the sanitizing enditions are removedor halted. Chemical metheds, where empatible, can be used on a wider variety of construction materials. These metheds typieally employ oxidizing agents steh as halogenated compounds, hydrogen peroxide, ozone, peracetic acid, or combinations thereof. Halogenated com peunds are effeetive sanitizers but are diffieult to flush from the system and may leave biofilms intact. Compounds such as hydrogen peroxide, ozone, and peracetic acid oxidize bacteria and biofilms by forming reactive peroxides and free radieals (netably hydroxyl radieals). The shert half life of these compounds, partieularly ozone, may require that it be added continuously during the sanitization process. Hy drogen peroxide andozone rapidly degrade to water andox ygen; peracetic acid degrades to acetic acid in the presence of ultraviolet light. It is important to note that mieroorga nisms in a biefilm can be extremely difficult to kill, even by aggressive oxidizing biocides. The less developed the biofllm, the more effective the biocidalaction. Therefore, eptimal biocide entrol is achieved by frequent biocide use that does not allow significant biofilm development be Killed but intact biofilms can become a
nutrient source for rapid biofilm regrowth after the sanitizing conditions are removed or halted. In such cases, a combination of routine thermal and periodic supplementation with chemical sanitization might be more effective. The more frequent the thermal sanitization, the more likely biofilm development and regrowth can be eliminated. Chemical methods, where compatible, can be used on a wider variety of construction materials. These methods typically employ oxidizing agents such as halogenated compounds, hydrogen peroxide, ozone, peracetic acid, or combinations thereof. Halogenated compounds are effective sanitizers but are difficult to flush from the system and may leave biofilms intact. Compounds such as hydrogen peroxide, ozone, and peracetic acid oxidize bacteria and biofilms by forming reactive peroxides and free radicals (notably hydroxyl radicals). The short half-life of ozone in particular, and its limitation on achievable concentrations require that it be added continuously during the sanitization process. Hydrogen peroxide and ozone rapidly degrade to water and oxygen; peracetic acid degrades to acetic acid in the presence of UV light. In fact, ozone's ease of degradation to oxygen using 254nm UV lights at use points allow it to be most effectively used on a continuous basis to provide continuously sanitizing conditions.

In-line UV light at a wavelength of 254 nm can also be used to continuously "sanitize" water ciculating in the system, but these devices must be properly sized for the water flow. Such devices inactivate a high percentage (but not $100 \%$ ) of microorganisms that flow through the device but cannot be used to directly control existing biofilm upstream or downstream of the device. However, when coupled with conventional thermal or chemical sanitization technologies or located immediately upstream of a microbially retentive filter, it is most effective and can prolong the interval between system sanitizations. The ultraviole light of
the proper wavelength also facilitates the degradation of hy drogen peroxide and ozone, peracetic acid, and ehlorinated

## water disinfectants.

It is important to note that microorganisms in a well-developed biofilm can be extremely difficult to kill, even by aggressive oxidizing biocides. The less developed and therefore thinner the biofilm, the more effective the biocidal action. Therefore, optimal biocide control is achieved by frequent biocide use that does not allow significant biofilm development between treatments.

Sanitization steps require validation to demonstrate the capability of reducing and holding microbial contamination at acceptable levels. Validation of thermal metheds sheuld inelude a heat distribution study to demenstrate that sanitization temperatures are achieved throughout the system. Va lidation of chemical methods require demonstrating adequate chemical concentrations throughout the system. In addition, when the sanitization process is completed, of feetive removal of chemieal residues must be demonstrated. The frequeney of sanitization is generally dietated by the results of systernern should include a heat distribution study to demonstrate that sanitization temperatures are achieved throughout the system, including the body of use point valves. Validation of chemical methods require demonstrating adequate chemical concentrations throughout the system, exposure to all wetted surfaces, including the body of use point valves, and complete removal of the sanitant from the system at the completion of treatment. Methods validation for the detection and quantification of residues of the sanitant or its objectionable degradants is an essential part of the validation program. The frequency of sanitization should be supported by, if not triggered by, the results of system microbial monitoring. Conclusions derived from trend analysis of the microbiological data should be used as the alert mechanism for
maintenance. The frequency of sanitization should be established in such a way that the system operates in a state of microbiological control and does not routinely exceed alert levels (see Alert and Action Levels and Specifications).

## OPERATION, MAINTENANCE, AND CONTROL

A preventive maintenance program should be established to ensure that the water system remains in a state of control. The program should include (1) procedures for operating the system, (2) monitoring programs for critical quality attributes and operating conditions including calibration of critical instruments, (3) schedule for periodic sanitization, (4) preventive maintenance of components, and (5) control of changes to the mechanical system and to operating conditions.

Operating Procedures-Procedures for operating the water system and performing routine maintenance and corrective action should be written, and they should also define the point when action is required. The procedures should be well documented, detail the function of each job, assign who is responsible for performing the work, and describe how the job is to be conducted. The effectiveness of these procedures should be assessed during water system validation.

Monitoring Program—Critical quality attributes and operating parameters should be documented and monitored. The program may include a combination of in-line sensors or automated instruments (e.g., for TOC, conductivity, hardness, chlorine, etc.), automated or manual documentation of operational parameters (such as flow rates or pressure drop across a carbon bed, filter, or RO unit), and laboratory tests (e.g., total microbial counts). The frequency of sampling, the requirement for evaluating test results, and the necessity for initiating corrective action should be included.

Sanitization-Depending on system design and the selected units of operation, routine periodic sanitization may be necessary to maintain the system in a state of microbial control. Technologies for sanitization are described above.

Preventive Maintenance-A preventive maintenance program should be in effect. The program should establish what preventive maintenance is to be performed, the frequency of maintenance work, and how the work should be documented.

Change Control-The mechanical configuration and operating conditions must be controlled. Proposed changes should be evaluated for their impact on the whole system. The need to requalify the system after changes are made should be determined. Following a decision to modify a water system, the affected drawings, manuals, and procedures should be revised.

## SAMPLING CONSIDERATIONS

Water systems should be monitored at a frequency that is sufficient to ensure that the system is in control and continues to produce water of acceptable quality. Samples should be taken from representative locations within the processing and distribution system. Established sampling frequencies should be based on system validation data and should cover critical areas including unit operation sites. The sampling plan should take into consideration the desired attributes of the water being sampled. For example, systems for Water for Injection because of their more critical microbiological requirements, may require a more rigorous sampling frequency.

Where possible, samples should be collected from use peints using the same delivery deviees, stuch as hoses, and procedures, sueh as prelimimary hose or outlet flushing, as are employed for normal water use from those use points. Where use points samples are not practical, specialsam-
pling ports may be used, but in both cases, consideration must be given to sample collection so that it aceurately represents the quality attributes of the water delivered by the system. This may include sampling pert or use point sanitization and thereugh flushing before a sample is taken if such practiees are employed during routine water use or delivery frem the system. Analyses of water samples often serve two purposes: in-process control assessments and final quality control assessments. In-process control analyses are usually focused on the attributes of the water within the system. Quality control is primarily concerned with the attributes of the water delivered by the system to its various uses. The latter usually employs some sort of transfer device, often a flexible hose, to bridge the gap between the distribution system use-point valve and the actual location of water use. The issue of sample collection location and sampling procedure is often hotly debated because of the typically mixed use of the data generated from the samples, for both in-process control and quality control. In these single sample and mixed data use situations, the worst-case scenario should be utilized. In other words, samples should be collected from use points using the same delivery devices, such as hoses, and procedures, such as preliminary hose or outlet flushing, as are employed by production from those use points. Where use points per se cannot be sampled, such as hard-piped connections to equipment, special sampling ports may be used. In all cases, the sample must represent as closely as possible the quality of the water used in production. If a point of use filter is employed, sampling of the water prior to and after the filter is needed because the filter will mask the microbial control achieved by the normal operating procedures of the system.
Samples containing chemical sanitizing agents require neutralization prior to microbiological analysis. Samples for microbiological analysis should be tested immediately,
or suitably refrigerated to preserve the original microbial attributes until analysis can begin. Samples of flowing water are only indicative of the concentration of planktonic (free floating) microorganisms present in the system. Biofilm microorganisms (those attached to water system surfaces) are usually present in greater numbers and are the source of the planktonic population recovered from grab samples. Microorganisms in biofilms represent a continuous source of contamination and are difficult to directly sample and quantify. Consequently, the planktonic population is usually used as an indicator of system contamination levels and is the basis for system Alert and Action Levels. The consistent appearance of elevated planktonic levels is usually an indication of advanced biofilm development in need of remedial control. System control and sanitization are key in controlling biofilm formation and the consequent planktonic population.

Sampling for chemical analyses is also done for in-process control and for quality control purposes. However, unlike microbial analyses, chemical analyses can be and often are performed using on-line instrumentation. Such on-line testing has unequivocal in-process control purposes because it is not performed on the water delivered from the system. However, unlike microbial attributes, chemical attributes are usually not significantly degraded by hoses. Therefore, through verification testing, it may be possible to show that the chemical attributes detected by the on-line instrumentation (in-process testing) are equivalent to those detected at the ends of the use point hoses (quality control testing). This again creates a single sample and mixed data use scenario. It is far better to operate the instrumentation in a continuous mode, generating large volumes of in-process data, but only using a defined small sampling of that data for QC purposes. Examples of acceptable approaches include using highest values for a given period, highest time-weighted average
for a given period (from fixed or rolling sub-periods), or values at a fixed daily time. Each approach has advantages and disadvantages relative to calculation complexity and reflection of continuous quality, so the user must decide which approach is most suitable or justifiable.

## CHEMICAL CONSIDERATIONS

The chemical attributes of USP Waters prior 1997-Purified Water and Water for Injection were specified by a series of chemistry tests for various specific and nonspecific attributes with the intent of detecting chemical species indicative of incomplete or inadequate purification. Many tests dated back to the 19th century, were nonquantitative, and represented long since outmeded analytieal teehnologies. While these methods could have been considered barely adequate to control the quality of these waters, they nevertheless stood the test of time. This was partly because the operation of water systems was, and still is, based on online conductivity measurements and specifications generally thought to these archaic chemistry attribute tests.
USP moved away from these chemical attribute tests to contemporary analytical technologies for the bulk waters Purified Water and Water for Injection. The intent was to upgrade the analytical technologies without tightening the quality requirements. The two contemporary analytical technologies employed were TOC and conductivity. The TOC test replaced the test for Oxidizable substances that primarily targeted organic contaminants. A multistaged Conductivity test which detects ionic (mostly inorganic) contaminants replaced, with the exception of the test for Heavy metals, all of the inorganic chemical tests (i.e., Ammonia, Calcium, Carbon dioxide, Chloride, Sulfate).

Replacing the heavy metals attribute was considered unnecessary because (a) the source water specifications (found in the NPDWR) for individual Heavy metals were tighter than the empirically determined limit found in the approximate limit of detection of the Heavy metals test for USP XXII Water for Injection and Purified Water menegraph (approximately 0.1 ppm ), (b) contemporary water system construction materials do not leach heavy metal contaminants, and (c) test results for this attribute have uniformly been negative-there has not been a confirmed occurrence of a singular test failure (failure of only the Heavy metals test with all other attributes passing) since the current heavy metal drinking water standards have been in place. Nevertheless, since the presence of heavy metals in Purified Water or Water for Injection could have dire consequences, its absence should at least be documented during new water system commissioning and validation or through prior test results records.

## The only remainimg original "inorganie" tests net eer ered by the eonduetivity specifteations were Total Solids

 and $p H$. Total solids and $p H$ are the only tests not covered by conductivity testing. The test for Total solids was considered redundant because the nonselective tests of conductivity and TOC could detect most chemical species other than silica, which could remain undetected in its colloidal form. Colloidal silica in Purified Water and Water for Injection is easily removed by most water pretreatment steps and even if present in the water, constitutes no medical or functional hazard except under extreme and rare situations. In such extreme situations, other attribute extremes are also likely to be detected. It is, however, the user's responsibility to ensure fitness for use. If silica is a significant component inthe source water, and the purification unit operations could be operated or fail and selectively allow silica to be released into the finished water (in the absence of co-contaminants detectable by conductivity), then either silica-specific or a total solids type testing should be utilized the af fecers to monitor and control this rather rare problem.

The pH attribute was eventually recognized to be redundant to the conductivity test (which included pH as an aspect of the test and specification); therefore, $p H$ was dropped as a separate attribute test.

The rationale used by USP to establish its conductivity specification took into consideration the conductivity contributed by the two least conductive former attributes of Chloride and Ammonia, thereby precluding their failure had those wet chemistry tests been performed. In essence, the Stage 3 conductivity specifications (see Water Conductivity $\langle 645\rangle$ ) were established from the sum of the conductivities of eontributing ions as a function of pH of chloride (from pH 5.0 to 6.2) or ammenia (from pH 6.3 to 7.0), plus the unavoidable contribution the limit concentrations of chloride ions (from pH 5.0 to 6.2 ) and ammonia ions (from pH 6.3 to 7.0 ), plus the unavoidable contribution of other conductivity-contributing ions from water $\left(\mathrm{H}^{+}\right.$and $\mathrm{OH}^{-}$), dissolved atmospheric $\mathrm{CO}_{2}$ (as $\mathrm{HCO}_{3}{ }^{-}$), and an elec-tro-balancing quantity of either $\mathrm{Na}^{+}$of $\mathrm{Cl}^{-}$, depending on the pH -induced ionic imbalance (see Table 1). The Stage 2 conductivity specification is the lowest value on this table, 2.1 $\mu \mathrm{S} / \mathrm{cm}$. The Stage 1 specifications, designed primarily for on-line measurements, were derived essentially by summing the lowest values in each column for a-series the contributing ion columns for each of a series of tables similar to Table 1, created for each $5^{\circ}$ increment between $0^{\circ}$ and $100^{\circ}$. For example purposes, the italicized values in Table 1, the conductivity data table for $25^{\circ}$, were summed to yield a con-
servative value of $1.3 \mu \mathrm{~S} / \mathrm{cm}$, the Stage 1 specification for a nontemperature compensated, nonatmosphere equilibrated water sample that actual had a measured temperature of
$25^{\circ}$ to $29^{\circ}$. Each $5^{\circ}$ increment table was similarly treated to yield the individual values listed in the table of Stage 1 specifications (see Water Conductivity $\langle 645\rangle$ ).

Table 1. Contributing Ion Conductivities of the Chloride-Ammonia Model as a Function of pH
(in atmosphere-equilibrated water at $25^{\circ}$ )

|  |  |  |  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |  |  |  |  |  |

As stated above, this rather radical change to a conductivity attribute as well as the inclusion of a TOC attribute allowed for on-line measurements. This was a major philosophical change and allowed major savings to be real-
ized by industry. The TOC and conductivity tests can also be performed "off-line" in the laboratories using collected samples, though sample collection tends to introduce oppor-
tunities for adventitious contamination that can cause false high readings. The collection of on-line data is not, however, without challenges. The continuous readings tend to create voluminous amounts of data where before only a single data point was available. Contimuous dataisexcellent for thelerstanding how a water system performs during allofits various usage and maintenance events in real time, but it tends to overwhelm quality control data systems that are de signed for far less data. In such situations, the user must deeide how to limit the data be used for routine quality control purposes. Examples of aceeptable approaches int elude using highest values for a given period, highest time-weighted average for agiven period (from fixedor roll ing subperiods), or values at a fixed daily time. Each approach has advantages and disadvantages relative to ealeulation complexity and reflection of contintrous quality, so the user must decide which approach is most sutable or justifiable. As stated under Sampling Considerations, continuous in-process data is excellent for understanding how a water system performs during all of its various usage and maintenance events in real time, but is too much data for QC purposes. Therefore, a justifiable fraction or averaging of the data can be used that is still representative of the overall water quality being used.

Packaged waters present a particular dilemma relative to the attributes of conductivity and TOC. The package itself is the source of chemicals (inorganics and organics) that leach over time into the water and can easily be detected. The irony of organic leaching from plastic packaging is that when the Oxidizable substances test was the only "organic contaminant" test for both bulk and packaged waters, that test's insensitivity to those organic leachables rendered their presence in packaged water at high concentrations (many times the TOC specification for bulk water) virtually undetectable. Similarly, glass containers can also leach inorganics, such as
sodium, which are easily detected by conductivity, but are undetected by the wet chemistry tests for water (other than pH or Total solids). Most of these leachables are considered harmless by current perceptions and standards at the rather significant concentrations present. Nevertheless, they effectively degrade the quality of the high-purity waters placed into these packaging system. Some packaging materials contain more leachables than others and may not be as suitable for holding water and maintaining its purity.

The attributes of conductivity and TOC tend to reveal more about the packaging leachables than they do about the water's original purity. These "allowed" leachables could render the packaged versions of originally equivalent bulk water essentially unsuitable for many uses where the bulk waters are perfectly adequate.

## MICROBIAL CONSIDERATIONS

The major exogenous source of microbial contamination of bulk pharmaceutical water is source or feed water. Feed water quality must, at a minimum, meet the quality attributes of Drinking Water for which the level of coliforms are regulated. A wide variety of other microorganisms, chiefly Gram-negative bacteria, may be present in the incoming water. These microorganisms may compromise subsequent purification steps. Examples of other potential exogenous sources of microbial contamination include unprotected vents, faulty air filters, backflow from contaminated outlets, drain air breaks, and replacement activated earbon, deionizer resins, and regenerant chemicals. ruptured rupture disks, backflow from contaminated outlets, unsanitized distribution system "openings" including routine component replacements, inspections, repairs, and expansions, inadequate drain and air-breaks, and replacement activated carbon, deionizer resins, and regenerant chemicals. In these situations, the exogenous contaminants may not
be normal aquatic bacteria but rather microorganisms of soil or even human origin. The detection of nonaquatic microorganisms may be an indication of a system component failure, which should trigger investigations that will remediate their source. Sufficient care should be given to system design and maintenance in order to minimize microbial contamination from these exogenous sources.

Unit operations can be a major source of endogenous microbial contamination. Microorganisms present in feed water may adsorb to carbon bed, deionizer resins, filter membranes, and other unit operation surfaces and initiate the formation of a biofilm. In a high-purity water system, biofilm is an adaptive response by certain microorganisms to survive in this low nutrient environment. Downstream colonization can occur when microorganisms are sloughed eff shed from existing biofilm-colonized surfaces and carried to other areas of the water system. Microorganisms may also attach to suspended particles such as carbon bed fines or fractured resin particles. When the microorganisms become planktonic, they serve as a source of contamination to subsequent purification equipment (compromising its functionality) and to distribution systems.

Another source of endogenous microbial contamination is the distribution system itself. Microorganisms can colonize pipe surfaces, rough welds, badly aligned flanges, valves, unidentified dead legs, etc. where they proliferate, forming a biofilm. and beoming a contintous soure of mierobial contamination. The smoothness and composition of the surface may affect the rate of initial microbial adsorption, but once adsorbed, biofilm development, unless otherwise inhibited by sanitizing conditions, will occur regardless of the surface. Once formed, the biofilm becomes a continuous source of microbial contamination.

## ENDOTOXIN CONSIDERATIONS

Endotoxins are lipopolysaccharides found in and shed from the cell envelope that is external to the cell wall of Gram-negative bacteria. Gram-negative bacteria that form biofilms can become a source of endotoxins in pharmaceutical waters. Endotoxins may occur as clusters of lipopolysaccharide molecules associated with living microorganisms, fragments of dead microorganisms or the polysaccharide slime surrounding biofilm bacteria, or as free molecules. The free form of endotoxins may be released from cell surfaces of the bacteria that colonize the water system, or from the feed water that may enter the water system. Because of the multiplicity of endotoxin sources in a water system, endotoxin quantitation in a water system is not a good indicator of the level of biofilm abundance within a water system.

Endotoxin levels may be minimized by controlling the introduction of free endotoxins and microorganisms in the feed water and minimizing microbial proliferation in the system. This may be accomplished through the normal exclusion or removal action afforded by various unit operations within the treatment system as well as through system sanitization. Other control methods include the use of ultrafilters or charge-modified filters, either in-line or at the point of use. The presence of endotoxins may be monitored as described in the general test chapter Bacterial Endotoxins Test $\langle 85\rangle$.

## MICROBIAL ENUMERATION CONSIDERATIONS

The objective of a water system microbiological monitoring program is to provide sufficient information to control and assess the microbiological quality of the water produced. Product quality requirements should dictate water quality specifications. An appropriate level of control may be maintained by using data trending techniques and, if
necessary, limiting specific contraindicated microorganisms. Consequently, it may not be necessary to detect all of the microorganisms species present in a given sample. The monitoring program and methodology should indicate adverse trends and detect microorganisms that are potentially harmful to the finished product, process, or consumer. Final selection of method variables should be based on the individual requirements of the system being monitored.

It should be recognized that there is no single method that is capable of detecting all of the potential microbial contaminants of a water system. The methods used for microbial monitoring should be capable of isolating the numbers and types of organisms that have been deemed significant relative to in-process system control and product impact for each individual system. Several criteria should be considered when selecting a method to monitor the microbial content of a pharmaceutical water system. These include method sensitivity, range of organisms types or species recovered, sample processing throughput, incubation period, cost, and methodological complexity. An alternative consideration to the use of the classical "culture" approaches is a sophisticated instrumental or hybrid apreach rapid test method that may yield more timely results. However, care must be exercised in selecting such an alternative approach to ensure that it has both sensitivity and correlation to classical culture approaches, which are generally considered the be "gold stadard" of accepted standards for microbial enumeration.

Consideration should also be given to the timeliness of microbial enumeration testing after sample collection. The number of detectable planktonic bacteria in a sample col-
lected in a scrupulously clean sample container will usually drop as time passes. The planktonic bacteria within the sample will tend to either die or to irretrievably adsorb to the container walls reducing the number of viable planktonic bacteria that can be withdrawn from the sample for testing. The opposite effect can also occur if the sample container is not scrupulously clean and contains a low concentration of some microbial nutrient that could promote microbial growth within the sample container. Because the number of recoverable bacteria in a sample can change positively or negatively over time after sample collection, it is best to test the samples as soon as possible after being collected. If it is not possible to test the sample within about 2 hours of collection, the sample should be held at refrigerated temperatures $\left(2^{\circ}\right.$ to $\left.8^{\circ}\right)$ for a maximum of about 12 hours to maintain the microbial attributes until analysis. In situations where even this is not possible (such as when using off-site contract laboratories), testing of these refrigerated samples should be performed within 48 hours after sample collection. In the delayed testing scenario, the recovered microbial levels may not be the same as would have been recovered had the testing been performed shortly after sample collection. Therefore, studies should be performed to determine the existence and acceptability of potential microbial enumeration aberrations caused by protracted testing delays.

## The Classical Culture Approach

Classical culture approaches for microbial testing of water include but are not limited to pour plates, spread plates, membrane filtration, and most probable number (MPN)
tests. These methods are generally easy to perform, are less expensive, and provide excellent sample processing throughput. Method sensitivity can be increased via the use of larger sample sizes. This strategy is used in the membrane filtration method. Culture approaches are further defined by the type of medium used in combination with the incubation temperature and duration. This combination should be selected according to the monitoring needs presented by a specific water system as well as its ability to recover the microorganisms of interest: those that could have a detrimental effect on the product or process uses as well as those that reflect the microbial control status of the system.

There are two basic forms of media available for traditional microbiological analysis: "high nutrient" and "low nutrient". High-nutrient media such as plate count agar (TGYA) and m-HPC agar (formerly m-SPC agar), are intended as general media for the isolation and enumeration of heterotrophic or "copiotrophic" bacteria. Low-nutrient media such as R2A agar and NWRI agar (HPCA), may be beneficial for isolating slow growing "oligotrophic" bacteria and bacteria that require lower levels of nutrients to grow optimally. Often some facultative oligotrophic bacteria are able to grow on high nutrient media and some facultative copiotrophic bacteria are able to grow on low-nutrient media, but this overlap is not complete. Low-nutrient and high-nutrient cultural approaches may be concurrently used, especially during the validation of a water system, as well as periodically thereafter. in order to determine if any additional mmmbers or types of bacteria are present so that their impact on the
determine if any additional numbers or types of bacteria can be preferentially recovered by one of the approaches. If so, the impact of these additional isolates on system control and the end uses of the water could be assessed. Also, the efficacy of system controls and sanitization on these stower growing baldial addional isolates could be assessed.

Duration and temperature of incubation are also critical aspects of a microbiological test method. Classical methodologies using high nutrient media are typically incubated at $30^{\circ}$ to $35^{\circ}$ for 48 to 72 hours. Because of the flora in certain water systems, incubation at lower temperatures (e.g., $20^{\circ}$ to $25^{\circ}$ ) for longer periods (e.g., 5 to 7 days) can recover higher microbial counts when compared to classical methods. Low-nutrient media are designed for these lower temperature and longer incubation conditions (sometimes as long as 14 days to maximize recovery of very slow growing oligotrophs or sanitant injured microorganisms), but even high-nutrient media can sometimes increase their recovery with these longer and cooler incubation conditions. Whether or not a particular system needs to be monitored using highor low-nutrient media with higher or lower incubation temperatures or shorter or longer incubation times should be determined during or prior to system validation and periodically reassessed as the microbial flora of a new water system gradually establish a steady state relative to its routine maintenance and sanitization procedures. The establishment of a "steady state" can take months or even years and can be perturbed by a change in use patterns, a change in routine and preventative maintenance or sanitization procedures, and frequencies, or any type of system intrusion, such as for component replacement, removal, or addition. The decision to use longer incubation periods should be made after
and the type of corrective actions required when an alert or action level is exceeded with the ability to recover the microorganisms of interest.

The advantages gained by incubating for longer times, namely recovery of injured microorganisms, slow growers, or more fastidious microorganisms, should be balanced against the need to have a timely investigation and to take corrective action, as well as the ability of these microorganisms to detrimentally affect products or processes. In no case, however, should incubation at $30^{\circ}$ to $35^{\circ}$ be less than 48 hours or less than 96 hours at $20^{\circ}$ to $25^{\circ}$.
Normally, the microorganisms that can thrive in extreme environments are best cultivated in the laboratory using conditions simulating the extreme environments from which they were taken. Therefore, thermophilic bacteria might be able to exist in the extreme environment of hot pharmaceutical water systems, and if so, could only be recovered and cultivated in the laboratory if similar thermal conditions were provided. Thermophilic aquatic microorganisms do exist in nature, but they typically derive their energy for growth from harnessing the energy from sunlight, from oxidation/reduction reactions of elements such as sulfur or iron, or indirectly from other microorganisms that do derive their energy from these processes. Such chemical/nutritional conditions do not exist in high purity water systems, whether ambient or hot. Therefore, it is generally considered pointless to search for thermophiles from hot pharmaceutical water systems owing to their inability to grow there.

The microorganisms that inhabit hot systems tend to be found in much cooler locations within these systems, for example, within use-point heat exchangers or transfer hoses. If this occurs, the kinds of microorganisms recovered are usually of the same types that might be expected from ambient
water systems. Therefore, the mesophilic microbial cultivation conditions described later in this chapter are usually adequate for their recovery.

## "Instrumental" Approaches

Examples of instrumental approaches include microscopic visual counting techniques (e.g., epifluorescence and immunofluorescence) and similar automated laser scanning approaches and radiometric, impedometric, and biochemically based methodologies. These methods all possess a variety of advantages and disadvantages. One adwage is their precision and acemracy. Advantages could be their precision and accuracy or their speed of test result availability as compared to the classical cultural approach. In general, instrument approaches often have a shorter lead time for obtaining results, which could facilitate timely system control. This advantage, however, is often counterbalanced by limited sample processing throughput due to extended sample collection time, costly and/or labor-intensive sample processing, or other instrument and sensitivity limitations.

## Instrumental appreaches are typieally destrutive becatuse

further isolate manipulation for characterization purposes is preeluded. Generally, some form of mierobial isolate characterization may be raquired element of water system menitering. Consequently, eulturing approaches have traditionally been preferred over instrumental approaches be eatse they offer a batance of desirable test attributes and inilies. Furthermore, instrumental approaches are typically destructive, precluding subsequent isolate manipulation for characterization purposes. Generally, some
form of microbial isolate characterization, if not full identification, may be a required element of water system monitoring. Consequently, culturing approaches have traditionally been preferred over instrumental approaches because they offer a balance of desirable test attributes and post-test capabilities.

## Suggested Methodologies

The following general methods were originally derived from Standard Methods for the Examination of Water and Wastewater, $17^{\text {th }}$ Edition, American Public Health Association, Washington, DC 20005. Even though this publication has undergone several revisions since its first citation in this chapter, the methods are still considered appropriate for establishing trends in the number of colony-forming units observed in the routine microbiological monitoring of pharmaceutical waters. It is recognized, however, that other combinations of media and incubation time and temperature may occasionally or even consistently result in higher numbers of colony-forming units being observed and/or different species being recovered.

The extended incubation periods that are usually required by some of the alternative methods available offer disadvantages that may outweigh the advantages of the higher counts
that may be obtained. The somewhat higher baseline counts that might be observed using alternate cultural conditions would not necessarily have greater utility in detecting an excursion or a trend. In addition, some alternate cultural conditions using low-nutrient media tend to lead to the development of microbial colonies that are much less differentiated in colonial appearance, an attribute that microbiologists rely on when selecting representative microbial types for further characterization. It is also ironical that the nature of some of the slow growers and the extended incubation times needed for their development into visible colonies may also lead to those colonies being largely nonviable, which limits their further characterization and precludes their subculture and identification.

Methodologies that can be suggested as generally satisfactory for monitoring pharmaceutical water systems are as follows. However, it must be noted that these are not referee methods nor are they necessarily optimal for recovering microorganisms from all water systems. The users mest decide should determine through experimentation with various approaches which methodologies are best for monitoring their water systems and recovering for in-process control and quality control purposes as well as for recovering any contraindicated species they may have specified.

| Drinking Water: | POUR PLATE METHOD OR MEMBRANE FILTRATION METHOD ${ }^{1}$ |
| :---: | :---: |
|  | Sample Volume- 1.0 mL minimum ${ }^{2}$ |
|  | Growth Medium-Plate Count Agar ${ }^{3}$ |
|  | Incubation Time-48 to 72 hours minimum |
|  | Incubation Temperature-30 ${ }^{\circ}$ to $35^{\circ}$ |
| Purified Water: | POUR PLATE OR MEMBRANE FILTRATION METHOD ${ }^{1}$ |
|  | Sample Volume- 1.0 mL minimum ${ }^{2}$ |
|  | Growth Medium-Plate Count Agar ${ }^{3}$ |
|  | Incubation Time-48 to 72 hours minimum |
|  | Incubation Temperature-30 ${ }^{\circ}$ to $35^{\circ}$ |
| Water for Injection: | MEMBRANE FILTRATION METHOD ${ }^{1}$ |
|  | Sample Volume-100 mL minimum ${ }^{2}$ |
|  | Growth Medium-Plate Count Agar ${ }^{3}$ |
|  | Incubation Time-48 to 72 hours minimum |
|  | Incubation Temperature $-30^{\circ} \mathrm{C}$ to $35^{\circ} \mathrm{C}$ |

[^269]
## IDENTIFICATION OF MICROORGANISMS

Identifying the isolates recovered from water monitoring methods may be important in instances where specific waterborne microorganisms may be detrimental to the products or processes in which the water is used. Microorganism information such as this may also be useful when identify-
ing the source of microbial contamination in a product or process. Often a limited group of microorganisms is routinely recovered from a water system. After repeated recovery and characterization, an experienced microbiologist may become proficient at their identification based on only a few recognizable traits such as colonial morphology and staining characteristics. This level of characterization may be ad-
equate for most situations. This may allow for a reduction in the number of identifications to representative colony types, or, with proper analyst qualification, may even allow testing short cuts to be taken for these microbial identifications.

## ALERT AND ACTION LEVELS AND SPECIFICATIONS

Water systems should be mierobiologieally monitored to eon frm that they continte to operate within their design specifieations and produce water of aceeptable quality. Menitoring data may be eempared to established proeess parameters or product specifiea tions.

A refinement to the use of process parameters and product speeiffeations is the establishment of Alert and Aetion Levels, which signal a shift in proeess performance. Alert and Aetion Levels are distinet frem proess parameters and product specifieations in that they are used for menitoring and control rather than aceept or reject decisions. Alert Levels are levels, events, or ranges that, when ex ceeded, indicate that a process may have drifted from its normat eperating eondition. Alewt Levels constitute a warning and do not necessarily require a corrective action. Action Levels are levels, events, or ranges that, when exceeded, indicate that a process has drifted from its nermal operating range. Exeeeding an Aetion tevel indientes that corrective action should be taken to bring the proeess back inte its normal operating range. Alert and Aetion Lev els are established within process and product specification toler ances and are based on a combination of technieal and product related considerations. Consequently, exeeding an Alert or Aetion tevel does not imply that product quality has been eompromised.

Technieal considerations used to establish Alert and Aetion Lev els should inelude a review of equipment design speciffeations to ensure that the prrification equipment is capable of achieving the required level of purity. In addition, samples should be collected and analyzed over a period of time to develep data reflecting nor mat water quality trends. Historieal or statistieally based levels ean be established using the above data. Levels established in this way measure process performanee and are independent of product con eems.

Product related Alert and Aetion Levels should represent both product quality concerns and the ability to effectively manage the purification process. These levels are typieally based on a review of process dat and an assessment of product sensitivity to ehemical and mierobiologieal contamination. The assessment of product suseeptibility might inelude preservative-efficacy, water activity, pH , ete. The levels should be set sueh that, when exeeed ed, product quality is not compromised. Menitoring data should be analyzed on an ongoing basis to enstre that the process contintes to perform within aceeptable limits. An analysis of data trends is often used to valuate precess performance. This information can be used to predict departures from established operating parameters, thereby signaling the need for appropriate preventative main tenamee.

It should be recosnized that the mierobial Alert and Aetion Lev elf established for any phamacentien water system are neeessarily linked to the monitoring method chosen. Using the suggested methodolegies above, generally considered maximmm Action Lev els are 500 colony forming units (efu) per mL for Drinking Water, 100 efuper mL for Purified Water and 10 efuper 100 mL for Water for Injection. However, if a given water system controls mieroor ganisms much more tightly than these levels, appropriate Alert and Aetion Levels should be lower to truly indieate when water systems may be starting to trend out of control. It is appropriate that, where
possible, these in process control parameters should be established well below mierobial levels that could be problematic for products and processes where used.

It should be emphasized that these in process eontrol guidelines are not intended to be totally inclusive for every sittation where ingredient waters are employed. For example, Gram negative mieroorganisms are not exeluded from ingredient waters, nor is the presence of Gram negative mierorgenisms prohibited in Drinking Water in the Federal Regulations. The reason for this is that these mierorgsanisms are ubiquitous to the aqueus envirenment and their exclusion would likely require a sterilization process that would not be appropriate or feasible in many manufacturing see narios. However, there are sittations where they might not be tol erated in certain products, sueh as some topieal products intended for use on broken skin or in some oral dosage forms. It is, therefore, ineumbent upen the manufacturer to supplement the general in process control guidelines to fit each partieular manufacturing and product use situation.

Though the use of alert and action levels is most often associated with microbial data, they can be associated with any attribute. In pharmaceutical water systems, almost every quality attribute, other than microbial quality, can be very rapidly determined with near-real time results. These short-delay data can give immediate system performance feedback, serving as ongoing process control indicators. However, because some attributes may not continuously be monitored or have a long delay in data availability (like microbial monitoring data), properly established Alert and Action Levels can serve as an early warning or indication of a potentially approaching quality shift occurring between or at the next periodic monitoring. In a validated water system, process controls should yield relatively constant and more than adequate values for these monitored attributes such that their Alert and Action Levels are infrequently broached.

As process control indicators, alert and action levels are designed to allow remedial action to occur that will prevent a system from deviating completely out of control and producing water unfit for its intended use. This "intended use" minimum quality is sometimes referred to as a "specification" or "limit". In the opening paragraphs of this chapter, rationale was presented for no microbial specifications being included within the body of the bulk water (Purified Water and Water for Injection) monographs. This does not
mean that the user should not have microbial specifications for these waters. To the contrary, in most situations such specifications should be established by the user. The microbial specification should reflect the maximum microbial level at which the water is still fit for use without compromising the quality needs of the process or product where the water is used. Because water from a given system may have many uses, the most stringent of these uses should be used to establish this specification.

Where appropriate, a microbial specification could be qualitative as well as quantitative. In other words, the number of total microorganisms may be as important as the number of a specific microorganism or even the absence of a specific microorganism. Microorganisms that are known to be problematic could include opportunistic or overt pathogens, nonpathogenic indicators of potentially undetected pathogens, or microorganisms known to compromise a process or product, such as by being resistant to a preservative or able to proliferate in or degrade a product. These microorganisms comprise an often ill-defined group referred to as "objectionable microorganisms". Because objectionable is a term relative to the water's use, the list of microorganisms in such a group should be tailored to those species with the potential to be present and problematic. Their negative impact is most often demonstrated when they are present in high numbers, but depending on the species, an allowable level may exist, below which they may not be considered objectionable.

As stated above, alert and action levels for a given process control attribute are used to help maintain system control and avoid exceeding the pass/fail specification for that attribute. Alert and action levels may be both quantitative and qualitative. They may involve levels of total microbial counts or recoveries of specific microorganisms. Alert levels are events or levels that, when they occur or are exceeded,
indicate that a process may have drifted from its normal operating condition. Alert level excursions constitute a warning and do not necessarily require a corrective action. However, alert level excursions usually lead to the alerting of personnel involved in water system operation as well as QA. Alert level excursions may also lead to additional monitoring with more intense scrutiny of resulting and neighboring data as well as other process indicators. Action levels are events or higher levels that, when they occur or are exceeded, indicate that a process is probably drifting from its normal operating range. Examples of kinds of action level "events" include exceeding alert levels repeatedly; or in multiple simultaneous locations, a single occurrence of exceeding a higher microbial level; or the individual or repeated recovery of specific objectionable microorganisms. Exceeding an action level should lead to immediate notification of both QA and personnel involved in water system operations so that corrective actions can immediately be taken to bring the process back into its normal operating range. Such remedial actions should also include efforts to understand and eliminate or at least reduce the incidence of a future occurrence. A root cause investigation may be necessary to devise an effective preventative action strategy. Depending on the nature of the action level excursion, it may also be necessary to evaluate its impact on the water uses during that time. Impact evaluations may include delineation of affected batches and additional or more extensive product testing. It may also involve experimental product challenges.
Alert and action levels should be derived from an evaluation of historic monitoring data called a trend analysis. Other guidelines on approaches that may be used, ranging from "inspectional" to statistical evaluation of the historical data have been published. The ultimate goal is to understand the normal variability of the data during what is considered a
typical operational period. Then, trigger points or levels can be established that will signal when future data may be approaching (alert level) or exceeding (action level) the boundaries of that "normal variability". Such alert and action levels are based on the control capability of the system as it was being maintained and controlled during that historic period of typical control.

In new water systems where there is very limited or no historic data from which to derive data trends, it is common to simply establish initial alert and action levels based on a combination of equipment design capabilities but below the process and product specifications where water is used. It is also common, especially for ambient water systems, to microbiologically "mature" over the first year of use. By the end of this period, a relatively steady state microbial population (microorganism types and levels) will have been allowed or promoted to develop as a result of the collective effects of routine system maintenance and operation, including the frequency of unit operation rebeddings, backwashings, regenerations, sanitizations, etc. This microbial population will typically be higher than was seen when the water system was new, so it should be expected that the data trends (and the resulting alert and action levels) will increase over this "maturation" period and eventually level off.

A water system should be designed so that performancebased alert and action levels are well below water specifications. With poorly designed or maintained water systems, the system owner may find that initial new system microbial levels were acceptable for the water uses and specifications, but the mature levels are not. This is a serious situation, which if not correctable with more frequent system maintenance and sanitization, may require expensive water system renovation or even replacement. Therefore, it cannot be
overemphasized that water systems should be designed for ease of microbial control, so that when monitored against alert and action levels, and maintained accordingly, the water continuously meets all applicable specifications.

An action level should not be established at a level equivalent to the specification. This leaves no room for remedial system maintenance that could avoid a specification excursion. Exceeding a specification is a far more serious event than an action level excursion. A specification excursion may trigger an extensive finished product impact investigation, substantial remedial actions within the water system that may include a complete shutdown, and possibly even product rejection.

Another scenario to be avoided is the establishment of an arbitrarily high and usually nonperformance based action level. Such unrealistic action levels deprive users of meaningful indicator values that could trigger remedial system maintenance. Unrealistically high action levels allow systems to grow well out of control before action is taken, when their intent should be to catch a system imbalance before it goes wildly out of control.

Because alert and action levels should be based on actual system performance, and the system performance data are generated by a given test method, it follows that those alert and action levels should be valid only for test results generated by the same test method. It is invalid to apply alert and action level criteria to test results generated by a different test method. The two test methods may not equivalently recover microorganisms from the same water samples. Similarly invalid is the use of trend data to derive alert and action levels for one water system, but applying those alert and action levels to a different water system. Alert and action levels are water system and test method specific.

Nevertheless, there are certain maximum microbial levels above which action levels should never be established. Water systems with these levels should unarguably be considered out of control. Using the microbial enumeration methodologies suggested above, generally considered maximum action levels are 100 cfu per mL for Purified Water and 10 cfu per 100 mL for Water for Injection. However, if a given water system controls microorganisms much more tightly than these levels, appropriate alert and action levels should be established from these tighter control levels so that they can truly indicate when water systems may be starting to trend out of control. These in-process microbial control parameters should be established well below the us-er-defined microbial specifications that delineate the water's fitness for use.

Special consideration is needed for establishing maximum microbial action levels for Drinking Water because the water is often delivered to the facility in a condition over which the user has little control. High microbial levels in Drinking Water may be indicative of a municipal water system upset, broken water main, or inadequate disinfection, and therefore, potential contamination with objectionable microorganisms. Using the suggested microbial enumeration methodology, a reasonable maximum action level for Drinking Water is 500 cfu per mL . Considering the potential concern for objectionable microorganisms raised by such high microbial levels in the feedwater, informing the municipality of the problem so they may begin corrective actions should be an immediate first step. In-house remedial actions may or may not also be needed, but could include performing additional coliform testing on the incoming water and pretreating the water with either additional chlorination or UV light irradiation or filtration or a combination of approaches. $\quad$ 2S (USP28)

## BRIEFING

$\langle 1232\rangle$ Instrumentation for Analysis of High Purity Pharmaceutical Waters, page 303 of PF 30(1) [Jan.-Feb. 2004]. It is proposed to (1) delete a sentence from the Technology Summary in the section on Total Organic Carbon (TOC) because it was reported to be inaccurate and (2) correct the formulas in the section on Conductivity. In addition, minor editorial style changes have been made.
(PW: F. Barletta) RTS-41177-1

## Add the following:

## ■ $<1232\rangle$ INSTRUMENTATION FOR ANALYSIS OF HIGH PURITY PHARMACEUTICAL WATERS

## INTRODUCTION

In the production of Purified Water and Water for Injection (WFI) the term "quality of water" is not rigorously defined, but it is generally accepted to mean "the concentration and type of impurities" found in the water. Advances in the science of water treatment have resulted in technologies that produce more water at lower cost and of higher quality. Consequently, the amount of impurities found in Purified Water and Water for Injection has decreased. The analytical methods have also improved to keep up with the improving water quality.

It would be impractical to describe all of the possible impurities because of the number of organic, inorganic, and ionic species that could enter a water system from the outside environment. The number of known chemicals is in the hundreds of thousands, and, theoretically, many could be found at a very low concentration in a water system. The nature of water treatment systems is such that very few unit operations are designed to selectively remove specific contaminants. There are notable exceptions such as water soft-
eners that are effective at displacing calcium and magnesium with sodium to protect systems from scale. It becomes expensive and very impractical to identify all impurity species in a pharmaceutical water system. The analytical instrumentation required to measure alkaline metal and heavy metal impurities (by atomic absorption or ion chromatography) is expensive, and the technology is not commercially available for measurement of specific organics in the $\mu \mathrm{g} / \mathrm{L}$ (ppb) range.

The more practical approach is to categorize impurities according to various attributes such as chemical properties, physical properties, organic/inorganic, oxidizability, toxicity, etc. One practical method of categorizing the impurity species is a determination of the degree of ionic behavior of the chemical moiety. For example, $\mathrm{H}^{+}, \mathrm{OH}^{-}, \mathrm{Na}^{+}, \mathrm{Ca}^{2+}$, $\mathrm{Mg}^{2+}, \mathrm{HCO}_{3}^{-}, \mathrm{Cl}^{-}, \mathrm{HSO}_{4}^{-}$, and other ionic species are commonly found in pharmaceutical water systems. All of these ions have a physical property in common: namely, that they are charged species and, therefore, detectable by conductivity. The majority of species that would be nonionic are organic. These consist of low molecular weight alcohols, ketones, and organic acids that, because of their size or polarity, are not completely removed by water systems. A valuable method for detecting these organic species is the use of a test for total organic carbon (TOC).

Both conductivity and TOC have the advantage of quantifying these types of impurities in the aggregate with great sensitivity. The advantage is also a disadvantage as neither measurement can distinguish or measure individual impurities, only the aggregate.

Not all types of impurities fall into the ionic/nonionic (conductive or TOC) category. Another class of impurities can be described as inorganic and nonionic (and therefore nonconductive). They include some dissolved metals, metal oxides, other metal forms, and semimetals such as those that
are silica-based. These species may be very weakly ionized and, therefore, would not be detectable by any conventional conductivity or TOC method. Particles also represent another class of impurity. These could be carbonaceous or silicabased, but they are not normally detectable by conductivity or TOC because they are typically nonionic and exist at concentrations undetectable by TOC analysis. However, the presence of substantive concentrations of these types of impurities is unlikely if the water treatment system is effective.
The final significant category of impurities consists of microorganisms. Although microorganisms are carbonaceous material, the detectability by conductivity or TOC is not practical because their molecular concentrations are too low to be detected by these methods. Microorganisms deserve special note because they can grow and interfere with drug chemistry and cause harm to the patient if they are not controlled (see Water for Pharmaceutical Purposes <1231〉).
Until USP 23, Supplement 5, the primary methods for ensuring the quality of bulk Purified Water and Water for Injection were a series of wet chemistry tests sitive to detect the presence of ammonia, calcium, chloride, carbon dioxide, sulfate, and oxidizable substances. The tests for these six species were subjective, unreliable, and not predictive of the true quality of water. The quality of water is better described by its conductivity and TOC and the primary methods for verifying water quality have shifted to these measurements.

Neither conductivity nor TOC are specific to any of the ions or species listed above. TOC is considered a one-forone replacement for the Oxidizable Substances (potassium permanganate) test, while conductivity is a sensitive test for all ionic (i.e., conductive) species. Both methods have
the advantages of being quantitative, numerical, robust, available for use on-line or off-line, and useful for quality control.

## TOTAL ORGANIC CARBON (TOC)

Organic chemistry is the study of carbon-containing compounds. The fully oxidized form of carbon, carbon dioxide $\left(\mathrm{CO}_{2}\right)$, is inorganic. $\mathrm{CO}_{2}$ is mildly reactive with water, and it is usually detected by its concomitant compounds and ions: carbonic acid $\left(\mathrm{H}_{2} \mathrm{CO}_{3}\right)$, bicarbonate $\left(\mathrm{HCO}_{3}{ }^{-}\right)$, and carbonate $\left(\mathrm{CO}_{3}{ }^{2-}\right)$. These three species are the result of the dissolution of $\mathrm{CO}_{2}$ in water and subsequent acid dissociation; they are not included in the TOC definition. Our concern is the remaining carbonaceous species that are not completely oxidized. These are the organic compounds that provide a fuel source for microorganisms, sustain biofilm, and may adversely impact drug chemistry.

Organic carbon enters the water system from several locations. The usual source of TOC is from the municipal water supply or from private wells. In January, 2002, the Environmental Protection Agency began regulating TOC levels in municipalities serving a population of 10,000 or more. Source water TOC can vary anywhere from 1 to 10 mg of carbon per L. The primary source of this TOC is the decomposition of plants and animals and subsequent runoff or leaching into the municipal feed water sources. The composition of these TOC products range from low molecular weight species such as urea to high molecular weight humic acids that give water an "iced tea" coloring. Other organic compounds found in water can be the direct result of industrial pollutants, pesticides, herbicides, and other man-made contaminants.

Other sources of TOC are the accidental introduction of TOC into the pharmaceutical water system and the degradation of water system components. The former is the result of
error, such as opening a wrong valve. The latter could be the breakdown of a plastic component in the water system or the presence of holes in the reverse osmosis (RO) membrane system. Regardless of the source, any of these TOC contaminants can be detrimental to the control of the water system.
Treatment methods to reduce TOC are discussed in Water for Pharmaceutical Purposes $\langle 1231\rangle$. In brief, various methods such as RO and filtration can reduce TOC concentration. Also, oxidizing agents such as chlorine and ozone can break up organic molecules. They are not, however, very selective and will attack nearly all organic molecules. The cleavage of large molecules creates smaller organic molecules that are easily digested and assimilated by microorganisms. Dead bacteria can also produce decomposition products called endotoxins that may produce a fever when injected into the body. The quantity of total organic carbon in pharmaceutical waters is of primary concern because it can enhance microorganism growth.

Volatile organic compounds are not a major contaminant in pharmaceutical water systems. Most contaminants are nonvolatile and are naturally occurring or anthropogenic organics. TOC measurements provide a single nonspecific measurement, detecting a broad spectrum of compounds without performing tests for individual contaminants.

## Laboratory TOC Technologies

TOC analysis was developed initially for the measurement of relatively high levels of TOC in water and waste water. Technological advances, however, have produced instruments that measure low levels of TOC in water down to sub-ppb levels, thus allowing for its application in the pharmaceutical industry. The principal TOC technologies are based on the oxidation of organic carbon to $\mathrm{CO}_{2}$ and subsequent detection of the $\mathrm{CO}_{2}$ by either conductometric or photometric means.

Some water samples contain dissolved $\mathrm{CO}_{2}$ (and $\mathrm{HCO}_{3}{ }^{-}$ and $\mathrm{CO}_{3}{ }^{2-}$ ) at the outset of the analysis, so the inorganic carbon (IC) must be removed or measured as part of the analysis. For any oxidation technology, depending on the TOC and IC levels, removal of the dissolved $\mathrm{CO}_{2}$ is always an option. In order to achieve accurate measurement of TOC in some samples, it is necessary to minimize the contribution of IC to the total signal. If it is determined that IC background is detrimental to the sample measurement, then the IC can be purged from the water sample by vacuum, nitrogen sparging, or acid addition, depending on the technology. This should not be necessary unless the TOC is very low and the IC very high. In pharmaceutical bulk water supplies, IC concentrations are typically low, and removal is not required for accurate TOC results. The basic oxidation and detection techniques used in TOC equipment are described below; however, other combinations of technologies that are not described may also be in use.

Combustion Oxidation/Nondispersive Infrared Detection (NDIR)—This technology combination is most often configured for laboratory use. Combustion oxidation uses oxygen and high temperatures ( $>600^{\circ}$ ) and a catalyst such as platinum ( Pt ) to facilitate the oxidation and convert the organic compounds to $\mathrm{CO}_{2}$. This technique has demonstrated high oxidation efficiency for both dissolved and particulate organics. The catalyst, however, can become poisoned and cause low recovery. NDIR is selective for $\mathrm{CO}_{3}$ in the preser. After oxidation of the sample, the $\mathrm{CO}_{2}$ is delivered to the detection chamber by a carrier gas. The concentration of $\mathrm{CO}_{2}$ is directly proportional to the absorption response according to Beer's Law. As with any absorption spectrophotometric method, NDIR is most sensitive at higher concentrations. Compared to oth-
er detectors, NDIR detectors can exhibit extended warm-up times at start-up. NDIR detectors typically require a comparatively higher calibration frequency.
Heated Persulfate Oxidation/NDIR Detection-Heated persulfate oxidation instruments generate hydroxyl radicals $(\cdot \mathrm{OH})$ by heating the persulfate to $>95^{\circ}$. The hydroxyl radicals act as powerful oxidizing agents. The cation form of the persulfate and its concentration vary, with concentrations ranging from $2 \%$ to $15 \%$. Heated persulfate is typically combined with the previously described NDIR detection method to measure $\mathrm{CO}_{2}$. This technology combination is typically applied in laboratory instrument configurations. Heated persulfate is a very efficient oxidation method. Its main disadvantages are the volume of reagent required.

UV Oxidation/NDIR Detection—UV oxidation uses UV light to generate hydroxyl radicals from the photolysis of water. In some instruments persulfate, which is activated by UV to increase the oxidative capacity, is added. This technology combination is most commonly found in laboratory configurations. The natural spectral output of a low pressure Hg lamp generates light of wavelength 253.7 and 184.9 nm . The shorter wavelength generates the oxidizing radicals, while both wavelengths are efficient at cleaving bonds in large and small organic molecules. This combination provides an efficient oxidation and measurement system. UV oxidation methods are particularly well suited for lower TOC concentrations found in pharmaceutical waters. The main advantage is the oxidation efficiency at lower TOC concentrations. The disadvantages are that the UV Hg lamps must be periodically replaced and that, as previously described, the NDIR detector systems are complex.

## UV/Persulfate Oxidation/Membrane Conductometric

Detection-In this technology, $\mathrm{CO}_{2}$ is generated by UV radiation (as described above), and the dissolved $\mathrm{CO}_{2}$ passes through a gas-permeable membrane to an on-board source
of low conductivity water. The resulting increase in conductivity in this water is directly proportional to the $\mathrm{CO}_{2}$ produced from the UV oxidation. Persulfate is typically added to enhance oxidation at TOC concentrations greater than 1 ppm. This technology combination makes use of the high sensitivity that conductivity measurements have at low concentrations of $\mathrm{CO}_{2}$, and the membrane separation helps to eliminate the typical chemical interferences that can disrupt conductivity measurements.

## Sampling Techniques for Laboratory Analysis-Be-

 cause compendial pharmaceutical waters have very low TOC (the USP limit is about $500 \mu \mathrm{~g}$ of carbon/L, but $<50 \mu \mathrm{~g}$ of carbon/L, and lower, is more likely), pharmaceutical waters require the following special handling to have valid TOC measurements.1. The water should be delivered from a hose or delivery receptacle in the same manner in which it is used in production.
2. The storage container may be any type that does not shed or leach TOC, and it must be scrupulously clean. Many plastic or polymeric containers are either unacceptable because of extractable TOC or they are too difficult to clean. Limited types of materials such as PTFE, PFA, and PVDF have found acceptance because of their low leach rates. Glass is an excellent material due to its negligible TOC leach rate and its cleanability. Cleaning of the glass according to Cleaning Glass Apparatus $\langle 1051\rangle$ is advised.
3. The container should be completely filled with the sample to keep the trapped air to a minimum. The container should be closed immediately to prevent atmospheric contamination.
4. The time between sampling and analysis should be kept to a minimum. If the samples are analyzed by an offsite laboratory, they should be refrigerated to minimize microbial growth.
5. The setting of the flow control valve should not be changed, and the sample bottle should not touch the port while taking the sample.
6. For compendial purposes, the water should be tested at a point that is equivalent to the quality of water used in production. This may require testing at several points, or at a location after the last-use point before the return to the tank in a recirculating system.

## On-Line TOC Technologies

The most common on-line TOC methods used in pharmaceutical applications employ UV oxidation and conductivity detection. These technologies are designed for exclusive use with low conductivity water supplies and with the device connected directly to the sample to eliminate exposure to the atmosphere. The low sample conductivity ensures an IC concentration so low that its removal is not necessary. No reagents are required because at TOC concentrations of 500 ppb or less, UV oxidation alone is usually sufficient for complete recovery.

UV oxidation can be applied on a fixed volume of sample or by irradiating a continuous stream to the UV source. Conductivity measurements are made during or immediately following the oxidation step. In one configuration, a gaspermeable membrane is used after the UV oxidation to separate $\mathrm{CO}_{2}$ from other potentially conductive oxidation by-products.

The main advantages of on-line technologies are the benefit of continuous unattended measurement of TOC, the availability of continuous trending of the water system, the
ability to respond to a disturbance immediately, and the elimination of sample collection, handling, and transportation errors.

## Sampling Techniques for On-Line TOC Analysis-

On-line TOC analysis has the advantage of being able to provide data continuously and without the difficulties in sample handling that accompany off-line TOC measurements. Typically, clean tubing is attached to the water system and water flow is directed to the inlet of the TOC instrument. Appropriate care should be taken to eliminate dead-legs and subsequent backflow of the sample line when the instrument is not in use.

## Technology Summary

Some of the oxidation and detection techniques work in tandem and are ideally suited for Purified Water and Water for Injection. These methods have the necessary resolution and sensitivity to perform the basic TOC measurement functions. The main differences between the technologies are the capital costs, consumables (UV lamps, gases, reagents), and maintenance and labor (preparing reagents, replacing catalysts, installing gas generators), and suitability for laboratory or on-line analysis.

Detection limits will vary by technology, and the analysis method must be able to meet the System Suitability requirements and detect the levels of TOC prescribed in Total Organic Carbon $\langle 643\rangle$. IR-based detection methods involve a well-established technique that requires a large sample size, a purge gas, long warm-up times, and frequent calibration. These detection methods are well suited to high TOC concentrations and are not susceptible to interferences that may be found in water. UV/eonductivity metheds are best suited
for on line process use in pharmaceutieal waters, where the sensitivity of conductivity measurements is ideally suited to meastring the conduetivity of $\mathrm{CO}_{2}$-containing solutions; the enductivity based techniques are capable of a much lower timitan The analysis time for each technology can vary from 0.5 to 30 minutes. Calibration requirements will also differ, varying from daily or weekly to annually. Calibration may be done by the user in-place or may require special attention by factory or trained personnel. Gases, chemicals, lamps, and other supplies will impact operating costs.

## CONDUCTIVITY

A conductivity measurement system is similar in concept to a TOC measurement system. A TOC analyzer cannot quantify individual organic species, only the aggregate carbon in the form of $\mathrm{CO}_{2}$. Likewise, a conductivity measurement does not distinguish between ions. It measures the total conductivity of charged ionic species.

A conductivity measurement is performed by measuring the AC resistance (conductance $=1 /$ resistance) between two electrodes of a known geometrical construction. The resistance of the fluid between the two electrodes will increase with electrode distance, $d$, and decrease with electrode area, $A$. To correct for this geometrical factor, the cell constant, $\phi$, of the sensor is equivalent to the distance between the electrodes divided by the area of the electrodes.

$$
\begin{equation*}
\varphi\left(\mathrm{cm}^{-1}\right)=\frac{d}{A} \tag{1}
\end{equation*}
$$

The cell constant normalizes the resistance, in $\Omega$, (or conductance, in $S$, to eliminate the impact of the sensor geometry, thereby resulting in the familiar water quality measurement of resistivity, $\rho$ (or conductivity, $\kappa$ ). The equations that relate these measurements are the following:

$$
\begin{align*}
& \frac{\text { resistance( } \Omega \text { ( } \Omega-\mathrm{cm})}{\varphi\left(\mathrm{cm}^{+1}\right)} \\
& \rho(\Omega-\mathrm{cm})=\frac{\operatorname{resistance}(\Omega)}{\varphi\left(\mathrm{cm}^{-1}\right)}  \tag{2}\\
& \kappa(\mathrm{S} / \mathrm{cm})=\text { conductance }(\mathrm{S}) \times \varphi\left(\mathrm{cm}^{-1}\right) \\
& \xrightarrow[\varphi(\mathrm{S} / \mathrm{cm})=-\frac{1}{\varphi(\Omega-\mathrm{cm})} \quad(4)]{ } \\
& \kappa(S / \mathrm{cm})=\frac{1}{\rho(\Omega-\mathrm{cm})} \tag{4}
\end{align*}
$$

A temperature device, such as a resistance temperature device (RTD) or thermistor, will be embedded in most conductivity sensors. The meter will measure the resistance of that device and convert it to a temperature according to its known temperature-resistance relationship.

The fundamental operation of conductivity measurement systems consists of measurement of the resistance between the electrodes, correction for the cell constant to get a conductivity or resistivity measurement, and then compensation for the raw measurement for temperature using an algorithm
in the meter. In order to meet the requirements of Water Conductivity $\langle 645\rangle$, the temperature compensation feature is disabled, and the uncompensated measurement is used to determine water quality acceptance.

## Impact of Water Chemistry on Conductivity

Electrical conductivity of water is a measure of the ionfacilitated flow of current between two electrodes through the water. The fundamental equation to describe the conductivity is the following:

$$
\begin{equation*}
\kappa=10^{-3} \sum_{i}^{\substack{\text { all } \\ \text { ions }}} \Lambda_{i}^{\circ} C_{i} \tag{5}
\end{equation*}
$$

in which $\kappa$ is the conductivity (Siemens $/ \mathrm{cm}$ ), $\Lambda_{i}$ is the limiting molar conductivity of ion $i$ (Siemens $-\mathrm{cm}^{2} / \mathrm{mol}$ ), and $C_{i}$ is the concentration of ion $i(\mathrm{~mol} / \mathrm{L})$. The equation is summed over all ions present in the water. If the concentrations are expressed in molality ( $\mathrm{mol} / \mathrm{kg}$ of water), then the equation is adjusted for the water density.

Water molecules dissociate into $\mathrm{H}^{+}$and $\mathrm{OH}^{-}$according to the following equation:

$$
\begin{equation*}
\mathrm{H}_{2} \mathrm{O} \rightleftharpoons\left[\mathrm{H}^{+}\right]+\left[\mathrm{OH}^{-}\right] \tag{6}
\end{equation*}
$$

and the extent of the reaction is determined by the dissociation constant, $K_{w}$.

$$
\begin{gather*}
K_{w}=\left[\mathrm{H}^{+}\right]\left[\mathrm{OH}^{-}\right]=1.00 \times 10^{-14} \text { at } 25^{\circ} \\
p K_{w}=-\log \left(K_{w}\right)=14 \text { at } 25^{\circ} \tag{8}
\end{gather*}
$$

In the absence of any other chemical species, electroneutrality and Equation 7 require that

$$
\begin{equation*}
\left[\mathrm{H}^{+}\right]=\left[\mathrm{OH}^{-}\right]=1 \times 10^{-7} \mathrm{~mol} / \mathrm{L} \tag{9}
\end{equation*}
$$

The limiting molar conductivities at $25^{\circ}$ of $\mathrm{H}^{+}$and $\mathrm{OH}^{-}$ are 349.8 and $198.6 \mathrm{~S}_{\mathrm{S}} \mathrm{cm}^{2} / \mathrm{mol}$, respectively. The resulting conductivity of pure water is $5.48 \times 10^{-8} \mathrm{~S} / \mathrm{cm}(0.0548 \mu \mathrm{~S} /$ cm ). The resistivity is the multiplicative inverse (Equation 4) of the conductivity, or 18.2 Megohm- $\mathrm{cm}(\mathrm{M} \Omega-\mathrm{cm})$.

At temperatures other than $25^{\circ}$ (the commonly used reference temperature), two phenomena directly impact the conductivity of pure water. First, the dissociation constant of water varies significantly over the range of $0^{\circ}$ to $100^{\circ}$. The value of $K_{w}$ changes by a factor of 400 , as the $p K_{w}$ is 14.9 at $0^{\circ}$ and 12.2 at $100^{\circ}$. The resulting change in $K_{w}$ causes a true increase in the ion concentrations as the temperature increases. The second effect is the temperature dependence of the ion mobility. [NOTE-The ion mobility, a measure of the ability of ions to conduct, is directly related to each ion's limiting molar conductivity.] The mobility of both ions increases by a factor of $\sim 3$ over the range of $0^{\circ}$ to $100^{\circ}$. The combination of these two effects causes the conductivity of pure water to increase from $0.0116 \mu \mathrm{~S} / \mathrm{cm}$ at $0^{\circ}$ to $0.777 \mu \mathrm{~S} / \mathrm{cm}$ at $100^{\circ}(86.1 \mathrm{M} \Omega-\mathrm{cm}$ to $1.29 \mathrm{M} \Omega-\mathrm{cm})$.

Although it is not unusual for some compendial water systems to produce pure water, most water treatment systems that produce Purified Water and Water for Injection have small amounts of impurities that pass through the water system. The impurities are usually simple alkali metal ions, possibly some lighter transition metal ions, and common counter ions such as $\mathrm{Cl}^{-}, \mathrm{SO}_{4}{ }^{2-}$, and $\mathrm{HCO}_{3}^{--}$. In addition, some gases, most notably $\mathrm{CO}_{2}$, readily dissolve in water and react to form $\mathrm{H}^{+}$and $\mathrm{HCO}_{3}^{-}$, predictably affecting conductivity and pH . Regardless of the ionic impurity, each has its
own characteristic limiting molar conductivity. Thus the measured conductivity of the water in a pharmaceutical system is determined from Equation 5, after consideration of all ions present at their respective concentrations.

## Temperature Compensation

Temperature compensation is the adjustment of a chemical or physical measurement at any temperature to its value at a reference temperature, $25^{\circ}$ in this case. The purpose of the compensation is to provide a universal reference point so that measurements taken at different temperatures can be properly compared. For example, if the conductivity of the water system is $0.11 \mu \mathrm{~S} / \mathrm{cm}$ at $37^{\circ}$, but later in the day it is $0.13 \mu \mathrm{~S} / \mathrm{cm}$ at $40^{\circ}$, the increase can be the result of the natural increase in ion mobility due to temperature, or it could be the result of more impurities in the water. The benefit of temperature compensation is that it can distinguish natural changes from water quality changes.

Prior to the application of microprocessors, temperature compensation was performed either by "correcting the signal" with the addition of analog circuitry or by numerically adjusting postmeasurement. Temperature compensation is currently performed automatically by the chemically-based numerical algorithms in the instrumentation.
Temperature compensation for conductivity measurements of pure water is difficult to perform accurately. For almost all types of fluids except pure water, the dependence of the conductivity on temperature is, on the average, about $1.9 \%$ to $2.2 \%$ per degree over the entire $0^{\circ}$ to $100^{\circ}$ range. This linear compensation factor applies for most process fluids and drinking waters, because the conductivity is dominated by the ions that are not related to water dissociation. However, because of the low impurity levels found in Purified Water or Water for Injection systems, the chemical composition of the ions in water is primarily due to $\mathrm{H}^{+}$and $\mathrm{OH}^{-}$,
with smaller (or similar) amounts of other ions. The temperature dependence of the conductivity, therefore, becomes less predictable because of the temperature dependence of the water chemistry. For example, at $0^{\circ}$ the conductivity of pure water changes at a rate of $>7 \%$ per degree, while at $100^{\circ}$ the temperature dependence is $<2.5 \%$ per degree. As the impurity levels increase, the temperature dependence moderates until it reaches $\sim 2 \%$ per degree. The appropriate correction for temperature compensation varies and must be accounted for correctly, depending on the temperature and the impurity level. On-line process instrumentation performs this correction automatically, but the algorithms remain trade secrets.

As the chapter Water Conductivity $\langle 645\rangle$ was being developed in the early 1990s, it was established that the measurements would be made in a nontemperature-compensated mode to eliminate the variability that is found from one instrument manufacturer to another. This resulted in the table, Stage 1-Temperature and Conductivity Requirements in the chapter Water Conductivity $\langle 645\rangle$ that set conductivity limits that are temperature dependent. The table takes into account the natural increase in conductivity as a function of temperature, while ensuring that certain impurity levels are not exceeded.

## Conductivity Technologies

Conductivity Sensors-A conductivity sensor used in pharmaceutical water measurements typically consists of two concentric electrodes, separated by an inert electrical insulator, with a cell constant that is usually anywhere from 0.01 to $0.1 \mathrm{~cm}^{-1}$. For on-line measurements, the sensor should be inserted into the tee of a piping system. Sidestream measurements are possible, but direct immersion into the piping are less costly (i.e., no water loss with no risk
to the water system). The electrode material should be compatible with the water system to prevent galvanic action between the water piping and the sensor. The insulator should be resistant to the water and to the processing conditions that may be present. The sensor design and geometry should be invariant to the high temperatures (up to steam sterilizable conditions at $131^{\circ}$ and 40 psia or higher), sanitization chemicals, UV, pressure, and flow rates that the sensor might be exposed to. Any Handling of the conductivity sensor is critical as any change in the geometric construction of the sensor will cause a change in the apparent measurement of the conductivity.

Stainless steel electrodes should be passivated, at a minimum, to reduce the possibility of corrosion or rouging. Passivation materials such as nitric acid, phosphoric acid, and citric acid are commonly used. Surface finishes having exposed surfaces with Roughness Average $\left(R_{a}\right)<10 \mu$ in (better than standard machine finishes) are readily attainable. The process connection to the water system can be any suit able connection type; however, a sanitary tri-clamp flange and gasket to provide a clean, tight seal between the sensor flange and water system are recommended. Welding of the electrodes to the flange should be clean and of pharmaceutical grade. Threaded process connections should be avoided to eliminate deadlegs; however, this parameter has no impact on the conductivity measurement.
The electrode material and insulator for off-line measurements are not critical, provided they give accurate measurements. Environmental factors are not present. To make accurate measurements, platinum electrodes should be avoided because a process called platinization is required periodically to recondition the surface of the electrode. However, this process is not robust, and it is difficult to determine when platinization is necessary, except by alternative verification measurements. An adverse impact to
measurement accuracy is also greatest at low conductivity. Common electrode materials include stainless steel, titanium, hastelloy, and graphite to a lesser extent. Titanium is widely used in the microelectronics industry because of its naturally passive surface and resistance to pure water. All of these electrode materials require low maintenance, if properly sanitized and cleaned. Repassivation of stainless steel electrodes may be needed if the material rouges or becomes scratched.

The concentric electrode design is not required, but it does result in mechanically rugged sensor construction that can withstand the pressures and flow changes in a water system. Also, the grounded shield design protects the sensor from any nearby surfaces that will impact the electric field and cause altered measurement in unshielded electrodes. Other subtle factors impacting sensor design and system accuracy are the electrode's macroscopic and microscopic properties. Large cell areas are preferable because this reduces the metal-water impedance that is formed at the electrode surface. Smaller cell areas can cause an undesirable increase in the measured cell resistance.

The two principal types of temperature devices are negative temperature coefficient (NTC) thermistors and 100 or 1000 platinum resistance temperature devices (RTDs). Both device types operate on the principle that their resistance changes in known and precise ways as a function of temperature. Both types are low in cost and have desirable electrical response characteristics. NTC thermistors have a very high, nonlinear sensitivity over a narrow temperature range, and their sensitivity drops markedly as the temperature increases. Platinum RTDs have a more linear response over a very wide dynamic range, and they are mechanically more robust than NTC thermistors. Repeatability of the resis-tance-temperature response for RTDs tends to be better than NTC thermistors.

Conductivity Instrumentation-The primary function of the conductivity meter is to make the AC resistance and the temperature measurements and to display the conductivity. The frequency of the AC measurement is critical to the accuracy of the measurement. At lower conductivity, lower measurement frequencies ( $<200 \mathrm{~Hz}$ ) are utilized to provide enough time to charge up the sensor to make an accurate measurement. At higher conductivity (nonpharmaceutical water), the AC measurement is made at a much higher frequency (up to $10,000 \mathrm{~Hz}$ ). High frequencies are required to reduce polarization (collection of ions) at the electrodes. If the AC frequency is too low and the ion concentration is too high, ions will collect at each electrode and disrupt the flow of current and subsequently disrupt the measurement. Cable capacitance and fluid capacitance also greatly impact the measurement accuracy, especially at the lowest conductivity; therefore, unique analog measurement systems are applied to make accurate measurements.
Most conductivity meters have multiple circuits to operate at multiple frequencies over a wide dynamic range. This operating frequency and range of the meter are executed internally and automatically by the meter. Older instruments and some hand-held meters may require manual adjustment of the operating range.
A meter may be placed as far as 100 meters away from the sensor, so the capability of transferring analog or digital signals over these distances necessitates the use of appropriate cable shielding. Also, the use of 3 - and 4 -wire measurements is commonly applied to reduce the negative impact of leadwire resistance, especially for long cables.
Although temperature compensation is not intended in Water Conductivity $\langle 645\rangle$, temperature compensation is used by a pharmaceutical facility to monitor and control the water system, in which case accurate temperature measurement is critical. At $20^{\circ}$, a $1^{\circ}$ measurement error will re-
sult in a $5 \%$ error in the calculated compensated conductivity. At $80^{\circ}$, the same error will result in a $10 \%$ error in the calculated compensated conductivity. Accurate temperature calibration is necessary to ensure accurate measurements.

Other features found in on-line conductivity analyzers are multiple channel inputs, setpoint alarms, relay control, 0/420 mA output, digital output, and multiple types of measurements (conductivity, resistivity), multiple compensation options, and several units of expression. The common set of units is $\mathrm{S} / \mathrm{cm}$ or $\mu \mathrm{S} / \mathrm{cm}$, but there is a small growing trend toward displaying measurements in $\mathrm{S} / \mathrm{m}$, which is an SI unit. Another requirement in Water Conductivity $\langle 645\rangle$ is a display resolution of $0.1 \mu \mathrm{~S} / \mathrm{cm}$, though more resolution is typical.

## Conductivity System Calibration

When a complete conductivity system calibration is required, it should be performed in the following sequence. Calibrate the meter first, then the sensor afterwards. The sensor may be calibrated on the same meter or on a different, calibrated meter.

Conductivity Meter Calibration-The purpose of this calibration is to verify and adjust, if necessary, the temperature measurement circuit and AC conductivity measurement circuit of the meter. There is no requirement for accuracy of the temperature circuit in general chapter Water Conductivity $\langle 645\rangle$, but an accuracy of $\pm 0.25^{\circ}$ is typical. Calibration is performed by removing the sensor from the meter and replacing the sensor with a precision resistor of known value. The resistor is a simulator of a specific tem-
perature. Comparison of the simulated and measured temperature will result in an adjustment of the temperature measurement circuit. There should be a provision within the meter to adjust the circuit calibration for temperature.

The same procedure is done for the AC conductivity measurement circuit. Replace the sensor with another precision resistor. Compare the simulated and measured conductivity and adjust, if necessary. Because of the multiple AC measurement circuits in these meters, calibrate either all of the circuits or the circuit that is in use during normal operation. Specific details for selecting the resistor values and calibrating the meter are supplied by instrument manufacturers. The accuracy required in Water Conductivity $\langle 645\rangle$ is $\pm 0.1 \mu \mathrm{~S} /$ cm . There should be a provision within the meter to adjust the circuit calibration for conductivity.

Conductivity Sensor Calibration-Calibration of the sensor is performed by accurately measuring the cell constant. Standard manufacturing practices can generate sensors with repeatable nominal cell constants, but typical tolerances can lead to variations up to $\pm 10 \%$. Calibration of the sensor in solutions of known, traceable conductivity is the only acceptable method.

The sources of primary standard solutions for cell constant calibration include the following:

- The preparation of ASTM solutions according to D1125 or D5391
- NIST standard solutions
- Pure water with no impurities

Most commercial sensors are not calibrated in primary standard solutions, but they are calibrated in a solution whose conductivity is known by a secondary transfer con-
ductivity standard. The secondary standard is determined by calibration in the primary standard solutions, usually in an ASTM standard solution(s), and this secondary sensor is used to calibrate commercial sensors.

This presents a dilemma for the pharmaceutical user because the primary standard solutions are all $>100 \mu \mathrm{~S} / \mathrm{cm}$, while the user is operating at $<5 \mu \mathrm{~S} / \mathrm{cm}$, and commonly at $<0.2 \mu \mathrm{~S} / \mathrm{cm}$. This problem is solved in one of two ways. First, if the conductivity measurement system (sensor and meter) has sufficient dynamic range and it is demonstrably accurate over the applicable range-from the calibration solution to the normal operating condition-then the sensor can be calibrated in the higher conductivity solution and then used in the low conductivity pharmaceutical water. Another method is calibration of the sensor in a recirculating pure water system generated by a mixed-bed de-ionization loop. The conductivity of pure water as a function of temperature is well documented. With an accurate temperature measurement, the conductivity is accurately known and can be used as a primary reference in the normal operating range of the sensor and meter. This technique results in a sensor that is calibrated very accurately, but it is impractical for most end-users, themselves, to execute.

Calibration of sensors in standard solutions that are $<10$ $\mu \mathrm{S} / \mathrm{cm}$ is possible but has several nuances. Solutions in this conductivity range may be unstable, because of the intrusion of $\mathrm{CO}_{2}$ (from the air) into the solutions. Once the containers are opened, the $\mathrm{CO}_{2}$ reacts immediately with water to form carbonic acid $\left(\mathrm{H}_{2} \mathrm{CO}_{3}\right)$ that weakly dissociates into $\mathrm{H}^{+}$and $\mathrm{HCO}_{3}{ }^{-}$, and these can impact the conductivity by up to $1 \mu \mathrm{~S} /$ cm unless preventive measures are taken. Another difficulty
is the increased level of cleanliness that is needed to perform the calibration. If there is any residue on the sensor before immersion into the standard solution, the cleanliness and accuracy of the solution is compromised. The advantage of the high conductivity primary standard is that it can better tolerate trace impurities. The advantage of the pure water standard is that it never has impurities. In Water Conductivity $\langle 645\rangle$, calibration accuracy of the cell constant is required to be $\pm 2 \%$, and this is readily achieved.

Frequency of Calibration-Water Conductivity $\langle 645\rangle$ makes no recommendation on the frequency of calibrating conductivity meters or sensors. The frequency should be based on historical data, system performance, and the manufacturer's recommendations. For conductivity meters, a 6month calibration cycle, or longer, is typical. For sensors, the materials, type of construction, and operating conditions can influence the calibration cycle. A sensor calibration certificate with a 6 -month to 1 -year expiration is typical. Ultimately, it is the amount of risk the user is willing to take that is the deciding factor. Documentation of all calibrations is vital for regulatory purposes.
During normal operation, calibration of robust conductivity sensors should not be required more than every 6 months to 1 year. Only mechanical or chemical disturbances of the sensor should impact the cell constant. For example, 0.1 $\mathrm{cm}^{-1}$ sensors tend to be more robust than $0.01 \mathrm{~cm}^{-1}$ sensors because the higher cell constant sensors have greater spacing (d) between the electrodes than the lower cell constant sensors. As a result, minor mechanical disturbances have a greater impact on the lower cell constant sensors.

## Off-Line Conductivity Measurements

Care should be taken when conductivity measurements of Purified Water or Water for Injection are taken off-line, e.g., in a laboratory. If the water conductivity (measured on-line) is $<1 \mu \mathrm{~S} / \mathrm{cm}$, then virtually any measurement of that same water made in the laboratory will result in a higher conductivity. The immediate reaction of $\mathrm{CO}_{2}$ with the water will cause the formation of $\mathrm{H}_{2} \mathrm{CO}_{3}$ as described above, and cause the conductivity to rapidly and immediately increase. As a result, it is very difficult to correlate on-line measurements to laboratory measurements.

For example, a water system with filtration, reverse osmosis, and mixed-bed de-ionization may be consistently producing Purified Water with a nominal quality of $0.055 \mu \mathrm{~S} /$ $\mathrm{cm}(18 \mathrm{M} \Omega-\mathrm{cm})$ water. When the water conductivity is measured in-line, the measurement may vary from 0.054 to $0.057 \mu \mathrm{~S} / \mathrm{cm}$. However, when the same water is transported into the laboratory, the conductivity may vary from 0.8 to $1.5 \mu \mathrm{~S} / \mathrm{cm}$. The conductivity increase will be due solely to the $\mathrm{CO}_{2}$. The increase in the variability in this off-line measurement will also be significant (almost $100 \%$ ), while the on-line measurement varies about $5 \%$. The increased fluctuation is due to the variations in concentration of $\mathrm{CO}_{2}$ in the ambient area at the time. Pristine air will have a concentration of about $375 \mathrm{ppm} \mathrm{CO}_{2}$, but normal industrial conditions would have the $\mathrm{CO}_{2}$ concentration vary from 500 to 1200 ppm . The variability in the $\mathrm{CO}_{2}$ concentration is completely beyond the control of the analyst, but it grossly impacts the measurement and completely obscures any possible correlation of off-line with on-line measurements. $\boldsymbol{m}^{2 S}$ (USP28)

## DIETARY SUPPLEMENTS

## General Chapters-General Information

## Briefing

<2023〉Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements, page 3155 of the First Supplement. It is proposed to clarify the discussion of the Test for Aflatoxins in the section Absence of Objectionable Microorganisms. It is also proposed to change the entry for Teas in Tables 1 and 2 to Botanicals to be treated with boiling water before use.
(AMB: D. Porter) RTS-41615-1

## Change to read:

## SUPPLEMENT COMPONENTS

Raw materials, excipients, and active substances as components of nutritional and dietary supplements can be a primary source of microbiological contamination. Specifications should be developed and sampling plans and test procedures should be employed to guarantee the desired microbiological attributes of these materials. The nature and extent of microbiological testing should be based upon a knowledge of the material's origin, its manufacturing process, its use, and historical data and experience. For instance, materials of animal or botanical origin that are not highly refined might require special, more frequent testing than synthetic products.

Since members of the family Enterobacteriaceae are a major component of the normal epiphytic and endophytic microflora (e.g., members of genera Klebsiella, Enterobacter, and Erwinia) and have been associated with the seeds, pods, roots, leaves, and stems of plants of economic importance, Coliform or Enterobacteriaceae counts will not be an appropriate general microbiological criterion for botanicals. However, when it is considered advantageous, Coliform or Enterobacteriaceae counts may be included in the individual monographs. Typically on new leaves, bacteria predominate in the microflora, while yeast and filamentous fungi succeed bacteria and become dominant late in the growing season. With dried botanicals, the bacterial population will tend to change from Gram-negative bacteria to Gram-positive spore formers and fungi. Refinement of botanicals from chopped or powdered plant material to powdered extracts using alcoholic, alkaline, or acid hy-dro-alcoholic, or aqueous extracting materials will reduce the likelihood of vegetative microorganisms within the botanical material. The classification of botanical materials is contained in Table 1.

Table 1. Definitions of a Range of Botanical Materials

| Botanical Preparation | Definition |
| :--- | :--- |
| $\begin{array}{l}\text { Chopped or Powdered } \\ \text { Botanicals }\end{array}$ | $\begin{array}{r}\text { Hand-picked portions of the botanical (i.e., leaves, flowers, roots, } \\ \text { tubers, etc.) that are air dried, and chopped, flaked, sectioned, } \\ \text { ground, or pulverized to the consistency of a powder. } \\ \text { Extracts are solids or semisolid preparations of a botanical that are pre- } \\ \text { pared by percolation, filtration, and concentration by evaporation } \\ \text { of the percolate. The extracting material may by alcoholic, alkaline, } \\ \text { or acid hydro-alcoholic or aqueous in nature. Typically an extract } \\ \text { is } 4 \text { to } 10 \text { times as strong as the original botanical. The extracts } \\ \text { may be semisolids or dry powders termed powdered extracts. }\end{array}$ |
| Tinctures are solutions of botanical substances in alcohol obtained by |  |
| extraction of the powdered, flaked or sectioned botanical. |  |$\}$| Infusions are solutions of botanical principles obtained by soaking the |
| :--- |
| powdered botanical in hot or cold water for a specified time and |
| straining. Typically infusions are $5 \%$ in strength. |

## Change to read:

## MICROBIOLOGICAL TESTING

## Frequency of Sampling and Testing

Microbiological attribute sampling and testing plans vary widely. In some cases no sampling or testing is necessary; in other cases periodic monitoring is warranted; and yet for some articles each batch requires sampling and testing. The design of the sampling and testing plans and the kind of attributes examined depend on the application and the type of the product, the potential for contamination from components and processing, the growth promotion or inhibition properties of the formulation, and the target population for the supplement. For example, a powdered botanical may have highly variable microbiological attributes so that an incoming batch would be sampled and composite testing would not be advised, while a highly refined botanical extract may not require
routine microbial testing. Similarly, products with a low water activity will not be susceptible to microbial growth during their shelf life provided they are protected from elevated humidity by their containers.

## Microbial Enumeration Tests

See the Introduction under Microbial Enumeration Tests-Nutritional and Dietary Supplements $\langle 2021\rangle$. These tests provide meaningful information regarding the microbiological acceptability of excipients, active substances, and nonsterile supplement formulations. If the individual monograph does not specify microbial enumeration limits, the guidance provided in this chapter is used. Acceptable general limits of microbial levels for raw materials, excipients, and botanical products are shown in Table 2; and those for raw materials, excipients, active ingredients, and other nonsterile finished articles that are nutritional supplements but do not contain botanicals are shown in Table 3.

Table 2. Recommended Microbial Limits for Botanical Ingredients and Products

| Material | Recommended Microbial Limit Requirements (cfu/g or mL ) |
| :---: | :---: |
| Dried or Powdered Botanicals | Total Aerobic Microbial Count NMT 105 |
|  | Total Combined Yeast \& Mold Count NMT $10^{3}$ |
|  | Bile-tolerant Gram-negative Bacteria NMT 103 |
|  | Absence of Salmonella spp. \& E. coli in 10 g |
| Powdered Botanical Extracts | Total Aerobic Microbial Count NMT $10^{4}$ |
|  | Total Combined Yeast \& Mold Count NMT $10^{3}$ |
|  | Absence of Salmonella spp. \& E. coli in 10 g |
| Tinctures | Total Aerobic Microbial Count NMT $10^{4}$ |
|  | Total Combined Yeast \& Mold Count NMT $10^{3}$ |
| Fluidextracts | Total Aerobic Microbial Count NMT $10^{4}$ |
|  | Total Combined Yeast \& Mold Count NMT $10^{3}$ |
| Infusions/Decoctions | Total Aerobic Microbial Count NMT 10² |
|  | Total Combined Yeast \& Mold Count NMT 10 |
| Nutritional Supplements with Botanicals | Total Aerobic Microbial Count NMT 104 |
|  | Total Combined Yeast \& Mold Count NMT $10^{3}$ |
|  | Absence of Salmonella spp \& E. coli in 10 g |
| Teas | Total Aerobic Microbial Count NMT $10{ }^{5}$ |
|  | Total Combined Yeast \& Mold Count NMT $10^{3}$ |
| - Botanicals to be treated with boiling water before | Absence of E. coli in 10 g |
| $\mathrm{use}_{\mathbf{1} 2 \mathrm{~S} \text { (USP28) }}$ |  |

Table 3. Recommended Microbial Limits for Dietary Supplement Ingredients and Products
$\left.\begin{array}{ll}\hline \text { Material } & \begin{array}{c}\text { Recommended Microbial Limit Requirements } \\ (\mathrm{cfu} / \mathrm{g} \text { or mL) }\end{array} \\ \hline \begin{array}{l}\text { Other raw materials and dietary } \\ \text { supplement ingredients }\end{array} & \begin{array}{l}\text { Total Aerobic Microbial Count NMT 103 } \\ \text { Total Combined Yeast \& Mold Count NMT } 10^{2}\end{array} \\ \begin{array}{l}\text { Nutritional supplements with synthetic or } \\ \text { highly refined ingredients }\end{array} & \begin{array}{l}\text { Absence of } E \text {. coli in } 10 \mathrm{~g}\end{array} \\ \hline\end{array} \begin{array}{l}\text { Total Aerobic Microbial Count NMT 103 } \\ \text { Total Combined Yeast \& Mold Count NMT 102 } \\ \text { Absence of E. coli in } 10 \mathrm{~g}\end{array}\right]$

## Absence of Objectionable Microorganisms

See Introduction under Microbiological Procedures for Absence of Specified Microorganisms-Nutritional and Dietary Supplements $\langle 2022\rangle$. Absence of one or more species of objectionable microorganisms is required in some individual monographs.

Test for Aflatoxins-Dietary and nutritional articles containing botanical products with a history of mycotoxin contamination are also typically tested for aflatoxins, especially if the material is obtained from roots or rhizomes. Where nessary, this test is inelud ed in the individual menegraph. Details of the Test for Aftatexins may be found in Artieles of Botanical Origin- 564 ):

- See Articles of Botanical Origin $\langle 561\rangle$ for the details of a test for aflatoxins. Where necessary, this test is included in the individual monograph.■2S (USP28)

Solid Oral Dosage Forms-Among all dosage forms, solid oral dosage forms present the lowest microbiological risk because of their method of manufacture, low water activity, and route of administration. When justified, reduced microbiological testing may be appropriate.

Other Concerns-The presence of some microorganisms in articles can be an indicator of processes that are not under microbiological control. For example, Purified Water used at some stage of the manufacture of these products might contain a typical flora of Gram-negative microorganisms. As with pharmaceutical products, inadequate processing of water and poor maintenance of water systems may result in the contamination of processed formulations by Gram-negative microorganisms.

## REAGENTS, INDICATORS, AND SOLUTIONS Reagent Specifications

## BRIEFING

Piperazine. It is proposed to add this new reagent.
(HDQ: M. Marques) RTS-41497-1

## Add the following:

■Piperazine (Diethylenediamine), $\mathrm{C}_{4} \mathrm{H}_{10} \mathrm{~N}_{2} \cdot 6 \mathrm{H}_{2} \mathrm{O}-$ 194.23-Use a suitable grade.■2S (USP28)

## REFERENCE TABLES

## Briefing

Container Specifications for Capsules and Tablets, USP 27 page 2741, page 3352 of the Second Supplement, and page 1404 of PF 30(4) [May-June 2004].
(HDQ) RTS-39507-2; 39869-2; 40078-1; 40078-2; 40078-3; 41479-1; 41480-1

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the Packaging and storage requirements set forth in the individual monographs. It lists the capsules and tablets that are, or will be, official in the United States Pharmacopeia and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets
Container
Monograph Title Specification

Add the following:
-Acetaminophen
Tablets, Extended-Release $\quad \mathrm{T}_{\boldsymbol{\square} 1 \mathrm{~S}}$ (USP28)
Add the following:
${ }^{\boldsymbol{\Delta}}$ Alendronate Sodium Tablets $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$
Add the following:
-Benazepril Tablets
$\mathrm{W}_{\square 1 \mathrm{~S}(U S P 28)}$

Add the following:
■Bismuth Subsalicylate Tablets
$\mathrm{T}_{\mathbf{1 S} \text { (USP28) }}$

## Add the following:

-Cefaclor Tablets $\mathrm{T}_{\text {■1S (USP28) }}$

## Add the following:

${ }^{\bullet}$ Chromium Picolinate Tablets $\quad \mathrm{W}_{\boxed{\square 2 S}}$ (USP28)
Add the following:
-Clarithromycin Tablets, Extended-
Release
$\mathrm{W}_{\mathbf{\square} 1 \mathrm{~S}(\text { USP28) }}$

## Add the following:

-Black Cohosh Tablets
$\mathrm{T}, \mathrm{LR}_{\text {■1S (USP28) }}$
Add the following:
-Desogestrel and Ethinyl Estradiol
Tablets
$\mathrm{W}_{\mathbf{\square 1 S}(\text { USP28) }}$
Add the following:
■Diethylstilbestrol Diphosphate Tablets $\mathrm{W}_{\square 1 \mathrm{~S} \text { (USP28) }}$
Add the following:
■Fluoxetine Capsules, Delayed-Release $\mathrm{T}_{\text {■1S (USP28) }}$
Add the following:
-Gabapentin Capsules $\mathrm{W}_{\text {■1S (USP28) }}$

## Add the following:

-Ginkgo Capsules
$\mathrm{T}, \mathrm{LR}_{\mathbf{1} 1 \mathrm{~S}(U S P 28)}$

Container Specifications for Capsules and Tablets (Continued)

| Monograph Title | Container Specification |
| :---: | :---: |
| Add the following: |  |
| - Ginkgo Tablets | $\mathrm{T}, \mathrm{LR}_{\text {■ } 1 \mathrm{~S}}$ (USP28) |
|  |  |
| Asian Ginseng Capsules | T,LR - 1 (USP28) |
| Add the following: |  |
| -Indinavir Sulfate Capsules | $\mathrm{T}_{\mathbf{1} 1 \mathrm{~S} \text { (USP28) }}$ |
| Add the following: |  |
| -Irbesartan Tablets | $\mathrm{W}_{\mathbf{\square 1 S} \text { (USP28) }}$ |
| Add the following: |  |
| -Irbesartan and Hydrochlorothiazide |  |
| Tablets | $\mathrm{W}_{\mathbf{\square 1 S} \text { (USP28) }}$ |
| Add the following: |  |
| - Isosorbide Mononitrate Tablets | $\mathrm{T}_{\mathbf{1} 1 \mathrm{~S} \text { (USP28) }}$ |
| Add the following: |  |
| -Isosorbide Mononitrate Tablets, |  |
| Extended-Release | $\mathrm{T}_{11 \mathrm{~S} \text { (USP28) }}$ |
| Add the following: |  |
| ${ }^{\text {4 }}$ Isradipine Capsules | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |
| Add the following: |  |
| - Lysine Hydrochloride Tablets | $\mathrm{W}_{\mathbf{\square 2 S} \text { (USP28) }}$ |
| Add the following: |  |
| -Metformin Hydrochloride Tablets | $\mathrm{T}_{\mathbf{1 S} \text { (USP28) }}$ |
| Add the following: |  |
| -Modafinil Tablets | $\mathrm{T}_{\text {L2S (USP28) }}$ |
| Add the following: |  |
| -Naproxen Tablets, Delayed-Release | $\mathrm{W}_{\mathbf{\square 1 S} \text { (USP28) }}$ |
| Add the following: |  |
| - Norgestimate and Ethinyl Estradiol |  |
| Tablets | $\mathrm{W}_{\text {■1S (USP28) }}$ |

## Add the following:

-Indinavir Sulfate Capsules

## Add the following:

| Monograph Title | Container Specification |
| :---: | :---: |
| Add the following: |  |
| - Ginkgo Tablets | $\mathrm{T}, \mathrm{LR}_{\text {■ } 1 \mathrm{~S}}$ (USP28) |
|  |  |
| Asian Ginseng Capsules | T,LR - 1 (USP28) |
| Add the following: |  |
| -Indinavir Sulfate Capsules | $\mathrm{T}_{\mathbf{1} 1 \mathrm{~S} \text { (USP28) }}$ |
| Add the following: |  |
| -Irbesartan Tablets | $\mathrm{W}_{\mathbf{\square 1 S} \text { (USP28) }}$ |
| Add the following: |  |
| -Irbesartan and Hydrochlorothiazide |  |
| Tablets | $\mathrm{W}_{\mathbf{\square 1 S} \text { (USP28) }}$ |
| Add the following: |  |
| - Isosorbide Mononitrate Tablets | $\mathrm{T}_{\mathbf{1} 1 \mathrm{~S} \text { (USP28) }}$ |
| Add the following: |  |
| -Isosorbide Mononitrate Tablets, |  |
| Extended-Release | $\mathrm{T}_{11 \mathrm{~S} \text { (USP28) }}$ |
| Add the following: |  |
| ${ }^{\text {4 }}$ Isradipine Capsules | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |
| Add the following: |  |
| - Lysine Hydrochloride Tablets | $\mathrm{W}_{\mathbf{\square 2 S} \text { (USP28) }}$ |
| Add the following: |  |
| -Metformin Hydrochloride Tablets | $\mathrm{T}_{\mathbf{1 S} \text { (USP28) }}$ |
| Add the following: |  |
| -Modafinil Tablets | $\mathrm{T}_{\text {L2S (USP28) }}$ |
| Add the following: |  |
| -Naproxen Tablets, Delayed-Release | $\mathrm{W}_{\mathbf{\square 1 S} \text { (USP28) }}$ |
| Add the following: |  |
| - Norgestimate and Ethinyl Estradiol |  |
| Tablets | $\mathrm{W}_{\text {■1S (USP28) }}$ |

## Add the following:

-Isosorbide Mononitrate Tablets $\quad \mathrm{T}_{\mathbf{1 S} \text { (USP28) }}$

## Add the following:

-Isosorbide Mononitrate Tablets,
Extended-Release

## Add the following:

| Monograph Title | Container Specification |
| :---: | :---: |
| Add the following: |  |
| - Ginkgo Tablets | $\mathrm{T}, \mathrm{LR}_{\text {■ } 1 \mathrm{~S}}$ (USP28) |
|  |  |
| Asian Ginseng Capsules | T,LR - 1 (USP28) |
| Add the following: |  |
| -Indinavir Sulfate Capsules | $\mathrm{T}_{\mathbf{1} 1 \mathrm{~S} \text { (USP28) }}$ |
| Add the following: |  |
| -Irbesartan Tablets | $\mathrm{W}_{\mathbf{\square 1 S} \text { (USP28) }}$ |
| Add the following: |  |
| -Irbesartan and Hydrochlorothiazide |  |
| Tablets | $\mathrm{W}_{\mathbf{\square 1 S} \text { (USP28) }}$ |
| Add the following: |  |
| - Isosorbide Mononitrate Tablets | $\mathrm{T}_{\mathbf{1} 1 \mathrm{~S} \text { (USP28) }}$ |
| Add the following: |  |
| -Isosorbide Mononitrate Tablets, |  |
| Extended-Release | $\mathrm{T}_{11 \mathrm{~S} \text { (USP28) }}$ |
| Add the following: |  |
| ${ }^{\text {4 }}$ Isradipine Capsules | $\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$ |
| Add the following: |  |
| - Lysine Hydrochloride Tablets | $\mathrm{W}_{\mathbf{\square 2 S} \text { (USP28) }}$ |
| Add the following: |  |
| -Metformin Hydrochloride Tablets | $\mathrm{T}_{\mathbf{1 S} \text { (USP28) }}$ |
| Add the following: |  |
| -Modafinil Tablets | $\mathrm{T}_{\text {L2S (USP28) }}$ |
| Add the following: |  |
| -Naproxen Tablets, Delayed-Release | $\mathrm{W}_{\mathbf{\square 1 S} \text { (USP28) }}$ |
| Add the following: |  |
| - Norgestimate and Ethinyl Estradiol |  |
| Tablets | $\mathrm{W}_{\text {■1S (USP28) }}$ |

$\mathrm{T}_{\mathrm{n}}$ (USP28)

Container Specifications for Capsules and Tablets (Continued)


| Monograph Title |
| :---: |
| Container |
| Specification |

Add the following:
-Oxaprozin Tablets $\quad \mathrm{T}_{\mathrm{M}} \mathrm{LR}_{\text {1S (USP28) }}$
Add the following:
-Pygeum Capsules $\mathrm{T}_{\mathbf{1} \text { 1S (USP28) }}$

## Add the following:

-Quinapril Tablets $\mathrm{W}_{\mathbf{■ 1 S} \text { (USP28) }}$
Add the following:
-Stavudine Capsules $\mathrm{T}_{\mathbf{\square 1 S} \text { (USP28) }}$
Add the following:
-Tolcapone Tablets $\mathrm{T}_{\mathbf{\square 1 S}}$ (USP28)
Add the following:
-Valerian Capsules $\quad{\mathrm{T}, \mathrm{LR}_{\text {1S (USP28) }}}^{\text {( }}$

## Add the following:

- Valsartan and Hydrochlorothiazide

Tablets $\mathrm{W}_{\mathbf{1 S} \text { (USP28) }}$

$$
\mathrm{W}_{\boldsymbol{\square}} \text { IS (USP28) }
$$

Briefing
Description and Relative Solubility of USP and NF Articles,
USP 27 page 2747, page 3166 of the First Supplement, page 3352
of the Second Supplement, page 7017 of PF 24(5) [Sept.-Oct.
1998], page 8589 of PF 25(4) [July-Aug. 1999], page 8917 of
PF 25 (5) [Sept.-Oct. 1999], page 9254 of $P F 25(6)$ [Nov.-Dec.
1999], page 1135 of PF 26(4) [July-Aug. 2000], page 1385 of
$P F 26$ (5) [Sept.-Oct. 2000], page 1236 of $P F$ 28(4) [July-Aug.
2002], page 1542 of $P F 28(5)$ [Sept.-Oct. 2002], page 1953 of
PF 28(6) [Nov.-Dec. 2002], page 266 of PF 29(1) [Jan.-Feb.
2003], page 509 of $P F 29$ (2) [Mar.-Apr. 2003], page 812 of $P F$
$29(3)$ [May-June 2003], page 1262 of PF 29(4) [July-Aug.
2003], page 1684 of $P F$ 29(5) [Sept.-Oct. 2003], page 2057 of
PF 29(6) [Nov.-Dec. 2003], page 317 of PF 30(1) [Jan.-Feb.
2004]; page 650 of $P F 30(2)$ [Mar.-Apr. 2004]; page 1050 of
PF 30(3) [May-June 2004]; and page 1405 of PF 30(4) [July-
Aug. 2004.
(HDQ) RTS-41550-1; 41549-1; 39507-3; 41326-1; 41547-
1; 41125-7-1; 41251-1

## Add the following:

■Betaine Hydrochloride: White crystalline powder.
Soluble in water and in alcohol; practically insoluble in chloroform and in ether.■2S (USP28)

## Add the following:

■Etidronate Disodium: White powder, which may contain lumps. Freely soluble in water; practically insoluble in alcohol.■2S (USP28)

## Add the following:

-Modafinil: White, odorless, crystalline powder. Slightly soluble in alcohol; sparingly soluble in methanol; practically insoluble in water. $\quad$ 2S (USP28)

## Add the following:

-Myristic Acid: Hard, white or faintly yellow, somewhat glossy, crystalline solid or white or yellow-white powder. Soluble in alcohol, in chloroform, and in ether; practically insoluble in water. NF category: Antifoaming agent.■2S (USP28)

## Change to read:

Naproxen: White to off-white, practically odorless, crystalline powder. Freely
${ }_{\square}^{\square}$ 2S (USP28)
Soluble in chloroform, in dehydrated alcohol, seluble
$\square_{\text {and }}$ 2S (USP28).
in alcohol; sparingly soluble in ether; practically insoluble in water.

## Add the following:

-Prilocaine: White or almost white powder or crystal aggregates. Very soluble in alcohol and in acetone; slightly soluble in water. $\quad$ 2S (USP28)

## Add the following:

-Tagatose: White or almost white crystals, having a sweet taste. Very soluble in water; very slightly soluble in alcohol. NF category: Sweetener, humectant. ${ }^{2 S}$ (USP28)

Items from Earlier Numbers of PF that Have Not Yet Appeared in a Supplement, and are Therefore Candidates for Subsequent Supplements.

## GENERAL NOTICES AND REQUIREMENTS

Significant Figures and Tolerances-See PF Vol. 30 No. 2, page 424.

General Chapters-See PF Vol. 30 No. 2, page 424.
Tests and Assays-See PF Vol. 30 No. 3, page 795.
Preservation, Packaging, Storage, and Labeling-See PF Vol. 30 No. 3, page 798.

## USP MONOGRAPHS

Acepromazine Maleate-See PF Vol. 29 No. 6, page 1832.
Acepromazine Maleate Injection-See PF Vol. 30 No. 4, page 1161.

Acetaminophen Extended-Release Tablets-See PF Vol. 30 No. 4, page 1161.
Acetaminophen Oral Solution-See PF Vol. 30 No. 1, page 40.
Acetaminophen Oral Suspension-See PF Vol. 30 No. 1, page 40.
Acetaminophen and Aspirin Tablets-See PF Vol. 30 No. 1, page 41.

Capsules Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 43.
Oral Powder Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 44.
Oral Solution Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 44.
Tablets Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine-See PF Vol. 30 No. 1, page 42.
Tablets Containing at Least Three of the Following-Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine-See PF Vol. 30 No. 1, page 44.
Acetaminophen and Codeine Phosphate Capsules-See PF Vol. 30 No. 1, page 45.
Acetaminophen and Codeine Phosphate Oral Solution-See PF Vol. 30 No. 1, page 46.
Acetaminophen and Codeine Phosphate Oral Suspension-See PF Vol. 30 No. 1, page 46.
Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solu-tion-See PF Vol. 30 No. 1, page 46.
Acetaminophen and Diphenhydramine Citrate Tablets-See PF Vol. 30 No. 1, page 47.
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets-See PF Vol. 30 No. 1, page 47.
Acetaminophen and Pseudoephedrine Hydrochloride TabletsSee PF Vol. 30 No. 1, page 48.
Acetohydroxamic Acid Tablets-See PF Vol. 30 No. 1, page 49.
Acyclovir-See PF Vol. 30 No. 2, page 431.
Adenosine-See PF Vol. 29 No. 6, page 1834.
Medical Air-See PF Vol. 28 No. 4, page 1065.
Albendazole Oral Suspension-See PF Vol. 30 No. 4, page 1163.
Albumin Human-See PF Vol. 29 No. 4, page 992.
Albuterol Tablets-See PF Vol. 30 No. 1, page 50.
Alendronate Sodium-See PF Vol. 30 No. 2, page 437.
Alendronate Sodium Tablets-See PF Vol. 28 No. 3, page 740.
Alendronic Acid Tablets-See PF Vol. 30 No. 3, page 804.
Alfentanil Hydrochloride-See PF Vol. 29 No. 6, page 1834.
Allopurinol-See PF Vol. 28 No. 5, page 1386.
Alprazolam Tablets-See PF Vol. 30 No. 1, page 51.
Alprostadil-See PF Vol. 29 No. 5, page 1412.
Alteplase-See PF Vol. 29 No. 6, page 1835.

Altretamine-See PF Vol. 27 No. 3, page 2514.
Alumina, Magnesia, and Calcium Carbonate Tablets-See PF Vol. 29 No. 6, page 1835.
Alumina, Magnesia, and Calcium Carbonate Chewable TabletsSee PF Vol. 29 No. 6, page 1836.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tab-lets-See PF Vol. 29 No. 6, page 1837.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets-See PF Vol. 29 No. 6, page 1837.
Alumina, Magnesia, and Simethicone Tablets-See PF Vol. 29 No. 6, page 1841.
Alumina, Magnesia, and Simethicone Chewable Tablets-See PF Vol. 29 No. 6, page 1842.
Amantadine Hydrochloride Capsules-See PF Vol. 30 No. 1, page 51.

Amifostine-See PF Vol. 30 No. 1, page 52.
Aminocaproic Acid-See PF Vol. 29 No. 5, page 1414.
Aminopentamide Sulfate-See PF Vol. 30 No. 4, page 1163.
Aminophylline-See PF Vol. 29 No. 5, page 1414.
Aminosalicylate Sodium Tablets-See PF Vol. 30 No. 1, page 53.
Amitriptyline Hydrochloride-See PF Vol. 29 No. 6, page 1844.
Ammonium Chloride-See PF Vol. 29 No. 5, page 1415.
Ammonium Molybdate-See PF Vol. 29 No. 5, page 1416.
Amoxicillin Tablets-See PF Vol. 29 No. 1, page 48.
Amoxicillin and Clavulanate Potassium for Oral Suspension-See PF Vol. 30 No. 1, page 53.
Amoxicillin and Clavulanate Potassium Tablets-See PF Vol. 29 No. 3, page 605.
Amphetamine Sulfate-See PF Vol. 30 No. 3, page 807.
Amphetamine Sulfate Tablets-See PF Vol. 30 No. 1, page 54.
Amphotericin B Lotion-See PF Vol. 30 No. 2, page 444.
Amphotericin B Topical Emulsion-See PF Vol. 30 No. 2, page 445.

Ampicillin-See PF Vol. 28 No. 6, page 1766.
Ampicillin Capsules-See PF Vol. 30 No. 1, page 55.
Ampicillin Tablets-See PF Vol. 30 No. 1, page 56.
Anecortave Acetate-See PF Vol. 30 No. 2, page 445.
Anecortave Acetate Injectable Suspension-See PF Vol. 30 No. 2, page 447.
Anileridine-See PF Vol. 29 No. 6, page 1846.
Antithrombin III Human-See PF Vol. 30 No. 1, page 56.
Arginine Hydrochloride-See PF Vol. 30 No. 2, page 449.
Ascorbic Acid Tablets-See PF Vol. 30 No. 1, page 60.
L-Asparagine-See PF Vol. 29 No. 3, page 687.
Aspartic Acid-See PF Vol. 30 No. 4, page 1163.
Aspirin-See PF Vol. 30 No. 4, page 1164.
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules-See PF Vol. 30 No. 1, page 60.
Atenolol-See PF Vol. 29 No. 5, page 1416.
Atenolol Tablets-See PF Vol. 29 No. 1, page 49.
Atovaquone Oral Suspension-See PF Vol. 30 No. 2, page 449.
Atracurium Besylate-See PF Vol. 29 No. 6, page 1846.
Atracurium Besylate Injection-See PF Vol. 30 No. 3, page 808.
Atropine Sulfate-See PF Vol. 29 No. 6, page 1847.
Aurothioglucose-See PF Vol. 29 No. 6, page 1847.
Avobenzone-See PF Vol. 30 No. 4, page 1164.
Azaperone-See PF Vol. 29 No. 6, page 1847.
Azithromycin-See PF Vol. 30 No. 2, page 450.
Azithromycin Capsules-See PF Vol. 27 No. 6, page 3394.
Aztreonam-See PF Vol. 30 No. 1, page 61.
Baclofen Tablets-See PF Vol. 30 No. 1, page 61.
BCG Live-See PF Vol. 30 No. 2, page 452.
Benazepril Hydrochloride-See PF Vol. 29 No. 5, page 1422.
Benazepril Hydrochloride Tablets-See PF Vol. 29 No. 3, page 606.

Benzocaine-See PF Vol. 30 No. 3, page 809.
Benzoyl Peroxide Gel-See PF Vol. 30 No. 4, page 1165.
Benzoyl Peroxide Lotion-See PF Vol. 30 No. 2, page 456.
Benzoyl Peroxide Topical Emulsion-See PF Vol. 30 No. 2, page 456.

Benztropine Mesylate-See PF Vol. 29 No. 6, page 1848.

Benzyl Benzoate Lotion-See PF Vol. 30 No. 2, page 457.
Benzyl Benzoate Topical Emulsion-See PF Vol. 30 No. 2, page 457.

Betahistine Hydrochloride-See PF Vol. 29 No. 4, page 1008.
Betamethasone Oral Solution-See PF Vol. 30 No. 2, page 460.
Betamethasone Syrup-See PF Vol. 30 No. 2, page 460.
Betamethasone Tablets-See PF Vol. 30 No. 1, page 62.
Betamethasone Dipropionate Lotion-See PF Vol. 30 No. 2, page 458.

Betamethasone Dipropionate Topical Emulsion-See PF Vol. 30 No. 2, page 459.
Betamethasone Sodium Phosphate-See PF Vol. 30 No. 4, page 1166.

Betamethasone Valerate Lotion-See PF Vol. 30 No. 2, page 461.
Betamethasone Valerate Topical Emulsion-See PF Vol. 30 No. 2, page 461.
Bethanechol Chloride-See PF Vol. 29 No. 6, page 1848.
Bethanechol Chloride Tablets-See PF Vol. 29 No. 1, page 54.
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers-See PF Vol. 30 No. 1, page 63.
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions-See PF Vol. 30 No. 1, page 66.
Biperiden-See PF Vol. 29 No. 6, page 1851.
Bismuth Subsalicylate Oral Suspension-See PF Vol. 30 No. 4, page 1166.
Bismuth Subsalicylate Tablets-See PF Vol. 30 No. 4, page 1167.
Red Blood Cells-See PF Vol. 30 No. 1, page 69.
Whole Blood-See PF Vol. 30 No. 1, page 76.
Bretylium Tosylate-See PF Vol. 29 No. 5, page 1431.
Bromodiphenhydramine Hydrochloride and Codeine Phosphate Syrup-See PF Vol. 27 No. 5, page 2980.
Brompheniramine Maleate-See PF Vol. 29 No. 5, page 1431.
Brompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution-See PF Vol. 30 No. 1, page 79.
Brompheniramine Maleate and Pseudoephedrine Sulfate SyrupSee PF Vol. 30 No. 1, page 80.
Bumetanide-See PF Vol. 29 No. 5, page 1432
Bupivacaine Hydrochloride-See PF Vol. 29 No. 5, page 1432.
Bupropion Hydrochloride Extended-Release Tablets-See PF Vol. 30 No. 3, page 810.
Butalbital, Acetaminophen, and Caffeine Tablets-See PF Vol. 30 No. 1, page 80.
Butorphanol Tartrate-See PF Vol. 29 No. 6, page 1851.
Caffeine-See PF Vol. 30 No. 4, page 1168.
Caffeine Injection-See PF Vol. 30 No. 2, page 462.
Caffeine Oral Solution-See PF Vol. 30 No. 2, page 464.
Calamine Lotion-See PF Vol. 30 No. 2, page 466.
Phenolated Calamine Lotion-See PF Vol. 30 No. 2, page 466.
Calamine Topical Suspension-See PF Vol. 30 No. 2, page 467.
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$\dagger$ New cancellations in PF 30(5).

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## HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps (Stages).

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In $P F$, this stage appears as OFFICIAL INQUIRY STAGE 4 in the Harmonization section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

## Stage 5: Consensus

## A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

## B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.
HARMONIZATION ..... 1841
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Alcohol [new] (2 ${ }^{\text {nd }}$ Supp to USP28) ..... 1844
Dehydrated Alcohol (2nd Supp to USP28) ..... 1847
Dehydrated Alcohol [new] (2 ${ }^{\text {nd }}$ Supp to USP28) ..... 1848
Anhydrous Citric Acid [new] (2 ${ }^{\text {nd }}$ Supp to USP28) ..... 1851
Citric Acid Monohydrate [new] (2 ${ }^{\text {nd }}$ Supp to USP28) ..... 1854
Talc ( $2^{\text {nd }}$ Supp to USP28) ..... 1857
Talc ( $2^{\text {nd }}$ Supp to USP28) ..... 1859
MONOGRAPHS (NF) ..... 1862
Corn Starch [new] (2 ${ }^{\text {nd }}$ Supp to NF 23) ..... 1862
Potato Starch [new] (2 $2^{\text {nd }}$ Supp to NF 23) ..... 1865
Wheat Starch $[$ new $]$ (2 ${ }^{\text {nd }}$ Supp to NF 23) ..... 1868

## MONOGRAPHS (USP)

## BRIEFING

Alcohol, USP 27 page 59 and page 669 of $P F 30(2)$ [Mar.-Apr. 2004]. The European Pharmacopoeia is the coordinating pharmacopoeia for the international harmonization of compendial standards for the Alcohol monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Identification A | + | + | + |
| Identification B | + | + | + |
| Appearance | + | + | + |
| Acidity or alkalinity | + | + | + |
| Relative density | + | + | + |
| Absorbance | + | + | + |
| Volatile impurities | + | + | + |
| Residue on <br> evaporation | + | + | + |
| Storage | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters.
Definition and Relative density: Each pharmacopeia specifies a different range for the content; the values for relative density vary accordingly and, in addition, are expressed at different temperatures.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Differences between the ADOPTION STAGE 6 document and the current $U S P$ monograph include the following:
(1) Definition-No change.
(2) Packaging and storage-Storage conditions to protect from light are added.
(3) USP Reference standards-A reference standard for Alcohol is added for use in the Identification test.
(4) Identification-Tests $A$ and $B$ are replaced with a more definitive IR absorption test, and the test for specific gravity is moved under Identification.
(5) Clarity of solution-This test is added to comply with EP standards.
(6) Color of solution-This test is added to comply with EP standards.
(7) Specific gravity-No change.
(8) Acidity-This test is replaced by a test for Acidity or alkalinity to comply with EP standards.
(9) Limit of nonvolatile residue-The sample size is increased from 40 to 100 mL .
(10) Ultraviolet absorbance-The standards have been modified to comply with EP standards. Corrections are made to the cell dimensions to comply with the signed off draft.
(11) Water-insoluble substances-This test is deleted. Because the monograph contains tests for Nonvolatile residue and Volatile impurities, this test is no longer needed.
(12) Aldehydes and other foreign organic substances-This test is replaced with a Volatile impurities test.
(13) Amyl alcohol and nonvolatile, carbonizable substancesThis test is replaced with a Volatile impurities test.
(14) Ultraviolet absorbance-This test is added to comply with EP standards. Corrections are made to the cell dimensions to comply with the signed off draft.
(15) Limit of acetone and isopropyl alcohol-This test is replaced with a Volatile impurities test.
(16) Methanol-This test is replaced with a Volatile impurities test.
(17) Volatile impurities-This chromatographic test is added to limit a wide array of volatile impurities within a single test method. Clarification is made under Procedure to analyze all of the standard solutions.
(EMC: J. Lane) RTS-41486-3

## Change to read:

## Aleohel


$\mathrm{E}_{2} \mathrm{H}_{6} \Theta \quad 46.07$
Ethanol.
Ethylaleohel [64-17.5].
H-Aleohel contains net less than-92.3 percent and not more than 93.8 percent, by weight, correspending to not less than 94.9 pereent and not more than 96.0 pereent, by volume, at $15.56^{\circ}$, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Packaging and-storage Preserve-in tight containers, remote frem fire.

## Identifieation-

A: Mix 5 dreps in a small beaker with 1 mL of petassium per mangenate solution ( 1 in 100) and 5 dreps of 2 N sulfuric acid, and eover the beaker immediately with a filter paper meistened with a solution recently prepared by dissolving 0.1 g of soditm nitrofer ricymide and 0.25 gof piperazine in 5 mL of water: an intense blue eolor is produced on the filter paper, the color becoming paler after a few mintutes.

B: To 5 mL of a solution ( 1 in 10 ) add 1 mL of 1.0 N sodium hydroxide, then slowly (over a period of 3 minutes) add 2 mL of $\theta .1 \mathrm{~N}$ iodine: the odor of iodoform develops, and a yellow precipi tate is formed within 30 mintres.
Speeifie gravity $\langle 844\rangle$ :- between 0.812 and- 0.816 at $15.56^{\circ}$, in dicating between $92.3 \%$ and $93.8 \%$, by weight, or between $94.9 \%$ and $96.0 \%$, by volume, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Acidity To 50 mL , in a glass stoppered flack, add 50 mL of re cently boiled water. Add phenolphthalein TS, and titrate with 0.020 N sodim hydroxide to a pink color that persists for 30 sec ends: net mere than 0.90 mL of 0.020 N soditm hydrexide is required for neutralization.
Limit of nonvolatile residue-Evaporate 40 mL in a tared dishon a water bath, and dry at $105^{\circ}$ for 1 hour: the weight of the residue does not exeed 1 me.
Water-insoluble substances Dilute it with an equal volume of water: the mixture is clear and remains clear for 30 minutes after eooling to $10^{\circ}$.
Aldehydes and-0ther foreign-0rganic substances Place 20 mL in a glass-stoppered eylinder that has been thoroughly cleaned with hydrochlerie acid, then rinsed with water and fanally with the At eohol to be tested. Cool the contents to approximately $15^{\circ}$, and add, by means of a carefully cleaned pipet, 0.10 mL of 0.10 N pe tassium permanganate, neting aceurately the time of addition. Mix at once by inverting the stoppered cylinder, and allow it to stand at $15^{\circ}$ for 5 minutes: the pink color does not entirely disappear.
Amylaleoholandmonvolatile, carbonizable substanees-Allow 25 mL to evaperate spentaneously from a pereelain dish, careftlly protect frem dust, until the surface of the dish is barely moist: no redor brown color is produced immediately upen the addition of a few dreps of sulfuric acid.
Limit of aeetone and isopropylaleohol To 1.0 mL add 1.0 mL of water, 1.0 mL of a saturated solution of dibasic sodium phosphate, and 3.0 mL of a saturated solution of potassium permanga nate. Warm the mixture to $45^{\circ}$ to $50^{\circ}$, and allow to stand until the permanganatecolor is discharged. Add 3.0 mL of 2.5 N sodium hydroxide, and filter, without washing, through a sintered glass fit ter. Prepare a control by mixing 1.0 mL of the saturated solution of dibasic sodium phosphate, 3.0 mL of 2.5 N sodium hydroxide, 80 He of acetone, and 5.0 mL of water. To each solution add 1 mL of furfural solution ( 1 in 100), allow to stand for 10 minutes, then to 1.0 mL of each solution add 3 mL of hydrochloric acid: any pink eoler produced in the test solution is not more intense than that in the controt.
Methanol To 1 drop add 1-drop-of water, 1 drop-of dilute phesphoric acid ( 1 in 20), and 1 drep of potassimm permangenate solution ( 1 in 20). Mix, allour to stand for 1 minute, and add sodium metabisulfite solution ( 1 in 20), dropwise, until the permanga nate color is diseharged. If a brown color remains, add 1 drop of the dilute phosphoric acid. To the colorless solution add 5 mL of freshly prepared chromotropic acid TS, and heat on a water bath at $60^{\circ}$ for 10 minntes: any viole color should not exeed that produred by 0.04 mg of methanol in 1 mL of water, treated in the same way as the sample.

## Alcohol

$$
\mathrm{C}_{2} \mathrm{H}_{6} \mathrm{O} \quad 46.07
$$

Ethanol.

Ethyl alcohol [64-17-5].
» Alcohol contains not less than 92.3 percent and not more than 93.8 percent, by weight, corresponding to not less than 94.9 percent and not more than 96.0 percent, by volume, at $15.56^{\circ}$, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Packaging and storage-Preserve in tight containers, protected from light. and remotem from, sparks, or open flames.

USP Reference standards $\langle 11\rangle-U S P$ Alcohol $R S$.
Clarity of solution-[NOTE-The Test solution is to be compared to Reference suspension $A$ and to water in diffused daylight 5 minutes after preparation of Reference suspension $A$.]

Hydrazine solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Methenamine solution-Transfer 2.5 g of methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.
Primary opalescent suspension-[NOTE-This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of Hydrazine solution to the Methenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE-This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension
A. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension B.

Test solution $A$-The substance to be examined.
Test solution B-Dilute 1.0 mL of Test solution $A$ to 20 mL with water, and allow to stand for 5 minutes before testing.

Procedure-Transfer a sufficient portion of Test solution $A$ and Test solution $B$ to separate test tubes of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Reference suspension A, Reference suspension $B$, and water to separate matching test tubes. Compare Test solution A, Test solution B, Reference suspension $A$, Reference suspension $B$, and water in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and LightScattering $\langle 851\rangle$ ). [NOTE-The diffusion of light must be such that Reference suspension $A$ can readily be distinguished from water, and that Reference suspension $B$ can readily be distinguished from Reference suspension A.] Test solution $A$ and Test solution $B$ show the same clarity as that of water or their opalescence is not more pronounced than that of Reference suspension $A$.

## Color of solution-

Standard stock solution-Combine 3.0 mL of ferric chloride $\mathrm{CS}, 3.0 \mathrm{~mL}$ of cobaltous chloride $\mathrm{CS}, 2.4 \mathrm{~mL}$ of cupric sulfate CS , and 1.6 mL of dilute hydrochloric acid ( 10 g per L).

Standard solution-[NOTE-Prepare the Standard solution immediately before use.] Transfer 1.0 mL of Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix.

Test solution-The substance to be examined.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Standard solution and water to separate, matching test tubes. Compare the Test solution, Standard solution, and water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). The Test solution has the appearance of water or is not more intensely colored than the Standard solution.

## Identification-

A: It complies with the test for Specific gravity.
B: Infrared Absorption $\langle 197 \mathrm{~F}\rangle$ or $\langle 197 \mathrm{~S}\rangle$ neat.
Specific gravity $\langle 841\rangle$ : between 0.812 and 0.816 at $15.56^{\circ}$, indicating between $92.3 \%$ and $93.8 \%$, by weight, or between $94.9 \%$ and $96.0 \%$, by volume, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

## Acidity or alkalinity-

Phenolphthalein solution-Dissolve 0.1 g of phenolphthalein in 80 mL of alcohol, and dilute with water to 100 mL .

Procedure-To 20 mL of alcohol, add 20 mL of freshly boiled and cooled water and 0.1 mL of Phenolphthalein solution. The solution is colorless. Add 1.0 mL of 0.01 N sodium hydroxide. The solution is pink ( 30 ppm , expressed as acetic acid).

Ultraviolet absorption-Record the UV absorption spectrum of the test material from 200 to 400 nm in a $1-\mathrm{em} 5-$ cm cell: maximum absorbance 0.40 at $240 \mathrm{~nm}, 0.30$ between 250 and 260 nm , and 0.10 between 270 and 340 nm . Examine between 235 and 340 nm , in a $5-\mathrm{cm}$ cell, using water as the compensation liquid. The absorption curve is smooth.

## Volatile impurities-

Test solution $A$-The substance to be examined.
Test solution B—Add $150 \mu \mathrm{~L}$ of 4-methylpentan-2-o1 to 500.0 mL of the substance to be examined.

Standard solution A-Dilute $100 \mu \mathrm{~L}$ of methanol to 50.0 mL with the substance to be examined. Dilute 5.0 mL of the solution to 50.0 mL with the substance to be examined.

Standard solution B—Dilute $50 \mu \mathrm{~L}$ of methanol and 50 $\mu \mathrm{L}$ of acetaldehyde to 50.0 mL with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 10.0 mL with the substance to be examined.

Standard solution C-Dilute $150 \mu \mathrm{~L}$ of acetal to 50.0 mL with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 10.0 mL with the substance to be examined.

Standard solution D—Dilute $100 \mu \mathrm{~L}$ of benzene to 100.0 mL with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 50.0 mL with the substance to be examined.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector, maintained at about $280^{\circ}$, and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ fused silica capillary column bonded with a $1.8-\mu \mathrm{m}$ layer of phase G43. The carrier gas is helium with a linear velocity of about 35 cm per second and a split ratio of $1: 20$. The column temperature is maintained at $40^{\circ}$ for the first 12 minutes after an injection is made and is increased from $40^{\circ}$ to $240^{\circ}$ from 12 to 32 minutes after injection. During the period of 32 to 42 minutes after an injection is made the column temperature is maintained at $240^{\circ}$. The injection port temperature is maintained at $200^{\circ}$. Chromatograph Standard solution $B$, and record the peak responses as directed for Procedure: the resolution, $R$, between the first major peak (acetaldehyde) and the second major peak (methanol) is not less than 1.5 .

Procedure-Separately inject equal volumes ( $1.0 \mu \mathrm{~L}$ ) of Test solution $A$ and Test Bration Test solution B, Standard solution A, Standard solution C, and Standard solution D into the chromatograph, record the chromatograms, and measure the major peaks. Calculate the concentration of methanol in Test solution A: not more than half the area of the corresponding peak in the chromatogram obtained with Standard solution $A$ ( 200 ppm ).
Calculate the sum of the contents of acetaldehyde and acetal, expressed as acetaldehyde, using the following formula:

$$
\left[\left(10 \times A_{E}\right) /\left(A_{T}-A_{E}\right)\right]+\left[\left(30 \times C_{E}\right) /\left(C_{T}-C_{E}\right)\right],
$$

in which $A_{E}$ is the area of the acetaldehyde peak in the chromatogram obtained with the Test solution $A ; A_{T}$ is the area of the acetaldehyde peak in the chromatogram obtained with Standard solution $B ; C_{E}$ is the area of the acetal peak in the chromatogram obtained with Test solution $A$; and $C_{T}$ is the area of the acetal peak in the chromatogram obtained with Standard solution C: not more than 10 ppm , expressed as acetaldehyde is found.

Calculate the content of benzene using the following formula:

$$
\left(2 B_{E}\right) /\left(B_{T}-B_{E}\right),
$$

in which $B_{E}$ is the area of the benzene peak in the chromatogram obtained with Test solution $A$; and $B_{T}$ is the area of the benzene peak in the chromatogram obtained with Standard solution D: not more than 2 ppm is found. If necessary, the identity of benzene can be confirmed using another suitable chromatographic system (stationary phase with a different polarity).

The total of all other impurities in the chromatogram obtained with Test solution B: not more than the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with Test solution B (300 ppm).

Disregard any peaks that are 0.03 times the area of the peak corresponding to 4-methylpentan-2-ol in the chromatogram obtained with Test solution $B(9 \mathrm{ppm})$.

Limit of nonvolatile residue-Evaporate 100 mL in a tared dish on a water bath, and dry at $100^{\circ}$ to $105^{\circ}$ for 1 hour: the weight of the residue does not exceed 2.5 mg -2S (USP28)

## BRIEFING

Dehydrated Alcohol, USP 27 page 60 and page 673 of $P F$ 30(2) [Mar.-Apr. 2004]. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of compendial standards for the Dehydrated Alcohol monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia.

## Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Identification A | + | + | + |
| Identification B | + | + | + |
| Appearance | + | + | + |
| Acidity or alkalinity | + | + | + |
| Relative density | + | + | + |
| Absorbance | + | + | + |
| Volatile impurities | + | + | + |
| Residue on <br> evaporation | + | + | + |
| Storage | + | + | + |

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters.
Relative density: The values for relative density are expressed at different temperatures in the three pharmacopeias.

Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications

Differences between the ADOPTION STAGE 6 document and the current USP monograph include the following:
(1) Definition-No change.
(2) Packaging and storage-Storage conditions to protect from light are added.
(3) USP Reference standards-A reference standard for alcohol is added for the Identification test.
(4) Identification-Tests $A$ and $B$ are replaced with a more definitive Infrared absorption test, and the test for Specific gravity is moved under Identification.
(5) Clarity of solution-This test is added to comply with EP standards.
(6) Color of solution-This test is added to comply with EP standards.
(7) Specific gravity-No change.
(8) Acidity-This test is replaced by a test for Acidity or alkalinity to comply with EP standards.
(9) Limit of nonvolatile residue-The sample size is increased from 40 to 100 mL .
(10) Water-insoluble substances-This test is deleted. Because the monograph contains tests for Nonvolatile residue and Volatile impurities, this test is no longer needed.
(11) Aldehydes and other foreign organic substances-This test is replaced with a Volatile impurities test.
(12) Amyl alcohol and nonvolatile, carbonizable substancesThis test is replaced with a Volatile impurities test.
(13) Ultraviolet absorbance-The standards have been modified to comply with EP standards. Corrections are made to the cell dimensions to comply with the signed off draft.
(14) Limit of acetone and isopropyl alcohol-This test is replaced with a Volatile impurities test.
(15) Methanol-This test is replaced with a Volatile impurities test.
(16) Volatile impurities-This chromatographic test is added to limit a wide array of volatile impurities within a single test method. Clarification is made under Procedure to analyze all of the standard solutions.
(EMC: J. Lane) RTS-41486-4

## Change to read:

## Dehydrated Aleohol


$\mathrm{G}_{2} \mathrm{H}_{6} \Theta \quad 46.07$
Ethanel.
Ethylaleohel [64-175].
\# Dehydrated Aleohol contains not less than-99.2 pereent, by weight, correspending to not less than 99.5 pereent, by volume, at $15.56^{\circ}$, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Packaging and-storage Preserve in tight containers, remete frem fire.

## Identification-

A: Mix 5 drops in a small beaker with 1 mL of potassium per mangenate solution ( 1 in 100) and 5 dreps of 2 N sulfuric acid, and eover the beaker immediately with a filter paper moistened with a solution reeently prepared by dissolving 0.1 g of sodium nitrofer rieyanide and 0.25 g of piperazine in 5 mL of water: an intense blue eelor is produced on the filter paper, the color beeoming paler after a few minntes.

B: To 5 mL of a solution ( 1 i in 10) add 1 mL of 1.0 N sodium hydroxide, then slowly (over a period of 3 minutes) add 2 mL of 0.1 N iodine: the oder of iodoform develops, and a yellow precipi tate is formed within 30 mintutes.
Speeifie gravity $\langle 844\rangle$ : net more than 0.7962 at $15.56^{\circ}$, indieat ing not less than $99.2 \% \mathrm{Of}_{2} \mathrm{H}_{5} \mathrm{OH}$ by weight.
Aeidity $\mathrm{To}-50 \mathrm{~mL}$, in a glass stoppered flask, add 50 mL of reeently boiled water. Add phenolphthalein-TS, and titrate-with 0.020 N sodium hydroxide to a pink coler that persists for 30 sec ends: not more than 0.90 mL of 0.020 N sodium hydroxide is required for neutralization.
Limil of nonvolatile residte-Evaporate -40 mL in a arad dish on a water bath, and dry at $105^{\circ}$ for 1 heur: the weight of the residue does not exeed 1 mg .
Water insoluble substanees-Dilute it with an equal volume of water: the mixture is clear and remains clear for 30 minutes after eoting to $10^{\circ}$
Aldehydes and other foreign-organic substanees. Place 20 mL in a glass stoppered eylinder that has been thoroughly cleaned with hydrochloric acid, then rinsed with water and fanally with the De hydrated Alcohol to be tested. Cool the contents to approximately $15^{\circ}$, and add, by means of a carefully cleaned pipet, 0.10 mL of $\theta .10 \mathrm{~N}$ potassium permanganate, noting necurately the time of at dition. Mix at onee by inverting the stoppered eylinder, and allow it to stand at $15^{\circ}$ for 5 minntes: the pink color does not entirely dis аррепи.
Amylaleoholand nonvolatile, carbonizable substanees Allow 25 mL to evaporate spontaneously from a porcelain dish, carefully protected from dust, until the sufface of the dish is barely moist: ne red or brown color is produced immediately upen the addition of a few drops of sulfuric acid.
Utraviolet absorbanee-Record the UV absorption spectrumbetween 340 nm and 235 mm in a 1 cm cell, with water in a matehed eell in the reference beam: the absorbanee is not more than 0.08 at 240 nm , and 0.02 between 270 nm and 340 nm , and the curve drawn through these peints is smooth.
Limit of acetone and isopropylaleohol, To 1.0 mL add 1 mL of water, 1 mL of a saturated solution of dibasic sodimm phosphate, and $3-\mathrm{mL}$ of a saturated solation of petassium permanganate. Warm the mixture to $-45^{\circ}$ to $50^{\circ}$, and allow to stand until the per mangenate color is diseharged. 1 ddd 3 mL of 2.5 N sodimm hydrox ide, and fllter, without washing, through a sintered glass filter. Prepare a control containing 1 mL of the sattrated solution of dibasic sodium phosphate, 3 mL of 2.5 N sodium hydroxide, and 80 He of acetome in 9 mL . To each solution add 1 mL of furfural sotution ( 1 in 100 ), and allow to stand for 10 minntes, then $10-1.0 \mathrm{~mL}$ of each solution add $3-\mathrm{mL}$ of hydrochloric acid: any pink color produced in the test solution is not more intense than that in the eentrel.
Methanol To 1-drop add 1-drop-of water, 1 drep-of dilute phespheric acid ( 1 in 20 ), and 1 drep of potassium permanganate solution ( 1 in 20). Mix, allow to stand for 1 minnte, and add sodium metabisulfite solution ( 1 in 20), dropwise, until the permangn natecolor is diseharged. If abrown color remains, add 1 drop of the dilute phesphoric acid. To the colorless solution add 5 mL of fresh ly prepared chremetrepic acid TS, and heat on a water bath at $60^{\circ}$ for 10 mintutes: no violet coler appears.

## Dehydrated Alcohol

$$
\mathrm{H}_{3} \mathrm{C} \widehat{\mathrm{OH}}
$$

$\mathrm{C}_{2} \mathrm{H}_{6} \mathrm{O} \quad 46.07$

Ethanol.

Ethyl alcohol [64-17-5].

## " Dehydrated Alcohol contains not less than 99.2

 percent, by weight, corresponding to not less than
## 99.5 percent, by volume, at $15.56^{\circ}$, of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$.

Packaging and storage-Preserve in tight containers, protected from light. fremere freser

USP Reference standards $\langle 11\rangle$ —USP Dehydrated Alcohol RS.

Clarity of solution-[NOTE-The Test solution is to be compared to Reference suspension $A$ and to water in diffused daylight 5 minutes after preparation of Reference suspension A.]

Hydrazine solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours. Methenamine solution-Transfer 2.5 g of methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension-[NOTE-This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of Hydrazine solution to the Methenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE-This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension A. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension B.

Test solution $A$-The substance to be examined.
Test solution B-Dilute 1.0 mL of Test solution $A$ to 20 mL with water, and allow to stand for 5 minutes before testing.

Procedure-Transfer a sufficient portion of Test solution $A$ and Test solution $B$ to separate test tubes of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Reference suspension A, Reference suspension $B$, and water to separate, matching test tubes. Compare Test solution A, Test solution B, Reference suspension $A$, Reference suspension $B$, and water in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and LightScattering $\langle 851\rangle$ ). [NOTE-The diffusion of light must be such that Reference suspension $A$ can readily be distinguished from water, and Reference suspension $B$ can readily be distinguished from Reference suspension A.] Test solution $A$ and Test solution $B$ show the same clarity as that of water, or their opalescence is not more pronounced than that of Reference suspension A.

## Color of solution-

Standard stock solution-Combine 3.0 mL ferric chloride CS, 3.0 mL cobaltous chloride CS, 2.4 mL cupric sulfate CS , and 1.6 mL dilute hydrochloric acid ( 10 g per L ).

Standard solution-[NOTE-Prepare the Standard solution immediately before use.] Transfer 1.0 mL of Standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix.

Test solution-The substance to be examined.
Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Standard solution and water to separate matching test tubes. Compare the Test solution, Standard solution, and water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). The Test solution has the appearance of water or is not more intensely colored than the Standard solution.

## Identification-

A: It complies with the test for Specific gravity.
B: Infrared Absorption $\langle 197 \mathrm{~F}\rangle$ or $\langle 197 \mathrm{~S}\rangle$ neat.
Specific gravity $\langle 841\rangle$ : not more than 0.7962 at $15.56^{\circ}$, indicating not less than $99.2 \%$ of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$, by weight.

## Acidity or alkalinity-

Phenolphthalein solution-Dissolve 0.1 g of phenolphthalein in 80 mL of alcohol, and dilute with water to 100 mL .

Procedure-To 20 mL of alcohol, add 20 mL of freshly boiled and cooled water and 0.1 mL of Phenolphthalein solution. The solution is colorless. Add 1.0 mL of 0.01 N sodium hydroxide. The solution is pink ( 30 ppm , expressed as acetic acid).

Ultraviolet absorption-Record the UV absorption spectrum of the test material from 200 to 400 nm in a $1-\mathrm{em} 5$ cm cell: maximum absorbance 0.40 at $240 \mathrm{~nm}, 0.30$ between 250 and 260 nm , and 0.10 between 270 and 340
nm . Examine between 235 and 340 nm , in a $5-\mathrm{cm}$ cell, using water as the compensation liquid. The absorption curve is smooth.

## Volatile impurities-

Test solution $A$-The substance to be examined.
Test solution B—Add $150 \mu \mathrm{~L}$ of 4-methylpentan-2-ol to 500.0 mL of the substance to be examined.

Standard solution A-Dilute $100 \mu \mathrm{~L}$ of methanol to 50.0 mL with the substance to be examined. Dilute 5.0 mL of the solution to 50.0 mL with the substance to be examined.

Standard solution B-Dilute $50 \mu \mathrm{~L}$ of methanol and 50 $\mu \mathrm{L}$ of acetaldehyde to 50.0 mL with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 10.0 mL with the substance to be examined.

Standard solution C-Dilute $150 \mu \mathrm{~L}$ of acetal to 50.0 mL with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 10.0 mL with the substance to be examined.

Standard solution D-Dilute $100 \mu \mathrm{~L}$ of benzene to 100.0 mL with the substance to be examined. Dilute $100 \mu \mathrm{~L}$ of the solution to 50.0 mL with the substance to be examined.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector, maintained at about $280^{\circ}$, and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ fused silica capillary column bonded with a $1.8-\mu \mathrm{m}$ layer of phase G43. The carrier gas is helium with a linear velocity of about 35 cm per second and a split ratio of $1: 20$. The column temperature is maintained at $40^{\circ}$ for the first 12 minutes after an injection is made and is increased from $40^{\circ}$ to $240^{\circ}$ from 12 to 32 minutes after injection. During the period of 32 to 42 minutes after an injection is made the column temperature is maintained at $240^{\circ}$. The injection port temperature is maintained at $200^{\circ}$. Chromatograph Standard solution $B$, and record the peak responses as directed for

Procedure: the resolution, $R$, between the first major peak (acetaldehyde) and the second major peak (methanol) is not less than 1.5 .

Procedure-Separately inject equal volumes $(1.0 \mu \mathrm{~L})$ of Test solution A, Testion B Test solution B, Standard solution A, Standard solution C, and Standard solution $D$ into the chromatograph, record the chromatograms, and measure the major peaks. Calculate the concentration of methanol in Test solution A: not more than half the area of the corresponding peak in the chromatogram obtained with Standard solution $A$ ( 200 ppm ).
Calculate the sum of the contents of acetaldehyde and acetal, expressed as acetaldehyde, using the following formula:

$$
\left[\left(10 \times A_{E}\right) /\left(A_{T}-A_{E}\right)\right]+\left[\left(30 \times C_{E}\right) /\left(C_{T}-C_{E}\right)\right],
$$

in which $A_{E}$ is the area of the acetaldehyde peak in the chromatogram obtained with the Test solution $A ; A_{T}$ is the area of the acetaldehyde peak in the chromatogram obtained with Standard solution $B ; C_{E}$ is the area of the acetal peak in the chromatogram obtained with Test solution $A$; and $C_{T}$ is the area of the acetal peak in the chromatogram obtained with Standard solution $C$ : not more than 10 ppm , expressed as acetaldehyde is found.

Calculate the content of benzene using the following formula:

$$
\left(2 B_{E}\right) /\left(B_{T}-B_{E}\right),
$$

in which $B_{E}$ is the area of the benzene peak in the chromatogram obtained with Test solution $A$, and $B_{T}$ is the area of the benzene peak in the chromatogram obtained with Standard solution $D$ : not more than 2 ppm is found. If necessary, the
identity of benzene can be confirmed using another suitable chromatographic system (stationary phase with a different polarity).

The total of all other impurities in the chromatogram obtained with Test solution $B$ is not more than the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with Test solution $B$ ( 300 ppm ). Disregard any peaks that are 0.03 times the area of the peak corresponding to $4-$ methylpentan-2-ol in the chromatogram obtained with Test solution $B(9 \mathrm{ppm})$.

Limit of nonvolatile residue-Evaporate 100 mL in a tared dish on a water bath, and dry at $100^{\circ}$ to $105^{\circ}$ for 1 hour: the weight of the residue does not exceed 2.5 mg . $\mathbf{n}^{2 S}$ (USP28)

## Briefing

Citric Acid, Anhydrous, page 677 of PF 30(2) [Mar.-Apr. 2004]. It is proposed to add Packaging and storage requirements.
(EMC: J. Lane; PSD: C. Okeke) RTS-41486-1

## Add the following:

## ©Citric Acid, Anhydrous Anhydrous Citric Acid


$\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7} \quad 192.13$

1,2,3-Propanetricarboxylic acid, 2-hydroxy-.
Citric acid [77-92-9].
» Anhydrous Citric Acid contains not less than 99.5 percent and not more than 100.5 percent of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7}$, calculated on the anhydrous basis.

## Add the following:

-Packaging and storage-Preserve in tight containers. No storage requirements specified. ${ }^{2 S}$ (USP28)

Labeling-Where it is intended for use in dialysis solutions, it is so labeled. Where Anhydrous Citric Acid must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled. Where Anhydrous Citric Acid is sterile, it is so labeled.

USP Reference standards $\langle 11\rangle$ —USP Citric Acid RS.
Clarity of solution-[NOTE-The Test solution is to be compared to Reference suspension $A$ in diffused daylight 5 minutes after preparation of Reference suspension A.]

Hydrazine sulfate solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours before use.

Hexamethylenetetramine solution Methenamine solu-tion-Transfer 2.5 g of Hexamethylenetetramine Methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.
Primary opalescent suspension-[NOTE-This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of Hydrazine sulfate solution to the Hex Methenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE-This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000 mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension A. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension $B$.

Test solution-Dissolve 2.0 g of Anhydrous Citric Acid in about 5 mL of water, dilute with water to 10 mL , and mix.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Reference suspension $A$, Reference suspension $B$, and water to separate matching test tubes. Compare the Test solution, Reference suspension $A$, Reference suspension $B$, and water in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and LightScattering $\langle 851\rangle$ ). [NOTE-The diffusion of light must be such that Reference suspension $A$ can readily be distinguished from water, and that Reference suspension $B$ can readily be distinguished from Reference suspension $A$.] The Test solution shows the same clarity as that of water.

## Color of solution-

Standard stock solutions-Prepare three solutions, $A, B$, and $C$, containing, respectively, the following parts of ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and dilute hydrochloric acid ( 10 g per L ):

$$
\begin{aligned}
& A-2.4: 0.6: 0: 7.0 \\
& B-2.4: 1.0: 0.4: 6.2 \\
& C-9.6: 0.2: 0.2: 0
\end{aligned}
$$

Standard solutions-[NOTE-Prepare the Standard solutions immediately before use.] Transfer 2.5 mL of Standard stock solution $A$ to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix to obtain Standard solution A. Transfer 2.5 mL of Standard stock solution $B$ to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix to obtain Standard solution B. Transfer 0.75 mL of Standard stock solution $C$ to a $100-\mathrm{mL}$ volumetric flask, dilute with dilute hydrochloric acid ( 10 g per L ) to volume, and mix to obtain Standard solution C.

Test solution-Use the Test solution prepared as directed in the test for Clarity of solution.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Standard solution A, Standard solution B, and Standard solution C, and water to separate matching test tubes. Compare the Test solution, Standard solution A, Standard solution B, and Standard solution $C$, and water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). The Test solution is not more intensely colored than Standard solutions $A, B$, $C$, or water.

Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$-Dry the substance to be examined at $105^{\circ}$ for 2 hours.

Bacterial endotoxins $\langle 85\rangle$-If intended for use in the manufacturing of parenteral dosage forms, without a further appropriate procedtre for the removal of bacterial endetoxins, net mere that 0.5 I . U. of endetoxin per milligram. The level of bacterial endotoxins are such that the requirement under the relevant dosage form monograph(s) in which Anhydrous Citric Acid is used can be met. Where the label states that Anhydrous Citric Acid must be subjected to further process-
ing during the preparation of injectable dosage forms, the level of bacterial endotoxins are such that the requirement under the relevant dosage form monograph(s) in which Anhydrous Citric Acid is used can be met.

Sterility $\langle 71\rangle$ —Where the label states that Anhydrous Citric Acid is sterile, it meets the requirements for Sterility $\langle 71\rangle$ under the relevant dosage form monograph(s) in which Anhydrous Citric Acid is used.

Water, Method I $\langle 921\rangle$ : not more than $1.0 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on 1.0 g .

Readily carbonizable substances-Transfer 1.0 g of powdered Anhydrous Citric Acid to a $22-\times 175-\mathrm{mm}$ test tube previously rinsed with 10 mL of sulfuric acid TS and allowed to drain for 10 minutes. Add 10 mL of sulfuric acid TS, agitate until solution is complete, and immerse in a water bath at $90 \pm 1^{\circ}$ for $60 \pm 0.5$ minutes, keeping the level of the acid below the level of the water during the entire period. Cool the tube in running water, and transfer the acid to a color-comparison tube: the color of the acid is not darker than that of a similar volume of Matching Fluid K (see Color and Achromicity $\langle 631\rangle$ ) in a matching tube, the tubes being observed vertically against a white background.

## Sulfate-

Standard sulfate solution A-To 181 mg of dibasic potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of 30 percent alcohol, swirl to dissolve, dilute with 30 percent alcohol to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a $1000-\mathrm{mL}$ volumetric flask, dilute with 30 percent alcohol to volume, and mix. This solution contains $10 \mu \mathrm{~g}$ of sulfate per mL .

Standard sulfate solution B-To 181 mg of dibasic potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of water, swirl to dissolve, dilute with water to volume, and mix. Immediately before use, transfer 10.0 mL of this solu-
tion to a $1000-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. This solution contains $10 \mu \mathrm{~g}$ of sulfate per mL.

Citric acid solution-Dissolve 2.0 g of Anhydrous Citric Acid in about 10 mL of water, dilute with water to 30 mL , and mix.

Procedure-To 4.5 mL of Standard sulfate solution $A$ add 3 mL of a barium chloride solution (1 in 4), shake, and allow to stand for 1 minute. To 2.5 mL of the resulting suspension, add 15 mL of the Citric acid solution and 0.5 mL of 5 N acetic acid, and mix (test solution). Prepare the Standard solution in the same manner, except use 15 mL of Standard sulfate solution B instead of the Citric acid solution: any turbidity produced in the test solution after 5 minutes standing is not greater than that produced in the Standard solution (0.015\%).

Heavy metals $\langle 231\rangle$ : $0.001 \%$.
Limit of oxalic acid-Prepare a citric acid solution by dissolving 800 mg of Anhydrous Citric Acid in 4 mL of water. Add 3 mL of hydrochloric acid and 1 g of granular zinc, boil for 1 minute, and allow to stand for 2 minutes. Transfer the supernatant to a test tube containing 0.25 mL of a phenylhydrazine hydrochloride solution (1 in 100), and heat to boiling. Cool rapidly, transfer to a graduated cylinder, and add an equal volume of hydrochloric acid and 0.25 mL of a potassium ferricyanide solution (1 in 20). Shake, and allow to stand for 30 minutes (test solution). Concomitantly prepare a control solution in the same manner, except use 4 mL of an oxalic acid solution containing 0.10 mg per mL , equivalent to 0.0714 mg of anhydrous oxalic acid per mL , instead of the citric acid solution: any pink color produced in the test solution is not more intense than that produced in the control solution ( $0.036 \%$ ).

Limit of aluminum (where it is labeled as intended for use in dialysis)-

Standard aluminum solution-To 352 mg of aluminum potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of water, swirl to dissolve, add 10 mL of diluted sulfuric acid, dilute with water to volume, and mix. Immediately before use, transfer 1.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.
pH 6.0 Acetate buffer-Dissolve 50 g of ammonium acetate in 150 mL of water, adjust with glacial acetic acid to a pH of 6.0 , dilute with water to 250 mL , and mix.

Test solution-Dissolve 20.0 g of Anhydrous Citric Acid in 100 mL of water, and add 10 mL of pH 6.0 Acetate buffer. Extract this solution with successive portions of 20, 20, and 10 mL of a $0.5 \%$ solution of 8 -hydroxyquinoline in chloroform, combining the chloroform extracts in a $50-\mathrm{mL}$ volumetric flask. Dilute the combined extracts with chloroform to volume, and mix.

Standard solution-Prepare a mixture of 2.0 mL of Standard aluminum solution, 10 mL of pH 6.0 Acetate buffer, and 98 mL of water. Extract this mixture as described for the Test solution, dilute the combined extracts with chloroform to volume, and mix.

Blank solution-Prepare a mixture of 10 mL of pH 6.0 Acetate buffer and 100 mL of water. Extract this mixture as described for the Test solution, dilute the combined extracts with chloroform to volume, and mix.

Procedure-Determine the fluorescence intensities of the Test solution and the Standard solution in a fluorometer set at an excitation wavelength of 392 nm and an emission wavelength of 518 nm , using the Blank solution to set the instrument to zero. The fluorescence of the Test solution does not exceed that of the Standard solution $(0.2 \mu \mathrm{~g} \mathrm{per} \mathrm{g})$. Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

Assay—Place about 0.550 g of Anhydrous Citric Acid in a tared flask, and weigh accurately. Dissolve in 50 mL of water, add 0.5 mL of phenolphthalein TS, and titrate with 1 N sodium hydroxide VS. Each mL of 1 N sodium hydroxide is equivalent to 64.03 mg of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7 \cdot \mathbf{\Delta U S P 2 8}}$

## BRIEFING

Citric Acid Monohydrate, page 681 of PF 30(2) [Mar.-Apr. 2004]. It is proposed to add Packaging and storage requirements.
(EMC: J. Lane; PSD: C. Okeke) RTS-41486-2

## Add the following:

## ©Citric Acid Monohydrate


$\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7} \cdot \mathrm{H}_{2} \mathrm{O} \quad 210.14$

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, monohydrate [5949-29-1].
» Citric Acid Monohydrate contains one molecule of water of hydration. It contains not less than 99.5 percent and not more than 100.5 percent of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7}$, calculated on the anhydrous basis.

## Add the following:

■Packaging and storage-Preserve in tight containers. No storage requirements specified.■2S (USP28)

Labeling-Where it is intended for use in dialysis solutions, it is so labeled. Where Citric Acid Monohydrate must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled. Where Citric Acid Monohydrate is sterile, it is so labeled.

USP Reference standards $\langle 11\rangle-U S P$ Citric Acid $R S$.
Clarity of solution-[NOTE-The Test solution is to be compared to Reference suspension $A$ in diffused daylight 5 minutes after preparation of Reference suspension $A$.]

Hydrazine sulfate solution-Transfer 1.0 g of hydrazine sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours before use.

Methenamine solution-Transfer 2.5 g of methenamine to a $100-\mathrm{mL}$ glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension-[NOTE-This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of Hydrazine sulfate solution to the Me thenamine solution in the $100-\mathrm{mL}$ glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard-[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the Primary opalescent suspension to a 1000 mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions-Transfer 5.0 mL of the Opalescence standard to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension
A. Transfer 10.0 mL of the Opalescence standard to a second $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix to obtain Reference suspension $B$.

Test solution-Dissolve 2.0 g of Citric Acid Monohydrate in about 5 mL of water, dilute with water to 10 mL , and mix.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Reference suspension $A$, Reference suspension $B$, and water to separate matching test tubes. Compare the Test solution, Reference suspension $A$, Reference suspension $B$, and water in diffused daylight, viewing vertically against a black background (see Visual Comparison under Spectrophotometry and LightScattering $\langle 851\rangle$ ). [NOTE-The diffusion of light must be such that Reference suspension $A$ can readily be distinguished from water, and that Reference suspension $B$ can readily be distinguished from Reference suspension $A$.] The Test solution shows the same clarity as that of water.

## Color of solution-

Standard stock solutions-Prepare three solutions, $A, B$, and $C$, containing, respectively, the following parts of ferric chloride CS, cobaltous chloride CS, cupric sulfate CS , and dilute hydrochloric acid ( 10 g per L ):

$$
\begin{aligned}
& A-2.4: 0.6: 0: 7.0 \\
& B-2.4: 1.0: 0.4: 6.2 \\
& C-9.6: 0.2: 0.2: 0
\end{aligned}
$$

Test solution-Use the Test solution prepared in the Clarity of solution test.

Procedure-Transfer a sufficient portion of the Test solution to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm . Similarly transfer portions of Standard solution A, Standard solution B, and Standard solution C, and water to separate matching test tubes. Compare the Test
solution, Standard solution A, Standard solution B, Standard solution $C$, and water in diffused daylight, viewing vertically against a white background (see Visual Comparison under Spectrophotometry and Light-Scattering $\langle 851\rangle$ ). The Test solution is not more intensely colored than Standard solutions $A, B$, $C$ or water.

Identification, Infrared Absorption $\langle 197 \mathrm{~K}\rangle$ — Dry the substance to be examined at $105^{\circ}$ for 2 hours.

Bacterial endotoxins $\langle 85\rangle$-If intended for use in the manufacturing of parenteral dosage forms, witheut a futher appropriate procedure for the removal of bacterial endotoxins, not more that 0.5 IU . of endotoxin per milligram. The level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Citric Acid Monohydrate is used can be met. Where the label states that Citric Acid Monohydrate must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Citric Acid Monohydrate is used can be met.

Sterility $\langle 71\rangle$-Where the label states that Citric Acid Monohydrate is sterile, it meets the requirements for Sterility $\langle 71\rangle$, under the relevant dosage form monograph(s) in which Citric Acid Monohydrate is used.

Water, Method I $\langle 921\rangle$ : between $7.5 \%$ and $9.0 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$, determined on 1.0 g .

Readily carbonizable substances-Transfer 1.0 g of powdered Citric Acid Monohydrate, to a $22-\times 175-\mathrm{mm}$ test tube previously rinsed with 10 mL of sulfuric acid TS , and allow to drain for 10 minutes. Add 10 mL of sulfuric acid TS, agitate until solution is complete, and immerse in a water bath at $90 \pm 1^{\circ}$ for $60 \pm 0.5$ minutes, keeping the level of the acid below the level of the water during the entire period. Cool the tube in running water, and transfer the
acid to a color-comparison tube: the color of the acid is not darker than that of a similar volume of Matching Fluid K (see Color and Achromicity $\langle 631\rangle$ ) in a matching tube, the tubes being observed vertically against a white background.

## Sulfate-

Standard sulfate solution A-To 181 mg of dibasic potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of 30 percent alcohol, swirl to dissolve, dilute with 30 percent alcohol to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a $1000-\mathrm{mL}$ volumetric flask, dilute with 30 percent alcohol to volume, and mix. This solution contains $10 \mu \mathrm{~g}$ of sulfate per mL .

Standard sulfate solution B-To 181 mg of dibasic potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of water, swirl to dissolve, dilute with water to volume, and mix. Immediately before use, transfer 10.0 mL of this solution to a $1000-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. This solution contains $10 \mu \mathrm{~g}$ of sulfate per mL .

Citric acid solution-Dissolve 2.0 g of Citric Acid Monohydrate in about 10 mL of water, dilute with water to 30 mL , and mix.

Procedure-To 4.5 mL of Standard sulfate solution $A$ add 3 mL of a barium chloride solution (1 in 4), shake, and allow to stand for 1 minute. To 2.5 mL of the resulting suspension, add 15 mL of the Citric acid solution and 0.5 mL of 5 N acetic acid, and mix (test solution). Prepare the Standard solution in the same manner, except use 15 mL of Standard sulfate solution B instead of the Citric acid solution: any turbidity produced in the test solution after 5 minutes standing is not greater than that produced in the Standard solution (0.015\%).

Heavy metals $\langle 231\rangle$ : $0.001 \%$.

Limit of oxalic acid—Prepare a citric acid solution by dissolving 800 mg of Citric Acid Monohydrate in 4 mL of water. Add 3 mL of hydrochloric acid and 1 g of granular zinc, boil for 1 minute, and allow to stand for 2 minutes. Transfer the supernatant to a test tube containing 0.25 mL of a phenylhydrazine hydrochloride solution (1 in 100), and heat to boiling. Cool rapidly, transfer to a graduated cylinder, and add an equal volume of hydrochloric acid and 0.25 mL of a potassium ferricyanide solution (1 in 20). Shake, and allow to stand for 30 minutes (test solution). Concomitantly prepare a control solution in the same manner, except use 4 mL of an oxalic acid solution containing 0.10 mg per mL , equivalent to 0.0714 mg of anhydrous oxalic acid per mL , instead of the citric acid solution: any pink color produced in the test solution is not more intense than that produced in the control solution ( $0.036 \%$ ).

Limit of aluminum (where it is labeled as intended for use in dialysis)-

Standard aluminum solution-To 352 mg of aluminum potassium sulfate in a $100-\mathrm{mL}$ volumetric flask, add a few mL of water, swirl to dissolve, add 10 mL of diluted sulfuric acid, dilute with water to volume, and mix. Immediately before use, transfer 1.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.
pH 6.0 Acetate buffer-Dissolve 50 g of ammonium acetate in 150 mL of water, adjust with glacial acetic acid to a pH of 6.0 , dilute with water to 250 mL , and mix.

Test solution-Dissolve 20.0 g of Citric Acid Monohydrate in 100 mL of water, and add 10 mL of pH 6.0 Acetate buffer. Extract this solution with successive portions of 20, 20 , and 10 mL of a $0.5 \%$ solution of 8 -hydroxyquinoline in chloroform, combining the chloroform extracts in a $50-\mathrm{mL}$ volumetric flask. Dilute the combined extracts with chloroform to volume, and mix.

Standard solution-Prepare a mixture of 2.0 mL of Standard aluminum solution, 10 mL of pH 6.0 Acetate buffer, and 98 mL of water. Extract this mixture as described for the Test solution, dilute the combined extracts with chloroform to volume, and mix.
Blank solution-Prepare a mixture of 10 mL of pH 6.0 Acetate buffer and 100 mL of water. Extract this mixture as described for the Test solution, dilute the combined extracts with chloroform to volume, and mix.

Procedure-Determine the fluorescence intensities of the Test solution and the Standard solution in a fluorometer set at an excitation wavelength of 392 nm and an emission wavelength of 518 nm , using the Blank solution to set the instrument to zero. The fluorescence of the Test solution does not exceed that of the Standard solution ( $0.2 \mu \mathrm{~g}$ per g ). Assay—Place about 0.550 g of Citric Acid Monohydrate in a tared flask, and weigh accurately. Dissolve in 50 mL of water, add 0.5 mL of phenolphthalein TS, and titrate with 1 N sodium hydroxide VS. Each mL of 1 N sodium hydroxide is equivalent to 64.03 mg of $\mathrm{C}_{6} \mathrm{H}_{8} \mathrm{O}_{7 \cdot \Delta}$ USP28

## Briefing

Talc, USP 27 page 1764. The European Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Talc monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the ADOPTION STAGE 6 document, is based on the corresponding monograph for Talc that was prepared by the European Pharmacopoeia. The European Pharmacopoeia draft was based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia.

Pharmacopeial Discussion Group Sign-Off Document

| Attributes | EP | JP | USP |
| :--- | :---: | :---: | :---: |
| Definition | + | + | + |
| Production ${ }^{*}$ | + | + | + |
| Labeling | + | + | + |
| Identification A | + | + | + |
| Acidity or alkalinity | + | + | + |
| Aluminum | + | + | + |
| Calcium | + | + | + |
| Iron | + | + | + |
| Lead | + | + | + |
| Magnesium | + | + | + |
| Loss on ignition |  | + | + |

* In USP, this section will be included under "Absence of asbestos."

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Characters, Water-soluble substances, Labeling, Microbial contamination, Packaging and storage.

Specific local attributes:
Acid-soluble substances, Arsenic (JP).
Identification B and C (USP).
Reagents and reference materials: Each pharmacopeia will adapt the text to take account of local reference substances and spectra and reagent specifications.

Proposed changes from the current $U S P$ monograph include the following:

1. Definition-A more detailed definition that includes the predominant minerals in Talc is used.
2. Packaging and storage-No change.
3. Labeling-A requirement that the labeling indicate its suitability for oral or topical administration is added. A requirement that the labeling indicate the absence of asbestos is also added.
4. Identification-Tests for Infrared absorption and silicates are added.
5. Microbial limits-Requirements are added for topical and oral administration.
6. Acidity and alkalinity-This test is added to better characterize the article.
7. Loss on ignition-The ignition temperature and limit are increased to comply with EP standards.
8. Acid-soluble substances-This test is omitted. Tests for calcium, aluminum, and magnesium are added to strengthen the monograph.
9. Reaction and soluble substances-This test is renamed as Wa-ter-soluble substances.
10. Water-soluble substances-Previously named Reaction and soluble substances.
11. Water-soluble iron-This test is replaced with a quantitative procedure.
12. Limit of iron-This test replaces the previous Water-soluble iron test.
13. Arsenic, Heavy metals, and Lead-This test is replaced with tests for Limit of lead and Limit of aluminum.
14. Absence of asbestos-This section is added to ensure that the article does not contain asbestos. Talc derived from deposits that are known to contain associated asbestos is not suitable for pharmaceutical use.
15. Content of magnesium-This test is added to quantify the major components of Talc.
(EMC: J. Lane; AMB: D. Porter) RTS-41405-1

## Change to read:

## Fate

H-Tale is a native, hydreus magnesitm- silicate, sometimes containing a small propertion of aluminum silieate.

Packaging and-storage-Preserve in well closed containers.
Identification Mix abut 200 mg of anhydrous sodium carbenate with 2 g of anhydrous potassium carbonate, and melt in a plat inum crueible. To the melt add 100 me of the substance under test, and continte heating until fusion is complete. Cool, and transfer the fused mixture to a dish or beaker with the aid-of about 50 mL of hot water. Add hydrechloric acid to the liquid until efferveseence ceases, then add 10 mL more of the acid, and evaporate the mixture on a stem bath to dryness. Cool, add 20 mL of water, boil, and filter the mixture: an insoluble residue of siliea remains. Dissolve in the filtrate about 2 g of ammenimm chloride, and add 5 mL of 6 N ammonimm hydroxide. Filter, if neessary, and add dibasie sodium phesphate TS to the filtrate: a white, crystalline precipitate of magnesitm ammenitm phesphate separates.
Mierobial limits- $\langle 64\rangle$-The total-bacterial count does not exceed 500 per है.
Loss-on ignition- $\langle 733$ ) Weigh neeurately about 1 g and ignite at $1000^{\circ}$ to constant weight: it loses net more than $6.5 \%$ of its weight.
Acid-soluble-substanees-Digest 1.00 s with 20 mL of 3 N hy drochloric acid at $50^{\circ}$ for 15 mintutes, add water to restore the orig inal volume, mix, and filter. To 10 mL of the filtrate add 1 mL of 2 N sulfuric acid, evaporate to dryness, and ignite to constant weight: the weight of the residue does not exeed 10 mg ( $2.0 \%$ ).
Reaction and soluble substanees-Beil 10 g with 50 mL of water for 30 minutes, adding water from time to time omaintain apprex imately the original volume, and filter: the filtrate is neutral to lit mus paper. Evaperate one half of the filtrate to drymess, and dry at $105^{\circ}$ for 1 hour: the weight of the residue does not exceed 5 mg ( $0.1 \%$ ).
Water-soluble iren Slightly acidify with hydrechloric acid the remaining half of the filtrate obtained in the test for Reaction and soluble substanes, and add 1 mL of potassitm ferrecyanide TS: the liquid does not aequire a blue color.

## Arsenie, Heary metals, andHead-

Test solution Transfer 10.0 s a 250 mL flack, and add 50 mL of 0.5 N hydrechloric acid. Attach a reflux eondenser to the flask, heat on a steam bath for 30 minutes, cool, transfer the mixture to a beaker, and allow the undissolved material to settle. Deeant the st pernatant liquid through thick, strong, medium-speed flter paper into 100 mL volumetric flask, retrining as mueh as possible of the insoluble material in the beaker. Wash the slury and beaker with three 10 mL pertions of het water, deennting each washing threugh the filter into the flask. Finally, wash the fllter paper with 15 mL of het water, cool the filtrate to room temperature, dilute with water to volume, and mix. Use this Test solution for the fot fowing tests.

Arsenic, Method $I\langle z 14\rangle$-Use 10 mL of the Test soldtion in preparing the Test Preparation. The limit is 3 ppm.

Heary metals- $\langle 234\rangle$-Use 5 mL of the Test solution in preparing the Test Prepatation. The limit is $0.004 \%$.

Leat $\langle 254\rangle$ - 45 mL pertion of the Test solution contains net
mere than 5 4ig of lead $(0.001 \%)$.

## ■Talc

» Talc is a powdered, selected, natural, hydrated magnesium silicate. Pure talc has the formula $\mathrm{Mg}_{3} \mathrm{Si}_{4} \mathrm{O}_{10}(\mathrm{OH})_{2}$. It may contain variable amounts of associated minerals among which chlorites (hydrated aluminum and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate), and dolomite (calcium and magnesium carbonate) are predominant.

Packaging and storage-Preserve in well-closed containers.

Labeling-The label states, where applicable, that the substance is suitable for oral or topical administration. The certificate of analysis states the absence of asbestos. It also indicates which method specified under the test for Absence of asbestos was used for analysis.

## Identification-

A: The IR spectrum of a potassium bromide dispersion of it exhibits maxima at $3677 \pm 2 \mathrm{~cm}^{-1}$, at $1018 \pm 2 \mathrm{~cm}^{-1}$, and at $669 \pm 2 \mathrm{~cm}^{-1}$.

B: Mix about 200 mg of anhydrous sodium carbonate with 2 g of anhydrous potassium carbonate, and melt in a platinum crucible. To the melt add 100 mg of the substance under test, and continue heating until fusion is complete. Cool, and transfer the fused mixture to a dish or beaker with the aid of about 50 mL of hot water. Add hydrochloric acid to the liquid until effervescence ceases, then add 10 mL
more of the acid, and evaporate the mixture on a steam bath to dryness. Cool, add 20 mL of water, boil, and filter the mixture: [NOTE-Save the insoluble residue for use in Identification test C.] To 5 mL of the filtrate add 1 mL of 6 N ammonium hydroxide and 1 mL of ammonium chloride TS. Filter, if necessary, and add 1 mL of dibasic sodium phosphate TS to the filtrate: a white crystalline precipitate of magnesium ammonium phosphate is formed.

C: In a lead or platinum crucible and using a copper wire, mix about 100 mg of the insoluble residue as obtained in Identification test $B$ with about 10 mg of sodium fluoride and a few drops of sulfuric acid to give a thin slurry. Cover the crucible with a thin transparent plate of plastic under which a drop of water is suspended, and warm gently. Within a short time, a white ring is rapidly formed around the drop of water.

Microbial limits $\langle 61\rangle$-If intended for topical administration, the total aerobic microbial count does not exceed 100 cfu per g , and the total combined molds and yeasts count does not exceed 50 cfu per g . If intended for oral administration, the total aerobic microbial count does not exceed 1000 cfu per $g$, and the total combined molds and yeasts count does not exceed 100 cfu per $g$.

Acidity and alkalinity-Boil 2.5 g of talc with 50 mL of carbon dioxide-free water under reflux. Filter under vaccum. To 10 mL of the filtrate, add 0.1 mL of bromothymol blue TS. Not more than 0.4 mL of 0.01 N hydrochloric acid is required to change the color of the indicator. To 10 mL of the filtrate, add 0.1 mL of phenolphthalein TS: not more than 0.3 mL of 0.01 N sodium hydroxide is required to change the color of the indicator to pink.

Loss on ignition $\langle 733\rangle$-Weigh accurately about 1 g and ignite at $1075 \pm 25^{\circ}$ to constant weight: it loses not more than $7.0 \%$ of its weight.

Water-soluble substances-To 10.0 g add 50 mL of carbon dioxide-free water, heat to boiling, and boil under a reflux condenser for 30 minutes. Allow to cool, filter, and dilute to 50.0 mL with carbon dioxide-free water: the filtrate is neutral to litmus paper. Evaporate 25.0 mL of the filtrate to dryness, and dry at $105^{\circ}$ for 1 hour: the weight of the residue does not exceed $5 \mathrm{mg}(0.1 \%)$.

## Limit of iron-

Test stock solution-Weigh 10.0 g of Talc into a conical flask fitted with a reflux condenser, gradually add 50 mL of 0.5 N hydrochloric acid while stirring, and heat on a water bath for 30 minutes. Allow to cool. Transfer the mixture to a beaker, and allow the undissolved material to settle. Filter the supernatant into a $100-\mathrm{mL}$ volumetric flask, retaining as much as possible of the insoluble material in the beaker. Wash the residue and the beaker with three $10-\mathrm{mL}$ portions of hot water. Wash the filter with 15 mL of hot water, allow the filtrate to cool, and dilute with water to 100.0 mL .

Test solution- Transfer 2.5 mL of the Test stock solution to a $100-\mathrm{mL}$ volumetric flask, add 50.0 mL of 0.5 N hydrochloric acid, and dilute with water to volume.
Standard iron stock solution- Transfer 863.4 mg of ferric ammonium sulfate to a $100-\mathrm{mL}$ volumetric flask, dissolve in water, add 10 mL of 2 N sulfuric acid, and dilute with water to volume. Pipet 25 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, add 10 mL of 2 N sulfuric acid, dilute with water to volume, and mix. This solution contains the equivalent of $250 \mu \mathrm{~g}$ of iron per mL .

Standard iron solutions-Into four $100-\mathrm{mL}$ volumetric flasks, each containing 50.0 mL of 0.5 N hydrochloric acid, transfer respectively $2.0,2.5,3.0$, and 4.0 mL of the Standard iron stock solution, and dilute each flask with water to volume.

Procedure-Concomitantly determine the absorbance of the Test solution and the Standard iron solutions at the iron emission line of 248.3 nm with an atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) equipped with an iron hollow-cathode lamp and an air-acetylene flame. Make any correction using a deuterium lamp: not more than $0.25 \%$ of iron is found.

## Limit of lead-

Test solution-Use the Test stock solution, prepared as directed in the test for Limit of iron.

Lead standard stock solution-Dissolve 160 mg of lead nitrate in 100 mL water that contains 1 mL of nitric acid, and dilute with water to 1000 mL . Pipet 10 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of $10 \mu \mathrm{~g}$ of lead per mL .

Lead standard solutions-Into four identical $100-\mathrm{mL}$ volumetric flasks, each containing 50.0 mL of 0.5 N hydrochloric acid transfer respectively $5.0,7.5,10.0$, and 12.5 mL of Lead standard stock solution, and dilute with water to volume.

Procedure-Concomitantly determine the absorbance of the Test solution and the Standard lead solutions at the lead emission line of 217.0 nm with an atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) equipped with a lead hollow-cathode lamp and an air-acetylene flame: not more than $0.001 \%$ of lead is found.

## Limit of calcium-

Cesium chloride solution-Dissolve 2.53 g of cesium chloride in 100 mL of water, and mix.
Lanthanum chloride solution-To 5.9 g of lanthanum oxide slowly add 10 mL of hydrochloric acid, and heat to boiling. Allow to cool, and dilute with water to 100 mL .

Test stock solution-[Caution-Perchlorates mixed with heavy metals are known to be explosive. Take proper precautions while performing this procedure.] Weigh 500 mg of Talc in a $100-\mathrm{mL}$ polytetrafluoroethylene dish, add 5 mL of hydrochloric acid, 5 mL of lead-free nitric acid, and 5 mL of perchloric acid. Stir gently, then add 35 mL of hydrofluoric acid, and evaporate slowly on a hot plate to moist dryness (until about 0.5 mL remains). To the residue, add 5 mL of hydrochloric acid, cover with a watch glass, heat to boiling, and allow to cool. Rinse the watch glass and the dish with water, and transfer into a $50-\mathrm{mL}$ volumetric flask containing 5 mL of the Cesium chloride solution. Rinse the dish again with water, and dilute with water to volume.

Test solution-Transfer 5.0 mL of the Test stock solution to a $100-\mathrm{mL}$ volumetric flask, add 10.0 mL of hydrochloric acid and 10 mL of Lanthanum chloride solution, and dilute with water to volume.

Calcium standard stock solution-Dissolve 3.67 g of calcium chloride dihydrate in diluted hydrochloric acid, and dilute with the same solvent to 1000 mL . Immediately before use, pipet 10 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of $100 \mu \mathrm{~g}$ of calcium per mL .

Calcium standard solutions-Into four identical 100-mL volumetric flasks, each containing 10.0 mL of hydrochloric acid and 10 mL of Lanthanum chloride solution, transfer respectively $1.0,2.0,3.0$, and 4.0 mL of Calcium standard stock solution, and dilute each flask with water to volume.

Procedure-Concomitantly determine the absorbance of the Test solution and the Standard calcium solutions at the calcium emission line of 422.7 nm with an atomic absorption spectrophotometer (see Spectrophotometry and LightScattering $\langle 851\rangle$ ) equipped with a calcium hollow-cathode lamp and a nitrous oxide-acetylene flame: not more than $0.9 \%$ of calcium is found.

## Limit of aluminum-

Cesium chloride solution and Test stock solution-Proceed as directed in the test for Limit of calcium.

Test solution-Transfer 5.0 mL of the Test stock solution to a $100-\mathrm{mL}$ volumetric flask, add 10 mL of the Cesium chloride solution and 10.0 mL of hydrochloric acid, and dilute with water to volume.

Aluminum standard stock solution- Dissolve 8.947 g of aluminum chloride in water, and dilute with water to 1000 mL . Immediately before use, pipet 10 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of $100 \mu \mathrm{~g}$ of aluminum per mL.

Standard aluminum solutions-Into four identical 100mL volumetric flasks, each containing 10.0 mL of hydrochloric acid and 10 mL of Cesium chloride solution, transfer respectively $5.0,10.0,15.0$, and 20.0 mL of Aluminum standard stock solution, and dilute with water to volume.

Procedure-Concomitantly determine the absorbance of the Test solution and the Standard aluminum solutions at the aluminum emission line of 309.3 nm with an atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) equipped with an aluminum hol-low-cathode lamp and a nitrous oxide-acetylene flame: not more than $2.0 \%$ of aluminum is found.

Absence of asbestos- [NOTE-Suppliers of Talc may use one of the following methods to determine the absence of asbestos.] Proceed as directed for test $A$ or test $B$. If either test is positive, perform test $C$.

A: The IR absorption spectrum of a potassium bromide dispersion of it at the absorption band at $758 \pm 1 \mathrm{~cm}^{-1}$, using scale expansion, may indicate the presence of tremolite or of chlorite. If the absorption band remains after ignition of the substance at $850^{\circ}$ for at least 30 minutes, it indicates
the presence of the tremolite. In the range $600 \mathrm{~cm}^{-1}$ to 650 $\mathrm{cm}^{-1}$ using scale expansion, any absorption band or shoulder may indicate the presence of serpentines.

B: X-ray diffraction $\langle 941\rangle$ employing the following conditions: $\mathrm{Cu} \mathrm{K} \alpha$ monochromatic 40 kV radiation, 24 mA to 30 mA ; the incident slit is set at $1^{\circ}$; the detection slit is set at $0.2^{\circ}$; the goniometer speed is $1 / 10^{\circ} 2 \Theta$ per minute; the scanning range is $10^{\circ}$ to $13^{\circ} 2 \Theta$ and $24^{\circ}$ to $26^{\circ} 2 \Theta$; the sample is not oriented. Prepare a random sample, and place on the sample holder. Pack and smooth its surface with a polished glass microscope slide. Record the diffractograms: the presence of amphiboles is detected by a diffraction peak at $10.5 \pm 0.1^{\circ} 2 \Theta$, and the presence of serpentines is detected by diffraction peaks at $24.3 \pm 0.1^{\circ} 2 \Theta$ to $12.1 \pm 0.1^{\circ}$ $2 \Theta$.

C: The presence of asbestos (see Optical Microscopy $\langle 776\rangle$ ) is shown if there is a range of length to width ratios of $20: 1$ to $100: 1$, or higher for fibers longer than $5 \mu \mathrm{~m}$; if there is a capability of splitting into very thin fibrils; and if there are two or more of the following four criteria: (1) parallel fibers occurring in bundles, (2) fiber bundles displaying frayed ends, (3) fibers in the form of thin needles, or (4) matted masses of individual fibers and/or fibers showing curvature.

## Content of magnesium-

Lanthanum chloride solution and Test stock solution-
Prepare as directed in the test for Limit of calcium.
Test solution-Dilute 0.5 mL of Test stock solution with water to 100.0 mL . Transfer 4.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, add 10.0 mL of hydrochloric acid and 10 mL of Lanthanum chloride solution, and dilute with water to volume.

Magnesium standard stock solution-Dissolve 8.365 g of magnesium chloride in diluted hydrochloric acid, and dilute with the same solvent to 1000 mL . Pipet 5 mL of this solution into a $500-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. This solution contains the equivalent of $10 \mu \mathrm{~g}$ of magnesium per mL .

Standard magnesium solutions-Into four identical 100mL volumetric flasks, each containing 10.0 mL of hydrochloric acid and 10 mL of Lanthanum chloride solution, transfer respectively $2.5,3.0,4.0$, and 5.0 mL of Magnesium standard stock solution, and dilute with water to volume.
Procedure-Concomitantly determine the absorbance of the Test solution and the Standard magnesium solutions at the magnesium emission line of 285.2 nm with an atomic absorption spectrophotometer (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) equipped with a magnesium hol-low-cathode lamp and an air-acetylene flame: between $17.0 \%$ to $19.5 \%$ of magnesium is found. $\quad$ 2S (USP28)

## MONOGRAPHS (NF)

## Briefing

Corn Starch, page 1457 of $P F$ 30(4) [July-Aug. 2004]; Potato Starch, page 1460 of $P F$ 30(4) [July-Aug. 2004]; Wheat Starch, page 1462 of $P F$ 30(4) [July-Aug. 2004]. In the Packaging and storage section it is proposed to add that no storage requirements are specified. The revision proposed in $P F 30(2)$, to change the name of the section from Packaging and storage to Packaging, was canceled.
(EMC: J. Lane; PSD: C. Okeke) RTS-41285-3

## Add the following:

## ©Corn Starch

» Corn Starch consists of the starch granules separated from the mature grain of corn [Zea mays Linné (Fam. Gramineae)].

## Change to read:

Packaging and storage-Preserve in well-closed containers. -No storage requirements specified. $\mathbf{L S S}_{\text {(NF23) }}$

Labeling-Where Corn Starch is intended for use in preparing Absorbable Dusting Powder, it is so labeled and the label states that it must be subjected to further processing during the preparation of Absorbable Dusting Powder.

## Change to read:

## Identification-

A: Under a microscope, using not less than $20 \times$ magnification and using a mixture of glycerin and water $(1: 1)$ as a mounting agent, it appears as either angular polyhedral granules of irregular sizes with diameters ranging from about $2 \mu \mathrm{~m}$ to about $23 \mu \mathrm{~m}$ or as rounded or spheroidal granules of irregular sizes with diameters ranging from about $25 \mu \mathrm{~m}$ to about $35 \mu \mathrm{~m}$. The central hilum consists of a distinct cavity or a two- to five-rayed cleft, and there are no concentric striations. Between crossed nicol prisms, the starch granules show a distinct black cross intersecting at the hilum.

B: Suspend 1 g of it in 50 mL of water, boil for 1 min ute, and cool: a thin, cloudy mucilage is formed.

C: To 10 mL of the mereilage obtained in Identification test $B$, add 0.04 mL of iodine and potassium iodide TS: an erange red to datk blue color is prodtueed, which disappears en heating.

C: To 1 mL of the mucilage obtained in Identification test $B$, add 0.05 mL of tine - iodine and potassium iodide TS 2: $\quad$ 1S (NF23) an orange-red to dark blue color is produced, which disappears on heating.

Iodinesolution Dissolve 12.7gofiodine and 20gofpe-tassitmmiodide-in water, and diltte-with water to 1000.0 mL . Fe 10.0 mL of this seltation, ade 0.6 of of petassitm iodide, and dilute with water to 100.0 mL . Prepare immediately be fereuser ■ils (NF23)

Microbial limits $\langle 61\rangle$ —The total aerobic microbial count does not exceed 1000 cfu per g , the total combined molds and yeasts count does not exceed 100 cfu per g , and it meets the requirements of the test for the absence of Escherichia coli. Where it is intended for use in preparing Absorbable Dusting Powder, it also meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa.
$\mathbf{p H}\langle\mathbf{7 9 1}\rangle$ —Prepare a slurry by weighing 5.0 g of Corn Starch, transferring to a suitable nonmetallic container, and adding 25.0 mL of freshly boiled and cooled water. Agitate continuously at a moderate rate for 1 minute. Stop the agitation, and allow to stand for 15 minutes. Determine the pH to the nearest 0.1 unit: the pH , determined potentiometrically, is between 4.0 and 7.0.

Loss on drying $\langle 731\rangle$ —Dry about 1 g , accurately weighed, at $130^{\circ}$ for 90 minutes: it loses not more than $15.0 \%$ of its weight.

## Change to read:

Residue on ignition $\langle 281\rangle$ : not more than $0.6 \%$, determined on a $1.0-\mathrm{g}$ test specimen. Ignition temperature $600 \pm 50^{\circ}-\square_{\text {■1S (NF23) }}$

Limit of iron-Shake 1.5 g of Corn Starch with 15 mL of 2 N hydrochloric acid, and filter. Transfer 10 mL of the filtrate to a test tube, add 2 mL of citric acid solution (2 in 10), 0.1 mL of thioglycolic acid, and mix. Add 10 N ammonium hydroxide until the solution is distinctly alkaline to litmus, dilute with water to 20 mL , and mix (Test Solution). Prepare a Standard Iron Solution containing the equivalent of $10 \mu \mathrm{~g}$ of iron per mL as directed under Iron $\langle 241\rangle$. Immediately before use, quantitatively dilute an accurately measured volume of this solution with water to obtain a Diluted Standard Iron Solution containing the equivalent of $1 \mu \mathrm{~g}$ of iron per mL . Prepare the Standard Solution by transferring 10 mL of the Diluted Standard Iron Solution to a test tube and proceeding in the same manner as directed for the preparation of the Test Solution, beginning with "add 2 mL of citric acid solution (2 in 10)." After 5 minutes, any pink color in the Test Solution is not more intense than that in the Standard Solution, corresponding to a limit of $10 \mu \mathrm{~g}$ of iron per g .

Limit of oxidizing substances-Transfer 4.0 g to a glassstoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is
equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate is required ( $20 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ).

Limit of sulfur dioxide-Not more than $50 \mu \mathrm{~g}$ per g . REAGENTS-

Carbon dioxide-Use carbon dioxide, with a flow regulator that will maintain a flow of $100 \pm 10 \mathrm{~mL}$ per minute.
Bromophenol blue indicator solution-Dissolve 100 mg of bromophenol blue in 100 mL of dilute alcohol (1 in 5), and filter if necessary.

Hydrogen peroxide solution-Dilute $30 \%$ hydrogen peroxide with water to obtain a $3 \%$ solution. Just before use, add 3 drops of Bromophenol blue indicator solution, and neutralize to a violet-blue endpoint with 0.01 N sodium hydroxide. Do not exceed the endpoint.
APPARATUS-In this test, the sulfur dioxide is released from the test specimen in a boiling acid medium and is removed by a stream of carbon dioxide. The separated gas is collected in a dilute hydrogen peroxide solution where the sulfur dioxide is oxidized to sulfuric acid and titrated with standard alkali. The apparatus consists essentially of a 500mL three-neck, round-bottom boiling flask, a separatory funnel having a capacity of 100 mL or greater, a gas inlet tube of sufficient length to permit introduction of the carbon dioxide within 2.5 cm of the bottom of the boiling flask, a reflux condenser having a jacket length of 200 mm , and a delivery tube connecting the upper end of the reflux condenser to the bottom of a receiving test tube. Apply a thin film of stopcock grease to the sealing surfaces of all of the joints except the joint between the separatory funnel and the boiling flask, and clamp the joints to ensure tightness.

PROCEDURE-Add 150 mL of water to the boiling flask. Close the stopcock of the separatory funnel, and begin the flow of carbon dioxide at a rate of $100 \pm 5 \mathrm{~mL}$ per minute through the Apparatus. Start the condenser coolant flow.

Add 10 mL of Hydrogen peroxide solution to a receiving test tube. After 15 minutes, without interrupting the flow of carbon dioxide, remove the separatory funnel from the boiling flask, and transfer 25.0 g of test specimen into the boiling flask with the aid of 100 mL of water. Apply stopcock grease to the outer joint of the separatory funnel, and replace the separatory funnel in the boiling flask. Close the stopcock of the separatory funnel, and add 80 mL of 2 N hydrochloric acid to the separatory funnel. Open the stopcock of the separatory funnel to permit the hydrochloric acid solution to flow into the boiling flask, guarding against the escape of sulfur dioxide into the separatory funnel by closing the stopcock before the last few mL of hydrochloric acid drain out. Position the Apparratus in a water bath, and Boil the mixture for 1 hour. Remove the receiving test tube, and transfer its contents to a $200-\mathrm{mL}$ wide-necked, conical flask. Rinse the receiving test tube with a small portion of water, add the rinsing to the $200-\mathrm{mL}$ conical flask, and mix. Heat on a water bath for 15 minutes, and allow to cool. Add 0.1 mL of Bromophenol blue indicator solution, and titrate the contents with 0.1 N sodium hydroxide VS until the color changes from yellow to violet-blue, with the color change lasting for at least 20 seconds. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Calculate the content, in $\mu \mathrm{g}$ per g , of sulfur dioxide in the test specimen taken by the formula:

$$
1000(32.03) V N / W,
$$

in which 32.03 is the milliequivalent weight of sulfur dioxide; $V$ is the volume, in mL , of titrant consumed; $N$ is the normality of the titrant; and $W$ is the weight, in g , of test specimen taken.

Organie volatile imptrities, Method $H\langle 467$ ): meets the requirements. $\Delta$ NF23

## BRIEFING

Potato Starch, page 1460 of PF 30(4) [July-Aug. 2004]-See briefing under Corn Starch.
(EMC: J. Lane; PSD: C. Okeke) RTS-41285-2

## Add the following:

## © Potato Starch

» Potato Starch is obtained from the tuber of So-

## lanum tuberosum $L$.

## Change to read:

Packaging and storage-Preserve in well-closed containers. ${ }^{-N o}$ storage requirements specified. ${ }^{2 S}$ (NF23)

## Change to read:

## Identification-

A: Under a microscope, using a mixture of glycerin and water ( $1: 1$ ) as a mounting agent, it presents granules, either irregularly shaped, ovoid, or pear-shaped, usually $30 \mu \mathrm{~m}$ to $100 \mu \mathrm{~m}$ in size, but occasionally exceeding $100 \mu \mathrm{~m}$, or rounded, $10 \mu \mathrm{~m}$ to $35 \mu \mathrm{~m}$ in size. There are occasional compound granules having two or four components. The ovoid and pear-shaped granules have an eccentric hilum and the rounded granules acentric or slightly eccentric hilum. All granules show clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum.

B: Suspend 1 g of it in 50 mL of water, boil for $1 \mathrm{mi}-$ nute, and cool: a thin, cloudy mucilage is formed.

C: To 1 mL of the mucilage obtained in Identification test $B$, add 0.05 mL of iodine and potassium iodide TS
 duced, which disappears on heating.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed 1000 cfu per g , the total combined molds and yeasts count does not exceed 100 cfu per g , and it meets the requirements of the test for the absence of Escherichia coli.
$\mathbf{p H}\langle 791\rangle$ —Prepare a slurry by weighing 5.0 g of Potato Starch, transferring to a suitable nonmetallic container, and adding 25.0 mL of freshly boiled and cooled water. Agitate continuously at a moderate rate for 1 minute. Stop the agitation, and allow to stand for 15 minutes. Determine the pH to the nearest 0.1 unit: the pH , determined potentiometrically, is between 5.0 and 8.0.

Loss on drying $\langle 731\rangle$-Dry about 1 g , accurately weighed, at $130^{\circ}$ for 90 minutes: it loses not more than $20.0 \%$ of its weight.

## Change to read:

Residue on ignition $\langle 281\rangle$ : not more than $0.6 \%$, determined on a $1.0-\mathrm{g}$ test specimen. Ignition-temperature $600 \pm 50^{\circ}$. "■ $^{1 S}$ (NF23)

Limit of iron—Shake 1.5 g of Potato Starch with 15 mL of 2 N hydrochloric acid, and filter. Transfer 10 mL of the filtrate to a test tube, add 2 mL of citric acid solution (2 in 10), 0.1 mL of thioglycolic acid, and mix. Add 10 N ammonium hydroxide until the solution is distinctly alkaline to litmus, dilute with water to 20 mL , and mix (Test Solution). Prepare a Standard Iron Solution containing the equivalent of $10 \mu \mathrm{~g}$ of iron per mL as directed under Iron $\langle 241\rangle$. Immediately before use, quantitatively dilute an accurately measured volume of this solution with water to obtain a Diluted Standard Iron Solution containing the equivalent of $1 \mu \mathrm{~g}$ of iron per
mL . Prepare the Standard Solution by transferring 10 mL of the Diluted Standard Iron Solution to a test tube and proceeding in the same manner as directed for the preparation of the Test Solution, beginning with "add 2 mL of citric acid solution (2 in 10)." After 5 minutes, any pink color in the Test Solution is not more intense than that in the Standard Solution, corresponding to a limit of $10 \mu \mathrm{~g}$ of iron per g .

Limit of oxidizing substances-Transfer 4.0 g to a glassstoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate is required ( $20 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ).

Limit of sulfur dioxide: not more than $50 \mu \mathrm{~g}$ per g .

## REAGENTS-

Carbon dioxide - Use carbon dioxide, with a flow regulator that will maintain a flow of $100 \pm 10 \mathrm{~mL}$ per minute.

Bromophenol blue indicator solution-Dissolve 100 mg of bromophenol blue in 100 mL of dilute alcohol (1 in 5), and filter if necessary.

Hydrogen peroxide solution-Dilute 30\% hydrogen peroxide with water to obtain a $3 \%$ solution. Just before use, add 3 drops of Bromophenol blue indicator solution, and neutralize to a violet-blue endpoint with 0.01 N sodium hydroxide. Do not exceed the endpoint.

APPARATUS-In this test, the sulfur dioxide is released from the test specimen in a boiling acid medium and is removed by a stream of carbon dioxide. The separated gas is collected in a dilute hydrogen peroxide solution where the sulfur dioxide is oxidized to sulfuric acid and titrated with standard alkali. The apparatus consists essentially of a 500mL three-neck, round-bottom boiling flask, a separatory funnel having a capacity of 100 mL or greater, a gas inlet tube of sufficient length to permit introduction of the carbon dioxide within 2.5 cm of the bottom of the boiling flask, a reflux condenser having a jacket length of 200 mm , and a delivery tube connecting the upper end of the reflux condenser to the bottom of a receiving test tube. Apply a thin film of stopcock grease to the sealing surfaces of all of the joints, except the joint between the separatory funnel and the boiling flask, and clamp the joints to ensure tightness. PROCEDURE-Add 150 mL of water to the boiling flask. Close the stopcock of the separatory funnel, and begin the flow of carbon dioxide at a rate of $100 \pm 5 \mathrm{~mL}$ per minute through the Apparatus. Start the condenser coolant flow. Add 10 mL of Hydrogen peroxide solution to a receiving test tube. After 15 minutes, without interrupting the flow of carbon dioxide, remove the separatory funnel from the boiling flask, and transfer 25.0 g of test specimen into the boiling flask with the aid of 100 mL of water. Apply stopcock grease to the outer joint of the separatory funnel, and replace the separatory funnel in the boiling flask. Close the stopcock of the separatory funnel, and add 80 mL of 2 N
hydrochloric acid to the separatory funnel. Open the stopcock of the separatory funnel to permit the hydrochloric acid solution to flow into the boiling flask, guarding against the escape of sulfur dioxide into the separatory funnel by closing the stopcock before the last few mL of hydrochloric acid drain out. Pesition the Apparatus in a water bath, and Boil the mixture for 1 hour. Remove the receiving test tube, and transfer its contents to a $200-\mathrm{mL}$ wide-necked, conical flask. Rinse the receiving test tube with a small portion of water, add the rinsing to the $200-\mathrm{mL}$ conical flask, and mix. Heat on a water bath for 15 minutes, and allow to cool. Add 0.1 mL of Bromophenol blue indicator solution, and titrate the contents with 0.1 N sodium hydroxide VS until the color changes from yellow to violet-blue, with the color change lasting for at least 20 seconds. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Calculate the content, in $\mu \mathrm{g}$ per g , of sulfur dioxide in the test specimen taken by the formula:

$$
1000(32.03) \mathrm{VN} / \mathrm{W},
$$

in which 32.03 is the milliequivalent weight of sulfur dioxide; $V$ is the volume, in mL , of titrant consumed; $N$ is the normality of the titrant; and $W$ is the weight, in g , of test specimen taken.

Organic volatile impurities, Method $\Psi\langle(467)$ : meets the requirements._ANF23

## Briefing

Wheat Starch, page 1462 of $P F$ 30(4) [July-Aug. 2004]—See briefing under Corn Starch.
(EMC: J. Lane; PSD: C. Okeke) RTS-41285-1

## Add the following:

## $\Delta$ Wheat Starch

» Wheat Starch is obtained from the caryopsis of Triticum aestivum L. (T. vulgare Vill.).

## Change to read:

Packaging and storage -Preserve in well-closed containers. - No storage requirements specified.■2S (NF23)

## Change to read:

## Identification-

A: Under a microscope, using a mixture of glycerin and water $(1: 1)$ as a mounting agent, it presents large and small granules, and very rarely, intermediate sizes. The large granules, usually $10 \mu \mathrm{~m}$ to $60 \mu \mathrm{~m}$ in diameter, are discoid or, more rarely, reniform when seen face-on. The central hilum and striations are invisible or barely visible and the granules sometimes show cracks on the edges. Seen in profile, the granules are elliptical and fusiform and the hilum appears as a slit along the main axis. The small granules, rounded or polyhedral, are $2 \mu \mathrm{~m}$ to $10 \mu \mathrm{~m}$ in diameter. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum.

B: Suspend 1 g of it in 50 mL of water, boil for $1 \mathrm{mi}-$ nute, and cool: a thin, cloudy mucilage is formed.

C: Te 1 mL of the murilage obtained in Itdentification test $B$, add 0.05 mL of iodine and potassium-iodide TS: a dark blue celor is produced, which disappears on heating.

C: To 1 mL of the mucilage obtained in Identification test $B$, add 0.05 mL of dine solution: ■iodine and potassium iodide TS 2: $\mathbf{I S ~ ( N F 2 3 ) ~}$ an orange-red to dark blue color is produced, which disappears on heating.

Iodine solution Dissolve 12.7g of iodine and 20gof po assitum iodide in water, and dillte with water to 1000.0 mL . Fe 10.0 mL of this selution, add 0.6 g of petassitum-iodide, and dilute with water to 100.0 mL . Prepare immediately before use.mis (NF23)

Microbial limits $\langle 61\rangle$ —The total aerobic microbial count does not exceed 1000 cfu per g , the total combined molds and yeasts count does not exceed 100 cfu per $g$, and it meets the requirements of the test for the absence of Escherichia coli.
$\mathbf{p H}\langle 791\rangle$ —Prepare a slurry by weighing 5.0 g of Wheat Starch, transfer to a suitable nonmetallic container, and add 25.0 mL of freshly boiled and cooled water. Agitate continuously at a moderate rate for 1 minute. Stop the agitation, and allow to stand for 15 minutes. Determine the pH to the nearest 0.1 unit: the pH , determined potentiometrically, is between 4.5 and 7.0.

Loss on drying $\langle 731\rangle$-Dry about 1 g , accurately weighed, at $130^{\circ}$ for 90 minutes: it loses not more than $15.0 \%$ of its weight.

## Change to read:

Residue on ignition $\langle 281\rangle$ : not more than $0.6 \%$, determined on a $1.0-\mathrm{g}$ test specimen. Ignition-temperature $600 \pm 50^{\circ} \cdot \square_{1 S}$ (NF23)

Total protein: not more than $0.3 \%$ of total protein (corresponding to $0.048 \%$ of nitrogen $\left[\mathrm{N}_{2}\right]$, conversion factor: 6.25).

Procedure-Accurately weigh 6.0 g of test substance containing about 2 mg of nitrogen, transfer to a combustion flask, and add 4 g of a powdered mixture of 100 g of potassium sulfate, 5 g of cupric sulfate, and 2.5 g of selenium, and three glass beads. Wash any adhering particles from the neck into the flask with 5 mL of sulfuric acid, allowing it to run down the sides of the flask, and mix the contents by rotation. Close the mouth of the flask loosely (e.g., by means of a glass bulb with a short stem) to avoid excessive loss of sulfuric acid. Heat gradually at first, then increase the temperature until there is vigorous boiling with condensation of sulfuric acid in the neck of the flask. [NOTE--Precautions should be taken to prevent the upper part of the flask from becoming overheated.] Continue the heating for 30 minutes, unless otherwise directed. Cool, dissolve the solid material by cautiously adding to the mixture 25 mL of water, cool again, and place in a steam distillation apparatus. Add 30 mL of sodium hydroxide solution (42 in 100), and distill immediately by passing steam through the mixture. Collect about 40 mL of distillate in 20.0 mL of 0.01 N hydrochloric acid and enough water to cover the tip of the condenser. Towards the end of the distillation, lower the receiver so that the tip of the condenser is above the surface of the acid. [NOTE-Take precautions to prevent any water on the outer surface of the condenser from reaching the contents of the receiver.] Titrate the distillate with 0.01 N sodium hydroxide, using methyl purple TS as indicator ( $n_{1} \mathrm{~mL}$ of 0.01 N sodium hydroxide).

Repeat the test using about 50 mg of glucose in place of the substance to be examined ( $n_{2} \mathrm{~mL}$ of 0.01 N sodium hydroxide).

$$
\text { Content of nitrogen }=\left[0.01401\left(n_{2}-n_{1}\right)\right] / m,
$$

Limit of iron-Shake 1.5 g of Wheat Starch with 15 mL of 2 N hydrochloric acid, and filter. Transfer 10 mL of the filtrate to a test tube, add 2 mL of citric acid solution (2 in 10), 0.1 mL of thioglycolic acid, and mix. Add 10 N ammonium hydroxide until the solution is distinctly alkaline to litmus, dilute with water to 20 mL , and mix (Test Solution). Prepare a Standard Iron Solution containing the equivalent of $10 \mu \mathrm{~g}$ of iron per mL as directed under Iron $\langle 241\rangle$. Immediately before use, quantitatively dilute an accurately measured volume of this solution with water to obtain a Diluted Standard Iron Solution containing the equivalent of $1 \mu \mathrm{~g}$ of iron per mL . Prepare the Standard Solution by transferring 10 mL of the Diluted Standard Iron Solution to a test tube and proceeding in the same manner as directed for the preparation of the Test Solution, beginning with "add 2 mL of citric acid solution (2 in 10)." After 5 minutes, any pink color in the Test Solution is not more intense than that in the Standard Solution, corresponding to a limit of $10 \mu \mathrm{~g}$ of iron per g .

Limit of oxidizing substances-Transfer 4.0 g to a glassstoppered, $125-\mathrm{mL}$ conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, $50-\mathrm{mL}$ centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, $125-\mathrm{mL}$ conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to $34 \mu \mathrm{~g}$ of oxidant, calculated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate is required ( $20 \mu \mathrm{~g}$ per g , calculated as $\mathrm{H}_{2} \mathrm{O}_{2}$ ).
where $m$ is the amount of test substance weighed, in g .

Limit of sulfur dioxide: not more than $50 \mu \mathrm{~g}$ per g . REAGENTS-

Carbon dioxide-Use carbon dioxide, with a flow regulator that will maintain a flow of $100 \pm 10 \mathrm{~mL}$ per minute.

Bromophenol blue indicator solution-Dissolve 100 mg of bromophenol blue in 100 mL of dilute alcohol (1 in 5), and filter if necessary.

Hydrogen peroxide solution-Dilute $30 \%$ hydrogen peroxide with water to obtain a $3 \%$ solution. Just before use, add 3 drops of Bromophenol blue indicator solution, and neutralize to a violet-blue endpoint with 0.01 N sodium hydroxide. Do not exceed the endpoint.
aPPARATUS-In this test, the sulfur dioxide is released from the test specimen in a boiling acid medium and is removed by a stream of carbon dioxide. The separated gas is collected in a dilute hydrogen peroxide solution where the sulfur dioxide is oxidized to sulfuric acid and titrated with standard alkali. The apparatus consists essentially of a 500mL three-neck, round-bottom boiling flask, a separatory funnel having a capacity of 100 mL or greater, a gas inlet tube of sufficient length to permit introduction of the carbon dioxide within 2.5 cm of the bottom of the boiling flask, a reflux condenser having a jacket length of 200 mm , and a delivery tube connecting the upper end of the reflux condenser to the bottom of a receiving test tube. Apply a thin film of stopcock grease to the sealing surfaces of all of the joints, except the joint between the separatory funnel and the boiling flask, and clamp the joints to ensure tightness.

PROCEDURE-Add 150 mL of water to the boiling flask.
Close the stopcock of the separatory funnel, and begin the flow of carbon dioxide at a rate of $100 \pm 5 \mathrm{~mL}$ per minute through the Apparatus. Start the condenser coolant flow. Add 10 mL of Hydrogen peroxide solution to a receiving test tube. After 15 minutes, without interrupting the flow
of carbon dioxide, remove the separatory funnel from the boiling flask, and transfer 25.0 g of test specimen into the boiling flask with the aid of 100 mL of water. Apply stopcock grease to the outer joint of the separatory funnel, and replace the separatory funnel in the boiling flask. Close the stopcock of the separatory funnel, and add 80 mL of 2 N hydrochloric acid to the separatory funnel. Open the stopcock of the separatory funnel to permit the hydrochloric acid solution to flow into the boiling flask, guarding against the escape of sulfur dioxide into the separatory funnel by closing the stopcock before the last few mL of hydrochloric acid drain out. Position the Apparatus in a water bath, and Boil the mixture for 1 hour. Remove the receiving test tube, and transfer its contents to a $200-\mathrm{mL}$ wide-necked, conical flask. Rinse the receiving test tube with a small portion of water, add the rinsing to the $200-\mathrm{mL}$ conical flask, and mix. Heat on a water bath for 15 minutes, and allow to cool. Add 0.1 mL of Bromophenol blue indicator solution, and titrate the contents with 0.1 N sodium hydroxide VS until the color changes from yellow to violet-blue, with the color change lasting for at least 20 seconds. Perform a blank determination, and make any necessary correction (see Titrimetry $\langle 541\rangle$ ). Calculate the content, in $\mu \mathrm{g}$ per g , of sulfur dioxide
in the test specimen taken by the formula:

$$
1000(32.03) \mathrm{VN} / W,
$$

in which 32.03 is the milliequivalent weight of sulfur dioxide; $V$ is the volume, in mL , of titrant consumed; $N$ is the normality of the titrant; and $W$ is the weight, in g , of test specimen taken.

[^270]
## PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the Staff Directory to find the contact information).

Briefings Each Preview is preceded by a Briefing in the following format:

## Briefing

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being used, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see How To Use PF), the name of the scientific staff liaison who handled this item, and the USP tracking correspondence number, as shown in the example below:
(PA5: K. Russo) RTS-55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.

## STIMULI TO THE REVISION PROCESS

This section may contain the following:

- reports or statements of authoritative committees
- original research reports
- evaluations of new and existing pharmacopeial methods
- commentaries
- articles relevant to compendial issues

These items are published to stimulate discussion and continual review of Pharmacopeial standards. Generally, if an Expert Committee publishes an article on which they are specifically seeking comment, this will be clearly stated in the article. Readers may submit comments on issues raised in this section, but comment is not as critical as that for the In-Process Revision and Pharmacopeial Previews sections. Readers interested in submitting comments should see Instructions to Authors.
STIMULI TO THE REVISION PROCESS ..... 1873
Instructions to Authors ..... 1875
Changes to USP General Chapter Heavy Metals $\langle 231\rangle$, John T. Geary ..... 1876
Development of a New Official Compendium, Separate from USP-NF, for Articles Not Legally Marketed in the U.S., Council of Experts Executive Committee, Ad Hoc Council of Experts Committee, and USP Staff ..... 1877
Microbial Identification in the Pharmaceutical Industry, Scott V.W. Sutton and Anthony M. Cundell ..... 1884
Proposal and Qualification of a Harmonized Anti-Factor 11a Assay for Unfractionated Heparin PotencyDetermination, Patrick N. Shaklee, Elaine Gray, Peter Rigsby, Emmanuelle Charton, Toine Overbeeke,G.W.K.van Dedem, Erwin Coyne, Mette Schrøder, and Kristian B. Johansen1895
Sterilizing Filtrations with Microporous Membranes, Maik W. Jornitz and Theodore H. Meltzer ..... 1903
The USP Perspective to Minimize the Potential Risk of TSE Infectivity in Bovine-Derived Articles Used in the Manufacture of Medical Products, Ian DeVeau, Roger Dabbah, and Scott Sutton ..... 1911

## Instructions to Authors

Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to $U S P-N F$ revision will be considered for publication in the Pharmacopeial Forum under the section Stimuli to the Revision Process. Manuscripts are received with the explicit understanding that they have not been published previously and that they are not simultaneously under consideration by any other publication.

All manuscripts are subject to review by USP headquarters staff, Committee members, or qualified outside referees, and if accepted for publication will be subject to editing by USP staff. Accepted manuscripts become the property of the USP Convention, Inc., (USPC) and may not be published elsewhere without written permission from the USPC. Authors are also responsible for obtaining permission for reprinting any illustrations that have been published elsewhere.

Abstract-Include an abstract of not more than 250 words stating the purpose and the results or conclusions of the article.
References-Consult a current copy of the Pharmacopeial Forum and the ACS Style Guide for assistance with reference style.

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Contact Person-When submitting a manuscript, designate one author of the article as correspondent and include that author's full address, telephone number, fax number, and e-mail address.

Submission Instructions-Manuscripts must be submitted both as an electronic file and as a printed copy of the electronic file. Submit the text in Microsoff ${ }^{\mathbb{B}}$ Word or another current word-processing application. The preferred format for graphics submitted electronically is tagged image file format (TIFF). Graphics that cannot be submitted electronically must be cameraready, of easily reproducible quality and size, and clearly labeled. Photocopies are not acceptable. Manuscripts submitted for publication should be addressed to:

Pharmacopeial Forum
Executive Secretariat, USP
12601 Twinbrook Pkwy.
Rockville, MD 20852

# Changes to USP General Chapter Heavy Metals $\langle 231\rangle$ 

John T. Geary ${ }^{*}$


#### Abstract

USP General Chapter Heavy Metals $\langle 231\rangle$ has been the subject of discussion within the industry for several years, and its deficiencies were discussed during a USP Open Conference that was convened in June, 2003 in Philadelphia, PA. This Stimuli article reviews a few of the problems with USP $\langle 231\rangle$ and outlines the changes USP is considering for a future proposal.


USP General Chapter Heavy Metals $\langle 231\rangle$ has been the subject of discussion within the industry for several years. Deficiencies of the method were recently the topic of the USP Open Conference on Analytical Methods and General USP Topics that was held in June 2003 in Philadelphia. The Basel Working Group on the Determination of Metal Traces presented a thorough discussion of the problems encountered using $\langle 231\rangle$ for heavy metals screening. To summarize their paper, "USP $\langle 231\rangle$ was never intended to be a universal test for heavy metals as it is currently applied."

Methods I, II, and III suffer to some degree from the lack of specificity using colorimetric detection. Not all heavy metals are detected by the procedure. The method is capable only of detecting metals precipitated by sulfide and those that produce a black or brown precipitate. The use of a $600{ }^{\circ} \mathrm{C}$ ignition temperature causes loss of analyte, especially mercury, and has been confirmed as a cause of false negative results.

USP is proposing the following changes to Heavy Metals $\langle 231\rangle$ : The Method II preparation using high-temperature ignition will be withdrawn. Methods $I$ and $I I I$ will be continued. Colorimetric detection for these preparations will be continued, but an alternative method of detection, Inductively Coupled Plasma/Atomic Emission Spectroscopy (ICP/AES), will be approved for both Method I and Method III, which will permit the user to choose either method of detection. USP intends to seek additional alternatives to colorimetric detection, such as x-ray fluorescence, atomic absorption, and electroanalytical methods. These alternatives will be proposed when sufficient data are available to attest to their effectiveness.

[^271]
# Development of a New Official Compendium, Separate from USP-NF, for Articles Not Legally Marketed in the U.S.* 

Council of Experts Executive Committee, ${ }^{\dagger}$ Ad Hoc Council of Experts Committee, $\ddagger$ and USP Staff ${ }^{\ddagger}$


#### Abstract

At a July 2003 meeting, the Council of Experts Executive Committee voted to include monographs in the United States Pharmacopeia and National Formulary for articles that are not legally marketed in the United States but are available in international commerce. Subsequently, the USP Board of Trustees formed a Task Force to monitor progression of this decision and related activities. The Board Task Force requested that USP develop a Stimuli article to solicit input related to how the decision of the Council of Experts Executive Committee might be implemented. This article (1) proposes that the clearest and most definitive way to effect the Council of Experts decision would be a separate official compendium, (2) provides additional information, and (3) requests comments.


## INTRODUCTION

Delegates representing regional medical societies from four regions of the country met in Washington, DC, in January 1820 to determine the contents of the first Pharmacopoeia of the United States of America (USP), which presented the best medicines, named them, and provided recipes for their preparation by practitioners of the day. Over time, with the rise in modern pharmaceutical manufacturing, the task of making a drug has shifted from practitioners to pharmaceutical manufacturers. A residuum of the original approach remains with practitioners who compound a medicine, using at times a $U S P$ preparation monograph pursuant to a physician's prescription. Today, only a relatively small fraction of prescriptions in the United States are compounded.

USP was incorporated in 1900 as the United States Pharmacopoeial Convention under federal law relating to the District of Columbia. It is now classified as a 501 (c)(3) nonprofit scientific corporation working in the public interest. Convention delegates meet at 5 -year intervals to elect the officers of the Convention, the Board of Trustees, and the Council of Experts, and to consider resolutions. With staff support, the Council of Experts creates content for two compendia, the original $U S P$ and, following its purchase in 1975, the National Formulary ( $N F$ ). $U S P$ and $N F$ are separate compendia but are published annually in a combined text with two Supplements. The USP is published as a continuing revision of the 1820 text, but each new $N F$ is a new edition. The current USP 27-NF 22 became official on Jan-

[^272]uary 1,2004 , and contains monographs for prescription and over-the-counter drugs, biologics, and allied therapeutic products (including some devices). In the current revision of $U S P$, a separate section is devoted to dietary supplements. Excipient monographs appear in $N F$. With some exceptions, all articles in $U S P-N F$ are legally marketed in the U.S. An example of such an exception is a dosage form containing four drugs to treat tuberculosis. Also, $U S P-N F$ contains ingredient and product monographs for many articles that have not undergone a regulatory approval in the U.S. These include drug products marketed in the U.S. prior to 1938, drug products marketed in the U.S. after 1938 without a regulatory filing, compounded preparations, dietary supplements, several positron emission tomography products, and some medical devices. Drug substances and excipients are reviewed but not formally approved as part of a regulatory filing for a dosage form in the U.S.
$U S P$ and $N F$ are unusual among compendia of the world because they are published independently from government. As an organization, USP depends for its success on many factors but certainly on its ability to evolve with the times. This Stimuli article postulates the need for a new compendium, separate from $U S P-N F$, to account for an increasing need for public monographs that serve a broad range of constituencies. This need is similar to, if not identical with, motivations that called delegates to the 1820 Convention.

## USP, FDA, AND THE U.S. MARKET

USP publishes $U S P-N F$ independently of statute under the authority of its charter and its Constitution and Bylaws. The original mandatory character of $U S P$, to the extent that it existed at all, devolved from practitioners who declared it to be their "official compendium" and agreed to abide by its standards. Over time, the two compendia have been adopted and made enforceable by various bodies, including both U.S. federal and state governments. Standards in USP $-N F$ also may be adopted by regulatory bodies and other parties
throughout the world when a local standard does not exist or requires modification. The U.S. Federal Food, Drug, and Cosmetic Act (FDCA), created in 1938, specifies what aspects of the USP FDA shall enforce. It does not empower or limit what USP can publish.

Various terms and words-at times confusing and subject to misinterpretation-are used to describe the character of $U S P-N F$ and the relationship of the two texts to the FDCA. USP uses the term official to describe the two compendia. For example, after the content of the USP is adopted by the Council of Experts, the USP Board of Trustees designates the date when the text becomes official. Use of the term in this context indicates that a standard emanating from the Council of Experts is authorized by the Board to be effective at a specified date. In Section 201(j) the FDCA designates the $U S P$, the $N F$, and the Homeopathic Pharmacopeia and their supplements as official compendia of the U.S. This designation in itself confers no enforcement authority. It is instead a drafting mechanism for making standards that appear in a supplement enforceable without having to adopt new regulations or legislation. Because monograph requirements are factual determinations made by USP's Council of Experts, USP functions as a fact-finding body, with conclusions based on these facts reflected in the decisions of the Council of Experts. Facts can change, but the law remains constant. That helps explain why changes appearing in $U S P-N F$ and its Supplements are enforceable without subsequent adoption by a legislature or agency. USP's continuous revision facilitates rapid updating to allow for advances in science and technology. These updates focus on new analytical procedures and acceptance criteria that generally improve over time. In contrast, antibiotic drug monographs, previously provided in the Code of Federal Regulations, were cumbersome to finalize and update and were eliminated in the 1997 Food and Drug Administration Modernization Act with deletion of Section $507 .{ }^{1}$

Other sections of the law indicate to FDA what aspects to enforce, e.g., Section 501(b). This section provides that an article that is a drug recognized in USP or $N F$ shall be deemed to be adulterated unless it complies with the standards of strength, quality, and purity contained therein. Noncompliance of a product with compendial requirements is to be determined in accordance with procedures defined in a monograph. USP can publish only information or facts upon which laws can operate. It has no enforcement authority, nor can it make legal requirements unilaterally.

Recognizing that certain aspects of the monograph are enforceable by FDA, USP has sought to clarify what parts of the two compendia are informational only. For example, USP has placed a chevron ( $>$ ) at the beginning of the Definition section in the monograph to separate informational items from enforceable items. The material above the chevron (e.g., the chemical structure and chemical formula) is informational and not enforceable. A similar approach has

[^273]been taken for General Chapters. Many General Chapters numbered below 1000 contain techniques or procedures, sometimes with acceptance criteria, that are referenced in a monograph as a means of conserving text space. USP has declared Chapters numbered above 1000 to be informational. To clarify this point, the following is stated in the General Notices section of the Second Supplement to USP 27-NF 22:

Articles recognized in this compendia must comply with the official standards and tests and assays in the General Notices, relevant monographs, and General Chapters numbered below 1000 .
General Chapters numbered above 1000 are considered to be interpretative of a subject. They contain no requirements unless specifically referenced in the monograph or elsewhere in the Pharmacopeia. As with any other parts of $U S P-N F$, other parties may recognize and incorporate these General Chapters above 1000 no matter what their subjects and make them enforceable. This is outside of USP's control. ${ }^{2}$
USP strives at all times to create the most complete, relevant, science-based standards for therapeutic articles and is under the direction of its Board of Trustees to do so. These standards arise from well-established processes that allow the standards to be authoritative, credible, and unbiased. Because the Council of Experts is an elected body and reaches its conclusions through majority-based balloting, it is not consensus based. Its character and the standards it creates are in and of themselves voluntary. They become mandatory and thus enforceable by action of other parties.
In the years of their existence, USP and FDA, together with pharmaceutical manufacturers and compounding professionals, have strived to work harmoniously in various ways that, in the aggregate, have resulted in a broad array of articles, both ingredients and preparations, that are among the best in the world. To the extent allowed by law, FDA representatives are welcomed in USP conclaves, either as representatives of the Agency or as members of the Expert Committees of the Council of Experts. FDA is constrained in working with USP to the extent that it is constrained in working with any non-U.S. government organization. However, unlike participation in voluntary consensus bodies, which is governed by the National Technology Transfer Act of 1995, FDA is specifically authorized to cooperate in the revision of USP pursuant to Circular OMB A-119 and 21 USC 377. This law was added by the Labor-Federal Security Appropriations Act of 1944 because USP standards are not considered voluntary but rather enforceable under the FDCA. Certain information available to FDA in regulatory filings may not be shared with USP, either because of laws protecting trade secret information or because of constraints on resources needed to fulfill provisions of the Freedom of Information Act.

[^274]FDA may not change a USP standard, but it can publish alternative methodology in a regulation if it believes that USP methodology is deficient. FDA has never resorted to this because of the cooperative relationship between the two bodies. If USP's analytical procedures are not suitable for a particular substance or product, a firm may submit alternative methodology to USP for incorporation in the relevant monograph. A firm may claim an article is not "USP" or " $N F$ " if it differs from the standards of strength, quality, or purity established for the article in USP and if the difference is stated on the product's label.

Both FDA and USP have executed different roles and responsibilities over the years. For example, taking advantage of the USP selection process to determine the "best drugs," the U.S. Government, turning to USP rather than FDA with passage of Medicare legislation in the 1960s, recognized articles included or approved for inclusion in the USP as a basis for certain types of reimbursement. ${ }^{3}$ More recently, the expansion of FDA's responsibilities-and perhaps in particular passage of the 1984 Drug Price Competition and Patent Term Restoration Act-has had a significant impact on USP.

Although the details of this impact are broad and certainly extend beyond USP, they relate, insofar as USP is concerned, to reduced incentives for manufacturers to voluntarily provide the information needed to support a public monograph, either because of the intensely competitive environment created by the 1984 law or because of a desire to avoid a dual review-an increasingly stringent one at FDA to achieve the private standard and, at times, a more protracted one with USP to achieve the public standard. In addition, with better control of an article's quality, the public monograph necessarily has moved beyond a "one size fits all" approach to a more accommodating one that accounts for different routes of synthesis and different dosage form performance characteristics. This results in what USP now terms the flexible monograph. Various aspects of a monograph are covered in a Guideline designed to assist sponsors in submitting Requests for Revision in support of a new monograph or a monograph revision (http://www.usp.org/ standards/revisionguideline/index.html). Further details about the complex relationship between FDA and USP are presented in an Appendix to this article.

## STATUS OF MONOGRAPHS

## New Monographs and Missing Monographs

Each year, FDA approves many new drugs, including biologics, with release in the market requiring conformance to private and/or public standards. Over time, the private standard may become public through USP processes. Despite the challenges and barriers discussed in the previous

[^275]section, USP continues to believe strongly in the value of public monographs for these articles and, when needed, associated official USP Reference Standards to support firstparty (manufacturer, compounding professional), secondparty (purchaser, distributor), and third-party (independent body) testing. In a world where counterfeit and substandard drugs are on the rise and control over market zones is either declining or nonexistent and where health professionals no longer have "hands-on" control over the quality of the medications they use, the value of a public science-based monograph appears as strong as, if not stronger than, the value perhaps perceived by the 1820 Convention delegates. The value may be even greater for therapeutic articles marketed outside the U.S., where regulatory control is diminished, a pharmacopeia may not be present, and the possibility of counterfeit and/or substandard drugs is more likely. In recognition of this value, delegates to the 1995 Quinquennial Meeting passed the following resolution:

USP is encouraged to determine the feasibility and advisability of providing upon request, authoritative standards for pharmaceuticals and related products, and health care technologies utilized by other countries that rely upon $U S P-N F$, where no national standard currently exists.
USP has always supported the activities of the World Health Organization (WHO) in creation of the International Pharmacopeia. To assist WHO, USP finalized a four-drug combination dosage form monograph for the treatment of tuberculosis. This monograph can assist manufacturers and public health authorities throughout the world in ensuring the availability of a good-quality fixed-combination dosage form to assist practitioners in treating patients with this dread disease. Note that this monograph now is part of official text in $U S P-N F$, but it has no implications for FDA or manufacturers marketing in the U.S., given that an article conforming to this monograph is not legally marketed in the U.S. Should such an article become available through FDA's new drug application process, the monograph might have to be adjusted based on the FDA regulatory review.

## Missing Monographs

In 1980, the USP Convention voted to change the scope of $U S P$ so that by 1990 it would include monographs for all drug entities (drug substances) and, to the extent possible, drug products marketed in the U.S. Because USP usually relies on voluntary donations of both information and reference standard candidate material to support $U S P-N F$ content and associated official USP Reference Standards, the two compendia over time-predominantly for the reasons discussed previously in this article-have failed, increasingly, to meet this goal. For example, USP is missing 323 non-complex drug substance monographs and approximately twice that number of dosage form monographs. Taken together, the total number of monographs missing from $U S P-N F$ is about a third; i.e., 2000 monographs of a potential cohort of about 6000 are not available to the public. The challenge is particularly acute for complex ingredi-
ents and dosage forms, in which cases creation of a public monograph is generally not deemed in the interest of some manufacturers.

## Monograph Updating

USP has requested the involved Council of Experts Expert Committees to review currently available monographs to determine how many contain outdated procedures. Reports received to date emphasize the need to modernize some test procedures and to include impurity tests in the monographs. New International Conference on Harmonization approaches to the USP tests, particularly the Impurity test, suggest that a drug substance monograph may need to have different Impurity test procedures to account for impurities arising from different routes of synthesis. For these reasons, many monographs need updating to better control ingredient and dosage form impurities. Again, the rationale for sponsors to submit these requests for revision is frequently lacking, given the resources needed to update a monograph and the lack of incentive to do so. This is a challenge also shared by FDA in maintaining private standards in an application. ${ }^{4}$

## A NEW APPROACH

For the various reasons delineated in this article, USP believes a new approach is needed not only to avoid an increasingly deficient monograph cohort in $U S P-N F$ but also for USP to better serve the international community. The approach will entail a search for sponsors of articles not legally marketed in the U.S.-i.e., sponsors who are willing to submit Requests for Revision for new monographs, with an increased emphasis on using USP's stan-dards-setting and laboratory capabilities to create the information needed to support a monograph. ${ }^{5}$ The overall approach was solidified by a formal decision of the Council of Experts in July 2003 to create monographs for articles not legally marketed in the U.S. ${ }^{6}$ This formal decision is extremely important, but it is also important to note that USP had already taken similar decisions in the past, including, as noted, the four-drug dosage form monograph to treat tuberculosis. In addition, the Preface to earlier editions of $N F$ indicated an intent to allow excipient monographs that were not part of FDA-approved dosage forms.

Working with the Council of Experts Executive Committee, USP has considered several ways to indicate the status of a monograph for an article not legally marketed in the U.S. Despite the overall complexity of the issue, the presen-

[^276]tation allows only a few possibilities. These include placing such monographs in (1) a separate section of Pharmacopeial Forum, (2) USP-NF with distinguishing marks, (3) $U S P-N F$ in a separate section, and (4) a separate compendium. Although the authors welcome comments on all possibilities, we believe that the most useful and clearest way would be to create a separate compendium. This would be an official compendium of USP but would not be an official compendium of the U.S. under the FDCA. The few monographs for articles not legally marketed in the U.S. that are currently in $U S P-N F$ would be transferred to the new compendium, as perhaps would General Chapters and other useful information.

## JUSTIFICATION

The new approach is justified by the support it provides, for both non-U.S. and U.S. constituencies. Non-U.S. constituencies who may benefit from a separate USP compendium include international public health officials, manufacturers marketing good-quality, safe and effective drugs, and the public at large.

- Public health officials throughout the world are expected to benefit from the proposed approach. The preface to the third edition of the International Pharmacopeia emphasizes the availability of monographs primarily for ingredients and dosage forms on the list of essential drugs, as determined by the WHO Expert Committee on the Selection of Essential Drugs. This list comprises 325 drug substances and 260 dosage forms, which leaves many hundreds of ingredients and dosage forms without modern monographs and associated reference standards. The proposed approach would allow USP thus to assist WHO in several ways. First, USP could aid WHO in providing monographs/ reference standards for medicines on the essential drug list. Second, USP would assist WHO in providing monographs/reference standards for articles moving in international commerce but not included in the essential drug list. In a separate compendium, USP might also follow WHO's lead in providing classical procedures (less demanding tests), as well as basic and screening tests, to help reduce the circulation of counterfeit and substandard drugs.
- For international regulatory agencies, the availability of modern ingredient and dosage form monographs in a separate USP compendium should facilitate review processes, given that validated analytical procedures and associated official USP Reference Standards would be available. The approach thus could alleviate constraints on regulatory resources, which in some locales is severe. The approach also would be useful to other government and nongovernment groups, including customs inspectors and international relief groups wishing to purchase good-quality drugs. Many of these groups engage in testing as a means of ensuring the quality of therapeutic articles. At this time, absence of
a monograph in any of the world's major pharmacopeias, including $U S P-N F$, means that such testing is either impeded or not possible. Although a separate compendium is proposed, USP intends to use Pharmacopeial Forum as a means of eliciting public comment on draft monographs for the separate compendium. Public comments would be encouraged from nonU.S. constituencies who might rely on tests, procedures, and acceptance criteria in a separate compendium.
- For manufacturers wishing to move ingredients and dosage forms in international commerce, the availability of modern ingredient and dosage form monographs in a separate USP compendium, coupled with the availability of official USP Reference Standards, will assist in applying the best, most appropriate procedures in support of work with regulatory agencies, international funding agencies, other manufacturers, and in country constituencies, including practitioners and patients.
U.S. constituencies who may benefit from the new approach include FDA, some manufacturers marketing or intended to market products in the U.S., and the U.S. public at large.
- For FDA, the value of the approach lies in the availability of validated analytical monograph procedures and associated official USP Reference Standards for articles moving in international commerce but not available on the U.S. market. Many of the articles in international commerce may have the same names and otherwise be similar to articles legally marketed in the U.S., with differences revealed perhaps only in certain testing, e.g., the USP Impurities test or the Performance test (dissolution, disintegration). If USP is able to publish monographs for these articles and make available official USP Reference Standards, FDA would have access to procedures/standards that would allow border control and detection of counterfeit and substandard medicines. The approach would facilitate efforts to keep such articles out of U.S. commerce rather than allowing safe harbors for articles legally marketed in the U.S. In addition, the proposed monographs/reference standards for international products and substances might be useful for legally marketed U.S. articles, given that many of the international monograph procedures would still be applicable for consideration as alternative methods for FDA-approved products. For example, if there were a question about strength, the official USP Reference Standard material might be used to test the U.S. product, even though the monograph was for an article not legally marketed in the U.S. Of course, due consideration would have to be given to the suitability of the method for this purpose. As a further advantage, it is also possible that the proposed approach would gener-
ate updates to USP monographs and private standards in FDA application files-a goal that FDA itself has championed. USP emphasizes, however, that the proposed approach is not intended to influence any product legally marketed in the U.S. Control of this market is entirely the responsibility of the U.S. government working through FDA and not that of USP.
- For U.S. manufacturers, the value of the proposed approach would be the ability to view modern specifications in ingredient and dosage form monographs, even though the article might not be legally marketed in the U.S. USP occasionally hears that manufacturers would like confirmed analytical procedures to test competing products. The proposed approach would fulfill that need. In addition, for U.S. generic manufacturers, the proposed approach offers the possibility of placing, with Council of Experts approval, ingredient and dosage form monographs in the separate compendium pending an FDA regulatory decision. With conclusion of a positive Agency decision and provision of regulatory judgments about acceptance criteria for impurities, dissolution, and other procedures, the monographs could move to $U S P-N F$. At present, a manufacturer is sometimes caught between FDA, which may wish to have final monographs in $U S P-N F$ for articles pending Agency approval, and USP, which states that it cannot conclude such a monograph pending receipt of final Agency decisions for acceptance criteria. [NOTEUSP's Council of Experts considered the possibility of keeping monographs for articles in Pharmacopeial Forum ( $P F$ ) pending an FDA decision. With FDA approval and availability of needed regulatory judgments, the monographs could move to $U S P-N F$. This approach, however, would detract from the finality of the monographs in that USP does not regard $P F$ to be an official compendium.]
- The U.S. public at large would benefit through increased assurance of good-quality products moving in U.S. commerce, avoidance of delays in regulatory approvals, and improved border control. Specifically, a separate compendium would indicate articles (and provide test procedures for them) that should not be in U.S. commerce. Legislative changes are under consideration to expand importation of ingredients and products. Should the approach be finalized, a separate compendium with public ingredient and dosage monographs would allow testing of possibly counterfeit or substandard imported drugs with modern analytical procedures, using associated official USP Reference Standards, subject to the conclusions of the USP Council of Experts.


## SPECIAL CONSIDERATIONS

A modern pharmacopeial monograph usually incorporates both regulatory and compendial decisions. For example, USP's Council of Experts now reviews extensive information in a Request for Revision that allows validated analytical procedures to appear in a monograph. It does not, as a rule, review isolation, characterization, and qualification data that support acceptance criteria (limits) for impurities. Similarly, USP does not usually review bioavailability and bioequivalence data to justify acceptance criteria used in a USP Performance test, such as dissolution or disintegration, for a dosage form. In addition, USP does not engage in extensive testing of candidate ingredient or dosage form material with a proposed monograph to ensure that the compendial procedures are adequate. These are left to manufacturers and FDA. ${ }^{7}$ To allow the new approach, USP might rely on information such as certain regulatory acceptance criteria, providing they were based on review by selected regulatory authorities, ${ }^{8}$ or USP could develop the necessary information itself. The new approach will require careful consideration of the information needed to support a monograph for articles not legally marketed in the U.S., coupled with an understanding of the resources needed to obtain this information.

## CONCLUSION

The international market for manufactured pharmaceuticals is changing at a rapid pace, leading to a global environment that is at least as challenging as that confronting Convention delegates in 1820. Like early practitioners in the U.S., modern practitioners in many parts of the world beyond the U.S. may confront a bewildering array of poorly named therapeutic ingredients and products with uncertain safety, efficacy, and quality. Yet unlike 1820, the possibility of uniform, good-quality, safe, and effective therapeutic agents today offers health care opportunities that could not be imagined by the practitioners who formed the early pharmacopeia. This Stimuli article is presented to further discuss how USP could-and perhaps should-evolve in the coming years to serve public health both nationally and internationally. The specific suggestion is to create a separate official USP compendium, clearly distinguished from USP, to support international needs and, as feasible, national interests as well. The approach offered has broad and complex underpinnings. At no point in the approach is it intended that the national relationship with FDA and manufacturers of articles legally marketed in the U.S. be al-

[^277]tered. Instead, the approach is designed to facilitate the availability of useful public analytical information to all constituencies of USP throughout the world. In an era of counterfeit drugs, substandard drugs, drugs with unclear names and quality, drugs with uncertain safety and efficacy, in an era when infectious diseases such as HIV, malaria, and tuberculosis threaten public health advances, in an era when therapeutic agents offer hope and promise to all the world's people, and in a world where therapeutic products move across national borders with increasing speed, there are overarching justifications for a separate compendium. We welcome comments.

## APPENDIX

## Drugs

The FD\&C Act defines drugs as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and "articles (other than food) intended to affect the structure or any function of the body of humans or other animals." USP's goal is to have substance and preparation (product) monographs for all FDA-approved drugs. USP also develops monographs for therapeutic products not approved by FDA, e.g., pre-1938 drugs and compounded preparations. The complex set of procedures that result in validation of private regulatory methods submitted in NDAs, ANDAs, NADAs, and ANADAs and the subsequent transition to a public official procedure in USP, coupled with availability of a verified reference standard material, have been described elsewhere. Although submission of information needed to develop a monograph by the Council of Experts is voluntary, compliance of an article bearing a USP name, with a $U S P-N F$ monograph, if available, is not.
Names for drug substances are established through the efforts of the United States Adopted Names (USAN) Council. USP participates in this activity together with the American Pharmacists Association, the American Medical Association, and the Food and Drug Administration. Drug product names can be established by FDA but more often are developed cooperatively with USP in activities of the Council of Experts Nomenclature and Labeling Expert Committee. Oversight of brand names is the responsibility of FDA, working with applicants.

## Biologics

Originating in 1938, the FDCA includes provisions of the Public Health Service Act (PHSA) and many subsequent amendments, e.g., the provisions of the Dietary Supplement Health and Education Act (DSHEA). As defined in the PHSA, biological products are any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivatives, allergenic product, analogous product, arsphenamine or its derivatives, or any trivalent arsenic compound applicable to the prevention, treatment, or cure of diseases or injuries in humans. Through Intercenter agreements, many
macromolecules and mixtures manufactured through recombinant technology are regulated in CBER, except for hormone biologics, which are generally regulated in CDER. CDER also regulates small molecules manufactured through recombinant technology. Therefore, biologics regulated by CDER under NDAs are subject to the compendial standard requirements under the FDCA regarding adulteration and misbranding. Biologic products regulated under the PHSA are required to bear "proper" names, not "established" names like drugs. Provisions of the FDCA apply to biological products regulated under the PHSA-except that, if licensed, a biologic product does not need an approved application under Section 505 of the FDCA. For this reason, biological drug products approved under the PHSA should comply with the adulteration and misbranding provisions of the FDCA in Section 501(b) and 502(g) and, thus, should conform to official monographs if available.

## Medical Devices

Section 201(h) of the FDCA defines a device as an article/ instrument, apparatus, or component recognized in $U S P-$ NF. Section 502(e) defines the established name of a device in the absence of an FDA designation of the official name as the official title in an official compendium. Despite these statutory provisions, there is no comparable recognition of USP's standard-setting authority and ability to define the medical device as exists for other FDA-regulated therapeutic products. Under the Food and Drug Administration Modernization Act, CDRH recognizes national and international consensus standards, including some USP tests and assays for medical devices.

## Dietary Supplements

As with drugs and biologics, the FD\&C Act names $U S P$, $N F$, and the Homeopathic Pharmacopeia as official compendia for dietary supplements. Under section 403(s)(2)(D), a dietary supplement may be deemed misbranded if it is covered by the specification in an official compendium, is represented as conforming to its specification, and fails to conform. Therefore, unlike articles classified as drugs, the dietary supplement must assert conformance to the $U S P-N F$ monograph in order for the compendial standards to apply. Compliance with a $U S P-$ $N F$ monograph is thus voluntary on the part of a dietary supplement manufacturer. In contrast, a drug approved under the FDCA must conform to an "official compendium" if compendial standards exist, unless it declares nonconformance.

## Compounded Preparations

Preparation monographs may also provide information or standards applicable in compounding. Compounding means the preparation, mixing, assembling, packaging, or labeling of a drug or device or other article as the result of a practitioner's order or in anticipation of such an order based on routine regularly observed prescribing patterns. FDAMA defines the difference between pharmaceutical manufacturing and compounding. Statements in $U S P-N F$ for compounded preparations may be enforced both at the federal and state levels.

# Microbial Identification in the Pharmaceutical Industry 

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#### Abstract

A review of the microbial identification methods that are available to support compendial testing was undertaken to determine the state of the art within the pharmaceutical industry and to stimulate the USP revision process. Emphasis was given to the preliminary screening of microbial isolates for cellular morphology, staining, and diagnostic biochemical reactions to either characterize the microorganisms or support decisions for using different microbial identification schema and the rapid microbial identification methods that are available. The relative advantages of phenotypic and genotypic microbial identification methods are discussed. Due to the complexity of the topic, the authors believe that treatment of alternative microbial identification systems warrants a guidance chapter separate from the proposed General Chapter $\langle 1227\rangle$ Validation of Alternative Microbiological Methods.


## INTRODUCTION

Microorganisms found in pharmaceutical ingredients, water for pharmaceutical use, the manufacturing environment, intermediates, and finished products are frequently identified to assist in product investigations. This is especially common if their numbers exceed alert and/or action levels for the material or process environment tested. Routine monitoring might include characterization by colony morphology, cellular morphology (rod, cocci, etc.), gram reaction, and key enzyme activities. This information may be sufficient to confirm that the bacteria found in the material are typical for that material or process environment or indicative of no change in the level of environmental control in an aseptic processing area. However, there may be a need for more precise identification methods during an investigation to assign a species name to the microorganism. Microbiological identification systems are based on different analytical techniques, and each has restrictions due to method and/or database limitations and each has inherent shortcomings in terms of accuracy, reproducibility, technical complexity, rapidity, and cost. A decision must be made regarding the appropriate technology to use in the routine pharmaceutical microbiological testing laboratory with these limits in mind as well as a thought to the need for the level of identification (genus, species, strain) needed for the particular situation.

## REGULATORY GUIDANCE ON MICROBIAL IDENTIFICATION

What is the status of microbial identification in the compendia and pharmaceutical regulations? There is no USP chapter that specifically addresses microbial identification. However, the need for microbial identification is specifically

[^278]cited in USP General Chapter $\langle 61\rangle$ Microbial Limit Tests, where it is recommended that microorganisms demonstrating characteristic cellular and colonial morphology on selective and/or diagnostic agar media in the absence of specified microorganisms tests be confirmed, if necessary, by other suitable cultural and biochemical tests.
The proposed Microbial Limit Tests harmonization document (1) does not include this specific text, but it does allow for the use of alternative microbiological tests. The Australian Therapeutic Goods Administration (TGA) recommends testing for the absence of all pseudomonads in topical preparations (2) but does not provide specific means for identification. FDA, in their 1993 Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories, references the FDA Bacteriological Analytical Manual (3) for microbial identification techniques in reviewing microbial limits tests that relies heavily on selective and differential media.
USP General Chapter $\langle 71\rangle$ Sterility Tests (harmonized with the JP and Ph. Eur. January 1, 2004) allows for invalidation of the test if "after determination of the identity of the microorganisms isolated from the test, the growth of this species (or these species) may be ascribed unequivocally to faults with respect to the material and or the technique used in conducting the sterility test procedure." The TGA document contains similar wording (4) but has gone on record that this identification must be performed at the level of DNA (5). FDA has also argued that invalidation of a sterility test requires identification of microorganisms at the DNA level in its draft aseptic processing guideline (0).
The manufacturing area is also a concern for microbial identification. USP informational chapter $\langle 1116\rangle$ Microbiological Evaluation of Clean Rooms and Other Controlled Environments recommends that microbial isolates be identified at an appropriate level to support the environmental monitoring program. The recent FDA draft guidance document on aseptic processing (6) recommends the use of genotypic microbial identification methods because of the
increased accuracy and precision of these methods. The authors believe that this statement should be critically reviewed.

There is obviously a great deal of interest in microbial identification but little guidance about precisely how to conduct it. Although the draft USP informational chapter〈1223〉 Validation of Alternative Microbiological Methods provides some guidance (7), the treatment is not complete. There is very little guidance about precisely how to qualify different methods of microbial identification, and there are many methods to choose from.

## CHARACTERIZATION OF BACTERIA IN THE PHARMACEUTICAL ENVIRONMENT

## Historic Background

The pioneer in the classification of bacteria was the German biologist Cohn, who first suggested in 1870 the division of bacteria into groups based on their cellular morphology as determined by light microscopy. At the time it was a revolutionary idea that there are many different species of bacteria. Cohn recognized six genera without the advantages of pure culture and staining techniques, emphasizing that bacteria occur with different species. They were Micrococcus (ball or egg-shaped), Bacterium (short, rod-like), Bacillus (straight, fiber-like), Vibrio (wavy, curllike), Spirillum (short, screw-like), and Spirochete (long, flexible, spiral).

In 1884, the Danish microbiologist Christian Gram developed the differential staining of bacteria that is universally used to classify them as negatively or positively reactive to what is now called the Gram's stain. The established system of bacterial classification based on colony morphology and color, cellular morphology, differential staining, motility, physiology, biochemical reactions, and substrate utilization used by American microbiologists was systematized in the 1923 Bergey's Manual of Determinative Bacteriology. The routine identification methods employed in the food, clinical, and microbiology laboratory continue to be based on the determination of the morphology, differential staining, and physiology of a microbial isolate by means of miniaturized and automated substrate utilization screening methods to speciate the isolate, e.g., API, Vitek, and Biolog microbial identification systems (8-10).

## MICROBIAL ISOLATION

Microorganisms are present in a variety of milieux in the pharmaceutical manufacturing environment. The first step to identification is to isolate a pure colony for analysis. This purification is normally accomplished by subculturing one or more times on solid media to ensure purity, each time streaking for single colonies. This technique also allows full phenotypic expression and growth of sufficient inoculum for the identification.

It should be recognized that expressions of the microbial phenotype, i.e., cell size and shape, sporulation, cellular composition, antigenicity, biochemical activity, sensitivity to antimicrobial agents, etc. frequently depend on the media and growth conditions (Table 1). These conditions will include the better-known variables such as temperature, pH , redox potential, and osmolality and lesser-known variables such as nutrient depletion, vitamin and mineral availability, growth cycle, water activity of solid media, static or rotatory liquid culture, and solid versus liquid media culture, as well as colony density on the plate.

Table 1. Phenotypic characteristics that may be employed in microbial taxonomy

| Categories | Characteristics |
| :--- | :--- |
| Cultural | Colony morphology, colony color and <br> size, and pigment production |
| Morphological | Cellular morphology, cell size, flagella <br> type, reserve material, gram reaction <br> and spore, and acid-fast staining. |
| Physiological | Oxygen tolerance, pH range, tempera- <br> ture optimum and range, and salinity <br> tolerance |
| Biochemical | Carbon utilization, carbohydrate oxida- <br> tion or fermentation, and enzyme pat- <br> terns |
| Inhibition | Bile salt-tolerance, antibiotic suscep- <br> tibility, and dye tolerance |
| Serological | Agglutination <br> Chemo- |
| Taxty acid profile, microbial toxins, and |  |
| whole cell composition |  |

In contrast, the microbial genotype is highly conserved and is independent of the culture conditions, so the identifications may be conducted on uncultured test material-primary enrichments that increase the amount of nucleic acid available for analysis, the primary isolation cultures from microbial limit testing ( $\langle 61\rangle$ ), or environmental monitoring plates. For example, a recent publication (11) confirmed the stability of repetitive-sequence PCR patterns of the bacteria E. coli, P. aeruginosa, E. faecalis, S. epidermidis, and $A$. baumannii with respect to both the age of the culture and 5,10 , and 15 subcultures. Table 2 lists a number of genotypic characteristics that may be determined.

Table 2. Genotypic/phylogenic characteristics that may be employed in microbial taxonomy

| Categories | Characteristics |
| :--- | :--- |
| Genotypic | DNA base ratio $(G+C$ content $)$, restric- <br> tion fragment patterns, and DNA |
| phylogenic | probes <br> DNA-DNA hybridization, and 16S and <br> 23S rRNA codon sequences |

## PRELIMINARY SCREENING OF MICROBIAL ISOLATES

Microorganisms isolated from pharmaceutical ingredients, water for pharmaceutical use, the manufacturing environment, intermediates, and finished products on compendial media in all likelihood will be physiologically stressed. The microorganisms will go from a metabolic status suitable for slow or no growth for survival under adverse conditions to rapid growth under laboratory culture conditions. This transition can be managed by careful handling of the isolates. Individual representative colonies from the primary isolation media are streaked onto solid media as described above in preparation for identification. The first step is to determine the gram reaction and cellular morphology of the bacteria isolates. This is a critical step for phenotypic identification schemes. If the wrong gram reaction and/or cellular morphology are assigned to an isolate, subsequent testing may be conducted using the wrong microbial identification kit, resulting in an incorrect or nonsensical result. Several common preliminary screening tests are described below.

## Gram Staining

Gram staining methods employed include the four-step method: Crystal violet (primary stain); iodine (mordant); alcohol (decolorizer); safranin (counter stain) or the three-step method in which the decolorization and counter-staining step are combined. Done correctly, Gram-positive organisms retain the crystal violet stain and appear blue; Gramnegative organisms lose the crystal violet stain and contain only the counter-stain safranin and thus appear red. Common pitfalls in this method are that heat fixation may cause Gram-positive cells to stain Gram-negative and older cultures may give Gram-variable reaction; using too much decolorizer could result in a false Gram-negative result and not using enough decolorizer may yield a false Gram-positive result. One variation that has advantages in some situations is to perform a methanol fix of the bacterial smear on the microscope slide; this may be preferable to a heat fix for consistent results.

Because the Gram-staining reaction must be read under a microscope, this method provides two pieces of information: the Gram-staining characteristics and the cell morphology (i.e., rods or cocci, single cells or chains or clumps or clusters, etc.). The use of a semi-automated cell-staining device such as the Aerospray Gram-staining instrument (Wescor, Inc., Salt Lake City, UT) to give more consistent results is recommended.

## Spore Staining

Spore staining methods employed include a two-step method: malachite green (primary stain) and safranin (counter stain). The fixed bacterial smear is stained with 7.6\% aqueous malachite green solution for 10 minutes, rinsed, and counter stained with a $0.25 \%$ aqueous safranin solution
for 15 seconds, rinsed, and blotted dry. This procedure stains the spores green, but the rest of the bacterial cell is stained red.

## Biochemical Screening

Key biochemical screening tests are the oxidase test to separate Gram-negative rod-shaped bacteria into nonfermenters (oxidase positive) and enteric (oxidase negative) bacteria, the catalase test to separate Staphylococci (catalase positive) from Streptococci (catalase negative), and the coagulase test to separate staphylococci into coagulase negative (presumptively nonpathogenic) and coagulase positive (more likely pathogenic) staphylococci.
For many types of investigations, these few tests may provide enough information to trend data. However, there are much more definitive bacterial identification schemes or systems available to the pharmaceutical microbiologist.

## MICROBIAL IDENTIFICATION BY PHENOTYPIC METHODS

Phenotypic methods utilize expressed gene products to distinguish among different microorganisms. Generally, these require a large number of cells in pure culture. Disadvantages of culture methods for microbial enumeration and identification are well known and include the long incubation times, the inability of most environmental microorganisms to grow on artificial media, the specific growth requirements of many microorganisms, the unintentional selectiveness of culture methods, and the need to fully express phenotypic properties of recently isolated stressed microorganisms by subculture from primary isolation, selective, or diagnostic media prior to microbial identification. However, the carbon utilization and biochemical reaction patterns for microbial species in the database for a microbiological identification system are always based on inocula development for that identification system on specified culture media and incubation conditions to achieve consistency of identification. Despite these limitations, phenotypic microbial identification methods are successfully employed in the routine food, water, clinical, and pharmaceutical microbiological testing laboratory. An excellent overview of manual and automated systems for the detection and identification of microorganisms may be found in the 8th Edition of the ASM Manual of Clinical Microbiology (12).

## Carbon Utilization and Biochemical Reaction Methods

A compendial example of this approach is $\langle 61\rangle$ Microbial Limit Tests, which utilizes general and selective enrichment broth and diagnostic solid media to demonstrate the absence of specified microorganisms. These methods can be conducted in any microbiology laboratory.

There are several microbial identification kits based on carbon utilization and biochemical reactions that are readily available. The API strip takes what originally required racks of tubes and reduces them in size and complexity to several
small, prepackaged strips. The Vitek Microbial Identification System takes this concept a step further, miniaturizing the reaction tubes in cards and coupling the assay with automated incubation and reading. However, these traditional biochemical methods are not the only phenotypic test methods available to the pharmaceutical microbiologist.

The Biolog Microbial Identification System has an identification scheme based on carbohydrate utilization. A 96well microtiter plate holds a variety of media containing specified carbohydrates and a redox indicator. If growth occurs in a particular well, the reduced conditions within that well result in the redox dye tetrazolium turning dark, signifying catabolism of the substrate. This reaction is easily read manually or by a photometric plate reader, and the result is a semi-automated identification system that complements the traditional methods.

In addition to the carbohydrate utilization method, Biolog has also developed a "Phenotype MicroArrays" system that utilizes the same basic technology but can monitor, either directly or indirectly, a large number of different aspects of cell function. The range of phenotypes monitored includes cell-surface structure and transport functions, catabolism of carbon, nitrogen, phosphorus, and sulfur compounds, biosynthesis of small molecules, cellular respiratory functions, and finally, stress and repair functions. This offers the small lab an opportunity to delve into greater detail during an investigation and to provide finer differentiation among isolates.

In addition to the phenotypic methods used to identify microorganisms based on their gram reaction, cellular morphology, carbon utilization patterns, and biochemical reactions are methods based on the cellular composition of the microorganisms grown on specified media. These include the MIDI (gas-liquid chromatographic fatty acid ester analysis) Microbial Identification System and the MicroMass MALDI TOF mass spectrometry with the MicrobeLynx pattern recognition software.

## Fatty Acid Analysis

When bacteria are grown on defined and reproducible media, the fatty acid composition of their membranes is consistently expressed as a phenotypic characteristic. The MIDI Microbiological Identification System utilizes this characteristic. Fatty acids are extracted from cell cultures and es-
terified, and the patterns of fatty acid esters are then determined using gas-liquid chromatography. This system then identifies microorganisms based on the unique fatty acid pattern of each strain. The system uses gas chromatographs, proprietary microbial databases, and pattern recognition software to identify each strain.

## Mass Spectrometric Methods

Less well known than the fatty acid analysis (and far less utilized), MALDI TOF mass spectrometry has promise as a technique for the rapid identification of microorganisms. Whole bacterial cell analysis has yielded unique mass spectra from charged macromolecules from common species of bacteria. The absence of sample preparation, coupled with rapid analysis and high throughput make the technology attractive as a rapid microbial identification method. The method involves applying the bacterial cultures to the instrument plate wells, overlying the whole cells with a solvent matrix of alpha-cyano-4-hydroxycinnamic acid for Gram-negative bacteria and 5-chloro-2-mercaptobenzothiazole for Gram-positive bacteria. The wells are then bombarded with a nitrogen laser that causes desorption of ionized cellular components that travel down a tube toward a detector. The time for the charged components to reach the detector operated in a positive ion detection mode using an acceleration voltage of +15 kV is a function of their kinetic energy, i.e., mass and charge. The detector signal is captured as a unique fingerprint for different species/stains of microorganism in the acquisition mass range of 500 to 10,000 Daltons. The MicroMass MALDI TOF mass spectrome-try-MicrobeLynx database currently has approximately 3500 spectral entries covering more than 100 genera and more than 400 different species. The time to process a sample is on the order of 3 minutes, so the equipment could run at least 100 microbial identifications a day.

## Survey of Phenotypic Methods

Representative phenotypic microbial identification systems that are widely used in the pharmaceutical industry are listed in Tables 3 and 4. With the substrate utilization methods, the incubation time may be shortened from overnight to 2-4 hours by using higher inoculum levels.

Table 3. Representative phenotypic microbial identification methods for members of the family Enterobacteriacae

| Product | Manufacturer | Method | Incubation <br> Time |
| :--- | :--- | :--- | :--- |
| API 20E | bioMérieux, Durham, NC | Substrate utilization and <br> biochemical reactions | Overnight |
| BBL Crystal Enteric/ <br> Nonfermenter | BD Diagnostics, Sparks, DE | As above | 4 hours |
| GN Microplate <br> Vitek GNI Plus | Biolog, Hayward, CA <br> bioMérieux, Durham, NC | As above <br> As above | As above <br> 2 hours and/or <br> overnight |

Table 3. Representative phenotypic microbial identification methods for members of the family Enterobacteriacae (Continued)

|  |  |  | Mrubation |
| :--- | :--- | :--- | :--- |
| Product | Manufacturer | Method | Time |
| MIDI Sherlock <br> MALDI TOF Mass Spectrometry <br> with MicrobeLynx software | MIDI, Newark, DE | Waters Corp., Milford, MA | Fatty acid ester analysis <br> Spectral analysis of ionized <br> cellular components |

Table 4. Representative phenotypic microbial identification methods for Staphylococcus spp. and other Gram-positive cocci

| Product | Manufacturer | Method | Incubation <br> Time |
| :--- | :--- | :--- | :--- |
| API Staph | bioMérieux, Durham, NC | Substrate utilization and <br> biochemical reactions | Overnight |
| BBL Crystal Gram-Positive ID | BD Diagnostics, Sparks, DE | As above | 4 hours |
| System | bioMérieux, Durham, NC | As above | $2-15$ hours |
| Vitek GPI | Biolog, Hayward, CA | As above <br> Biolog GP | Fatty acid ester analysis |

## NUCLEIC ACID-BASED (GENOTYPIC) MICROBIOLOGICAL METHODS

## Historic Background

In 1953, Watson and Crick reported the chemical structure and the base pairing of the DNA molecule. Their Nobel prize-winning publication in the British scientific journal Nature was the beginning of the new field of molecular biology that revolutionized biology and medicine.

An important milestone in the development of molecular biology-based microbiological methods was the discovery by Kornberg in 1958 of the enzyme DNA polymerase, which is responsible for the replication of nucleic acid. This was followed by the use of DNA-DNA hybridization to show the DNA relatedness between enteric bacteria in 1969, as well as the discovery of restriction enzymes to cleave DNA into analyzable fragments (the basis of ribotyping) that same year. The first use of ribosomal 16S RNA gene homology in bacterial taxonomy was described by Woese in 1977, and that same year DNA sequencing was used in taxomony by Sanger. Eight years passed before polymerase chain reaction (PCR) was developed as a tool to rapidly amplify a DNA segment (Mullis in 1985), and the first complete DNA sequencing of the genome of a bacterium, Haemophilis influenzae, was achieved ten years later by Venter and his team in 1995. Additional information on these milestones may be found in the American Society for Microbiology website article titled "Significant Events of the Last 125 Years" (13).

By the end of 1999 there were 4313 validly named prokaryotic species and 849 validly named genera of Bacteria and Archaea reported in the second edition of Bergey's Manual of Systematic Bacteriology (14) based on 16S rRNA DNA sequence analysis. The phylogenetic organization, i.e., DNA relatedness at the species level of the manual is notable with references to the information contained in the species descriptions. The revolution in microbial taxonomy started by Woese in 1977 would seem to be complete.
The key to the whole field of nucleic acid-based identification of microorganisms was the introduction of the concept of molecular systematics using proteins and nucleic acids in 1965 by the American Nobel laureate, Linus Pauling. Because the sequence of nucleic acids in a particular microorganism is extremely conserved or constant, even over geological time, and the DNA and RNA molecules are relatively stable, they are excellent materials for the detection and identification of microorganisms. However, this is complicated by the fact that a single bacterial cell weighs $10^{-13} \mathrm{~g}$ and the nucleic acid sequences that are amplified by Polymerase Chain Reaction (PCR) may represent 100 to 100,000 times less than the weight of the bacterial cell. To analyze the nucleic acid from a microorganism one needs to culture the organism and/or amplify the nucleic acid.
More details of the historic development of microbiological methods can be found in a chapter by one of the authors in the book Rapid Microbial Methods in the Pharmaceutical Industry (14).

## Absence of Specified Microorganism Screening

To detect with a high probability a single Salmonella cell in 10 g of a pharmaceutical product as required by absence of specified microorganism screening, an enrichment culture would need to obtain at least $10^{3}$ cells per mL . The cells would be lyzed, the nucleic acid extracted, and a thermostable polymerase used to copy a nucleic acid strand using oligonucleotide primers specific for Salmonella. This is achieved using a set of cycling temperatures to denature the nucleic acid, hybridize it with the primers, and use poly-merase-mediated complementary-strand synthesis to produce more nucleic acid. Twenty to thirty thermocycles can increase the amount of target nucleic acid over a million times so it can be detected by its electrophoretic pattern after treatment with reverse transcriptase, reaction with chemiluminescent DNA probes, or rRNA base sequence. This technology has been commercialized for the detection of $E$. coli O157:H7, Listeria monocytogenes, and Salmonella spp. by Qualicon as the BAX Microbial Detection System; for the detection of E. coli O157:H7 by Applied Biosystems as the TaqMan Pathogenic E. coli Detection System; and for Salmonella spp. as the Roche LightCycler PCR Salmonella Detection System (see Table 5). With PCR technology it will be possible to develop a multiplex PCR system for the simultaneous detection of the USP indicator organisms $E$. coli, S. aureus, P. aeruginosa, and Salmonella spp. for absence of specified microorganism testing to meet microbial limits requirements for nonsterile pharmaceutical drug products as indicated in specific monographs.

## BAX Microbial Identification System

The BAX Microbial Detection System takes microbial enrichments according to standard protocols for the type of food to be examined. A heated lysis reagent solution ruptures the bacterial cell wall, thereby releasing the DNA that is added to a lyophilized PCR reagent, and the DNA is amplified in the thermocycler/detection instrumentation.

## Ribotyping

With the RiboPrinter Microbial Characterization System marketed by duPont Qualicon, DNA is extracted from the bacterial cell lysate of pure colonies picked from an agar plate; the cells are lyzed, and the DNA is cut into fragments by a restriction enzyme. The DNA fragments are separated by molecular size and charge using gel electrophoresis and are transferred to a membrane where they are hybridized with a labeled DNA probe. A chemiluminescent agent is added, and the emission of light is captured by a digitizing camera. The RiboPrint is compared to other patterns in a database, and the bacterium is identified or a stain comparison is made from the ribotyping patterns. The RiboPrinter has the capacity to identify on the order of 20 organisms daily.

## Bacterial Barcodes

Bacterial Barcodes developed a repetitive-sequence and PCR-based DNA fingerprinting (rep-PCR) technology that is combined with the Agilent 2100 Bioanalyzer and Caliper Technologies LabChip and the DiversiLab software to identify a range of bacterial stains of clinical significance. The rep-PCR technology is based on noncoding repetitive sequences that are found interspersed through bacterial DNA. When PCR is performed using primers complementary to these repetitive sequences, the DNA sequences lying between the repetitive sequences are amplified. These amplified sequences were initially separated by electrophoresis. The stained gel contains a banding pattern or barcode that is distinctive for the bacterial stain. Computer-based analyses of the digitized images of the banding generated dendrograms demonstrating the relatedness of the stains. The Bioanalyzer processes the LabChips DNA chips, replacing the standard gel electrophoresis with automated lab-on-a-chip microfluids. These components are capable of preparing samples, capturing DNA fingerprints, and analyzing the results within 5 hours.

## Ribosomal RNA Base Sequencing

The MicroSeq 500 16S rDNA Bacterial Sequencing Kit marketed by Applied Biosystems allows bacterial identification using the DNA sequence of the first 500 base pairs of the bacterium's 16 S rRNA gene, and the full-gene kit enables full characterization of the entire 16 S rRNA gene of the bacterium. The MicroSeq Bacterial Sequencing Kits have been validated for use on PCR thermal cyclers from Applied Biosystems. The nucleic acid is extracted from a loop of a bacterial colony and amplified. The amplification products are run on the capillary electrophoresis-based ABI PRISM 310 Genetic Analyzer for maximum automation or on the slab gel-based ABI PRISM 377 DNA Sequencer for maximum throughput. After sequencing, the MicroSeq system identifies a bacterium or its closest genetic relatives through dedicated software that compares the gene sequence of the sample against the MicroSeq 16S rDNA Database. This database includes the 16 S rDNA gene sequences of more than 1200 known organisms, and the microbial identification daily throughput ranges from 8 to 128 , depending on the sequencing instrumentation configuration.

## PCR Kit for the Detection of Salmonella in Food

The LightCycler Salmonella Detection Kit (RocheDiagnostics) was developed to detect low levels of Salmonella in food. Using sequence-specific primers in a PCR, the LightCycler amplifies and detects in real time, employing fluorescence hybridization probes, a fragment of the Salmonella DNA derived from an enrichment culture. This procedure, including PCR set and 36 - to 48 -cycle run, can be completed with 75 minutes with 30 samples included in the LightCycler run.

Table 5. Representative genotypic microbial identification methods

| Product | Manufacturer | Method | Processing Time |
| :---: | :---: | :---: | :---: |
| RiboPrinter Microbial Characterization System | DuPont Qualicon, Wilmington, DE | Ribotyping, i.e., restrictive enzyme cleavage, electrophoretic separation, and chemiluminescent probes | 8 hours |
| BAX Microbial Detection System | DuPont Qualicon, Wilmington, DE | Nucleic acid extraction, PCR amplification, and chemiluminescent probes | Overnight |
| MicroSeq 16S and 23S rRNA Gene Sequence Analysis | Applied Biosystems, Foster City, CA | Nucleic acid extraction, PCR amplification, and rRNA base sequencing | 2-4 hours |
| LightCycler PCR Salmonella Detection System | Roche Diagnostics, Indianapolis, IN | Nucleic acid extraction, PCR amplifica- tion, and chemiluminescent probes | 1-2 hours |

## IDENTIFICATION OF FUNGI

## Phenotypic Methods

Interest in fungal taxonomy has increased due the growing clinical importance of opportunistic fungal pathogens associated with immunocompromised patients due to the AIDS epidemic, leukemia, organ transplant, and invasive medical procedures. Fungi are classified and identified by their morphological features rather than their nutritional and biochemical differences. Fungal taxonomy is complicated by the existence of teleomorphs (sexual states) and anamorphs (asexual states) for the same fungus that develop at different times under different nutritional conditions, leading to dual species names (16). Clinical mycologists as well as pharmaceutical microbiologists are most familiar with Deuteromycetes (anamorphs) or, to use an older terminology, fungi imperfecti. Unfortunately, fungal taxonomy is
technically difficult and is usually limited to mycological specialists. Although classical identification methods based on morphology are generally applied to fungal identification, carbon utilization and biochemical reaction patterns have been successfully used to identify yeast, e.g., API 20C and the Biolog FF System. These methods are suitable for the routine microbiological testing laboratory. Table 6 presents a number of commercially available systems for phenotypic identification of fungi.
The Biolog Filamentous Fungi system employs redox chemistry similar to Biolog's other technology. Based on reduction of tetrazolium in response to metabolic activity, the reaction occurs in a 96 -well plate that allows the analysis of fungal growth via turbidimetric means. There is an option for workers to add their own patterns of carbon usage produced by new cultures outside of the Biolog database.

Table 6. Representative microbial phenotypic identification methods for fungi

| Product | Manufacturer | Method | Incubation <br> Time |
| :--- | :--- | :--- | :--- |
| API 20C (Yeast) | bioMérieux, Durham, NC | Substrate utilization and <br> biochemical reactions | $24-48$ hours |
| YT Microplate (Yeast) | Biolog, Hayward, CA <br> bioMérieux, Durham, NC | As above <br> Vitek YBC (Yeabove | As above |
| Biolog FF System (Filamentous <br> Fungi) | Biolog, Hayward, CA | As above | As above |
| Microbial Identification <br> System (MIS) | MIDI, Newark, DE | Fatty acid ester analysis | $4-14$ days |

## Genotypic Methods

rRNA gene sequencing and Ribotyping may also be applied to fungal identification. For example, recent studies using MicroSeq D2 ribosomal DNA sequencing to identify molds and yeasts found in a clinical setting determined that

58 and $93.9 \%$ of the molds and yeasts, respectively, that could be identified with those isolates were neither identified nor included in the MicroSeq or API microbial identification system libraries (17 and 18). Clearly the fungal MicroSeq library is inadequate for mold identification.

## THE RELATIVE MERITS OF PHENOTYPIC AND GENOTYPIC MICROBIAL IDENTIFICATION METHODS

Application in Clinical Microbiology

Whereas rRNA gene sequencing has had a profound effect on microbial taxonomy, it may be asked what are the appropriate applications of nucleic acid-based methods to pharmaceutical microbiology? In clinical microbiology genotypic identification methods have been successfully applied to the identification of fastidious organisms, e.g., Clamydia trachomatis and Neisseria gonorrhoeae, slowgrowing organisms, e.g., fungal pathogens, and Mycobacterium tuberculosis, rapid screening for pathogens e.g., group A Streptococcus confirmatory testing, and unculturable organisms, e.g., the Whipple's bacillus Tropheryma whippelii (19).

Because of medical reimbursement requirements, clinical microbiology is subject to greater cost controls than is pharmaceutical microbiology, and it is unlikely that rRNA gene sequencing will be a routine test method. However, in some instances the cost-effectiveness of the use of these methods can be demonstrated in better clinical outcomes, reduced hospital stays, or the prevention of future illness compared to conventional clinical microbiology testing. In contrast, it is difficult to justify genotypic identification methods for routine pathogen screening and identification, especially when the relatively few pathogens isolated from the screening of clinical samples that are usually sterile may be readily identified using phenotypic methods.

## Genotypic Methods

Genotypic microbial identification methods based on nucleic acid analyses may be less subjective, less dependent on the culture method, and theoretically more reliable because nucleic acid sequences are highly conserved by microbial species. These methods would include DNA-DNA hybridization, PCR, 16 S and 23 S rRNA gene sequencing, and analytical ribotyping. However, these methods are more technically challenging for the pharmaceutical microbiologist and are more expensive in terms of both equipment and current testing costs, and they often rely on a technology marketed by a single company. Their current use may be better suited to critical microbiological investigations associated with direct product failure or with the identifications conducted in a specialized research-oriented laboratory
within a pharmaceutical company or sent to a contract testing laboratory. The increased accuracy of identification with rRNA base sequencing and the ability to determine the strain of microorganism with ribotyping may be seen as molecular epidemiology tools that are best deployed to definitively determine the origin of the microbial contamination in media fill and sterility test failures and environmental monitoring excursions exceeding established action levels.

## Genotypic versus Phenotypic Methods

Phenotypic methods rely on the more subjective determination of cellular morphology, gram reaction, catalase, coagulase or oxidase activity, other biochemical reactions, and carbon utilization patterns for identification, which introduces some disadvantages in consistent identification. However, these are mature technologies that are marketed by multiple companies as consistent, prepackaged kits with well-established quality control procedures and mature instrumentation with extensive databases to identify the most commonly encountered microorganisms found in the pharmaceutical industry. Furthermore, their underlying technologies are familiar to microbiologists working in routine microbiological testing laboratories in both large and small pharmaceutical companies. In contrast, the technologies deployed in genotypic methods are not as well established and are better suited to a research environment. Typically a single company currently markets some technologies, and, in some cases, there is a lack of commercially available reagents, primers, and probes. In addition, the technology is unfamiliar to most pharmaceutical laboratories, and the tests may be subject to nucleic acid contamination if they are not run in an environment with suitable controls in place to eliminate such contamination. Also, the nucleic acid can be difficult to reliably extract from some organisms, and many of the systems lack validated and/or appropriate databases for environmental microorganisms encountered in the pharmaceutical industry. Additionally, the instrumentation is expensive, and the unit testing cost is greater than that for phenotypic methods, so the implementation of the technology may be limited to larger pharmaceutical companies. An important consideration with a microbial identification technology is the number and types of genera and species in the database compared to those in the public domain. A comparison of the database size of representative phenotypic and genotypic microbial identification methods is presented in Table 7.

Table 7. Comparison of the database size of representative phenotypic and genotypic microbial identification methods

| System | Classification | Database Size | Comments |
| :---: | :---: | :---: | :---: |
| Vitek Microbial Identification Systems | Phenotypic | 800+ species of bacteria and yeast | Stronger in clinical organisms |
| Microlog Microbial Identification Systems | Phenotypic | 1900 species of bacteria, yeast, and molds | Stronger in environmental organisms |
| Sherlock MIDI Microbial Identification System | Phenotypic | 2000 entries, including aerobic and anaerobic bacteria and yeasts | Wide applicability |
| MALDI TOF MS plus MicrobeLynx | Phenotypic | Approximately 3500 spectral entries covering more than 100 genera and more than 400 different species | Developed by a collaboration between Manchester Metropolitan University and NTTC |
| RiboPrinter | Genotypic | 6000 ribotypes consisting of 197 bacterial genera and 14,000 species | Type organisms and submitted isolates |
| MicroSeq 16S rRNA gene sequencing bacterial identification system | Genotypic | Bacterial full-gene and 500 basepair libraries have 1400+ entries | Includes an extensive coverage of Gram-negative nonfermenters, Bacillus, Coryneforms, Mycobacteria, and Staphylococcus |
| Microseq D2 LSU rDNA fungal identification system | Genotypic | 900 entries for yeast and filamentous fungi | Weak in both clinical and environmental fungi |
| Accugenix rRNA Gene Sequencing Systems | Genotypic | Accugenix bacterial database: 1607; Accugenix fungal database: 544 | Propriety database |
| Bergey's Manual of Systematic Bacteriology, 2nd ed. | Genotypic and Phenotypic | 849 genera and 4313 validly named prokaryotic species | Taxonomic authority |
| Ribosomal Database Release 2/06/04 | Genotypic | 87,860 aligned and annotated bacterial and archeal rRNA gene sequences | Extracted from primary sequence databases (DDBJ, EMBL, and GeneBank) |
| GeneBank (NCBI) | Genotypic | 1244 genera and 13,088 bacterial species | Public-domain database |

Driving the technology is the undisputed fact that these genotypic microbial identification methods, based on nucleic acid analyses, are less subjective, less dependent on the culture method, and theoretically more reliable because nucleic acids are highly conserved by microbial species. However, the microbiology laboratory cannot just buy the equipment, plug it in, and transfer a technician from performing other duties to running these methods. A significant investment in training, validation, and database development is required to successfully implement these methods.

The genotypic methods have some significant advantages; however their use should be limited to critical microbiological investigations associated with direct product failure, and identifications should be conducted in a specialized research-orientated laboratory within a pharmaceutical company (or sent to a qualified contact testing laboratory). The increased accuracy of identification with rRNA codon base sequencing and the ability to determine the strain of microorganism with ribotyping in some respects is a type of molecular epidemiology that seeks to more de-
finitively determine the origin of the microbial contamination in media fill and following sterility test failures and action level excursions during environmental monitoring.

## LITERATURE SURVEY

As stated earlier, in clinical microbiology genotypic identification methods have been successfully applied to the identification of fastidious organisms (e.g., Clamydia trachomatis and Neisseria gonorrhoeae), slow-growing organisms (e.g., fungal pathogens and Mycobacterium tuberculosis), rapid screening for pathogens (e.g., group A Streptococcus confirmatory testing), and unculturable organisms (e.g., the Whipple's bacillus Tropheryma whippelii) (19). Grazier et al. (20) looked at the ability of ribotyping to discriminate among Enterobacter cloacae isolates in comparison to a battery of conventional serological and biochemical assays and concluded that there was good agreement between identification by the genetic method and the combination of conventional methods. Clabouts et al. (21) performed a similar study with Clostridium difficile,

Martin et al. (22) with E. coli, Nielsen et al. (23) for Campylobacter jejuni, and Nadon et al. (24) for Listeria mono-cytogenes-all with similar results.

To date few publications have directly compared phenotypic and genotypic microbial identification methods. A study conducted at the Mayo Clinic reported using 72 unusual aerobic Gram-negative bacteria comparing the results achieved with the Sherlock MIDI system (cellular fatty acid profiles), MicroLog System (carbon utilization), and MicroSeq System (16S rRNA gene sequencing) against their clinical laboratory's conventional system (25). The agreement with the conventional system at the genus level was MicroSeq ( $97.2 \%$ ), MicroLog ( $87.5 \%$ ), and Sherlock ( $77.8 \%$ ). Drancourt et al. (26) demonstrated the need to accurately determine the gram reaction, oxidase and catalase activities, growth requirements, and appropriate biochemical profile determination to achieve accurate phenotypic identification; they used 16 S rDNA sequence analysis to identify previously unidentified environmental and clinical bacterial isolates. They also found that $10 \%$ of the environmental isolates could not be identified because they may be new species, and the sequencing could not separate Enterobacter and Pantoea isolates into species. In a poster at a recent ASM Annual Meeting, Waddington et al. compared genotypic and phenotypic methods for bacterial identification (27). They reported that with 18 ATCC cultures representing common environmental isolates the accuracy/reproducibility using MicroSeq DNA sequencing, Ribotyping, MIDI fatty acid ester analysis, Microlog substrate utilization, and Vitek 2 substrate utilization and biochemical reactions was $100 / 100 \%, 81 / 97 \%, 50 / 81 \%, 65 / 62 \%$, and $33 / 89 \%$, respectively. The selection of cultures readily identified by the DNA sequencing system may have unintentionally biased the outcome of the study.

Other studies using rRNA gene sequencing support the promise of the system for microbial identification but highlight the need to expand the database of the MicroSeq 500 16 S rRNA gene sequencing system. Furthermore, many microorganisms readily recognized by the phenotypic system do not require nucleic acid-based systems (28 and 29). However, a recent study by the National Reference Center for Mycology (Canada) shows that for difficult-to-cultivate mycobacteria these genetic approaches are actually more cost effective than conventional methods (30).

## DECISION MATRIX

Whereas rRNA gene sequencing has had a profound effect on microbial taxonomy, the appropriate role of nucleic acid-based identification methods in pharmaceutical microbiology is not yet clear. When companies are evaluating the suitability of microbial identification methods they are encouraged to consider a range of factors objectively in a decision matrix. Factors that must be considered and weighed are safety issues, breadth of application of the method, history of regulatory approval, equipment cost, unit-test cost, rapidity of the method, number of identification runs per day, number of vendors who can supply the equipment,
complexity of the method, ease of validation, training requirements, and potential cost savings. In addition, the use of the resultant information is a consideration. For example, there is no point to having highly detailed, expensive-to-obtain information to establish environmental trends in an aseptic manufacturing facility when identification to the genus level is sufficient to establish that the environment is in a state of control.
These considerations are common to all new microbiological methods. Recent publications discussing the adoption of new technology include the PDA Task Force Report (31), a recently published book on this topic (32), a USP Stimuli article discussing the relationship between rapid microbial methods and process analytical technology (33), and a recent In-Process Revision (7).

## VALIDATION OF MICROBIAL IDENTIFICATION METHODS

An excellent document that addresses both the selection and validation of microbial identification methods is Cumitech 31: Verification and Validation of Procedures in the Clinical Microbiology Laboratory (34). Another option is the AOAC International Official Methods program, which qualifies microbiological methods as official methods using interlaboratory collaborative studies (35). Additionally, USP has proposed a validation scheme (7). However, the proposed USP chapter is unsatisfactory in several regards, not least of which is that in an effort to address all aspects of the problem it has become so stilted and unwieldy that it is difficult to apply. The authors propose that the issue of microbial identification be removed from the draft general chapter $\langle 1223\rangle$ and be developed as a separate chapter utilizing available reference material.

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# Proposal and Qualification of a Harmonized Anti-Factor Ila Assay for Unfractionated Heparin Potency Determination 

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#### Abstract

In 1998, a working group was set up by the World Health Organization to address biological standardization of unfractionated heparin. The purpose of the working group was to examine the feasibility of replacing current pharmacopeial heparin assays with more modern test methods. A drafting group from within the working group was then given the task of testing and developing a suitable heparin assay, namely, the chromogenic Anti-Factor IIa (thrombin inhibition) method. The drafting group laboratories then conducted a multi-laboratory, multi-day qualification study of the proposed Anti-Factor IIa assay. In the present article, results of the drafting group qualification study are presented demonstrating the flexibility, precision, and robustness of the Anti-Factor IIa assay methodology. Based on the findings described herein, a proposal is put forth for conducting a larger collaborative study of the heparin Anti-Factor IIa assay. The larger collaborative study intends to assess suitability of the proposed Anti-Factor IIa method as a replacement for current pharmacopeial heparin assay methods involving animal plasmas.


## INTRODUCTION

The official USP monograph assay for measuring the potency of Unfractionated Heparin (heparin or UFH) has been in continuous, unchanged use since it was first introduced in 1949 (1). The USP heparin assay method is based on the ability of known amounts of heparin to inhibit the clotting of recalcified sheep plasma (2). The problems associated with the USP assay, including variability in sheep plasma sources, inability to automate the method, subjectivity in measuring the degree of clotting, and results being unsuitable for statistical evaluation, are well known and have been previously discussed (3). In a similar manner, the EP heparin potency assay involves measuring the extension of the clotting times when specified quantities of rabbit-brain cephalin and heparin are added to recalcified sheep plasma (widely known as the sheep plasma aPTT method; see refs. 4-6). No major difficulty has been reported with the EP assay, which has demonstrated robustness and reproducibility in two international collaborative studies (5, 6). However, the EP Assay relies on variable sheep-plasma and aPTT reagents that can, in turn, cause assay variability (3-5). Finally, the JP heparin assay procedure requires both sulfated bovine blood and bovine brain thrombokinase (8). Because of reports of bovine spongiphorm encephalopathy (BSE) in Europe, Japan, and the US, it is becoming increasingly difficult to obtain and/or import reagents for performing the assay using the JP procedure (9).

To circumvent the problems described above, a proposal for a new USP Heparin assay based on an Anti-Factor IIa (thrombin inhibition) procedure was put forth by Coyne et al. in a Pharmacopeial Forum Stimuli article in 1994 (3). A separate proposal was made by Johansen for an Anti-Factor IIa method as "a new pharmacopoeial assay for unfractionated heparin" during a 1998 meeting convened by the World Health Organisation (WHO) to establish the $5^{\text {th }}$ International Unfractionated Heparin Reference Standard (5, 10). Following the 1998 meeting, a Working Group (WG) was established consisting of representatives from WHO, the pharmacopoeias (i.e., USP, EP, and JP), industry, and national control authorities (11). The purpose of the WG was to examine the feasibility of using a chromogenic Anti-Factor IIa assay as a harmonized, global replacement assay for unfractionated heparin (11). A smaller Drafting Group was then established with a charge to "prepare a standard operating procedure for the proposed global Anti-Factor IIa chromogenic method" (11). During subsequent Drafting Group meetings (12,13), conditions were established for the harmonized Anti-Factor IIa method, and a validation study was designed and implemented by the Drafting Group members. One purpose of the present article is to present the design and findings of the Drafting Group Anti-Factor IIa method qualification study. A second purpose is to propose a future, larger collaborative study of the harmonized AntiFactor IIa procedure to assess suitability of the method as a replacement for current pharmacopeial heparin assays involving animal plasmas.

[^279]
## AIM OF STUDY

The aim of this study was to qualify the Anti-Factor IIa method finalized at the 2001 Drafting Group Meeting (13), using as reference and test materials the 5th International Standard for Unfractionated Heparin and a clinical preparation of unfractionated heparin, respectively (5). Six samples each of both reference and test heparin were sent to each of five participating laboratories for six separate days of AntiFactor IIa testing. Additionally, the study design required that participants use both common (provided) and in-house (local laboratory) antithrombin and thrombin assay components on each day of analysis and provide separate results for each set of reagents. Precision, robustness, and reagent effects were then assessed with a detailed statistical analysis of the results.

## SAMPLES

These two samples were sent to each of the participants:
S: The $5^{5 \mathrm{~h}}$ International Standard for Unfractionated Heparin, 97/578. Freeze-dried preparation. Potency 2031 IU/ampoule. T: A Clinical preparation of unfractionated heparin. Liquid preparation. Potency range $350-450 \mathrm{IU} / \mathrm{mL}$.
The participants were asked to use the potency range above as a guide and to adjust the initial dilutions of each heparin so that the responses for the dilutions in the assays were in a similar range.

In addition, a purified human antithrombin preparation (NIBSC, $95 / 808,5.0 \mathrm{IU} / \mathrm{ampoule})$ and a purified human thrombin preparation (NIBSC, $94 / 708$, specific activity $3400 \mathrm{IU} / \mathrm{mg}$, $20 \mathrm{IU} / \mathrm{ampoule}$ ) were also sent to participants. These were provided for use as common reagents in the overall study design (see below).

## PARTICIPANTS

The five laboratories listed in Appendix $A$ were the study participants. Each participating laboratory was arbitrarily assigned a number (see below), not necessarily representing the order of listing in Appendix $A$.

## ASSAY METHOD

Due to the fact that each laboratory utilized specialized equipment and technology, the assay method required only that certain time elements, as well as reagent and test article concentrations, be met by each participant's Anti-Factor IIa procedure. Thus, each participating laboratory was asked to perform the overall test method described, utilizing its own specific procedures in order to meet the assay requirements set forth below.

| Reagent | Method $^{\mathrm{A}}$ |
| :--- | :--- |
| Heparin, STD/Test | $0-10 \mathrm{mU}^{1}$ |
| Human AT | $0.075 \pm 0.025 \mathrm{IU} / \mathrm{mL}^{1}$ |
| Incubation | $37^{\circ} \mathrm{C} / 60 \mathrm{~s}$ |


| Reagent | Method $^{\mathrm{A}}$ |
| :--- | :--- |
| Thrombin | $0.56 \mathrm{IU} / \mathrm{mL}$ <br> (bovine/human) ${ }^{1, \mathrm{~B}}$ |
| Incubation <br> Substrate $\mathrm{B}^{\circ} \mathrm{C} / 60 \mathrm{~s}$ |  |
| Measurement | $0.278 \mathrm{mM}(\mathrm{S}-2238)^{2,3}$ |
| Kinetic/endpoint |  |

NOTE-Beyond meeting the assay requirements above, no further instructions were given to the participants. It should be noted that other chromogenic substrates for thrombin are commercially available and may be substituted for S-2238 (16).

## DESIGN AND NUMBER OF ASSAYS

All participants were requested to carry out 2 sets of 6 independent, daily assays ( 12 assays in total), one set using the common reagents provided and another set using inhouse (local) reagents. The same daily ampoules of standard and test article (and dilutions prepared from these) could be used for the assays performed using the different sets of reagents. An independent, daily assay was defined as one conducted with a completely fresh set of dilutions prepared from previously unopened ampoules of standard and test article.

## METHODS OF ANALYSIS

All assay results were analyzed using the principles of parallel line bioassay (14) comparing transformed assay response to log concentration. Here, an analysis of variance gives an assessment of the linearity and parallelism of the response lines, and tests for deviations from linearity and parallelism were performed at the $1 \%$ level of significance. For the majority of assays, the untransformed assay responses were found to give the best linearity with log concentration. In one laboratory, responses were transformed to percentages relative to the estimated upper and lower limits of the dose-response curve, and weighted regression of log response on $\log$ concentration was used.

All mean potencies were reported as unweighted geometric mean potencies. Variability between assays and laboratories were then expressed using geometric coefficients of variation (GCV; see ref. 15).

## RESULTS

Five laboratories presented results from 60 total assays. As previously mentioned, each laboratory was arbitrarily assigned a laboratory number. Lab 5 returned data for the
common reagents only. Lab 2 also provided data from an inhouse method (Method C) that was based on the proposed global method, using local in-house reagents. The Method C modifications to the final concentrations of the reagents were $0.06 \mathrm{IU} / \mathrm{mL}$ instead of $0.075 \mathrm{IU} / \mathrm{mL}$ of antithrombin; $0.48 \mathrm{IU} / \mathrm{mL}$ instead of $0.56 \mathrm{IU} / \mathrm{mL}$ of thrombin; 0.5 mM in-
stead of 0.28 mM of chromogenic substrate. Additionally, the incubation time between heparin and antithrombin was increased from 60 s to 90 s in Method C, and the incubation time of the heparin and antithrombin with thrombin was increased from 60 s to 180 s .

Table 1. Local in-house reagents

| Lab | Antithrombin | Thrombin | Readout | Instrumentation |
| :---: | :---: | :---: | :---: | :---: |
| 1 | Octapharma | Diagnostic Stago | Kinetic | Automated analyser |
|  |  | (human) |  |  |
| 2 | Chromogenix | Kordia (human) | Kinetic | Microtitre plate, robotic dilution |
| 3 | Chromogenix | Sigma (human) | Endpoint | Microtitre plate |
| 4 | Chromogenix | Biofac (bovine) | Kinetic | Automated analyser |
| 5 | - | - | Endpoint | Microtitre plate |

Table 1 shows the commercial sources of the in-house antithrombin and thrombin reagents used by the participants. Three laboratories used antithrombin preparations from the same manufacturer. Only one lab used thrombin of bovine origin; all other participants used thrombin of human origin. Two laboratories used automated analysers; two laboratories used microtitre plates with manual dilutions of samples, and one laboratory used microtitre plate with robotic dilutions of samples.

All raw results were reported and analyzed by the parallel line method (14). Tables $2 a-2 e$ show the result summaries for laboratories 1 to 5 , respectively, comparing potency estimates obtained using the common reagents and the local in-house reagents. Linearity and parallelism were deemed satisfactory for all results; exceptions were noted (see Tables $2 a-2 e$ ) in only 4 of the 60 assays analysed ( 2 assays with nonlinearity, 2 assays with nonparallelism).

Table 2a. Summary of results for lab 1

|  | Potency <br> Common <br> Reagents <br> (1) | In $\mathbf{m L})$ <br> Reagents <br> (2) | Ratio <br> $(\mathbf{1}):(2)$ |
| :---: | :---: | :---: | :---: |
| Assay | 396 | 397 | 1.00 |
| 1 | 414 | 404 | 1.02 |
| 2 | 397 | 397 | 1.00 |
| 3 | 405 | 407 | 0.99 |
| 4 | 408 | 412 | 0.99 |
| 5 | 412 | 407 | 1.01 |
| 6 | 405 | 404 | 1.00 |
| Mean (95\% <br> Confidence <br> Limits) | $(397-413)$ | $(398-410)$ | $(0.99-1.02)$ |
| Between- | $1.9 \%$ | $1.5 \%$ |  |
| Assay GCV | $(n=6)$ | $(n=6)$ |  |

Table 2b. Summary of results for lab 2

| Assay | Potency (IU/mL) |  | $\begin{aligned} & \text { Ratio } \\ & \text { (1):(2) } \end{aligned}$ | $\begin{gathered} \text { Potency } \\ \text { (IU/mL) } \\ \text { ("Method C") } \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: |
|  | Common Reagents <br> (1) | In-House Reagents <br> (2) |  |  |
| 1 | 439 | 421 | 1.04 | 458 |
| 2 | 419 | 425 | 0.98 | 399 |
| 3 | 430 | 398 | 1.08 | 431 |
| 4 | 405 | 450 | 0.90 | 412 |
| 5 | 446 | 406 | 1.10 | 413 |
| 6 | 432 | 415 | 1.04 | (412)* |
| Mean (95\% | 428 | 419 | 1.02 | 422 |
| Confidence | (413-444) | (401-438) | (0.95-1.10) | (395-451) |
| Limits) |  |  |  |  |
| Between-Assay | 3.5\% | 4.3\% |  | 5.5\% |
| GCV | ( $n=6$ ) | ( $n=6$ ) |  | ( $n=5$ ) |

[^280]Table 2c. Summary of results for lab 3

|  | Potency <br> Common <br> Reagents <br> $(\mathbf{1})$ | IU/mL) <br> In-House <br> Reagents <br> (2) | Ratio <br> (1):(2) |
| :---: | :---: | :---: | :---: |
| 1 | 393 | 396 | 0.99 |
| 2 | 383 | 384 | 1.00 |
| 3 | 434 | 428 | 1.01 |
| 4 | $(380)^{*}$ | 421 | $(0.90)$ |
| 5 | 389 | 470 | 0.83 |
| 6 | 353 | 382 | 0.92 |
| Mean (95\% <br> Confidence <br> Limits) | 390 | 412 | 0.95 |
| Between- | $756-426)$ | $(379-448)$ | $(0.85-1.05)$ |
| Assay |  |  |  |
| GCV | $(n=5)$ | $8.3 \%$ |  |

* invalid estimate (nonparallelism)

Table 2d. Summary of results for lab 4

| Potency (IU/mL) |  |  |  |
| :---: | :---: | :---: | :---: |
| Assay | Common Reagents (1) | In-House Reagents (2) | $\begin{aligned} & \text { Ratio } \\ & \text { (1):(2) } \end{aligned}$ |
| 1 | 378 | 381 | 0.99 |
| 2 | (399)* | 396 | (1.01) |
| 3 | 418 | 415 | 1.01 |
| 4 | 367 | 380 | 0.96 |
| 5 | 385 | 386 | 1.00 |
| 6 | 396 | 389 | 1.02 |
| Mean (95\% | 390 | 391 | 1.00 |
| Confidence Limits) | (372-409) | (378-405) | (0.97-1.02) |
| Between- | 4.3\% | 2.6\% |  |
| Assay | ( $n=5$ ) | ( $n=6$ ) |  |

[^281]Table 2e. Summary of results for lab 5

| Assay | Potency (IU/mL) <br> Common Reagents (1) |
| :---: | :---: |
| 1 | $(451)^{*}$ |
| 2 | 435 |
| 3 | 497 |
| 4 | 371 |
| 5 | 453 |
| 6 | 454 |
| Mean (95\% | 440 |
| Confidence Limits) | $(385-503)$ |
| Between-Assay | $11.4 \%$ |
| GCV | $(n=5)$ |
| ${ }^{*}$ invalid estimate (S nonlinear) |  |

A summary of each laboratory's overall mean potency estimates for sample T, in IU $/ \mathrm{mL}$, is presented in Table 3 and shown in histogram format in Figure 1. All the potency estimates shown in both Table 3 and Figure 1 were based on the same statistical method (14).


Fig. 1. Histogram showing potency estimates obtained using common and in-house reagents. The number in the squares indicates the laboratory number.

Table 3. Summary of intra-laboratory variability and overall mean potency estimates for sample $T$

| Potency (IU/mL) |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Laboratory | Common <br> Mean (95\% Confidence Limits) | (1) <br> BetweenAssay GCV | In-Hous <br> Mean (95\% Confidence Limits) | nts (2) BetweenAssay GCV | Mean (95\% Confidence Limits) |
| 1 | $\begin{gathered} 405 \\ (397-413) \end{gathered}$ | $\begin{aligned} & 1.9 \% \\ & (n=6) \end{aligned}$ | $\begin{gathered} 404 \\ (398-410) \end{gathered}$ | $\begin{aligned} & 1.5 \% \\ & (n=6) \end{aligned}$ | $\begin{gathered} 1.00 \\ (0.99-1.02) \end{gathered}$ |
| 2 | $\begin{gathered} 428 \\ (413-444) \end{gathered}$ | $\begin{aligned} & 3.5 \% \\ & (n=6) \end{aligned}$ | $\begin{gathered} 419 \\ (401-438) \end{gathered}$ | $\begin{aligned} & 4.3 \% \\ & (n=6) \end{aligned}$ | $\begin{gathered} 1.02 \\ (0.95-1.10) \end{gathered}$ |
| 3 | $\begin{gathered} 390 \\ (356-426) \end{gathered}$ | $\begin{aligned} & 7.5 \% \\ & (n=5) \end{aligned}$ | $\begin{gathered} 412 \\ (379-448) \end{gathered}$ | $\begin{aligned} & 8.3 \% \\ & (n=6) \end{aligned}$ | $\begin{gathered} 0.95 \\ (0.85-1.05) \end{gathered}$ |
| 4 | $\begin{gathered} 390 \\ (372-409) \end{gathered}$ | $\begin{aligned} & 4.3 \% \\ & (n=5) \end{aligned}$ | $\begin{gathered} 391 \\ (378-405) \end{gathered}$ | $\begin{aligned} & 2.6 \% \\ & (n=6) \end{aligned}$ | $\begin{gathered} 1.00 \\ (0.97-1.02) \end{gathered}$ |
| 5 | $\begin{gathered} 440 \\ (385-503) \\ \hline \end{gathered}$ | $\begin{gathered} 11.4 \% \\ (n=5) \end{gathered}$ | NT* | NT | - |

[^282]Between-assay variability was low: GCVs were $<10 \%$ (mean GCV 5.0\%) in all but one case. The mean ratios were not significantly different from 1.0 , indicating excellent agreement between results using different reagents.

The inter-laboratory variability was also low: GCV values measured $4.5 \%$ and $5.6 \%$ for in-house and common reagents assays, respectively. These findings also take into account that the common reagent used by lab 5 was the in-house reagent for lab 5. When all results were analyzed as a group, the overall GCV value was determined to be 4.4\% (see Table 4).

Table 4. Inter-laboratory variability

|  | \% GCV |
| :---: | :---: |
| Common Reagents | $5.6(n=5)$ |
| In-House Reagents | $4.5(n=5)$ |
| Mean | $4.4(n=9)$ |

The sensitivity of the assay was then investigated by comparing the fitted slopes obtained using the common reagents and the in-house reagents (see Table 5). Due to the fact that different participants utilized different readouts (endpoint or kinetic), it was not possible to compare the responses between laboratories, but it was feasible to compare results within each laboratory. For labs 1 and 2, fitted slopes were noted to be consistently steeper when using the common reagents. This situation was reversed for lab 4 . No such patterns were noted for lab 3 . Comparison of sensitivity could not be made for lab 5, because this participant carried out only assays using the common reagents.

Table 5. Fitted common slopes lab 1

| Assay | Common <br> Reagents | In-House <br> Reagents |
| :---: | :---: | :---: |
| 1 | 1.89 | 1.50 |
| 2 | 1.88 | 1.46 |
| 3 | 2.07 | 1.49 |
| 4 | 2.11 | 1.44 |
| 5 | 2.10 | 1.49 |
| 6 | 2.09 | 1.54 |

lab 2

| Assay | Common <br> Reagents | In-House <br> Reagents |
| :---: | :---: | :---: |
| 1 | 0.84 | 0.68 |
| 2 | 0.81 | 0.74 |
| 3 | 0.87 | 0.68 |
| 4 | 0.81 | 0.61 |
| 5 | 0.88 | 0.72 |
| 6 | 0.82 | 0.71 |

lab 3

| Assay | Common <br> Reagents | In-House <br> Reagents |
| :---: | :---: | :---: |
| 1 | 0.69 | 0.68 |
| 2 | 0.60 | 0.58 |
| 3 | 0.62 | 0.81 |
| 4 | - | 0.66 |
| 5 | 0.74 | 0.59 |
| 6 | 0.59 | 0.64 |


| lab 4 |  |  |
| :---: | :---: | :---: |
| Assay | Common <br> Reagents | In-House <br> Reagents |
| 1 | 0.31 | 0.50 |
| 2 | - | 0.49 |
| 3 | 0.26 | 0.46 |
| 4 | 0.27 | 0.46 |
| 5 | 0.26 | 0.45 |
| 6 | 0.24 | 0.46 |

## ADDITIONAL STUDY RESULTS

Because of known differences between the unit values of the USP assay Unit (U) and the International Unit (IU) for unfractionated heparin ( $5,11,17$ ), lab 1 conducted an additional and separate arm of the Anti-Factor IIa validation study described above. Briefly, lab 1 included separate dilutions of the USP Heparin Sodium Reference Standard (Lot K-5) in each of the 12 sets of assays described above ( 2 sets of reagents, 6 independent assays). The purpose of this separate study arm was to investigate what effect, if any, different standards would have on the measured potency of the test article ( $\mathbf{T}$ ).
Results of the separate study conducted by lab 1 are presented in Table 6. The results in Table 6 demonstrate mean test article potencies with $6 \%$ to $8 \%$ lower values when USP K-5 was utilized as the reference standard. The percentage differences measured with the present Anti-Factor IIa procedure are similar in scale to previously reported discrepancies noted between the International and USP Units (5, 17).

Table 6. Study of reference standard effects on test article potency values

|  | T Potency (IU/mL) with $\mathbf{5}^{\text {th }} \mathbf{~ I S}$ |  | T Potency (U/mL) with USP K-5 |  |
| :---: | :---: | :---: | :---: | :---: |
| Assay | Common | In-House | Common | In-House |
| 1 | 398 | 418 | 389 | 375 |
| 2 | 399 | 395 | 374 | 361 |
| 3 | 402 | 397 | 368 | 374 |
| 4 | 404 | 402 | 377 | 366 |
| 5 | 408 | 414 | 379 | 375 |
| 6 | 394 | 403 | 383 | 373 |
| Mean | 401 | 405 | 378 | 371 |

## NOTES-

1. All unit values were determined utilizing the slope/ratio procedure, which accounts for the slight differences in $\mathbf{T}$ $\mathrm{IU} / \mathrm{mL}$ values (above) from those listed in Table $2 a$.
2. Comparing the common/common reagent determinations, $\mathbf{T}$ mean U/mL Anti-Factor IIa potencies were $94 \%$ of the measured IU/mL values. When in-house/in-house reagent results were compared, $\mathbf{T}$ mean $\mathrm{U} / \mathrm{mL}$ values were $92 \%$ of the measured $\mathrm{IU} / \mathrm{mL}$ values.

## DISCUSSION

Although the laboratories participating in the study were experienced with other chromogenic test methods, this was the first multi-laboratory qualification study of the harmonized Anti-Factor IIa assay procedure involving unfractionated heparin. Considering this fact, the performance of the proposed Anti-Factor IIa assay method was excellent. The between-assay variability for both common reagents and in-house reagents was low, and the majority of GCV values were below $10 \%$. Higher \% GCVs were obtained by laboratories using the manual-dilution, microtitre plate methods. The inter-laboratory variability was equally low; the overall GCV was found to be only $4.4 \%$. There was a lower between-laboratory variability with the in-house reagents assays compared to the common reagents, but this was not statistically significant. There was no significant difference between the potency estimates obtained using the two types of reagents as indicated by the close to " 1 " ratio obtained between potency estimates by the different reagents. There was also no significant difference in the potency estimates between the potency estimates obtained using the different in-house reagents. In addition, there was also no significant difference between potency estimates obtained using kinetic or endpoint readouts for the assays.

The data presented also suggest that the proposed AntiFactor IIa method is easy to set up and sufficiently flexible to allow for differences in reagents and equipment among participants. Further evidence of flexibility was seen with results from the modified procedure (Method C) used by Lab 2, which reported potency estimates that were similar to those obtained by the other participants. Although only
a small number of laboratories were involved in this study, the data presented suggest that the proposed Anti-Factor IIa assay is sufficiently precise and robust to warrant further evaluation. A larger collaborative study is therefore proposed in order to further evaluate the proposed Anti-Factor IIa method as a possible replacement for current pharmacopeial heparin assays.

## ABBREVIATIONS

| AT | Antithrombin |
| :--- | :--- |
| BSE | Bovine spongiform encephalopathy |
| EP | European Pharmacopoeia |
| GCV | Geometric coefficient of variation |
| JP | Japanese Pharmacopoeia |
| NIBSC | National Institute for Biological Standards <br> and Control |
| USP | United States Pharmacopeia |
| WHO | World Health Organization |
| WG | Working group |

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# Sterilizing Filtrations with Microporous Membranes 

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#### Abstract

By definition (FDA, 1987), a sterilizing filter is one that withstands organism challenges of $1 \times 10^{7} \mathrm{cfu}^{\text {per } \mathrm{cm}^{2}}$ of effective filter area. The confronting organism is Brevundimonas diminuta ATCC 19146 cultivated according to Leahy and Sullivan (1978). Until rather recently, it was believed that the sterilization of fluids could be ensured by their filtration through a sterilizing membrane whose proper and pertinent identity was confirmed by its pore size rating, which was itself determined by integrity testing.

Developments in filtration practices showed this belief to be too generally founded. As the folk wisdom has it, "the devil is in the details." It was discovered that the positive conclusions based on pore size ratings were subject to modification by the physicochemical specificity of the organism-suspending fluid; by the individuality of the organism type in its size-changing response to the suspending fluid; in the possible alteration in the filter's pore size induced by the fluid; and by the adsorptive qualities of the membrane resulting from its particular polymeric composition-all influenced by the filtration conditions in their numerous varieties. This article reviews the present status of and knowledge about sterilizing filtrations with microporous membranes.


## THE PRESENT STATUS

What had once seemed simple was recognized as being quite complex. The certainty of obtaining sterile effluent requires far more than the identification of a "sterilizing filter" by a pore size rating. The complex of influences governing the outcome of an intended sterilizing filtration necessitates a careful validation of the process, including that of the filter (PDA Special Report \#26). The very drug preparation of interest, the exact membrane type, the precise filtration conditions, and the specific organism type(s) of concern must be employed in the necessary validation.

Sterilization-meaning the absence of all (organism) life becomes severely restricted by the present view of "sterilizing filtration." The practice becomes limited to the organisms of concern, possibly only to those tested in the validation exercise (Agalloco, 1998). B. diminuta proves not to be a universal model for all types of microorganisms. Bioburden isolates are to be preferred. However, a necessary condition of any test organisms is their amenity to identification and culturing. A more general conclusion regarding other organism types under the same processing conditions involves assumptions. "Reasoned" extrapolations to other drug preparations, or to other filters, or to other filtration conditions involve a degree of risk.

The same filter may not sterilize the same preparation under different filtration conditions, especially under dissimilar differential pressures (Leahy and Sullivan, 1978). A given membrane may or may not retain a particular organism type suspended in a different drug vehicle (Bowman et al., 1967). The organism type need not remain constant in size, but may alter in response to its suspending fluid (Gould

[^283]et al., 1993; Leo et al., 1997). The effect of the vehicle upon the polymeric membrane may cause a change in the pore size (Lukaszewicz and Meltzer, 1980).
This newer version of sterilizing filtration is short of the (illusory) certainties that accompanied the earlier beliefs based on pore size ratings, absolute filters, and an exclusivity of particle retention by the sieve retention mechanism. Perhaps not surprisingly, its implementation has lagged somewhat. Be that as it may, the situation is as described. The application of validation to sterilizing filtrations can endow the practice with the seriousness it deserves and with the reliability it requires (Jornitz and Meltzer, 1998; PDA Special Report \#26).

## MECHANISMS OF ORGANISM RETENTIONS

The axiom of solid geometry that a particle too large to enter an opening (pore) cannot pass through it is so supported by common experiences that it is the usual view of the mechanism of particle retention. It is the straightforwardness of this logic that served so firmly to bolster a belief in an unquestionable correlation of filtrative sterilization with pore size ratings (Johnston and Meltzer, 1979). However, organism (particle) retentions need not derive only from sieving, from the size exclusion mechanism that results from the particle size / pore size relationship. Adsorptive effects, including filter-surface impactions, can also be effective in this regard.
The adsorptive fixation of organisms to solid surfaces is reported in the literature. Pertsovskaya and Zvyagintsev (1971) state that different groups of different bacteria are adsorbed by polymeric films composed of polyamides, polyacrylates, polyethylenes, or cellulose acetate. That various bacteria adsorb onto various surfaces was also disclosed
by Gerson and Zajic (1978). Hjertin et al. (1974) studied the adsorption of yeasts on nonionogenic, hydrophobic agarose and the column adsorption of S. typhimurium.

Zierdt and his associates in 1997 at the National Institutes of Health noted that both gram-negative and gram-positive organisms were retained on the surfaces of polycarbonate and cellulose acetate membranes of pore sizes much larger than the bacteria. The organisms involved in the studies were Escherichia coli and Staphylococcus aureus. The adsorptive bonding of the bacteria to the polymeric filter surface withstood the mechanical and desorptive actions of washings with buffer solutions (Zierdt et al., 1977). SEM photographic evidence of $0.8-\mu \mathrm{m}$ S. aureus organisms retained on the surfaces of (track-etched) polycarbonate membranes of $12 \mu \mathrm{~m}$-rated pore size is shown in Figure 1 (Zierdt, 1978).


Figure 1.
The adsorptive removal of $B$. diminuta by a glass fiber prefilter in circumstances unattributable to sieve retention is shown in Figure 2 (Leahy and Sullivan, 1978). Tanny et al. (1979) challenged the exclusivity of sieve retention as the mechanism of organism removal by membrane filters. It was postulated that the retention of B. diminuta by 0.45 $\mu \mathrm{m}$-rated mixed esters of cellulose membranes involved adsorptive sequestration. An initial reluctance by some to accept this view stemmed from the firmly stated belief of earlier investigators that membrane filters were so uniform in their pore sizes, a condition favorable to sieving, as to serve solely as screen filters. Pore size distribution of membranes had early on been explored by mercury porosimetry and had been reported to be a narrow $5 \%$. The $0.45 \mu \mathrm{~m}-$ rated membrane was said to be $0.02 \mu \mathrm{~m}$ in its distribution; "It reflects an extraordinary degree of uniformity." (Dwyer, 1966). Subsequently, Marshall and Meltzer (1978) demonstrated the actual value to be closer to $100 \%$.


Figure 2.
De-emphasis of membrane pore size distribution delayed explanation of the dependence of organism retention on the challenge density. The exaggerated report of pore size uniformity confused the meaning of the pore size rating by trivializing its difference from the largest pores. Meant to signal the mean pore size, it came also to identify the set of largest pores, those that are the concern in particle retentions. Consequently, experts in the membrane field advised, "The membrane filter functions primarily as a screen filter. It retains all particles larger than the pore size of the filter." (emphasis added) (Dwyer, 1966). This is now known not to be so; nor does the pore size rating value represent the pore dimensions.
The erroneous concepts sustained belief in the exclusivity of sieve retention and catered to the comforting reliance on absolute filters. The reluctance to abandon the certainty of sieve retention, where it applies, in favor of the conditional actions of the adsorptive effect is evident even todayhence, the drive to use membranes of lower pore size ratings, more assertive of size exclusions, where $0.2 / 0.22$ $\mu \mathrm{m}$-rated filters do not yield sterile effluent. Not surprisingly, some 20 cases of such occurrences have been noted, B. diminuta not being a universal model for all organisms (Sundaram et al., 2001). Thus, $0.1 \mu \mathrm{~m}$-ratings are championed as alternatives to the more conventional use of the $0.2 / 0.22-\mu \mathrm{m}$ variety despite the observation that the organisms escaping capture by the latter are not necessarily retained by the former and also despite the penalty in flows where the advocated substitution is unnecessary (Kawamura et al., 2000).

## THE CHALLENGE DENSITY

The origins of the $1 \times 10^{7} / \mathrm{cm}^{2}$ value are unclear. Thermal sterilizations are seen as capable as achieving fewer than one failure in one million. Because of sampling limitations, sterilizing filtrations cannot ensure fewer than one failure per thousand. It may be that the $1 \times 10^{7}$ number was se-
lected to elevate reliability of the sterilizing technique. The target of one in 10 million also represents an attempt to match the number of challenging organisms to the number of pores calculated to be present in an area of membrane. The calculations, which take into account the total porosity of a membrane area and assume each pore to have the volume of a sphere $0.2 \mu \mathrm{~m}$ in diameter, are too presumptuous. Nevertheless, some calculations suggest there are 10 million pores, $0.2 \mu \mathrm{~m}$-rated, per square centimeter of microporous membrane. The object of the challenge is to ensure that even an occasional, single large pore will be confronted by an organism. The goal is statistically flawed. The attainment of the hoped-for organism/pore confrontation would not be realized. The organism disposition over the membrane would not be uniform but would follow the laws of probability via the Poisson distribution. Some of the pores would go unchallenged while some would be multi-challenged (Juran, 1974).

The $1 \times 10^{7} / \mathrm{cm}^{2}$ challenge far exceeds the degree of organism loadings that characterizes pharmaceutical preparations presented to final filters. It is, however, justified by the belief that a filter capable of withstanding a severe trial will assuredly resist lesser confrontations. Indeed, Elford (1933) found and Wallhäusser (1985) confirmed that higher organism densities resulted in greater probabilities of organism passage.

It should be pointed out, however, that not the total organism count itself but its state of dilution may influence the filter's retention qualities as an expression of its pore size distribution. The matter has been little investigated with organism, but with silica particles it is found that diluter suspensions are initially retained quite thoroughly; progressively suffer poorer retentions over time; but ultimately undergo improved removal efficiency (Zahka and Grant, 1991). The changes in particle removal over time are explained as follows: Despite the hydrodynamic flow being preferentially directed to the fewer larger pores present in the filter, it engages the overwhelmingly larger of numbers of smaller pores. Complete particle removal results, and the smaller pores thus encountered become blocked. In consequence, the proportion of larger pores increases. This promotes particle passage. As the particles accumulate at the larger pores, they become increasingly clogged and blocked. Increased particle retention then results (Jornitz and Meltzer, 2001).

The implications of these findings to the selection of challenge densities appropriate to the testing of pharmaceutical preparations are intriguing. Validation of the sterilizing filtration operation using the very drug preparation of interest, whatever its actual organism concentration, may finesse the problem.

## THE MODEL ORGANISM

FDA (1987) defines a sterilizing filter as one that retains $1 \times 10^{7}$ cfu of Brevundimonas diminuta ATCC 19146/per $\mathrm{cm}^{2}$ of effective filtration area (EFA). FDA, although cognizant of smaller organisms (Howard and Duberstein, 1980),
selected $B$. diminuta as the model organism for sterile filtrations. Although not the smallest organism known, B. dimin$u t a$ was considered diminutive enough to represent whatever smaller size organisms were likely to be present in pharmaceutical preparations.

It was this organism, then called Pseudomonas diminuta, that Bowman et al. (1963) found could be removed from its suspension by $0.45 \mu \mathrm{~m}$-rated microporous membrane except, surprisingly, in the presence of penicillinase. The $0.2 / 0.22 \mu \mathrm{~m}$-rated membrane was devised for its removal. Until the $0.45 \mu \mathrm{~m}-$ rated membrane exhibited its inability to retain $B$. diminuta in that situation, it was considered the "sterilizing filter." This appellation was passed to the $0.2 /$ $0.22 \mu \mathrm{~m}$-rated membrane that did so retain the organism. However, the $0.45 \mu \mathrm{~m}$-rated membrane otherwise did perform as the sterilizing filter for $B$. diminuta, as well as in other circumstances (Tanny et al., 1979; Trotter et al., 2002). It depends upon the filtration process. The point being made is that the attainment of sterility is dependent upon more than the pore-size rating. Process conditions and fluid properties also influence the retentivity. A universal type "sterilizing filter" is unlikely, given the variety and complexities of sterile filtrations (Jornitz and Meltzer, 2001).

The filtrative sterilization by $0.45 \mu \mathrm{~m}$-rated membranes of solutions containing $B$. diminuta had conventionally been ascribed to sieve retention. This was brought into question by the interfering action of penicillinase. It seemed unreasonable that penicillinase in solution could interfere with sieve retention. That the $0.45 \mu \mathrm{~m}-$ rated pores were too large to sterilize by sieve retention became evident in that no sterile effluent resulted. In the absence of the protein, it was rationalized, organism removal was governed by adsorptive sequestration. In its presence, penicillinase preemptively saturated the adsorption sites to competitively prevent organism sequestration. To effect the sieve retention of the organisms the smaller pore sized $0.2 / 0.22 \mu \mathrm{~m}$-rated membrane was necessitated. The penicillinase did not interfere with sieve retention.

The earlier reliance on pore size as a guarantor of sterility, as defined by $1 \times 10^{7} \mathrm{cfu} / \mathrm{cm}^{2}$ EFA of $B$. diminuta, was based on a correlation of membrane integrity test values (which differ for membranes of different polymeric compositions) with the degrees of retention (Reti, 1977; Pall and Kirnbauer, 1978; Johnston and Meltzer, 1979). The experimental work largely utilized organism suspensions in water or in saline lactose broth. At the time, sieve retention was considered the exclusive mechanism of particle removal by filters. Consequently, the limitations imposed by factors such as vehicle effects, etc., were neither appreciated nor investigated.

## PORE SIZE RATINGS

The microporous membrane filters are available from several manufacturers in a series of pore sizes, each with a pore-size distribution that remains undefined (Marshall and Meltzer, 1978) despite its contribution to the retention pic-
ture (Zahka and Grant, 1991; Jornitz et al., 2001). The poresize ratings, upon which the sterilizing ability of membranes was believed to depend, have uncertain values. The ratings are assigned individually by each manufacturer; there is no industry standard. Consequently, the same pore size rating from different manufacturers may represent different pore dimensions (Meltzer and Lindenblatt, 2002). The designated pore sizes, as is by now widely understood, do not describe actual pore dimensions. They serve as manufacturer's parts numbers.

Pore size designations were early on assigned on the basis of mercury intrusion measurements (Rootare, 1970; Meltzer, 1987) or from mean flow-pore analyses (ASTM 1980), not by particle retentions. To attempt to use organism retentions invites, among other complications, those influencing adsorptive sequestrations. Retention ratings have been attempted using latex beads in the presence of surfactants that suppress adsorptions (Wrasidlo and Mysels, 1984; Emory et al., 1993). In one study the manufacturer of nylon membranes reported that on the basis of latex particle retention its $0.1 \mu \mathrm{~m}$ rating would be labeled $0.28 \mu \mathrm{~m}$; its $0.2 \mu \mathrm{~m}-$ rated counterpart would be rated $0.46 \mu \mathrm{~m}$ (Krygier, 1986). As stated, the filter ratings are not standardized, and the manufacturers do not ordinarily disclose their pore size rating systems.

The first "sterilizing membrane" manufactured in the USA, on the original German technology (Zsygmondy, 1909), was rated as having a pore size of $0.45 \mu \mathrm{~m}$. As stated above, it was found, however, that B. diminuta was not removed by this filter when protein was present in the drug preparation. The pore size was reduced by half to effect sterilization (Bowman et al., 1967). The resulting "sterilizing membrane" was labeled 0.20 or $0.22 \mu \mathrm{~m}$-rated, depending upon its fabricator.

FDA's defining of a "sterilizing filter" as one capable of retaining the $B$. diminuta burden of $1 \times 10^{7} /$ per cm $^{2}$ led filter makers to label such filters $0.2 / 0.22 \mu \mathrm{~m}-$ rated. The relevant bacteria testing is performed under specified conditions during the membranes' development and production stages (ASTM, 1988). The $0.1 \mu \mathrm{~m}$-rated filters, being tighter, require no qualification. Yet, neither of these ratings always retains all the organism types that are encountered in pharmaceutical processing. The $0.45 \mu \mathrm{~m}-$ rated filters do not meet this retention qualification. Nevertheless, as demonstrated by Tanny et al. (1979) and Trotter et al. (2002), they
do perform as sterilizing filters under specified conditions. The point being made is that pore size ratings do not guarantee the attainment of sterilizing filtrations, as had previously been believed. Considerations other than pore size are involved. The drug preparation can affect sieve retentions by altering the pore size and/or organism size. It can also influence the adsorptive sequestration mechanism by modifying the adsorptive tendencies of the filter polymer. Additionally, the filtration conditions, such as temperature and pressure differentials, exert their own influences.

## PORE ARCHITECTURE

The membrane analogy is that of a polymeric sponge. The filter pores are pictured as being irregular and tortuous capillaries composed of interconnected spaces within the polymer matrix. The structure derives from a polymer solution which is deposited (cast) in a very precise thickness. Being in solution, the long-chain polymer molecules are in motion in the coiled, convoluted, and tangled forms normal to their ambient temperature. The chain segments are separated from one another by distances fixed by the polymer dilution. It is these interstitial spaces that in their interconnections prefigure the pores of the finished membrane. Casting formulae of different polymer concentrations give rise to different intersegmental separations, ultimately to different porosities, when by proper manipulation the polymer is precipitated as a gel, to be washed and dried to its solid, microporous membrane state. There is an ineluctable pore size distribution, and some anisotropic pore shape formation is inevitable (Kesting, 1985).

Williams and Meltzer (1983) hypothesize the formation of the microporous membrane structure according to known soap bubble clustering and in accord with zeolitic compositions. The open areas were prefigured in the casting solution. They are of various polygonal shapes, framed by polymeric struts and walls. They are interconnected by openings in their common walls. It is these openings that are the metering and retaining pores of the membrane. Figure 3 is of a detergent foam confined between glass plates. The polygonal structure is obvious. Figure 4 is of a reticulated polyurethane foam demonstrating the same polygonal forms.

## Detergent Foam

 Between Two Glass Plates

Figure 3.


Figure 4. Reticulated polyurethane foam

Too little is actually known about the pore shapes and sizes. The total porosity of the filter can be assayed, but the number of pores, however defined (Johnston, 2003), is estimated on the basis of oversimplifying assumptions. The number of the all-important retentive pores, or of the largest pores, cannot be assessed with confidence.

## VALIDATION

Given the complexity of factors that govern the attainment of a sterilizing filtration, the achievement of the objective requires documented experimental evidence. The necessary validation protocol has been amply described in the literature. PDA Technical Report \#26, Sterilizing Filtration of Liquids, is an excellent and detailed source. Jornitz and Meltzer (2001) also deal with the subject. Figure 5. from PDA Technical Report \#26 illustrates in chart form the validation strategies that are involved in the exercise.

*Concurrence of the appropriate regulatory agency should be sought prior to using this methodology.

Figure 5.

## RESTATEMENT OF PRESENT SITUATION

Until recently, the $0.2 / 0.22 \mu \mathrm{~m}$-rated membranes were considered the "sterilizing filters" based on their retention of Brevundimonas diminuta in the amount of $1 \times 10^{7}$ cfu per $\mathrm{cm}^{2}$ of filter surface. However, $B$. diminuta is not a suitable model for organisms encountered in all pharmaceutical settings. Some type organisms penetrate $0.2 / 0.22 \mu \mathrm{~m}$-rated membranes. When the organisms are known to be smaller, as in water purification contexts, $0.1 \mu \mathrm{~m}$-rated membrane should be employed. The $0.1 \mu \mathrm{~m}$-rated membranes are tighter than their 0.2 or $0.22 \mu \mathrm{~m}$-rated counterparts. Their pores being more restricted, they better retain smaller organisms based on the size-exclusion principle. However, their
unnecessary use will needlessly penalize flow rates and possibly throughputs.

Filters retain organisms by other than by the sieve retention mechanism. In liquid filtrations, the main mechanisms of microbial retention are sieve retention and impact and surface adsorptions. Depending upon the fluid vehicle, the organism type, the membrane polymer type, and the filtration conditions, cells may adhere to the pore surfaces as they negotiate the "tortuous pores" through the membranes. For gas filtrations, the same phenomena are at work, but the adsorptive phenomenon is enhanced by additional electrostatic interactions. These electrostatic interactions are so strong that, for a given filter rating, particle retention is significantly more efficient in gas filtration than in liquid filtration.

It is now recognized that a pore size of whatever rating, however confirmed by integrity testing, whether $0.2 / 0.22$, 0.1 , or 0.45 , is not enough to ensure sterile effluent. Other factors can influence the microbial retentive properties of microporous membranes for fluid filtration applications. These include the physicochemistry of the fluid; pH , viscosity, and chemical composition, and its compatibility with the filtration matrix. The filtration conditions are also influential: the filtration velocity/flow rate, the differential pressure across the filter membrane, and the duration of the filtration. Additionally, the surface properties of the filtration matrix, particularly its propensity for adsorptions, and the size and surface properties of the particles being filtered are important. The validation of the filtration process is necessitated by the many variables. Its proper implementation requires the use of the actual membrane type and the specific drug preparation under the actual use conditions.

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# The USP Perspective to Minimize the Potential Risk of TSE Infectivity in Bovine-Derived Articles Used in the Manufacture of Medical Products 

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#### Abstract

This Stimuli article on the potential risk of acquiring transmissible spongiform encephalopathy through the use of bovine-derived articles in the manufacture of medical products and on risk-reduction strategies to minimize this risk was prepared at the request of the USP Analytical Microbiology Expert Committee and USP Project Team 11. The article is divided into two major sections: a review of the illness and risk-reduction strategies. The review of the illness is intended to give the reader an overall view of the issues involved in transmissible spongiform encephalopathy and why it is a concern to the manufacturer, regulator, and consumer of health care products. The risk-reduction strategies are intended as a preliminary presentation of guidelines that may ultimately be included in a new general information chapter on the subject. Readers are invited to submit comments, suggested additions, changes, and revisions to the authors.


## INTRODUCTION

Articles of bovine origin are used extensively in the production of pharmaceuticals, biologics, medical devices, and dietary supplements; for many of these health care products, it is difficult to identify a single product from any one of the categories that does not contain or utilize in its production at least one component that can be derived from bovine sources. Bovine articles are used as active pharmaceutical ingredients, excipients, components of medical devices, or components of cell culture media used in the synthesis of biologics and biotechnological products. Since the first description and subsequent outbreaks of a transmissible spongiform encephalopathy (TSE) in cattle (bovine spongiform encephalopathy or BSE) capable of infecting other species, including humans, by the consumption of infected bovine products, there have been some concerns about the potential risk of TSE transmission through the use of health care products. Although there have been isolated reports of TSE transmission in domesticated animals linked to the use of vaccines (Agrimi et al., 1999; Caramelli et al., 2001), it is generally accepted that the TSE transmission risk through animal-derived articles used in the manufacture of health care products is very low (Bader et al., 1997; Cohen et al., 2003). Regardless of the very low risk potential, various US and international regulatory agencies have developed guidances to help manage and further reduce the potential transmission risks. The purpose of this article is to review the issues involved in TSE transmission risks and to outline general risk reduction strategies based upon current scientific studies and regulatory guidances.

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## REVIEW OF THE ILLNESS

TSEs are a family of transmissible animal and human diseases characterized by spongy degeneration of the brain with severe neurological signs and symptoms. No treatments for TSEs are available, and the disease is fatal in all known cases. TSEs are also characterized by relatively long incubation periods of several years and, within the brain, are accompanied by activation of microglial cells, hypertrophy and proliferation of astrocytes, and degenerative neuronal vacuolation. Clinical features include mental changes, ataxia, and loss of fine motor control of body homeostasis (Koster et al., 2003).
The first description of a TSE was published in the mid1700s in Europe for scrapie, a neurological disorder in sheep and goats. A human TSE, Creutzfeldt-Jakob disease (CJD) was first described in the early 1900s (Creutzfeldt, 1920). Other human spongiform encephalopathies described prior to 1995 include Kuru, Gerstmann-SträusslerScheinker syndrome, and fatal familiar insomnia. Additional TSEs include chronic wasting disease of elk and deer, which is endemic in certain parts of the United States and Canada (Williams and Young, 1980) and Transmissible Mink Encephalopathy (Marsh et al., 1976).
The causative agent of TSE (including BSE) is still controversial (Narang, 2002; Priola et al., 2003; Manuelidis and $\mathrm{Lu}, 2003$ ), but most studies point to proteinaceous infectious particles devoid of any nucleic acid and termed prions (Prusiner, 1991; Uptain and Lindquist, 2002; Caughey and Lansbury, 2003; King and Diaz-Avalos, 2004). Evidence suggests that a prion is a modified form of a normal cellular protein $\left(\mathrm{PrP}^{\mathrm{c}}\right)$. This protein is found predominantly on the surface of neurons; however, it is also found on lymphoid, lung, liver, spleen, and kidney tissues (Brown et al., 1994). Small amounts of the protein have also been reported on skeletal muscle (Thomzig et al., 2003) and blood cells (Cervenakova et al., 2003). It is a soluble glycoprotein with a
secondary structure containing about 42 percent and about 3 percent alpha helix and beta sheet, respectively. The modified form of $\mathrm{PrP}^{\mathrm{c}}, \mathrm{PrP}^{\mathrm{sc}}$ (for scrapie), is the putative disease agent. $\mathrm{Pr}^{\mathrm{Pc}}$ is relatively insoluble, accumulates in cytoplasmic vesicles of diseased individuals, and has the primary structure identical to $\operatorname{PrP}^{\mathrm{c}}$, but its secondary structure is about 30 percent and about 43 percent alpha helix and beta sheet, respectively (Pan et al., 1993). PrPc can bind to each other, forming large aggregates. Furthermore, when it is present $\mathrm{PrP}^{\text {sc }}$ catalyzes the conversion of $\operatorname{PrP}^{\mathrm{c}}$ to $\operatorname{PrP}^{\mathrm{sc}}$; expression of $\mathrm{PrP}^{\mathrm{c}}$ is required for infection with a TSE (Brandner et al., 1996).

The two forms of the prion protein differ greatly in their reaction to various biochemical, chemical, and physical agents known to either hydrolyze or denature proteins. $\operatorname{PrP}{ }^{\mathrm{c}}$ is completely digested by hydrolysis with proteinase K , readily hydrolyzed by relatively weak acids and bases, and denatured by high heat and chaotropic agents. Proteinase K removes only the N -terminal 67 amino acids of $\mathrm{PrP}^{\text {sc }}$, leaving a residue that is still infectious. $\mathrm{PrP}^{\mathrm{sc}}$ is also resistant to acid hydrolysis and denaturation by heat and chaotropic agents.

BSE was unknown until the 1980s, when it was first described in the United Kingdom (Wells et al., 1987). Before the causative agent and means of transmission were known, an outbreak of BSE occurred within the UK leading to the death of approximately 200,000 head of cattle diagnosed with the disease. In order to contain the illness, more than 4.5 million head of asymptomatic cattle were destroyed, devastating the British cattle industry (DTZ Pieda Consulting, 1998). Although the UK has had the greatest number of reported cases of BSE, the illness has also been reported throughout Europe, Israel, Japan, Canada, and, as of December 2003, the United States (OIE, 2004). In the vast majority of these diagnosed cases, the source of the BSE has been identified as originating in the UK. Because the sole incidence of BSE in the United States was in a cow traced back to Canada, the US Department of Agriculture (USDA) and the Office International des Epizooties considers this as a nonindigenous case. The only regions still reporting no cases of BSE are South America (excluding the Falkland Islands), Australia, and New Zealand.

The origin of BSE also is controversial. Two theories have been proposed. The more favored theory is that it arose from sheep and goat scrapie; this theory is, in part, supported by the fact that scrapie is widespread and remains one of the more common TSEs in domesticated animals. This theory is further supported by the discovery of a strain of sheep scrapie that has chemical properties similar to those of BSE (Hope et al., 2000). However, there are still some strain differences between scrapie prion and the BSE prion. Furthermore, scrapie and BSE differ in the signs, symptoms, and progression of the respective diseases. The alternative theory is that BSE arose spontaneously in a few cows within UK herds (Bostok, 2000). This theory is, in part, supported by the belief that the human TSE, CJD, occurs spontaneously in one in every one to five million people. It is thought that the spontaneous rate of BSE in cattle may be
similar. Although the origin of BSE is controversial, the amplification and subsequent spread of the causative agent is believed to be fairly well established (Lindenbaum, 2001; Collinge, 2001).
Prions are stabilized by fatty material, and extraction of lipids tends to make them more susceptible to heat denaturation. It is an international agricultural practice to feed cattle, especially dairy cows, high-protein supplements derived from rendered animal by-products. In the past, these animal by-products included the remains of sheep and goats, as well as cattle. Prior to the 1980 s, it was common practice to extract and market tallow from rendered animals. As the demand for tallow declined around 1980, renderers switched to a less expensive rendering process, which used lower temperature without removing lipids. This produced animal feed of higher fat content. Some speculate that a few TSE-infected animals entered into the rendering process, the process failed to inactivate prions, and the subsequent infected feed was given to healthy animals. Prions were able to withstand normal digestion, passed into the animals' circulatory systems, and eventually were deposited into nervous tissues, where they became amplified. As the infected animals were recycled through the rendering process, an amplification of the infectious materials occurred, resulting in the epidemic that was experienced in the UK (Wilesmith et al., 1991; Taylor et al., 1995).
Beginning in 1988, measures to control BSE in the UK were put into place, and numerous countries began to ban the importation of cattle and bovine products from the UK. Eventually, bans on the feeding of ruminant-derived animal feed to ruminants were adopted worldwide. Statistics on the illness in the UK indicate that the regulations put into place after the BSE outbreak, following an initial lag period caused by the long incubation period of the illness, have significantly reduced the incidence within that country. Incidences of BSE are still being reported, primarily in animals that were born prior to the institution and enforcement of the feed band (MAFF, 1998). Regardless of whether BSE represents cross-species transmission of scrapie or spontaneous eruption within cattle herds, there is a potential risk of additional BSE outbreaks in cattle herds in the future if the feed ban described above, which appears to have broken the cycle of transmission and amplification, is rescinded or if its enforcement is lax.
In the years intervening between the detection of BSE in the UK and the institution of measures to control its spread, infected cattle entered into the human food chain. Although CJD had been first described in the 1920s, starting in 1994 a new form of CJD, variant CJD (vCJD), began to appear in persons residing or having resided in the UK. The signs and symptoms of CJD (Will et al., 1996) include a mean age of onset of about 65 years; mean onset of clinical signs before death of about 4 months; displays of degrees of confusion and ataxia without abnormal behavior, and, upon autopsy, "florid" amyloid plaques usually absent from brain tissue. In contrast, the signs and symptoms of vCJD include a mean age of onset of about 29 years, mean onset of clinical signs before death of about 12 months, displays of abnormal be-
havior, and, upon autopsy, "florid" amyloid plaques always present (Ironside et al., 1997). Another difference between vCJD and CJD is that, to date, $100 \%$ of all vCJD patients are homozygous at codon 129 of the prion protein gene for methionine, whereas no such distinction is present in cases of CJD. In addition, when the brain material from the vCJD patients was strain typed using the mouse system, vCJD and BSE were found to be the same strain (Bruce et al., 1997). Furthermore, the size and glycosylation pattern of the prion molecule from CJD and vCJD are different; prions from patients with vCJD are identical to those found in cattle with BSE (Collinge et al., 1996). It has also been shown that for transgenic mice containing the human prion protein and infected with BSE, the incubation times are very similar to those of mice containing the bovine prion protein (Korth et al., 2003). These last three characteristics, along with geography of both the BSE and vCJD outbreaks, indicate that the source of vCJD was from the consumption of human food products of bovine origin. This indication suggests there may be a potential risk of TSE transmission to humans from the use of bovine-derived medicinal products. Currently, fewer than 150 patients with vCJD have been diagnosed in the UK; however, recent examination of lymphoid tissues surgically removed from appendicitis and tonsillitis UK patients leads to estimates that UK residents may harbor the infectious TSE agent at a rate of $49-692$ per million (Hilton et al., 2004).

Prions at high titer are found primarily within tissue of the central nervous system of infected animals. This includes the brain, spinal cord, and dorsal root ganglia; these tissues are referred to as high-infectivity tissues (WHO, 1999). In infected cattle, lower titers have been found in cerebrospinal fluid, lung, lymph tissue, spleen, kidney, liver, and ileum (Brown et al., 2001; Terry et al., 2003); these tissues are referred to as low-infectivity tissues. In cattle, no detectable infectivity was found in skeletal muscle, cardiac muscle, prostate, adrenal glands, clotted blood, fat, gingiva, intestine (except for the ileum), testis, thyroid, milk, mucus, feces, saliva, semen, serous exudate, sweat, tears, and urine; these tissues are regarded as noninfectious. However, other studies of TSE-infected hamsters have found prions in skeletal muscle (Thomzig et al., 2003). Studies using rodents have demonstrated the presence of TSE infectivity associated with blood (Cervenakova et al., 2003). This infectivity is associated mostly with the leukocyte and plasma fractions, and residual infectivity is associated with red blood cells. The transfusion of blood from preclinical sheep infected with either BSE or scrapie can infect naive sheep (Hunter et al., 2002). Moreover, the December 2003 report of a case of a human vCJD fatality in the United Kingdom, purportedly from a blood transfusion, indicates a potential TSE-infection risk associated with blood and blood products (Matthews et al., 2003). In addition, studies have found prions in the urine of TSE-infected rodents, cattle, and humans as detected by immunological methods; however, in-
tracerebral inoculation of hamsters with urine-derived prions did not cause clinical signs of prion disease even after a prolonged incubation period, suggesting urine-derived prions may differ in pathogenic properties from brain-derived prions (Shaked et al., 2001).

Animals and humans are currently diagnosed with TSE post-mortem using several types of tests. The classic diagnostic test is histological examination of brain tissue, looking for the characteristic vacuolar degeneration. There are also immunohistochemical tests that can confirm the presence of $\mathrm{PrP}^{\mathrm{sc}}$ in the vacuolated regions of the brain (Haritani et al., 1994). In addition, there are other, immunologically based tests, such as Western blots (Oesch et al., 2000) and ELISA (Grassi et al., 2001), that can quantitate the PrPsc present in tissues having high or moderately high titers. These tests typically take less time to perform than histological examination (6-8 hours versus weeks, respectively) and can be partially or fully automated. Although most of these are post-mortem tests, some of them can be used as ante-mortem tests of lymphoid tissue samples from the tonsils (Schreuder, et al., 1998) or from the third eyelid (O'Rourke et al., 2000) of infected animals. However, the immunochemical tests still require extensive sample collection and preparation and are expensive, limiting their feasibility for routine testing and monitoring the disease state of large herds. Current tests lack the sensitivity to detect prions in certain tissues, such as blood, where infectivity has been demonstrated. Moreover, current tests may not be able to detect infectivity in infected animals not yet showing clinical signs; negative results do not ensure the absence of infectivity. In these cases, the detection of infectivity is possible if suspect tissue is inoculated intracranially into experimental animals where the prions can become amplified. The disadvantage of the intracranial inoculation approach for detection of low infectivity is that it can take months to years to obtain a positive result. Although other analytical methods are under development for the detection and quantitation of prions from low-infectivity tissues such as blood (Schmerr et al., 1999; Schmitt et al., 2002), no currently available and fully available method is sensitive enough for routine ante-mortem screening of asymptomatic animals. Other factors hampering method development include an unclear understanding of what constitutes an infectious dose, the lack of Biosafety level 3 laboratories necessary for carrying out method development and validation, sample matrix interferences, and the lack of readily available, standardized reference materials for validation. In this situation, the best current approach to reduce the risk of transmitting TSE either via foods or health care products is through the appropriate sourcing of the animal-derived articles and the use of practices and procedures that have been shown to eliminate or destroy the infectivity. The following section will address these issues.

## RISK-REDUCTION STRATEGIES

This section considers measures for minimizing the potential risk of TSE transmission during the use of animal-derived materials, especially if the animal is a ruminant. Such materials may be used for the preparation of:

- active substances
- excipients
- raw or source materials and reagents used in production (e.g., bovine serum albumin, enzymes, culture mediaincluding those used to prepare working cell banks or new master cell banks)
- fermentation culture media (media used in establishment of stock microbial cultures should be evaluated only for contribution to final fermentation volume)
- medical devices
- reagents used to clean manufacturing equipment
- media used for media fills on equipment used to manufacture sterile products.
It is recommended that alternative, nonanimal source ingredients be substituted for animal-source ingredients whenever possible. However, in some cases, nonanimal source ingredients may not be suitable for the intended purpose. In these situations, animal-source ingredients are a necessity, and the implementation and maintenance of riskreduction strategies are a requirement.

These risk-reduction strategies are also applicable to materials that come into direct contact with the equipment used in the manufacture (and therefore have the potential to allow contamination) of, for example, test media used in plant and equipment validation. The proposed measures are especially applicable for bovine and other ruminant-derived material and may be adapted to include other animals if they are later shown to have the potential risk of transmitting the TSE agent.

In light of the current scientific knowledge and regardless of the geographic origin, milk is unlikely to present any risk of TSE contamination (Bader et al., 1997; Cohen et al., 2003). Therefore, milk and materials derived only from milk may be excluded from the scope of these strategies, provided the milk is sourced from healthy animals under the same conditions as milk collected for human food consumption. Derivatives of milk from ruminants prepared with the use of other ruminant materials (such as pancreatic-enzyme digest of casein), are not excluded from the scope of this article because of the use of these other ruminant materials.

Derivatives of wool and hair of ruminants, such as lanolin, wool alcohol, and amino acids are also excluded from the scope of this article, provided the wool and hair are sourced from live animals, because hair by itself is considered to have no potential of infectivity (Bader et al., 1997). Derivatives of wool and hair from ruminants prepared with the use of other ruminant materials (such as pancreatic enzymes) are not excluded from the scope of this article because of the use of these other ruminant materials.

## Manufacturing (Including Collection of Source Materials)

Ideally, the sourcing of materials of ruminant origin should be established closed herds. A closed herd is maintained in such a way as to minimize contact with other domestic ruminants to reduce the risk of contracting diseases, such as TSE, that are transferable to humans. The animals in a closed herd have not been suspected of scrapie, BSE, or other herd-threatening diseases. Members of the closed herd have documented female lineage, and each animal is uniquely identified. Adequate steps are taken to ensure that the animals of a closed herd do not come in contact with other animals not of the closed herd, although exposure to animals not thought to be of high risk of being TSE infected, such as horses, cats, and dogs, may be acceptable. Food provided to the animals of the closed herd contains no rumi-nant-derived protein or offal, and, preferably, all animal feed is produced within the confines of the closed herd facility to help guard against accidental exposure to TSE-infected feed. Once established, all cattle in a closed herd should be born to that herd. Furthermore, because research indicates that semen does not transmit TSE (WHO, 1999), new genetic variation should be introduced into a closed herd only as semen. A herd should be maintained under the conditions stated above for at least 6 years to ensure no latent TSE is present before it can be declared a closed herd (ES, 2000). The lowest possible potential risks of TSE transmission are through the use of bovine-derived articles originating from animals from closed herds, especially for bovine-derived articles that do not undergo processing to reduce infectivity.
Currently, due to the relatively small number of closed herds, bovine and other ruminant-derived articles from closed herds are in limited supply and tend to be more expensive than articles derived from open herds. When using closed herd-derived material is not feasible, additional details should be sought about the source of the bovine-derived materials and other measures taken to minimize the risk of transmission of TSE agents (as well as other animal diseases); the remaining part of this discussion will focus on the use of open-herd, animal-derived material. The manufacturer of the medicinal product should audit the supplier of these materials to ensure that the latter are sourced and handled in conformity with the principles outlined in this article and appropriate quality control systems.
The risk of transmission of infectious agents can be greatly reduced by controlling a number of parameters. These parameters include:

- geographic source of animals
- nature of animal tissue used in manufacture
- production process(es).

It is unlikely that any single approach will establish the safety of a product, and therefore the three approaches cited above need to complement each other to minimize the risk of contamination.

## Animals as Sources of Materials

Careful selection of source materials is the most important criterion for the safety of medicinal products. The most satisfactory sources of materials are closed herds, followed by open herds from countries that have not reported cases of endogenous BSE and have (OIE, 2003):

- compulsory notification
- compulsory clinical and laboratory verification of suspected cases.
Official certification of the origin should be available from the supplier, obtained and kept on file. In addition, firms should ensure that a risk of BSE infection is not introduced from the following factors:
- the importation of cattle from countries where a high incidence of BSE has occurred
- the importation of progeny of affected females
- the use in ruminant feed of meat and bone meal containing any ruminant protein.
Current US FDA recommendations prohibit the use of any bovine-derived materials that originate from countries reporting indigenous cases of BSE in any FDA-regulated product (CBER, 2000), with the exception of gelatin. For veterinary biologics, current Center for Veterinary Biologics (USDA) regulations indicate that ingredients of animal origin should be sourced from countries whose BSE status is either no or low risk as defined by the US National Center for Import and Export and 9 CFR 94.18 (CVB, 2001). However, suppliers and manufacturers should not rely on country of origin alone to ensure the safety of the animal-derived materials when additional and reasonable practices and procedures are available to further reduce the potential risk. The absence of reports of indigenous cases of BSE should not be interpreted as evidence of complete absence of BSE within a country or region.

Source animals should be born after the feeding ban was imposed. If the date of birth of the animals is not known, both the implementation date of the ban and the incubation period of TSE should be considered to determine the safety of the sourcing.

Along with these measures, manufacturers of a medicinal product should justify their strategy for sourcing, in relation to the category of materials, the quantity of source material, and the intended use of the finished medicinal product. In supplying countries, source materials from well-monitored herds may provide an extra safety margin.

## Parts of Animal Bodies, Body Fluids, and Secretions as Starting Materials

Table 1 is a partial list of articles of bovine origin commonly used to manufacture medical products; the table also includes the common source tissue from which the articles are derived. In a TSE-infected animal, different organs and secretions have different levels of infectivity. On the basis of data on natural scrapie, organs, tissues and fluids have been classified into four main groups bearing different potential risks, as shown in Table 2 (EMEA, 2001). Although the dis-
tribution of infectivity in BSE-affected cattle may be different, the classification of tissues and body fluids in Table 2 can be a consideration for the selection of bovine-source materials; cross-referencing the information contained in Table 1 with Table 2 can yield some indications about the relative potential risk of a particular bovine-derived article to carry TSE infectivity. It is important to note the following points:

- the classification of tissues shown in Table 2 is based on titration of infectivity in mice inoculated by the intracerebral route. In experimental models using strains adapted to laboratory animals, higher titers and a slightly different classification of tissues may occur
- in certain situations there could be cross-contamination of tissues of different categories of infectivity. The potential risk will be influenced by the circumstances in which tissues were removed, especially contact of material of a low-risk group with that of a high-risk group. Thus, the cross-contamination of some tissues may be increased if infected animals are slaughtered by penetrative brain stunning or if the brain and/or spinal cord are sawed. The risk of cross-contamination will be decreased if body fluids are collected with minimal damage to tissue and cellular components are removed and if fetal blood is collected without contamination from other maternal or fetal tissues, including placenta or amniotic and allantoic fluids
- the risk posed by cross-contamination will be dependent on several complementary factors, including:
- precautions adopted to avoid contamination during collection of tissues (see above)
- level of contamination (amount of the contaminating tissue)
- amount of material to be used
- processes to which the material will be subjected during the manufacturing process
- no detectable infectivity does not necessarily mean no infectivity. Suppliers and manufacturers should not rely upon the tissue origin of the ruminant-derived article alone to ensure the lowest potential TSE risk when additional and reasonable practices and procedures also are available to reduce the risk even further
- the potential risk of a bovine-derived article carrying TSE infectivity is a function of both the potential risk associated with a particular tissue and the processes involved in the extraction and isolation of the article from the tissue. The potential risk of articles derived from high TSE infectivity tissue can be reduced by processes that can clear the TSE agent.
Suppliers and manufacturers of medicinal products should assess the potential risk and adjust their practices and procedures accordingly to minimize the potential risk of TSE infective to the lowest practical level.

Table 1. Partial list of articles of bovine origin used in the production of pharmaceuticals, biologics, medical devices, and dietary supplements

| Bovine Article | Tissue of Origin | Use | Alternatives Currently Available |
| :---: | :---: | :---: | :---: |
| Amino acids | Hair/skin | API and cell culture media | Yes |
| Aprotinin bovine | Lung | API | No |
| Bone and bone derivatives | Bone | Medical devices | Limited |
| Bovine colostrum | Colostrum | Colostrum | No |
| Bovine immunoglobulins | Blood, colostrum | Cell culture media | Limited |
| Bovine serum | Blood | Cell culture media | Limited |
| Bovine serum albumin | Blood | Cell culture media | Limited |
| Calf serum | Blood | Cell culture media | Limited |
| Casein derivatives | Milk | Excipients and cell culture media | Limited |
| Cholesterol | Brain | Excipient | Yes |
| Chondroitin sulfate sodium | Bones | API and dietary supplement | Yes |
| Creatine | Muscle | Dietary supplement | Yes |
| Chymotrypsin | Pancreas | API and cell culture media | Limited |
| Collagen | Bone/hide | Medical device and cell culture media | Yes |
| Corticotropin | Pituitary | API | Yes |
| Diglycerides | Tallow | Excipient | Yes |
| Fatty acids | Tallow | Excipient | Yes |
| Fetal bovine serum | Bone | Cell culture media | Limited |
| Fibroblast growth factors | Multiple (including brain) | Cell culture media | Limited |
| Fibronectin | Blood | Cell culture media | Yes |
| Gelatin | Bone and hide | Excipient and cell culture media | Limited |
| Glucagon | Pancreas | API | Yes |
| Glycerin | Tallow | Excipient and cell culture media | Yes |
| Hard fat | Tallow | Excipient | Yes |
| Hemoglobin | Blood | Blood replacement | Limited |
| Heparin | Intestine | API | Limited |
| Hyaluronidase | Testis | API | Yes |
| Insulin | Pancreas | API | Yes |
| Lactitol | Milk | Excipient | No |
| Lactoferrin | Milk | Excipient | Limited |
| Lactose | Milk | Excipient | Limited |
| Lactulose | Milk | API | Limited |
| Levothyroxine sodium | Thyroid | API | Limited |
| Monoglycerides | Tallow | Excipient | Yes |
| Oxytocin | Pituitary | API | Yes |
| Pancreatin | Pancreas | API | Yes |
| Pancrelipase | Pancreas | API | Yes |
| Pegademase bovine | Intestine | API | No |
| Pepsin | Stomach | API and cell culture media | Yes |
| Peptone | Muscle | Cell culture media | Limited |
| Phospholipids | Brain | Excipient | Yes |
| Pituitary gland extract | Pituitary gland | Cell culture media | Limited |
| Polysorbate 80 | Tallow | Excipient and cell culture media | Yes |
| Smallpox vaccine | Living skin | Live vaccine | No |
| Stearates | Tallow | Excipients and cell culture media | Yes |
| Thrombin | Blood | API | No |
| Thyroid | Thyroid | API | Yes |
| Trypsin | Pancreas | API and cell culture media | Limited |
| Vasopressin | Pituitary | API | Yes |

Table 2. Relative scrapie infectivity titers in tissues and body fluids from naturally infected sheep and goats with clinical scrapie ${ }^{1}$

| Category I | High infectivity <br> Brain, spinal cord, (eye) <br> Category II <br> Medium infectivity |
| :---: | :---: |
| Category III | Ileum, lymph nodes, proximal colon, spleen, tonsil (dura mater, pineal gland, placenta), <br> cerebrospinal fluid, pituitary, adrenal gland <br> Low infectivity |
| Category IV | Distal colon, nasal mucosa, peripheral nerves, bone marrow, liver, lung, pancreas, thymus, <br> blood <br> No detectable infectivity |
|  | Clotted blood, feces, heart, kidney, mammary gland, milk, ovary, saliva, salivary gland, <br> seminal vesicle, serum, skeletal muscle, testis, thyroid, uterus, fetal tissue, (bile, bone), car- <br> tilaginous tissue, connective tissue, hair skin, urine) |

${ }^{1}$ Tissues in parentheses were not titrated in the original studies, but their relative infectivity is indicated by other data on spongiform encephalopathies. On the basis of their composition, materials not listed may be classified by analogy to those mentioned.
${ }^{2}$ No infectivity was transmitted in bioassays involving inoculation of up to 5 mg of tissue into rodent brains.

## Process Validation

Due to the documented resistance of TSE agents to most inactivation procedures, controlled sourcing is the most important criterion in achieving acceptable product safety. However, whenever possible, validation studies of processes developed to reduce or eliminate prions from potentially infected materials should be performed.

Caveats to performing such studies are that validation studies of removal/inactivation procedures may be difficult to interpret because it is necessary to take into consideration the nature of the spiked material and its relevance to the natural situation, the design of the study (including scalingdown of processes), and the method of detection of the agent (in vitro or in vivo assay), after spiking and after the treatment. Further research is needed to develop an understanding of the most appropriate methodology for validation studies. An additional problem in performing prion clearance validation studies is the lack of readily available, suitably well-characterized and standardized reference materials for spiking. Regardless, if claims are made for the ability of a specific manufacturing process to remove or inactivate TSE agents, these claims will have to be substantiated by appropriate validation studies with suitably characterized reference material. Because there are currently no validated analytical methods for the detection of small amounts of the TSE agent, TSE clearance validation studies typically employ the intracranial injection of in-processed material into rodents for amplification and detection of potential residual infectivity (Blum et al., 1998). Analysts should consult USP general chapter Design and Analysis of Biological Assays $\langle 111\rangle$ when developing their validation studies.

Beyond the particular limitations that apply to TSE validation studies and their interpretation, the major hurdle is identifying steps that will effectively remove or inactivate TSE agents during the manufacture of biological medicinal
products. Manufacturers are encouraged to continue their investigations into removal and inactivation methods to identify steps/processes that will have benefit in ensuring the removal or inactivation of TSE agents. In any event, a production process whenever possible should be designed taking note of available information about methods that are thought to inactivate or remove TSE agents. For example, certain production procedures such as those used in the manufacture of tallow, tallow derivatives, and gelatin may contribute considerably to the reduction of the risk of TSE contamination.

## TSE Reference Materials

As indicated previously, there are no readily available, well-characterized, and standardized TSE reference materials with which to perform TSE clearance validation studies. However, the acquisition of some forms of TSE reference materials, most frequently TSE-infected brain homogenate, is sometimes possible via academic sources. Within the United States, the possession, use, and transfer of TSE agents are regulated by USDA ( 9 CFR Part 121, 2002). Potential users of TSE reference materials should consult and comply with the regulations. When selecting materials to be used in validation studies, researchers should consider the relative resistance of the TSE reference materials to be cleared by a given procedural step. For example, certain TSE strains, such as mouse-adapted BSE strain 301 V , appear to be the most resistant to heat inactivation (Bostock, 2000). It is recommended that this strain, or a strain showing similar resistance to heat, be used to validate a heat treatment step. Although TSE-infected brain homogenate appears to be the most available type of TSE reference material, such material may not be the best for all situations. The brain matrix in which the TSE agent is found may promote or prevent the inactivation of a given procedural step. In such cases, the use of isolated prion protein may be more appropriate.

## Age of Animals

Because the accumulation of TSE infectivity occurs during an incubation period of several years, sourcing from young animals may be prudent. Because this consideration will be lot specific, the audit of the raw material supplier should include a review of records establishing this fact. In addition, the purchase contract should stipulate the maximum age of the source animals.

## Specific Products

Tallow. Tallow used as the starting material for the manufacture of tallow derivatives should be produced by a method at least as robust and rigorous as those referred to in international regulations (EMEA, 2001 and APAG, 2003). Tallow derivatives such as glycerol and fatty acids that are manufactured from tallow by rigorous processes have been the subject of specific consideration and are thought unlikely to be infectious. Examples of rigorous processes are:

- transesterification or hydrolysis at not less than $200^{\circ} \mathrm{C}$ for not less than 20 minutes under pressure (glycerol, fatty acids, and fatty acid ester production)
- saponification with 12 M NaOH (glycerol and soap production)
- batch processes: at not less than $95^{\circ} \mathrm{C}$ for not less than 3 hours
- continuous processes: at not less than $140^{\circ} \mathrm{C}$, at a pressure of 2 bars ( 2000 hPA ) for not less than 8 minutes, or equivalent.
Gelatin. Current US FDA guidance for industry on the use and sourcing of gelatin for health care products (FDA, 1997) allows for the use of bovine-derived gelatin from cattle from countries reporting BSE or from countries not meeting the latest international BSE-related standards (OIE, 2003) provided:
- importers, manufacturers, and suppliers of bovine materials determine the tissue, species, and country source of all such materials to be used in processing gelatin for human use. This requires thorough record keeping with a clear indication of chain of custody
- bones and hides from cattle, from any country, that show signs of neurological disease are not to be used as raw material for the manufacture of gelatin
- the slaughterhouse removes the heads, spines, and spinal cords immediately after slaughter and that the heads, spines, and spinal cords are not used in gelatin production
- the gelatin produced from the above countries is not to be used either in injectable, ophthalmic, or implanted FDA-regulated products, or in their manufacture. The gelatin may be used for oral dosage forms and cosmetics.
In order to reduce the potential risk of transmitting the TSE agent in gelatin produced from cattle originating and residing in BSE-free countries, it is recommended that the practice described in the third item above - the removal
of heads, spines, and spinal cord immediately after slaughter and the nonuse of heads, spines, and spinal cords in gelatin production - also be followed. Regardless of the country of origin of the bovine material, it is recommended that the alkaline process of manufacturing gelatin be performed, because this method has been shown to clear the TSE agent (Inveresk Research International, 1998a, 1998b, and 1999). Systems should be in place for monitoring of the production process and for batch delineation (i.e., definition of batch, separation of batches, cleaning between batches, etc.). The potential for cross-contamination with possible infectious material is to be avoided.

Other bovine-derived articles. The extraction and production of both tallow and gelatin from bovine tissues involve the prolonged exposure of the tissues to high moist heat and/or high pH , agents that have been shown to inactivate the TSE agent. However, such treatments are inappropriate for the extraction of many other types of bovinederived articles because those treatments will lead to the destruction of the article of interest. In these cases, other means to remove or destroy the TSE agents must be employed. In some situations, conventional chemical and biochemical extraction and isolation procedures may be sufficient to remove the infectious agent. For example, it has been shown that an extraction and isolation procedure involving multiple ammonium sulfate fractionation steps and ion-exchange chromatography, plus other conventional techniques, were sufficient to significantly reduce the TSE infectivity from an aprotinin preparation derived from bovine lungs that had been spiked with TSE-infected brain homogenate (Blum et al., 1998). Similar techniques may be effective for other bovine-derived articles.

## CONCLUDING REMARKS

The assessment of the risks associated with TSE requires careful consideration of all of the parameters cited, and the preferred option should be to avoid the use of material derived from animals known to be susceptible (other than by experimental challenge) to TSEs in the products produced by the pharmaceutical industry. The acceptability of a particular medicinal product containing the materials, or which as a result of manufacture could contain these materials, will be influenced by a number of factors, including:

- documented and recorded source of animals
- nature of animal tissue used in manufacture
- production process(es)
- route of administration
- quantity of tissue used in the medicinal products
- maximum therapeutic dosage (daily dosage and duration of treatment)
- intended use of the product.

Manufacturers of medicinal articles containing ingredients of animal origin are responsible for the selection and justification of adequate measures to reduce the potential risk of TSE infectivity. The state of science and technology must be taken into consideration. Notwithstanding the points and considerations raised above, it should be empha-
sized that the potential risks associated with a given medicinal product should be considered individually in the light of specific circumstances and any new development in the current understanding of TSEs. The various steps to be taken by USP should provide an additional and complementary prospective to the strategies developed in this Stimuli article, with the ultimate goal of benefiting the patient.

## USP's BSE-TSE Initiative

In 2002, USP initiated the formation of a Project Team to advise the USP Council of Experts on steps that USP could initiate to help ensure the safety of pharmaceutical products in terms of BSE-TSE contamination. The Project Team includes the following national and international experts:

Brian Nunnally - Eli Lilly and Co.
Byron Rippke - US Department of Agriculture
Chuck Filburn - Nutramax Laboratories, Inc
David Schoneker - Colorcon
Everett Flanigan - Advanced ChemTech
Hannelore Wilkommen -Clearant GmbH
James Akers - Akers, Kennedy and Associates
Jordi Ruiz-Combalia - BIOIBERICA, S.A.
Joseph Knapp - University of Pittsburgh, School of Pharmacy
Judd Aiken - University of Wisconsin, School of Veterinary Medicine
Kristen Blancard - Nutramax Laboratories, Inc.
Louis Blecher - International Specialty Products
Mary Jo Schmerr - Iowa State University, College of Veterinary Medicine
Peter Ganz - Health Canada
Ralph Gomez - Hoffmann-La Roche Inc.
Richard Moreton - Penwest Pharmaceuticals Co.
Scott Sutton - Vectech Consulting
Susan Schniepp - Abbott Laboratories
Taryn Rogalski-Salter - Merck \& Company
Thomas Kreil - Baxter BioScience
Ana Padilla - WHO
Debbie Cooper - Wyeth
The Project Team discussed the role of USP and highlighted the need for standardized methods and reference materials. USP is investigating the elaboration of reference materials, including brain homogenate, reagents, and analytical procedures, that could be useful in the manufacture of bovine-derived articles and medical products. USP recognizes that the next step could be the development of an information chapter based on this Stimuli article and the need to monitor the new analytical procedures in order to be able to standardize those procedures in the future. Furthermore, USP is developing two new general information chapters, Glycoprotein and Glycan Analysis $\langle 1084\rangle$ and Biological Assay Validation $\langle 1033\rangle$, which will provide additional framework for the standardization and validation of biological assays and glycoprotein analysis. These general information chapters should assist suppliers and medical
product manufacturers in the development and validation of procedures to minimize the potential risk of TSE contamination of bovine-derived articles.

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## NOMENCLATURE

This section includes supplements to the latest edition of the USP Dictionary of USAN and International Drug Names that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

## USP Dictionary of USAN and International Drug Names 2004 USP DICTIONARY SUPPLEMENT 3

IMPORTANT-Save this Supplement. This and all supplements appearing in $P F$ are needed to keep the 2004 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2004) edition will be included in the next complete edition of the Dictionary.

## New United States Adopted Names (USAN)

The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of $P F$ for other new USAN to supplement the Dictionary main volume.

Alagebrium Chloride [2004] ( $\mathrm{al} \mathrm{a}^{\prime \prime}$ je bree ${ }^{\prime}$ um). $\mathrm{C}_{13} \mathrm{H}_{14}$ ClNOS. 267.78. (1) Thiazolium, 4,5-dimethyl-3-(2-oxo-2-pheny-lethyl)-, chloride; (2) 4,5-Dimethyl-3-(2-oxo-2-phenylethyl)thiazolium chloride. CAS-341028-37-3. Prevention and treatment of cardiovascular complications of aging, diabetes, and end stage renal disease; diabetic multisymptom pathology (other than cardiovascular) including retinopathy, neuphropathy, neuropathy, and ulcers (advanced glycosylation endproduct $(A G E)$ crosslink inhibitor). (Alteon) $\diamond A L T$ 711

$\mathrm{Cl}^{-}$

Atilmotin [2004] ( $\mathrm{a}^{\prime \prime}$ til moe' tin). $\mathrm{C}_{86} \mathrm{H}_{135} \mathrm{~N}_{20} \mathrm{O}_{19}{ }^{+}$. 1753.00. (1) LLysinamide, $N$-[(2S)-1-oxo-3-phenyl-2-(trimethylammonio)-propyl]-L-valyl-L-prolyl-L-isoleucyl-L-phenylalanyl-L-threo-nyl-L-tyrosylglycyl-L- $\alpha$-glutamyl-L-leucyl-L-glutaminyl-D-ar-ginyl-L-leucyl-; (2) $N-[(2 S)-3-$ Phenyl-2-(trimethylammonio)propanoyl]-L-valyl-L-prolyl-L-isoleucyl-L-phenylalanyl-L-threonyl-L-tyrosylglycyl-L-glutamyl-L-leu-cyl-L-glutaminyl-D-arginyl-L-leucyl-L-lysinamide. CAS-533927-56-9. Intended for use in the stimulation of gastrointestinal motility (GI prokinetic agent)(motilin receptor agonist). (Baxter Anesthesia and Critical Care) $\diamond M O T-288$; OHM-11638; BAX-ACC-1638


Becatecarin [2004] (be" ka tek' ar in). $\mathrm{C}_{33} \mathrm{H}_{34} \mathrm{Cl}_{2} \mathrm{~N}_{4} \mathrm{O}_{7}$. 669.60. (1) $5 H$-Indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione, 1,11-dichloro-6-[2-(diethylamino)ethyl]-12,13-dihydro-12-(4-O-methyl- $\beta$-D-glucopyranosyl)-; (2) 1,11-Dichloro-6-[2-(diethylamino)ethyl]-12-(4-O-methyl- $\beta$-D-glucopyranosyl)-12,13-dihydro- 5 H -indolo [2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione. CAS-119673-08-4. Antineoplastic (rebeccamycin analogue). (Exelixis) $\diamond X L 119 ; B M S-181176 ; B M Y-$ 27557; NSC-655649


Cariporide Mesylate [2004] (kar ee por' ide).
$\mathrm{C}_{12} \mathrm{H}_{17} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S} . \mathrm{CH}_{4} \mathrm{O}_{3} \mathrm{~S} .379 .46$. [Cariporide is INN.] (1) Benzamide, $N$-(aminoiminomethyl)-4-(1-methylethyl)-3-(methylsulfonyl)-, monomethanesulfonate; (2) $N$-(Diamino-methylene)-4-isopropyl-3-(methylsulfonyl)benzamide monomethanesulfonate; (3) N -(4-Isopropyl-3-methanesulfonyl-benzoyl)-guanidine.CAS-159138-81-5; CAS-159138-80-4 [cariporide]. Reduction of death and non-fatal myocardial infarction in patients undergoing CABG surgery. (Aventis Pharma Deutschland GmbH$) \stackrel{\rightharpoonup}{ } \stackrel{\text { HOE }}{ } 642$


Ciclesonide [2004] (sik le son' ide). $\mathrm{C}_{32} \mathrm{H}_{44} \mathrm{O}_{7}$. 540.69. (1) Pregna-1,4-diene-3,20-dione, 16,17-[[( $R$ )-cyclohexylmethylene] bis-(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-, ( $11 \beta, 16 \alpha$ ); (2) $2 H$-Naphth [ $\left.2^{\prime}, 1^{\prime}: 4,5\right]$ indeno [1,2-d] [1,3] dioxole, pregna-1,4-diene-3,20-dione deriv. $C A S$-126544-47-6; CAS-141845-82-1. INN. Treatment of asthma as prophylactic therapy in adults and adolescents. Alvesco (Dynamit Nobel $\mathrm{GmbH}) \diamond R P R 251526$


Disufenton Sodium [2004] (dye soo fen' ton). $\mathrm{C}_{11} \mathrm{H}_{13} \mathrm{NNa}_{2} \mathrm{O}_{7} \mathrm{~S}_{2}$. 381.30. (1) 1,3-Benzenedisulfonic acid, 4-[[(1,1-dimethy-lethyl)oxidoimino]methyl]-, disodium salt; (2) Disodium 4-tert-butyliminomethyl)benzene-,3-disulfonate $N$-oxide; (3) Disodium 4-[[(1,1-dimethylethyl)imino]methyl]benzene-1,3disulfonate $N$-oxide. CAS-168021-79-2. INN. Neuroprotective agent used to treat ischemic stroke. (AstraZeneca) $\checkmark N X Y-059$


Eritoran Tetrasodium [2004] ( $\mathrm{er}^{\prime \prime}$ i tore' an). $\mathrm{C}_{66} \mathrm{H}_{122} \mathrm{~N}_{2} \mathrm{Na}_{4} \mathrm{O}_{19} \mathrm{P}_{2}$. 1402.00. (1) $\alpha$-D-Glucopyranose, 3- O-decyl-2-deoxy-6-O-[2-deoxy-3-O-[(3R)-3-methoxydecyl]-6-O-methyl-2-[[(11Z)-1-oxo-11-octadecenyl]amino]-4- $O$-phosphono- $\beta$-d-glucopyra-nosyl]-2-[(1,3-dioxotetradecyl)amino]-, 1-(dihydrogen phosphate), tetrasodium salt; (2) 3-O-Decyl-2-deoxy-6-O-[2-deoxy-3-O-[(3R)-3-methoxydecyl]-6-O-methyl-2-[(11Z)-oc-tadec-11-enoylamino]-4- $O$-phosphonato- $\beta$-D-glucopyrano-syl]-2-[(3-oxotetradecanoyl)amino]- $\alpha$-D-glucopyranosyl tetrasodium phosphate. CAS-185954-98-7. Treatment of sepsis and other diseases due to reaction to bacterial endotoxin (endotoxin antagonist). (Eisai Medical Research) $\diamond$ E5564; B1287


Lenalidomide [2004] (le na lid' oh mide). $\mathrm{C}_{13} \mathrm{H}_{13} \mathrm{~N}_{3} \mathrm{O}_{3}$. 259.30. (1) 2,6-Piperidinedione, 3-(4-amino-1,3-dihydro-1-oxo- 2 H -iso-indol-2-yl)-; (2) 3-(4-Amino-1-oxo-1,3-dihydro-2H-isoin-dol-2-yl)piperidine-2,6-dione. CAS-191732-72-6. Immunomulator intended for use in the treatment of multiple myeloma, myelodysplastic syndromes, solid tumors including glioma and metastatic melanoma, Crohn's disease, and heart failure. Revlimid (Celgene) $\diamond C C-5013 ; C D C-501$


Levalbuterol Tartrate [2004] (lev al byoo' ter ol).
$2\left(\mathrm{C}_{13} \mathrm{H}_{21} \mathrm{NO}_{3}\right) . \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$. 628.71. 1,3-Benzenedimethanol, $\alpha^{1}$ [ [(1,1-dimethylethyl)amino]methyl]-4-hydroxy-, ( $\left.\alpha^{1} \mathrm{R}\right)$-, (2R,3R)-2,3-dihydroxybutanedioate (2:1) (salt). CAS-661464-94-4. Anti-asthmatic and bronchodilator ( $\beta_{2}$-adrenergic receptor agonist). Xopenex HFA (Sepracor)


Midostaurin [2004] (mi doe stor' in). $\mathrm{C}_{35} \mathrm{H}_{30} \mathrm{~N}_{4} \mathrm{O}_{4}$. 570.64. (1) Benzamide, $N-[(9 S, 10 R, 11 R, 13 R)-2,3,10,11,12,13$-hexahy-dro-10-methoxy-9-methyl-1-oxo-9,13-epoxy- $1 \mathrm{H}, 9 \mathrm{H}$-diindolo [1,2,3-gh:3', $\left.2^{\prime}, 1^{\prime}-l m\right]$ pyrrolo[3,4-j][1,7]benzodiazonin-11-yl]-N-methyl-; (2) $N$-[(9S,10R,11R,13R)-10-methoxy-9-methyl-1-oxo-2,3,10,11,12,13-hexahydro-9,13-epoxy$1 H, 9 H$-diindolo [1,2,3-gh:3', 2', 1'-lm]pyrrolo[3,4-j][1,7]ben-zodiazonin-11-yl]-N-methylbenzamide. CAS-120685-11-2. INN. Antineoplastic; protein kinase C inhibitor. (Novartis) $\checkmark C G P 41251$; PKC 412


Paliperidone [2004] (pal ee per' i done). $\mathrm{C}_{23} \mathrm{H}_{27} \mathrm{FNH}_{4} \mathrm{O}_{3} .388 .50$. (1) $4 H$-Pyrido [1,2-a]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-; (2) (9RS)-3-[2-[4-(6-Fluoro-1,2-benzi-soxazol-3-yl)piperidin-1-yl]]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one.CAS-144598-75-4. INN. Treatment of schizophrenia. (Johnson \& Johnson) $\triangleleft R O 76477$


Paliperidone Palmitate [2004]. $\mathrm{C}_{39} \mathrm{H}_{57} \mathrm{FN}_{4} \mathrm{O}_{4}$. 664.90. (1) Hexadecanoic acid, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-pi-peridinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4H-pyri-do[1,2-a]pyrimidin-9-yl ester; (2) (9RS)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl hexadecanoate. CAS-199739-10-1. Treatment of schizophrenia. (Johnson \& Johnson) $\triangleleft R O 92670$


Radafaxine Hydrochloride [2004] (rad a fax' een).
$\mathrm{C}_{13} \mathrm{H}_{18} \mathrm{ClNO}_{2}$. HCl . 292.20. (1) 2-Morpholinol, 2-(3-chloro-phenyl)-3,5,5-trimethyl-, hydrochloride, $(2 S, 3 S)-;(2)(+)-$ ( $2 S, 3 S$ )-2-(3-Chlorophenyl)-3,5,5-trimethylmorpholin-2-ol hydrochloride. CAS-106083-71-0. Antidepressant; antianxiety. (GlaxoSmithKline) $\diamond G W 353162 A$


Selegiline [2004] (se lé ji leen). $\mathrm{C}_{13} \mathrm{H}_{17} \mathrm{~N} .187 .30$. (1) Benzeneethanamine, $N, \alpha$-methyl- $N$-2-propynyl-, $(\alpha R)-;(2)(-)-(N)$ -Methyl- $N$-[(1R)-1-methyl-2-phenylethyl]prop-2-yn-1-amine. CAS-14611-51-9. Antidepressant (MAO inhibitor). (BASF); (Abbott)


Trodusquemine [2004] (troe doo' skwe meen). $\mathrm{C}_{37} \mathrm{H}_{72} \mathrm{~N}_{4} \mathrm{O}_{5} \mathrm{~S}$. 685.10. (1) Cholestane-7,24-diol, 3-[[3-[[4-[(3-aminopropy-1)amino]butyl]amino]propyl]amino]-, 24-(hydrogen sulfate), $(3 \beta, 5 \alpha, 7 \alpha, 24 R)-;(2)(24 R)-3 \beta-[[3-[[4-[(3-a m i n o p r o p y l) a m i-$ no]butyl]amino]propyl]amino]-7 $\alpha$-hydroxy-5 $\alpha$-cholestan-24yl hydrogen sulfate. CAS-186139-09-3. Treatment of medically significant obesity. (Genaera) $\diamond M S I-1436$


Vestipitant Mesylate [2004] (ves tee pit' ant). $\mathrm{C}_{23} \mathrm{H}_{24} \mathrm{~F}_{7} \mathrm{~N}_{3} \mathrm{O}$.$\mathrm{CH}_{4} \mathrm{O}_{3} \mathrm{~S}$. 587.60. (1) 1-Piperazinecarboxamide, $N-[(1 R)$-1-[3,5-bis(trifluoromethyl)phenyl]ethyl]-2-(4-fluoro-2-methyl-phenyl)- $N$-methyl-, (2S)-, monomethanesulfonate; (2) ( + )-(2S)- $N$-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl]-2-(4-fluoro-2-methylphenyl)- $N$-methylpiperazine-1-carboxamide methanesulfonate. CAS-334476-64-1. Antidepressant/antianxiety; prevention of nausea and vomiting; used in the treatment of functional dyspepsia, irritable bowel syndrome and $G E R D$. (GlaxoSmithKline) $>G W 597588 B$


## Proposed and Recommended International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Helath Organization (WHO).

Under its charter, the WHO is empowered simply to recommend specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as proposals ("Proposed International Nonproprietary Names"). A period of four months from the date of publication in WHO Drug Information is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested par-
ties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as recommendations ("Recommended International Nonproprietary Names"), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

## Proposed International Nonproprietary Names

The following 55 names have been selected by the World Health Organization (WHO) as Proposed International Nonproprietary Names. This list, with chemical names or descriptions and the molecular formulae, appears in WHO Drug Information, Vol 17, No. 3, 2003.

| Proposed INN | Therapeutic Indication |
| :--- | :--- |
| Adargileukin Alfa | Antiviral; antineoplastic |
| Alamifovir | Antiviral |
| Aprinocarsen | Antineoplastic |
| Belimumab | Immunomodulator |
| Cantuzumab Mertansine | Treatment of tumors that |
|  | express C242 antigen |
| Cimicoxib | Cycloxygenase-2 inhibitor |
| Dabuzalgron | Alfarl-adrenoreceptor agonist |
| Dacinostat | Antitumor agent, inhibitor of |
|  | histone deacetylase |
| Deligoparin Sodium | Anticoagulant |
| Desvenlafaxine | Antidepressant |
| Dibotermin Alfa | Growth factor |
| Diquafosol | P2Y receptor agonist |
| Disermolide | Antineoplastic |
| Edifoligide | Oligonucleotide |
| Edratide | Treatment of systemic lupus |
|  | erythematosus |
| Elsilimomab | Immunomodulator |
| Elvucitabine | Antiviral |
| Epitumomab Cituxetan | Immunomodulator |
| Eptotermin Alfa | Growth factor |
| Exatecan Alideximer | Antineoplastic |
| Exenatide | Antidiabetic |
| Firocoxib | Cycloxygenase-2 inhibitor |
| Fispemifene | Antiestrogen |
| Fluorescein Lisicol | Diagnostic aid |
| Freselestat | Elastase inhibitor |
| Galiximab | Immunomodulator |
| Hemoglobin Raffimer | Oxygen carrier |
| Icofungipen | Antifungal |
| Icrocaptide | Anti-inflammatory |
| Iferanserin | Serotonin receptor antagonist |
|  |  |

Any comments or formal objections to the proposed names should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Proposed INN | Therapeutic Indication |
| :--- | :--- |
| Istradefylline | Antiparkinsonian |
| Ixabepilone | Antineoplastic |
| Ladostigil | Cholinesterase and monamine |
| Lapatinib | oxidase inhibitor |
| Lomeguatrib | Antineoplastic |
| Odiparcil | Alkylluavanine alkyltransferase |
| Omiganan | inhibitor |
| Pactimibe | Antithrombotic |
| Patupilone | Antimicrobial |
| Pertuzumab | Antiatherosclerotic |
| Pixantrone | Antineoplastic |
| Pritumumab | Immunomodulator |
| Ralfimamide | Antineoplastic |
|  | Antineoplastic |
| Rebimastat | Analgesic, sodium channel |
| Segestrone | blocker |
| Semapimod | Matrix metalloproteinase |
| Sufugolix | inhibitor |
|  | Contraceptive |
|  | Immunomodulator |
| Tafluprost | Luteinizing hormone-releas- |
| Talizumab | ing-hormone (LHRH) |
| Technetium (99m Tc) | antagonist |
| Nitridocade | Antiglaucoma |
| Tesofensine | Immunomodulator |
| Tifenazoxide | Radiodiagnostic agent |
| Tisocalcitate | Antiparkinsonian |
| Ulifloxacin | Antidiabetic |
| Varenicline | Vitamin D analog |
|  | Antibacterial |
|  | Nicotinic acetylcholine |
|  | receptor agonist |

## Suggested United States Adopted Names

The United States Adopted Names (USAN) program is the specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs while the drugs are still in the investigational stages. The American Medical Association (AMA), the American Pharmaceutical Association (APhA), and the United States Pharmacopeial Convention (USPC) jointly sponsor the USAN program with representation from the FDA.

Each U.S. Adopted Name is chosen with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official United States Pharmacopeia or National Formulary. A measure of the prestige and recognition of the value of the USAN program can be found in the following regulations published by the Commissioner of Food and Drugs and the Secretary of Health and Human Services in the Federal Register of February 1988.

All who are concerned with the prescription, dispensing, use, sale or manufacture of drugs may, in the absence of the designation of an official name by the FDA, rely on the current compendial name or the U.S. Adopted Name (USAN) listed in this volume as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act.
A formal procedure ${ }^{1}$ is followed by the USAN Council in selecting an established name for a drug. The USAN Council Secretary is also an ex officio member of the International Nonproprietary Names (INN) Committee. USAN Guiding Principles are concordant with World Health Organization (WHO) principles, and all USANs for substances also named by the INN Committee are sys-

| Suggested USAN | Category |
| :---: | :---: |
| Aerofilcon | Hydrophilic contact lens |
| Hyperfilcon | material |
| Oxsilfilcon |  |
| Silfilcon |  |
| Afboximab | Anti-angiogenic agent to treat |
| Afociximab | solid tumors and age-related |
| Afotuximab | macular degeneration |
| Boxatuximab |  |
| Valiximab |  |
| Volociximab |  |
| Volotuximab |  |
| Alkarginine Acetate | Treatment of cardiogenic shock |
| Arloginine Acetate | complicating acute myocardial |
| Marginine Acetate | infarction |
| Monarginine Acetate |  |
| Targinine Acetate |  |
| Tilarginine Acetate |  |
| Aloglustratide Hydrochloride | Antineoplastic [activated by |
| Canfosfamide Hydrochloride | gluathione S-transferase |
| Canglustrac Hydrochloride | (GST) P1-1] |
| Canglustrafos Hydrochloride |  |
| Canglustramide Hydrochloride Canglustratide Hydrochloride |  |
|  |  |
| Ampaglufuran | Treatment of schizophrenia |
| Ampaxazole |  |
| Farampator |  |

tematically processed through the INN Committee. This ensures that, with very rare exceptions, USANs are identical to INNs and available for world-wide use.

A suggestion for a USAN originates usually from a firm or an individual who has developed a substance of potential therapeutic utility to the point where there is a distinct possibility of its being marketed in the United States of America. Occasionally, the initiative is taken by the USAN Council in the form of a request to parties interested in a substance for which a nonproprietary name appears to be lacking.
Submissions to the USAN Council are expected to conform to the established Guiding Principles ${ }^{2}$ and to be reasonably free from conflict with other names, including both trademarks and nonproprietary names. An effort is made to discourage the occasional, undesirable practice of incorporating in trademarks the syllables used in an established nonproprietary name, or syllables recommended for USAN. Such trademarks may act as a bar to the subsequent adoption of appropriate nonproprietary names for closely related drugs.

The suggested nonproprietary names for the drugs described in the following list are under consideration by the USAN Council. The name(s) being considered for each drug substance, and the applicable category, are separated by double spacing from the name(s) and category for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Suggested USAN | Category |
| :--- | :--- |
| Amyglybril | Treatment of mild-to-moderate <br> Amytargam <br> Betamilod <br> Prevamilod <br> Preveglybril <br> Prevetargam |
| Zeprebral disease, treatment |  |
| Zeprotargam |  |
| Zontargam |  |
| Amyglybril |  |
| Amytargam |  |
| Fibramilod |  |
| Fibritargam | Amyloidosis |
| Prevamilod |  |
| Preveglybril |  |
| Zontargam |  |
| Aptumumab |  |
| Lontumumab |  |
| Tractumumab | Treatment of cancer |
| Aplindore Fumarate |  |
| Indopagon Fumarate | Antischizophrenic (low intrin- |
| Molindore Fumarate | sic activity modulator of human |
| Moloxindore Fumarate |  |
| Oxindafren Fumarate |  |
| Padoxinor Fumarate |  |
| Palindore Fumarate |  |
| Paloxindore Fumarate |  |

[^285]| Suggested USAN | Category | Suggested USAN | Category |
| :---: | :---: | :---: | :---: |
| Atratinib Malate | Treatment of cancer | Etemucret | Treatment of dry eye (stimu- |
| Sunaritinib Malate |  | Icomucret | lates glycoprotein secretion) |
| Sunitinib Malate |  | Idroxicotrent |  |
| Susitinib Malate |  |  |  |
|  |  | Evandiracetam | Treatment of epilepsy, hyperki- |
| Axiaracetam | Treatment of epilepsy, neuro- | Seletracetam | netic movement disorders |
| Axivaracetam | pathic pain and essential tre- | Vantiracetam |  |
| Ziaracetam | mor |  |  |
|  | Treatment of rheumatoid ar- | Iloprost Trometamol | Treatment of pulmonary arterial hypertension |
| Crelizumab | thritis |  |  |
| Lolizumab |  | Ipronicline | Treatment of cognitive and |
| Relizumab |  | Promenicline | memory disorders |
| Ubelizumab |  | Sarenicline |  |
| Bioctadekin | Antineoplastic | Levotofisopam | Anxiolytic, treatment of auto- |
| Iboctadekin |  | Levtofisopam | nomic instability |
| Immunoctadekin |  |  |  |
| Munoctadekin |  | Selanzymin | Relief of pain and inflammation |
|  |  | Selezymin |  |
| Cenicline | Treatment of ulcerative colitis | Selmimase |  |
| Rivinicline |  | Selmimetase |  |
| Rovanicline |  | Somimase |  |
|  |  | Somimetase |  |
| Dalbavancin | Antibiotic | Sumimetase |  |
|  |  | Suprozymin |  |
| Darifenacin Hydrochloride | Treatment of overactive bladder | Zormimase |  |
|  |  | Selnefacap | Anti-inflammatory |
| Dexamfetamine Lysine | Treatment of ADHD (central | Selneficap |  |
| Dimesylate . | nervous system stimulant) | Sernefacap |  |
| Dextroamphetamine Lysine |  |  | Analgesic |
| Lidamfetamine Dimesylate |  |  |  |
| Lidamphetamine Dimesylate |  | Tolevamer Potassium | Treatment and prevention of |
| Lidexamfetamine Dimesylate |  |  | Clostridium difficile associated |
| Lidextroamphetamine |  |  | diarrhea |
|  |  | Valepcitabine Hydrochloride | Treatment of hepatitis C (HCV |
| Dronedarone Hydrochloride | Antiarrhythmic | Valeprucitabine Hydrochloride Valopcitabine Hydrochloride | RNA polymerase inhibitor) |
| Elatacept | Prevention of certain graft re- | Valopicitabine Hydrochloride |  |
| Leatacept | jections in solid organ and bone marrow transplants; treatment of autoimmune diseases and conditions such as rheumatoid arthritis and Type 1 diabetes | Valpercitabine Hydrochloride |  |

## Suggested International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO). INNs for substances originating within the United States are applied for through the USAN Council. INN and USAN Guiding Principles are concordant, which assures that, with very few exceptions, INNs and USANs are identical.

Under its charter, the WHO is empowered simply to recommend specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as proposals ("Proposed International Nonproprietary Names"). A period of four months from the date of publication in WHO Drug Information is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event
that no objection is received, the WHO proceeds with listing and publishing the names so devised as recommendations ("Recommended International Nonproprietary Names"), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

The names for the drugs that are categorized in the following list are under consideration for the selection of new Proposed International Nonproprietary Names. The name(s) being considered for each drug substance, and the applicable category, are separated by double spacing from the name(s) and category for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Suggested INN | Category |
| :---: | :---: |
| Acetaxel Exetaxel | Anti-tumor, especially those that overexpress P-glycoproteins |
| Ampaglufaran <br> Ampaneopion <br> Ampaxazole <br> Farampator | Treatment of schizophrenia |
| Aplindore Palindore | Antischizophrenic |
| Azifloxacin Bazofloxacin Endofloxacin | Antibacterial agent |
| Benzcapone Nibenzcapone Nibicapone | Treatment of Parkinson's disease |
| Canfosfamide Canglustratide | Antineoplastic agent |
| Dalbavancin | Antibiotic |
| Etemucret Icomucret | Treatment of dry eye (stimulates glycoprotein secretion) |
| Glicidelin Indacidelin Indantin | Treatment of neuropathic pain |
| Iboctadekin | Antineoplastic |
| Iloprost | Treatment of pulmonary arterial hypertension |
| Levotofisopam Levtofisopam | Anxiolytic, treatment of autonomic instability |
| Manitlimus | Immunosuppressive |
| Padorporfin Topadiporfin | Photosensitizer used in the treatment of prostate cancer |


| Suggested INN | Category |
| :---: | :---: |
| Pancarcinomab Nafenatox <br> Pancarcinomab Optimotox <br> Pantumomab Nafenatox <br> Pantumomab Optimotox <br> Ultimomab Nafenatox <br> Ultimomab Optimotox | Treatment of cancer |
| Parexyprisnil Pontiprisnil Spetoxyprisnil | Contraceptive (selective progesterone receptor modulator) |
| Pentadol <br> Tapentadol | Analgesic |
| Petaprost <br> Rivenprost <br> Voluprost | Treatment of fractures resulting from osteoporosis |
| Recamline <br> Ricamfoline <br> Ricamline | Anti-inflammatory, anti-rheumatic |
| Sapavaptan | Treatment of congestive heart failure, SIADH, liver cirrhosis with ascites and water retention, brain edema, nephritic syndrome associated with generally high AVP plasma levels and hyponatremia |
| Targinine Acetate Tilarginine Acetate | Treat cardiogenic shock complicating acute myocardial infarction (MI) |
| Tovelamer | Treatment and prevention of Clostridium difficile associated diarrheal disease |
| Transferrin Difitox | Treatment of glioblastoma multiform and high grade glioma |
| Volociximab | Anti-angiogenic agent to treat solid tumors and age-related macular degeneration |

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## USP CATALOG

## New Items at a Glance

See what's new in USP Reference Standards. For your convenient and quick reference, here's a list of Reference Standards released by USP over the past year.

This list is continuously updated with the newest Reference Standards released within the past 12 months.

| Cat. No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1012699 | Alcohol Determination-Acetonitrile ( $5 \mathrm{~mL} /$ ampule; 5 ampules) | F0C419 | \$156 |
| 1012688 | Alcohol Determination-Alcohol ( $5 \mathrm{~mL} /$ ampule; 5 ampules) | F0C399 | \$156 |
| 1048619 | Benazepril Hydrochloride (125 mg) | F0C250 | \$156 |
| 1048641 | Benazepril Related Compound C $(50 \mathrm{mg})$ | F0C425 | \$487 |
| 1071439 | Positive Bioreaction (3 strips; $10 \mathrm{~cm} \times 1$ cm) | F0D014 | \$325 |
| 1076206 | Powdered Black Cohosh Extract (1.5 g) | F0D086 | \$520 |
| 1076341 | Boric Acid (1 g) (AS) | F0D036 | \$200 |
| 1082708 | Butylated Hydroxytoluene ( 500 mg ) (AS) | F0D122 | \$156 |
| 1086334 | Calcium Acetate (1 g) (AS) | F0D156 | \$156 |
| 1086403 | Calcium Carbonate (1 g ) (AS) | F0D099 | \$156 |
| 1086436 | Calcium Chloride (1 g) (AS) | F0D153 | \$156 |
| 1086855 | Calcium Hydroxide (1 g) (AS) | F0D168 | \$156 |
| 1087701 | Candelilla Wax ( 250 mg ) | F0D123 | \$156 |
| 1091505 | Caprylocaproyl Polyoxylglycerides $(200 \mathrm{mg})$ | F0C312 | \$175 |
| 1098118 | Cefpiramide ( 300 mg ) | F0C203 | \$156 |
| 1098027 | Cefpodoxime Proxetil ( 350 mg ) | F0C192 | \$156 |
| 1105009 | Powdered Chaste Tree Extract (1.5 g) | F0C406 | \$520 |
| 1111001 | Chlorhexidine ( 200 mg ) | F0C306 | \$156 |
| 1111103 | Chlorhexidine Acetate ( 500 mg ) | F0C281 | \$156 |
| 1111307 | Chlorhexidine Related Compounds $(50 \mathrm{mg})$ | F0D017 | \$487 |
| 1115545 | Chlorogenic Acid ( 50 mg ) | F0C420 | \$156 |
| 1140349 | Clonazepam Related Compound C $(25 \mathrm{mg})$ | F0C340 | \$487 |
| 1140393 | Clonidine ( 200 mg ) | F0C401 | \$156 |
| 1140418 | Clonidine Related Compound A ( 25 mg ) | F0C373 | \$487 |
| 1140429 | Clonidine Related Compound B ( 25 mg ) | F0C403 | \$487 |
| 1152701 | Cyclandelate ( 200 mg ) | F0C384 | \$156 |
| 1187080 | Dibutyl Phthalate ( 200 mg ) | F0D125 | \$156 |
| 1224959 | Dolasetron Mesylate ( 200 mg ) | F0C319 | \$156 |
| 1224960 | Dolasetron Mesylate Related Compound A $(25 \mathrm{mg})$ | F0C321 | \$487 |
| 1231728 | Powdered Echinacea Purpurea Extract (1 g) | F0D018 | \$520 |
| 1231706 | Powdered Echinacea Angustifolia Extract (1 g) | F0D019 | \$520 |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | \$520 |
| 1269414 | Fenbendazole Related Compound A ( 30 mg ) | F0D009 | \$487 |
| 1269425 | Fenbendazole Related Compound B ( 30 mg ) | F0D008 | \$487 |
| 1272204 | Fludarabine Phosphate ( 300 mg ) | F0C374 | \$156 |
| 1279837 | Fluoxetine Related Compound C ( 15 mg ) | F0C352 | \$487 |
| 1288317 | Ganciclovir Related Compound A $(15 \mathrm{mg})$ | F0C288 | \$624 |


| Cat. No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1288463 | Gemcitabine Hydrochloride ( 200 mg ) | F0D037 | \$156 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 | \$156 |
| 1305507 | 2E, 4E-Hexadienoic Acid Isobutylamide $(25 \mathrm{mg})$ | F0C353 | \$540 |
| 1311306 | Homopolymer Polypropylene (3 Strips) | F0C096 | \$156 |
| 1349014 | Isoflurane Related Compound A (0.1 mL ) | F0C232 | \$487 |
| 1349025 | Isoflurane Related Compound B (0.1 mL ) | F0C233 | \$487 |
| 1356836 | Lamivudine ( 200 mg ) | F0C361 | \$156 |
| 1356847 | Lamivudine Resolution Mixture A ( 10 mg ) | F0D024 | \$487 |
| 1356950 | Lauroyl Polyoxylglycerides ( 500 mg ) (AS) | F0D020 | \$156 |
| 1358503 | Leuprolide Acetate (200 mg) | F0C430 | \$1,525 |
| 1367708 | Linoleoyl Polyoxylglycerides (100 mg) | F0C283 | \$156 |
| 1370270 | Loratadine (200 mg) | F0C414 | \$260 |
| 1374260 | Magnesium Hydroxide (1 g) (AS) | F0D158 | \$156 |
| 1375127 | Manganese Chloride (1 g) (AS) | F0D150 | \$156 |
| 1375149 | Manganese Sulfate (1 g) (AS) | F0D151 | \$156 |
| 1378012 | Medroxyprogesterone Acetate Related Compound A ( 25 mg ) | F0C427 | \$500 |
| 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution ClI ( 0.5 mL ) | F0C368 | \$560 |
| 1441232 | Metoprolol Related Compound A $(20 \mathrm{mg})$ | F0C343 | \$520 |
| 1441243 | Metoprolol Related Compound B ( 50 mg ) | F0C377 | \$520 |
| 1441254 | Metoprolol Related Compound C $(20 \mathrm{mg})$ | F0C344 | \$520 |
| 1441265 | $\underset{(50 \mathrm{mg})}{\substack{\text { Metoprolol Related Compound D }}}$ | F0C378 | \$520 |
| 1441298 | Metoprolol Succinate ( 200 mg ) | F0C415 | \$156 |
| 1444279 | Mirtazapine ( 350 mg ) | F0D155 | \$800 |
| 1445211 | Mitoxantrone System Suitability Mixture ( 0.3 mg ) | F0D010 | \$500 |
| 1449530 | Nabumetone Related Compound A $(15 \mathrm{mg})$ | F0D165 | \$487 |
| 1457469 | Naratriptan Hydrochloride (125 mg) | F0C360 | \$208 |
| 1460703 | Nevirapine Anhydrous ( 100 mg ) | F0D159 | \$156 |
| 1460714 | Nevirapine Hemihydrate (100 mg) | F0D034 | \$156 |
| 1460725 | Nevirapine Related Compound A ( 15 mg ) | F0D035 | \$487 |
| 1460736 | Nevirapine Related Compound B $(15 \mathrm{mg})$ | F0D033 | \$487 |
| 1478152 | Oleoyl Polyoxylglycerides (100 mg) | F0C313 | \$156 |
| 1485125 | Oxybutynin Related Compound B ( 20 mg ) | F0D061 | \$487 |
| 1485136 | Oxybutynin Related Compound C $(20 \mathrm{mg})$ | F0D062 | \$487 |
| 1535020 | Phenytoin Related Compound B ( 50 mg ) | F0C157 | \$487 |
| 1547925 | Polysorbate 20 (2 g) (AS) | F0D130 | \$156 |
| 1547947 | Polysorbate $60(2 \mathrm{~g})$ (AS) | F0D131 | \$156 |
| 1547969 | Polysorbate 80 (2 g) (AS) | F0D132 | \$156 |
| 1548101 | Potassium Benzoate (1 g) (AS) | F0D161 | \$156 |
| 1548134 | Potassium Bicarbonate (1 g) (AS) | F0D074 | \$156 |
| 1548167 | Potassium Carbonate (1 g) (AS) | F0D075 | \$156 |
| 1548190 | Potassium Chloride (1 g) (AS) | F0D127 | \$156 |
| 1548280 | Potassium Iodide (1 g) (AS) | F0D078 | \$156 |

## New Items at a Glance (Continued)

| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1572208 | Propionic Acid (1.5 mL/ampule; 3 ampules) (AS) | F0D029 | \$156 |
| 1601102 | Residual Solvents Mixture - Class 1 ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C407 | \$156 |
| 1601146 | Residual Solvent Class 1 - Benzene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C408 | \$156 |
| 1601168 | Residual Solvent Class 1 - Carbon Tetrachloride ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C409 | \$156 |
| 1601180 | Residual Solvent Class 1-1,2Dichloroethane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C412 | \$156 |
| 1601204 | Residual Solvent Class 1-1,1Dichloroethene ( $1.2 \mathrm{~mL} / \mathrm{ampule}$; 3 ampules) | F0C411 | \$156 |
| 1601226 | Residual Solvent Class 1-1,1,1Trichloroethane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C410 | \$156 |
| 1601340 | Residual Solvent Class 2 - Acetonitrile ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D049 | \$156 |
| 1601361 | Residual Solvent Class 2 Chlorobenzene ( $1.2 \mathrm{~mL} / \mathrm{ampule}$; 3 ampules) | F0D048 | \$156 |
| 1601420 | Residual Solvent Class 2-1,2Dichloroethene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D040 | \$156 |
| 1601521 | Residual Solvent Class 2-1,4-Dioxane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D050 | \$156 |
| 1601623 | Residual Solvent Class 2 - Methanol ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D045 | \$156 |


| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1601689 | Residual Solvent Class 2 - <br> Methylcyclohexane ( 1.2 mL /ampule; 3 ampules) | F0D044 | \$156 |
| 1601441 | Residual Solvent Class 2 - Methylene Chloride ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D046 | \$156 |
| 1601770 | Residual Solvent Class 2 - <br> Tetrahydrofuran ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D043 | \$156 |
| 1601805 | Residual Solvent Class 2 - Toluene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D042 | \$156 |
| 1601849 | Residual Solvent Class 2 - Xylenes ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D041 | \$156 |
| 1604508 | Rimantadine Hydrochloride ( 300 mg ) | F0C266 | \$156 |
| 1610090 | Scopoletin ( 20 mg ) | F0C329 | \$156 |
| 1613407 | Sodium Acetate (1 g) (AS) | F0D083 | \$156 |
| 1613757 | Sodium Carbonate Anhydrous (1 g) (AS) | F0D100 | \$156 |
| 1614396 | Sodium Metabisulfite (1 g) (AS) | F0D111 | \$156 |
| 1614454 | Sodium Nitrite (1 g) (AS) | F0D117 | \$156 |
| 1614807 | Sodium Sulfate Anhydrous (1 g) (AS) | F0D112 | \$156 |
| 1617408 | Sotalol Hydrochloride ( 300 mg ) | F0C234 | \$182 |
| 1667290 | Tiamulin Fumarate ( 250 mg ) | F0C327 | \$156 |
| 1667337 | Tiamulin Related Compound A ( 50 mg ) | F0C328 | \$494 |
| 1667585 | Titanium Dioxide (1 g) (AS) | F0D079 | \$156 |
| 1708762 | Valsartan (350 mg) | F0C147 | \$156 |
| 1711155 | Vecuronium Bromide ( 50 mg ) | F0C367 | \$156 |
| 1724769 | Zinc Sulfate (1 g) (AS) | F0D133 | \$156 |

## USING AND ORDERING USP REFERENCE STANDARDS

## Official Reference Standards

USP Reference Standards are required for use in pharmacopeial assays and tests in the official standards publication, the United States Pharmacopeia-National Formulary (USP-NF). USP Reference Standards help to ensure compliance with the official, FDA-enforceable quality requirements in the $U S P-N F$. The Reference Standards also lend themselves to many other applications, including measurements required to attain accurate and reproducible results in modern chromatographic and spectrophotometric methods.

## Rigorous Testing and Quality Control

USP Reference Standards are selected for their high purity, critical characteristics, and suitability for the intended purpose. Unless a USP Reference Standard label states a specific potency or content, the USP Reference Standard is taken as being $100 \%$ pure for the USP purposes for which it is provided. As a service to our customers, labeled purity values for Reference Standards and Authentic substances released after January 1, 2004 are listed in this catalog. See p. 9 for explanation of how values are calculated.

Heterogeneous substances, of natural origin, are also designated "Reference Standards" where needed. Usually these are the counterparts of international standards.

USP Reference Standards are established through a process of rigorous testing, evaluation, and quality control. They are independently tested in three or more laboratories-USP, FDA, and academic and industrial laboratories throughout the United States. The Reference Standards are released under the authority of USP's Board of Trustees, on the recommendation of the USP Reference Standards Expert Committee, which approves selection and suitability of each lot.

## Reference Standards Categories

USP offers more than 1,560 Reference Standards for pharmaceuticals, excipients, and dietary supplements. On pages $12-57$ of this catalog, you'll find a full list of available USP and NF Reference Standards, with information updated through May 2004. The list includes:

- Reference Standards required by the current official edition of $U S P-N F$.
- Reference Standards not required in the current $U S P-N F$, but for which sufficient demand remains.
- Reference Standards specified in the current edition of the Food Chemicals Codex (FCC).
- Authentic Substances (AS)—highly purified samples of chemicals, including substances of abuse, required by analytical, clinical, pharmaceutical, and research laboratories.

The distribution of controlled substances is subject to the regulations and licensing provisions of the Drug Enforcement Administration (DEA) of the U.S. Department of Justice.

USP also collaborates with the World Health Organization in its program to provide international biological standards and chemical reference materials for antibiotics, biologicals, and chemotherapeutic agents. Some USP Reference Standards are standardized in terms of the corresponding international standards.

## Proper Use of USP Reference Standards

USP Reference Standards are provided primarily for quality control use in conducting the pharmacopeial assays and tests described in the $U S P-N F$. Neither Reference Standards nor Authentic Substances are intended for use as drugs, dietary supplements, or medical devices.

To serve its intended purpose, each USP Reference Standard must be properly stored, handled, and used. Users of USP Reference Standards should refer to General Chapter $\langle 11\rangle$ in the $U S P-N F$ :

## Listing and directions in USP-NF

- Refer to the list of revisions, additions, and deletions of individual USP Reference Standards in USP 27-NF 22. Individual $U S P$ or $N F$ monographs specify the USP Reference Standard(s) required for assay and test procedures. The USP 27-NF 22 General Test Chapter $\langle 11\rangle$ USP Reference Standards provides additional information and instructions for proper use and storage. Note that if specific instructions for use appearing on the label of a USP Reference Standard differ from the instructions in Chapter $\langle 11\rangle$, the instructions on the label take precedence.
- Consult the cumulative updates to Reference Standards information provided in $U S P-N F$ Supplements and also in $U S P-N F$ Interim Revision Announcements, which are published in USP's bimonthly journal, Pharmacopeial Forum.


## Suitability for use

- The user must ascertain that the Reference Standards they are using are an official lot.


## USING AND ORDERING USP REFERENCE STANDARDS

- The user must determine the suitability of Reference Standards for applications and uses not in the $U S P-N F$.


## Storing

- Ensure that the USP Reference Standards are stored in their original stoppered containers, according to any special label directions, away from heat and humidity, and protected from light.


## Weighing

- Ensure that Reference Standard substances are accurately weighed-taking due account of relatively large errors potentially associated with weighing small masses-where it is directed that a standard solution or a standard preparation be prepared for a quantitative determination. See USP 27-NF 22 General Chapters $\langle 41\rangle$ Weights and Balances and $\langle 31\rangle$ Volumetric Apparatus, and USP-NF General Notices, for information regarding appropriate use of USP Reference Standards.


## Drying

- Use a clean and dry vessel, and not the original container, as the drying vessel where a USP Reference Standard is required to be dried before use.
- Make sure not to dry a specimen repeatedly at temperatures above 25 degrees.
- Follow any special drying requirements specified on the Reference Standards label or in specific sections of USP or NF monographs (note that any specific instructions on the label or in the monograph supersede the usual instructions in Procedures under Tests and Assays in $U S P-N F$ General Notices).
- Follow Method I under USP-NF General Chapter $\langle 921\rangle$ Water Determination where the titrimetric determination of water is required at the time a Reference Standard is to be used. Instrumental or microanalytical methods are acceptable for this purpose. When using typical amounts, users must titrate about 50 mg of the Reference Standard with a fourfold dilution of the reagent.


## ORDERING USP REFERENCE STANDARDS

## Four convenient ways to order

1. Phone: Call USP with your requirements: (800) 227-8772 from the U.S. or Canada and (301) 881-0666 from other countries. Please note that DEA controlled substances cannot be placed over the phone.

Hours of operation:

Monday-Friday
8:30AM-5:00PM
Fax: Fax your orders to (301) 816-8148.
Online: Order through the World Wide Web at http://store.usp.org. Please note that DEA controlled substances cannot be ordered online.
Mail: Send all mail orders to:
USP
Customer Service Department
12601 Twinbrook Parkway
Rockville, MD 20852, USA

## Important Order/Policy Information

For fax and mail orders, please use the order form at the back of this catalog. Official purchase orders on company letterhead may also be used to order USP Reference Standards. The purchase orders must have billing and shipping addresses and should include the catalog number, the name of the official Reference Standard, and the number of units ordered. Lot numbers need not be specified on written purchase orders as USP only ships current official lots. Confirmation orders may be sent and must clearly be designated as such. The USP does not assume responsibility for duplication of orders not clearly marked as confirmation orders.

## Pricing

USP Reference Standards must be ordered in whole units. Please note that one unit may include several individual containers.

Reference Standards unit prices included in the product listings from pages 12-57 of this catalog are effective until December 31, 2004. Please note that prices and package sizes are subject to change without notice.

## No Returns or Exchanges

USP Reference Standards may not be returned or exchanged for refund.

## Quantity Discounts

A 5\% discount is allowed for 5-24 units of any one Reference Standard in a single order, and a $10 \%$ discount for 25 or more units of any one Reference Standard in a single order. These discounts are subject to change without notice.

## USING AND ORDERING USP REFERENCE STANDARDS

## Shipping

- Reference Standards orders can only be shipped to a street address and not to P.O. boxes.
- Orders to the U.S. and Ontario, Canada are shipped via air courier of USP's choice at a charge of $\$ 11$ or via air courier of the customer's choice at an additional $\$ 25$ charge.
- Non-controlled substance orders to Canadian provinces other than Ontario are shipped via air courier of USP's choice at a charge of U.S. $\$ 70$. Carriers of the customer's choice incur an additional $\$ 25$ charge.
- Non-controlled substance orders to be shipped outside the U.S. and Canada are accepted directly by USP only when customs forms related to export are not required. They are shipped via air courier of USP's choice at a charge of U.S. $\$ 70$. Carriers of the customer's choice incur an additional $\$ 25$ charge.
- Shipping in cold pack can be done at customer request for an extra charge of \$25.
- Controlled substance orders to anywhere outside the U.S. are shipped via air courier of USP's choice with a charge of U.S. $\$ 220$.
- An additional shipping charge may be assessed for dangerous goods shipments.
- An additional shipping charge of $\$ 75$ will be assessed for rush/ same-day shipments.
- Customers may provide their shipping account numbers to have shipping charged directly.


## Payment

- Full payment in advance, in U.S. dollars, is required for all U.S. orders unless open account status has been granted by USP's Finance Department. To apply for open account status, an application can be requested by calling (301) 816-8177.
- Full payment in advance, in U.S. dollars, is required for all non-U.S. orders.
- Payment may be made by check, money orders, credit cards (VISA, MasterCard, American Express), and electronic wire transfer (please call (301) 816-8177 to get bank information for wire transfers). The customer is responsible for any bank fees and must include it in the payment. The customer is also responsible for any other fees such as customs duties, taxes, or tariffs.


## List Chemicals

The following Reference Standards are "List Chemicals": Dihydroergotamine Mesylate
*Ephedrine Sulfate
Ergonovine Maleate
Ergotamine Tartrate
Methylergonovine Maleate
Phenylpropanolamine Bitartrate
Phenylpropanolamine HCl
Pseudoephedrine HCl
Pseudoephedrine Sulfate

An organization in the United States seeking to purchase a List Chemical Reference Standard for resale to another customer must have a DEA registration (either a controlled substance or List Chemical registration). If an organization in the United States is purchasing the List Chemical Reference Standard for its own analytical use, it must provide USP with a letter on company letterhead describing the reason for the purchase.

## CONTROLLED DRUG SUBSTANCE ORDER

## DEA Requirements (U.S. Orders)

For all orders for controlled drug substances-regulated by the U.S. Drug Enforcement Administration (DEA)-to be shipped within the U.S., a copy of the customer's current DEA Registration Certificate must be on file with USP. To order Schedule I and II standards, customers must submit, with their order forms or purchase orders, a DEA Form 222-C, properly completed. In addition, customers ordering DEA Schedules III and IV must provide appropriate DEA registration numbers for those schedules on their order forms or purchase orders.

## DEA Requirements (International Orders)

For all international controlled drug substance orders, please contact Julie Smith at (301) 816-8164 or foreigncontrols@ usp.org.

All orders for controlled drug substances-regulated by the U.S. Drug Enforcement Administration (DEA)-to be shipped outside the U.S. must be accompanied by:

1. Full payment.

## USING AND ORDERING USP REFERENCE STANDARDS

2. An import permit (in English or with an English translation attached) valid at least 6 months from the date of its receipt by USP Customer Service.
3. A statement of non-reexport and use for medical or scientific purposes (in English or with an English translation attached).
4. Purchase Order or Price Quote given by USP.

On receiving the order, USP takes 2-3 business days to:

- Review all documents to make sure they are adequate and appropriate.
- Complete and legally approve the required DEA forms.
- Forward the forms to the DEA office to obtain the necessary Export Permits.

USP cannot ship items without an Export Permit. While it typically takes 6-10 weeks to get the permit from the DEA, USP has no control over the time in which permits are issued. On receiving the Export Permit, USP completes processing of the order in 1-3 days and ships out the materials through its freight forwarder.

Controlled substances (CI, CII, CIII, CIV, CV) and List Chemicals shipped to an international address, including Canada, add $\$ 25$ per unit.

For controlled substance orders to be shipped to Mexico, in addition to the DEA processing period, an additional week is required to obtain a certificate from the Mexican Embassy, authorizing the shipment to enter the country. Customers will pay an additional $\$ 114$ to cover the fee charged by the Mexican Embassy per import permit.

## Back Orders

USP will ship a back-ordered item if that item becomes available within 30 days of the date the order is placed if there is a valid open P.O. or payment for the item. If the order is more than 30 days old when the item becomes available, the customer will receive a Notice of Availability (NOA), indicating that the item is available. Such items will be shipped only after USP receives written authorization by the customer. The order will be canceled if the Reference Standard does not become available within six months of the original order. NOAs not replied to within 45 days of generation will be cancelled, and the customer account will be credited appropriately.

Customers may send confirmation orders for back-ordered Reference Standards that subsequently become available. They must clearly designate the confirmation orders as such-USP is not responsible for duplication of orders not clearly designated.

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## HOW TO READ PRODUCT LISTINGS

Column 1 (Catalog Number): Catalog number currently assigned to each Reference Standard and Authentic Substance. Please include this number in your orders.

Column 2 (Description): Product description as designated in $U S P-N F$, the product label, and / or the Drug Enforcement Administration Control Schedule, as applicable. The quantity of material per container follows the name in parentheses (all materials are in single containers unless otherwise specified).

Column 3 (Current Lot): Current lot designation of each official item being distributed as of the date of this catalog. If the current lot is blank, the item is not in distribution.

Column 4 (Purity Values) Assigned purity value as it appears on the RS or AS label. Code interpretations for the basis of purity assignments are as follows:
Basis Interpretation

## Code

| (ai) | as is |
| :--- | :--- |
| (dr) | dried |
| (an) | anhydrous |
| (fb) | free base |

Column 5 (Change Code): Codes that identify any change in USP Reference Standards status or information since the July/Aug. 2004, official Catalog. Code interpretations are as follows:

| Change <br> Code | Interpretation |
| :---: | :--- |
| 1 | New Reference Standard |
| 2 | New lot |
| 3 | Change in package size or description |
| 4 | Correction of typographical error |
| 5 | New catalog number-use for all orders |
| 6 | Previous lot no longer official; only <br> current lot to be used |
| 7 | Valid use date of previous lot extended <br> Change in catalog number and / or name, <br> 8 |
| see cross-reference section <br> Discontinued |  |

Column 6 (Previous Lot/Valid Use Date): Lot designations for recent lots no longer being distributed. The indicated month and year in parenthesis indicates the date (last day of the month) through which that lot was valid as an official USP Reference Standard. (e.g. "F-1 (06/00)" means lot F-1 is no longer being distributed, but was considered official through June 30, 2000.)

Column 7 (CAS Number) ${ }^{*}$ : Chemical Abstracts Service number, when available, for USP Reference Standards and Authentic Substances. In case of mixtures, typically, the CAS number of the analyte of interest is listed.

Column 8 (Price) List price of the reference standard.

[^287]New Lots in Distribution

| Cat. No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \text { CAS } \\ \text { No. } \\ \hline \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1005706 | Glacial Acetic Acid ( $1.5 \mathrm{~mL} /$ /ampule; 3 ampules) (AS) | F0D002 | 99.9\% (ai) | 1 |  | [64-19-7] | \$156 |
| 1012699 | Alcohol Determination-Acetonitrile ( 5 mL /ampule; 5 ampules) | F0C419 | 2\% v/v (ai) | 1 |  | n/f | \$156 |
| 1012688 | Alcohol Determination-Alcohol ( $5 \mathrm{~mL} /$ ampule; 5 ampules) | F0C399 | 1.96\% v/v (ai) | 1 |  | n/f | \$156 |
| 1076206 | Powdered Black Cohosh Extract (1.5 g) | F0D086 |  | 1 |  | [84776-26-1] | \$520 |
| 1076341 | Boric Acid (1 g) (AS) | F0D036 | 100.0\% (dr) | 1 |  | [10043-35-3] | \$200 |
| 1082708 | Butylated Hydroxytoluene ( 500 mg ) (AS) | F0D122 | >99.0\% (ai) | 1 |  | [128-37-0] | \$156 |
| 1086334 | Calcium Acetate (1 g) (AS) | FOD156 | 100.0\% (an) | 1 |  | [62-54-4] | \$156 |
| 1086403 | Calcium Carbonate (1 g ) (AS) | F0D099 | 99.1\% (dr) | 1 |  | [471-34-1] | \$156 |
| 1086436 | Calcium Chloride (1 g) (AS) | F0D153 | 101.9\% (ai) | 1 |  | [10035-04-8] | \$156 |
| 1086855 | Calcium Hydroxide ( 1 g ) (AS) | F0D168 | 98.1\% (ai) | 1 |  | [1305-62-0] | \$156 |
| 1087701 | Candelilla Wax ( 250 mg ) | F0D123 |  | 1 |  | [8006-44-8] | \$156 |
| 1091505 | Caprylocaproyl Polyoxylglycerides ( $200 \mathrm{mg} \mathrm{)}$ | F0C312 |  | 1 |  | n/f | \$175 |
| 1187080 | Dibutyl Phthalate (200 mg) | F0D125 |  | 1 |  | [84-74-2] | \$156 |
| 1288463 | Gemcitabine Hydrochloride (200 mg) | F0D037 | $0.997 \mathrm{mg} / \mathrm{mg}$ (ai) | 1 |  | [122111-03-9] | \$156 |
| 1356950 | Lauroyl Polyoxylglycerides ( 500 mg ) (AS) | F0D020 |  | 1 |  | n/f | \$156 |
| 1374260 | Magnesium Hydroxide (1 g) (AS) | F0D158 | 98.5\% (dr) | 1 |  | [1309-42-8] | \$156 |
| 1375127 | Manganese Chloride (1 g) (AS) | F0D150 | 99.6\% (dr) | 1 |  | [13446-34-9] | \$156 |
| 1375149 | Manganese Sulfate (1 g) (AS) | F0D151 | 99.8\% (ai) | 1 |  | [10034-96-5] | \$156 |
| 1444279 | Mirtazapine ( 350 mg ) | F0D155 | $0.999 \mathrm{mg} / \mathrm{mg}$ (an) | 1 |  | [61337-67-5] | \$800 |
| 1449530 | Nabumetone Related Compound A (15 mg) (1-(6-Methoxy-2-naphthyl)-but-1-en-3-one) | F0D165 |  | 1 |  | n/f | \$487 |
| 1460703 | Nevirapine Anhydrous ( 100 mg ) | FOD159 | $0.997 \mathrm{mg} / \mathrm{mg}$ (ai) | 1 |  | [129618-40-2] | \$156 |
| 1547925 | Polysorbate 20 (2 g) (AS) | F0D130 |  | 1 |  | [9005-64-5] | \$156 |
| 1547947 | Polysorbate 60 (2 g) (AS) | FOD131 |  | 1 |  | [9005-67-8] | \$156 |
| 1547969 | Polysorbate 80 (2 g) (AS) | F0D132 |  | 1 |  | [9005-65-6] | \$156 |
| 1548101 | Potassium Benzoate (1 g) (AS) | F0D161 | $0.999 \mathrm{mg} / \mathrm{mg}$ (an) | 1 |  | [582-25-2] | \$156 |
| 1548167 | Potassium Carbonate (1 g) (AS) | F0D075 | 99.8\% (dr) | 1 |  | [584-08-7] | \$156 |
| 1548190 | Potassium Chloride (1 g) (AS) | F0D127 | 100.0\% (dr) | 1 |  | [7447-40-7] | \$156 |
| 1548280 | Potassium lodide (1 g) (AS) | F0D078 | 100.0\% (dr) | 1 |  | [7681-11-0] | \$156 |
| 1572208 | Propionic Acid ( $1.5 \mathrm{~mL} /$ ampule; 3 ampules) (AS) | F0D029 | 99.8 \% w/w (ai) | 1 |  | [79-09-4] | \$156 |
| 1601689 | Residual Solvent Class 2 - Methylcyclohexane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D044 | $5.46 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1613407 | Sodium Acetate (1 g) (AS) | F0D083 | 99.8\% (dr) | 1 |  | [127-09-3] | \$156 |
| 1613757 | Sodium Carbonate Anhydrous (1 g) (AS) | FOD100 | 100.0\% (dr) | 1 |  | [497-19-8] | \$156 |
| 1614396 | Sodium Metabisulfite (1 g) (AS) | F0D111 | 98.6\% (ai) | 1 |  | [7681-57-4] | \$156 |
| 1614454 | Sodium Nitrite (1 g) (AS) | F0D117 | 99.6\% (dr) | 1 |  | [7632-00-0] | \$156 |
| 1614807 | Sodium Sulfate Anhydrous (1 g) (AS) | F0D112 | 99.8\% (dr) | 1 |  | [7757-82-6] | \$156 |
| 1667585 | Titanium Dioxide (1 g) (AS) | F0D079 | 99.6\% (dr) | 1 |  | [13463-67-7] | \$156 |
| 1724769 | Zinc Sulfate (1 g) (AS) | F0D133 | 56.4\% (ai) | 1 |  | [7446-20-2] | \$156 |
| 1015008 | Alprazolam CIV (200 mg) | H1C133 |  | 2 | H (06/05) | [28981-97-7] | \$207 |
| 1029910 | Ammonio Methacrylate Copolymer Type B ( 100 mg ) | F2C082 |  | 2 | $\begin{aligned} & \text { F-1 }(06 / 05) \\ & \text { F (05/00) } \end{aligned}$ | [33434-24-1] | \$156 |
| 1071009 | Bethanechol Chloride (200 mg) | G1D088 | $1.00 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{aligned} & \mathrm{G}(03 / 05) \\ & \mathrm{F}-3(07 / 01) \\ & \hline \end{aligned}$ | [590-63-6] | \$156 |
| 1078802 | Buspirone Hydrochloride (200 mg) | H0B301 |  | 2 | G (05/05) | [33386-08-2] | \$156 |
| 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) | O0C331 | 0.990 mg/mg (dr) | 2 | N-1 (06/05) N (06/00) | [137-08-6] | \$156 |

[^288]New Lots in Distribution

| Cat. No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1097750 | Cefonicid Sodium (1 g) | H0D105 | $887 \mathrm{ug} / \mathrm{mg}$ (an) | 2 | G (06/05) | [61270-78-8] | \$156 |
| 1140407 | Clonidine Hydrochloride (200 mg) | H0D106 | $1.000 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | G (05/05) | [4205-91-8] | \$156 |
| 1235300 | Enalapril Maleate (200 mg) | J1C267 | $0.992 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | $\begin{array}{\|l\|} \hline J(05 / 05) \\ I(06 / 01) \\ \hline \end{array}$ | [76095-16-4] | \$156 |
| 1250008 | Estradiol ( 500 mg ) | L0C337 | $0.996 \mathrm{mg} / \mathrm{mg}$ (an) | 2 | $\begin{array}{\|l\|} \hline \text { K1B007 (07/05) } \\ \text { K (04/03) } \\ \hline \end{array}$ | [50-28-2] | \$156 |
| 1303501 | Halothane ( 1 mL ) | G0D068 |  | 2 | F-1 (03/05) | [151-67-7] | \$156 |
| 1333003 | Hydroxyzine Hydrochloride ( 500 mg ) | I0C385 | $0.998 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | H (05/05) | [2192-20-3] | \$156 |
| 1392705 | Mesalamine ( 200 mg ) | H0C341 |  | 2 | $\begin{array}{\|l\|} \hline \text { G1B001 (06/05) } \\ \text { G (01/03) } \\ \text { F-1 (03/00) } \\ \hline \end{array}$ | [89-57-6] | \$156 |
| 1436006 | Methylprednisolone Acetate (200 mg) | H0D148 | $0.995 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | $\begin{aligned} & \text { G-2 (05/05) } \\ & \text { G-1 }(02 / 00) \\ & \hline \end{aligned}$ | [53-36-1] | \$156 |
| 1440808 | Metoclopramide Hydrochloride ( 500 mg ) | H0D121 | $0.999 \mathrm{mg} / \mathrm{mg}$ (an) | 2 | $\begin{aligned} & \text { G (06/05) } \\ & \mathrm{F}-2(06 / 99) \end{aligned}$ | [54143-57-6] | \$156 |
| 1443500 | Miconazole Nitrate (200 mg) | J0D011 | 0.997 mg/mg (dr) | 2 | $\begin{array}{\|l\|} \hline I(06 / 06) \\ H(06 / 99) \\ \hline \end{array}$ | [22832-87-7] | \$156 |
| 1446950 | Moricizine Hydrochloride ( $250 \mathrm{mg} \mathrm{)}$ | F1D057 | $0.999 \mathrm{mg} / \mathrm{mg}$ (an) | 2,3 | F (03/05) | [29560-58-5] | \$390 |
| 1449700 | Nadolol (200 mg) | G0C308 | $0.995 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | $\begin{array}{\|l\|} \hline \text { F-3 (04/05) } \\ \text { F-2 (04/02) } \\ \hline \end{array}$ | [42200-33-9] | \$156 |
| 1454008 | Nandrolone CIII ( 50 mg ) | F4D144 | $1.00 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | F-3 (04/05) | [434-22-0] | \$560 |
| 1463304 | Nicotine Bitartrate Dihydrate ( 500 mg ) | G1C070 |  | 2 | $\begin{aligned} & \hline \text { G (05/05) } \\ & \text { F (05/99) } \\ & \hline \end{aligned}$ | [6019-06-3] | \$156 |
| 1474005 | Nortriptyline Hydrochloride (200 mg) | I1D054 | $1.000 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{aligned} & \mathrm{I}(05 / 052) \mathrm{H}(04 / \\ & 00) \\ & \hline \end{aligned}$ | [894-71-3] | \$156 |
| 1478582 | Ondansetron Hydrochloride ( 300 mg ) | G0D154 | $0.993 \mathrm{mg} / \mathrm{mg}$ (an) | 2 | F0C222 (05/05) | [103639-04-9] | \$208 |
| 1495005 | Papain (1 g) | 10C389 | 6700 USP units/ mg (ai) | 2,6 | $\begin{aligned} & \hline \text { H }(06 / 04) \\ & G(12 / 01) \\ & \hline \end{aligned}$ | [9001-73-4] | \$156 |
| 1546707 | Polyethylene, High Density (3 strips) | G1D115 |  | 2 | $\begin{array}{\|l\|} \hline \mathrm{G}(06 / 05) \\ \mathrm{F}-1(04 / 01) \end{array}$ | [9002-88-4] | \$156 |
| 1575002 | Propoxyphene Napsylate CII (1 g) | H1C323 | $0.993 \mathrm{mg} / \mathrm{mg}$ (an) | 2 | H (05/05) | [26570-10-5] | \$207 |
| 1008002 | Propoxyphene Related Compound B ( 50 mg ) (alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane) | H0D012 | $0.94 \mathrm{mg} / \mathrm{mg}$ (ai) | 2,8 | G-3 (05/05) | n/f | \$487 |
| 1623670 | Sulbactam (250 mg) | H0C396 | $0.976 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | $\begin{array}{\|l\|l\|} \hline \text { G (05/05) } \\ \text { F-1 }(05 / 00) \\ \hline \end{array}$ | [68373-14-8] | \$156 |
| 1647001 | Testosterone Cypionate CIII (200 mg) | H0D162 | $1.000 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | $\begin{aligned} & \text { G-1 (03/05) } \\ & \text { G (08/01) } \end{aligned}$ | [58-20-8] | \$207 |
| 1682206 | Triclosan (200 mg) | G0D001 | $0.997 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | FOB135 (05/05) | [3380-34-5] | \$156 |
| 1705006 | L-Tyrosine ( 500 mg ) | K0C141 | $1.00 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | J (05/05) | [60-18-4] | \$156 |
| 1708729 | Valproic Acid Related Compound A ( 0.25 mL ) (diallylacetic acid) | F2C386 |  | 2 | $\begin{aligned} & \text { F1B156 (05/05) } \\ & \text { F (01/03) } \end{aligned}$ | [99-67-2] | \$208 |
| 1707908 | Valerenic Acid (15 mg) | H0D126 | $1.00 \mathrm{mg} / \mathrm{mg}$ (ai) | 2,3 | $\begin{array}{\|l\|} \hline \text { G0B146 (05/05) } \\ \text { F (01/04) } \\ \hline \end{array}$ | [3569-10-6] | \$696 |
| 1711009 | Vanillin Melting Point Standard (1 g) (Approximately 82 degrees) | J1C303 |  | 2 | $\begin{array}{\|l} \hline J(06 / 05) \\ I-1(03 / 03) \\ I(11 / 00) \\ \hline \end{array}$ | [121-33-5] | \$92 |

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## USP Reference Standards and Authentic Substances

| Cat. <br> No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1000601 | Acebutolol Hydrochloride ( 125 mg ) | F-1 |  |  |  | [34381-68-5] | \$156 |
| 1001003 | Acenocoumarol (200 mg) | F |  |  |  | [152-72-7] | \$156 |
| 1001502 | Acepromazine Maleate ( 250 mg ) | F-2 |  |  | F-1 (05/02) | [3598-37-6] | \$156 |
| 1002505 | Acesulfame Potassium ( 200 mg ) | F0C136 |  |  |  | [55589-62-3] | \$260 |
| 1003009 | Acetaminophen (400 mg) | J-1 |  |  | $\begin{array}{\|l\|} \hline J(05 / 02) \\ I(05 / 99) \\ \hline \end{array}$ | [103-90-2] | \$124 |
| 1004001 | Acetanilide Melting Point Standard ( 500 mg ) (Approximately 114 degrees) | M0A029 |  |  | $\begin{array}{\|l\|} \hline \text { L (06/04) } \\ \mathrm{K}(02 / 00) \\ \hline \end{array}$ | [103-84-4] | \$75 |
| 1005004 | Acetazolamide (2 g) | $J$ |  |  |  | [59-66-5] | \$156 |
| 1005706 | Glacial Acetic Acid ( 1.5 mL /ampule; 3 ampules) (AS) | F0D002 | 99.9\% (ai) | 1 |  | [64-19-7] | \$156 |
| 1006007 | Acetohexamide (250 mg) | H |  |  | G-1 (06/99) | [968-81-0] | \$156 |
| 1006506 | Acetohydroxamic Acid ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  | F (03/03) | [546-88-3] | \$156 |
| 1007000 | Acetophenazine Maleate ( 200 mg ) | F-1 |  |  |  | [5714-00-1] | \$156 |
| 1008501 | Acetylcholine Chloride ( 200 mg ) | G |  |  |  | [60-31-1] | \$156 |
| 1009005 | Acetylcysteine ( $200 \mathrm{mg} \mathrm{)}$ | H1B169 |  |  | H (01/04) | [616-91-1] | \$156 |
| 1009901 | Acetyltributyl Citrate ( 500 mg ) | G0C120 |  |  | F (05/04) | [77-90-7] | \$156 |
| 1009923 | Acetyltriethyl Citrate ( 500 mg ) | F-1 |  |  | F (05/02) | [77-89-4] | \$156 |
| 1012065 | Acyclovir (300 mg) | J0C149 |  |  | 1 (06/04) | [59277-89-3] | \$197 |
| 1012101 | Adenine ( 200 mg ) | G-1 |  |  | G (06/00) | [73-24-5] | \$156 |
| 1012123 | Adenosine ( 200 mg ) | G0C295 |  |  | $\begin{array}{\|l\|} \hline \text { F1B058 (01/05) } \\ \text { F (04/03) } \\ \hline \end{array}$ | [58-61-7] | \$156 |
| 1012145 | Agigenin ( 25 mg ) | F |  |  |  | n/f | \$156 |
| 1012509 | L-Alanine ( 200 mg ) | F-2 |  |  | F-1 (04/01) | [56-41-7] | \$156 |
| 1012553 | Albendazole (200 mg) | G |  |  | F-1 (01/00) | [54965-21-8] | \$156 |
| 1012600 | Albuterol ( 200 mg ) | 1 |  |  | H (12/00) | [18559-94-9] | \$156 |
| 1012633 | Albuterol Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | $J$ |  |  | I (04/00) | [51022-70-9] | \$156 |
| 1012757 | Alclometasone Dipropionate ( 300 mg ) | H |  |  | G (01/00) | [66734-13-2] | \$156 |
| 1012699 | Alcohol Determination-Acetonitrile ( $5 \mathrm{~mL} / \mathrm{am}$ pule; 5 ampules) | F0C419 | 2\% v/v (ai) | 1 |  | n/f | \$156 |
| 1012688 | Alcohol Determination-Alcohol ( $5 \mathrm{~mL} /$ ampule; 5 ampules) | F0C399 | 1.96\% v/v (ai) | 1 |  | n/f | \$156 |
| 1012780 | Alendronate Sodium (200 mg) | F0B315 |  |  |  | [121268-17-5] | \$156 |
| 1012906 | Alfentanil Hydrochloride CII ( 500 mg ) | F0B016 |  |  |  | [70879-28-6] | \$207 |
| 1012939 | Allantoin (200 mg) | FOC169 |  |  |  | [97-59-6] | \$156 |
| 1012950 | Alliin (25 mg) | F |  |  |  | [556-27-4] | \$1,525 |
| 1013002 | Allopurinol (250 mg) | JoC186 |  |  | $\begin{array}{\|l\|} \hline \text { I-1 (01/05) } \\ \text { I (07/02) } \\ \hline \end{array}$ | [315-30-0] | \$156 |
| 1013024 | Allopurinol Related Compound A ( 50 mg ) (3-Amino-4-carboxamidopyrazole Hemisulfate) | G |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-3 (05/02) } \\ \text { F-2 (04/99) } \\ \hline \end{array}$ | n/f | \$487 |
| 1013057 | S-Allyl-L-Cysteine (25 mg) | F |  |  |  | n/f | \$487 |
| 1014005 | Alphaprodine Hydrochloride CII (250 mg) | F |  |  |  | [561-78-4] | \$207 |
| 1015008 | Alprazolam CIV (200 mg) | H1C133 |  | 2 | H (06/05) | [28981-97-7] | \$207 |
| 1016000 | Alprostadil ( 25 mg ) | H |  |  |  | [745-65-3] | \$1,525 |
| 1017105 | Altretamine ( 500 mg ) | F |  |  |  | [645-05-6] | \$156 |
| 1017502 | Dried Aluminum Hydroxide Gel ( $200 \mathrm{mg} \mathrm{)}$ | F2B120 |  |  | F-1 (01/04) | [21645-51-2] | \$156 |
| 1018505 | Amantadine Hydrochloride ( 200 mg ) | H |  |  | G (04/01) | [665-66-7] | \$156 |
| 1019202 | Amcinonide (200 mg) | G0B260 |  |  | F-1 (03/04) | [51022-69-6] | \$156 |
| 1019417 | Amifostine Disulfide ( 25 mg ) | F0C152 |  |  |  | [112901-68-5] | \$487 |
| 1019508 | Amikacin (200 mg) | I |  |  | H (08/00) | [37517-28-5] | \$156 |

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## USP Reference Standards and Authentic Substances

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1019701 | Amiloride Hydrochloride ( 500 mg ) | H |  |  |  | [17440-83-4] | \$156 |
| 1019756 | Aminobenzoate Potassium (200 mg) | F-1 |  |  | F (06/01) | [138-84-1] | \$156 |
| 1019767 | Aminobenzoate Sodium (200 mg) | F |  |  |  | [55-06-6] | \$156 |
| 1019803 | Aminobenzoic Acid ( 200 mg ) ( p -aminobenzoic acid) | H1C083 |  |  | $\begin{aligned} & \mathrm{H}(10 / 04) \\ & \mathrm{G}(10 / 00) \\ & \hline \end{aligned}$ | [150-13-0] | \$156 |
| 1020008 | Aminobutanol ( 500 mg ) | G-1 |  |  | G (06/99) | [13054-87-0] | \$389 |
| 1021000 | Aminocaproic Acid (200 mg) | F-4 |  |  |  | [60-32-2] | \$156 |
| 1021703 | N-(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methy-lene)-aminoj-glycine ( 25 mg ) | F-1 |  |  |  | n/f | \$487 |
| 1022808 | 2-Amino-5-chlorobenzophenone ( 25 mg ) | 1 |  |  | H-1 (01/03) | [719-59-5] | \$487 |
| 1025205 | Aminoglutethimide ( 200 mg ) | F |  |  |  | [125-84-8] | \$156 |
| 1025307 | m -Aminoglutethimide ( $100 \mathrm{mg} \mathrm{)}$ | G |  |  | F (05/01) | n/f | \$487 |
| 1025351 | Aminohippuric Acid ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  |  | [61-78-9] | \$156 |
| 1025806 | 2-[3-Amino-5-(n-methylacetamido)-2,4,6-triiodo-benzamido]-2-deoxy-d-glucose ( 25 mg ) | F |  |  |  | n/f | \$487 |
| 1025908 | Aminopentamide Sulfate (200 mg) | F0B273 |  |  |  | [60-46-8] | \$156 |
| 1026004 | m-Aminophenol ( 300 mg ) | F |  |  |  | [591-27-5] | \$487 |
| 1026401 | Aminosalicylic Acid (125 mg) | F-1 |  |  | F (03/99) | [65-49-6] | \$124 |
| 1026605 | 3 -Amino-2,4,6-triodobenzoic Acid ( 50 mg ) | G |  |  |  | [3119-15-1] | \$487 |
| 1027007 | 5-Amino-2,4,6-triiodo-N-methylisophthalamic Acid ( 50 mg ) | F-1 |  |  |  | [2280-89-9] | \$487 |
| 1028000 | Amitraz (200 mg) | F0C042 |  |  |  | [33089-61-1] | \$156 |
| 1029002 | Amitriptyline Hydrochloride (200 mg) | J0A004 |  |  | $1(03 / 03)$ | [549-18-8] | \$156 |
| 1029909 | Ammonio Methacrylate Copolymer Type A ( 100 mg ) | F-1 |  |  | F (06/01) | [33434-24-1] | \$156 |
| 1029910 | Ammonio Methacrylate Copolymer Type B ( 100 mg ) | F2C082 |  | 2 | $\begin{aligned} & \hline \text { F-1 (06/05) } \\ & \text { F (05/00) } \\ & \hline \end{aligned}$ | [33434-24-1] | \$156 |
| 1029953 | Ammonium Chloride (200 mg) | F0C134 |  |  |  | [12125-02-9] | \$156 |
| 1030001 | Amobarbital CII (200 mg) | F-2 |  |  |  | [57-43-2] | \$207 |
| 1031004 | Amodiaquine Hydrochloride ( 500 mg ) | H0B238 |  |  | G-1 (04/03) | [6398-98-7] | \$156 |
| 1031401 | Amoxapine ( 200 mg ) | G |  |  | F-1 (04/02) | [14028-44-5] | \$156 |
| 1031503 | Amoxicillin (200 mg) | J0C043 |  |  | 1 (07/04) | [61336-70-7] | \$156 |
| 1032007 | Amphotericin B (125 mg) | J3C246 | $1009 \mathrm{ug} / \mathrm{mg}$ (dr) |  | $\begin{array}{\|l\|} \hline \mathrm{J}-2(01 / 05) \\ \mathrm{J}-1(07 / 02) \\ \hline \end{array}$ | [1397-89-3] | \$124 |
| 1033000 | Ampicillin (200 mg) | J-1 |  |  | J (12/01) | [69-53-4] | \$156 |
| 1033203 | Ampicillin Sodium ( 125 mg ) | G-1 |  |  | G (10/99) | [69-52-3] | \$124 |
| 1033407 | Ampicillin Trihydrate (200 mg) | G |  |  |  | [7177-48-2] | \$156 |
| 1034002 | Amprolium (200 mg) | G0C317 | 0.991 mg/mg (dr) |  | $\begin{aligned} & \hline F-1(04 / 05) \\ & F(04 / 02) \\ & \hline \end{aligned}$ | [121-25-5] | \$156 |
| 1034308 | Amrinone ( 500 mg ) | G |  |  |  | [60719-84-8] | \$156 |
| 1034320 | Amrinone Related Compound A (100 mg) (5-carboxamide[3,4'-bipyridin]-6(1H)-one) | F |  |  |  | [62749-46-6] | \$487 |
| 1034341 | Amrinone Related Compound B ( 100 mg ) ( N -(1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-yl)-2-hydroxypropanamide) | F-1 |  |  | F (03/00) | n/f | \$487 |
| 1034363 | Amrinone Related Compound C ( 50 mg ) (1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-carbonitrile) | F-1 |  |  | F (05/00) | n/f | \$487 |
| 1036008 | Anileridine Hydrochloride CII (250 mg) | F |  |  |  | [126-12-5] | \$207 |
| 1036507 | 3-Anilino-2-(3,4,5-trimethoxybenzyl) acrylonitrile ( 25 mg ) | G-1 |  |  |  | [30078-48-9] | \$487 |
| 1038003 | Antazoline Phosphate (200 mg) | H |  |  | G-1 (04/02) | [154-68-7] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1039006 | Anthralin (200 mg) | IOB221 |  |  | H (11/02) | [1143-38-0] | \$156 |
| 1040005 | Antipyrine (200 mg) | G |  |  | F-4 (09/01) | [60-80-0] | \$156 |
| 1040708 | Apigenin-7-glucoside ( $30 \mathrm{mg} \mathrm{)}$ | F |  |  |  | n/f | \$487 |
| 1041008 | Apomorphine Hydrochloride ( 250 mg ) | H |  |  | G (01/03) | [41372-20-7] | \$162 |
| 1041609 | Apraclonidine Hydrochloride ( 100 mg ) | H0B112 |  |  | G (06/03) | [73218-79-8] | \$479 |
| 1042000 | Aprobarbital CIII (200 mg) (AS) | F-1 |  |  |  | [77-02-1] | \$207 |
| 1042500 | L-Arginine (200 mg) | G-1 |  |  | G (09/00) | [74-79-3] | \$156 |
| 1042601 | Arginine Hydrochloride ( 125 mg ) | G0B060 |  |  | F-1 (05/03) | [1119-34-2] | \$124 |
| 1042703 | Arsanilic Acid ( 25 mg ) | F |  |  |  | [98-50-0] | \$156 |
| 1043003 | Ascorbic Acid (1 g) (Vitamin C) | Q0B012 |  |  | P (04/03) | [50-81-7] | \$156 |
| 1043706 | Aspartame ( 200 mg ) | H1B125 |  |  | H (05/03) | [22839-47-0] | \$156 |
| 1043750 | Aspartame Acesulfame (200 mg) | F0C137 |  |  |  | [106372-55-8] | \$156 |
| 1043728 | Aspartame Related Compound A ( 75 mg ) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid) | H |  |  | G-1 (10/99) | [5262-10-2] | \$487 |
| 1043819 | Aspartic Acid (100 mg) | F0B087 |  |  |  | [6899-03-2] | \$156 |
| 1044006 | Aspirin (500 mg) | H |  |  | G-1 (11/02) | [50-78-2] | \$156 |
| 1044301 | Astemizole (200 mg) | F |  |  |  | [68844-77-9] | \$156 |
| 1044403 | Atenolol (200 mg) | H1C320 | 998 ug/mg (dr) |  | $\begin{aligned} & \mathrm{H}(01 / 05) \\ & \mathrm{G}(08 / 01) \\ & \hline \end{aligned}$ | [29122-68-7] | \$156 |
| 1044651 | Atovaquone ( 200 mg ) | FOB190 |  |  |  | [95233-18-4] | \$156 |
| 1044662 | Atovaquone Related Compound A ( 25 mg ) (cis-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4naphthoquinone) | FOB188 |  |  |  | n/f | \$487 |
| 1044800 | Atracurium Besylate ( 100 mg ) | FOB143 |  |  |  | [64228-81-5] | \$156 |
| 1045009 | Atropine Sulfate ( 500 mg ) | M0B098 |  |  | $\begin{array}{\|l} \hline \text { L-2 (04/03) } \\ \mathrm{L}-1(06 / 02) \\ \mathrm{L}(10 / 00) \\ \hline \end{array}$ | [5908-99-6] | \$156 |
| 1045337 | Avobenzone ( 500 mg ) | G0B280 |  |  | F (09/03) | [70356-09-1] | \$156 |
| 1045508 | Aurothioglucose (100 mg) | H0B224 |  |  | $\begin{aligned} & \hline \text { G (10/03) } \\ & \text { F (12/01) } \end{aligned}$ | [12192-57-3] | \$156 |
| 1045600 | Azaerythromycin A (100 mg) | G |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-1 (02/02) } \\ \hline \\ \hline \end{array}$ | [76801-85-9] | \$156 |
| 1045756 | Azaperone ( 200 mg ) | F |  |  |  | [1649-18-9] | \$156 |
| 1045803 | Azatadine Maleate (200 mg) | G0B300 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (04/04) } \\ \text { F (06/00) } \\ \hline \end{array}$ | [3978-86-7] | \$156 |
| 1046001 | Azathioprine (200 mg) | H |  |  | G-1 (02/00) | [446-86-6] | \$156 |
| 1046056 | Azithromycin (100 mg) | H0C212 |  |  | $\begin{aligned} & \text { G (11/04) } \\ & \text { F (06/00) } \end{aligned}$ | [117772-70-0] | \$156 |
| 1046103 | Azlocillin Sodium (200 mg) | F |  |  |  | [37091-65-9] | \$156 |
| 1046147 | Azo-aminoglutethimide ( 100 mg ) | F |  |  |  | n/f | \$487 |
| 1046205 | Aztreonam ( 200 mg ) | G0C077 |  |  | F-1 (03/04) | [78110-38-0] | \$156 |
| 1046307 | Aztreonam E-Isomer ( 50 mg ) | F1D056 |  |  | F (04/05) | n/f | \$156 |
| 1046409 | Open Ring Aztreonam ( 25 mg ) | G0D071 |  |  | F (12/04) | [87500-74-1] | \$156 |
| 1047300 | Bacampicillin Hydrochloride ( 200 mg ) | G0B053 |  |  | F (11/02) | [37661-08-8] | \$156 |
| 1047503 | Bacitracin (1 g) (Susceptibility disk standard) | G1C254 |  |  | G (07/04) | [1405-87-4] | \$156 |
| 1048007 | Bacitracin Zinc (200 mg) | N0A024 |  |  | $\begin{aligned} & \mathrm{M}-1(11 / 02) \\ & \mathrm{M}(02 / 00) \\ & \hline \end{aligned}$ | [1405-89-6] | \$156 |
| 1048200 | Baclofen ( 500 mg ) | 1 |  |  |  | [1134-47-0] | \$156 |
| 1048222 | Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone) | H1C289 |  |  | H (11/04) | n/f | \$389 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1048506 | Beclomethasone Dipropionate (200 mg) | K |  |  | J (12/00) | [5534-09-8] | \$156 |
| 1048619 | Benazepril Hydrochloride ( 125 mg ) | F0C250 |  |  |  | [86541-74-4] | \$156 |
| 1048620 | Benazepril Related Compound A (15 mg) ((3R)-3-[[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]ami-nol-2,3,4,5-tetrahydro-2-oxo-1H-1-benazapine-1-acetic acid, monohydrochloride) | F0C252 |  |  |  | n/f | \$487 |
| 1048630 | Benazepril Related Compound B (15 mg) ((3S)-3-[[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]ami-no]-2,3,4,5-tetrahydro-2-oxo-1H-1-benazapine-1-acetic acid, monohydrochloride) | F0C256 |  |  |  | n/f | \$487 |
| 1048641 | Benazepril Related Compound C (50 mg) ((3S)-3-[[(1S)-1-carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1H-1-benazepine]-1acetic acid) | F0C425 | $1.00 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | [86541-78-8] | \$487 |
| 1049000 | Bendroflumethiazide (200 mg) |  |  |  | G-1 (06/05) | [73-48-3] | \$156 |
| 1050009 | Benoxinate Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  |  | F-1 (10/99) | [5987-82-6] | \$124 |
| 1051001 | Benzalkonium Chloride ( 5 mL of approx. $10 \%$ aqueous solution) | K0B151 |  |  | J (06/03) | [8001-54-5] | \$156 |
| 1054000 | Benzocaine ( 500 mg ) | J0C130 |  |  | I (12/04) | [94-09-7] | \$156 |
| 1055002 | Benzoic Acid ( 300 mg ) | F6B173 |  |  | $\begin{aligned} & \text { F-5 }(03 / 04) \\ & \text { F-4 }(07 / 01) \\ & \hline \end{aligned}$ | [65-85-0] | \$156 |
| 1056005 | Benzonatate (1 g) | 10B003 |  |  | H (01/03) | [104-31-4] | \$156 |
| 1056504 | 1,4-Benzoquinone (200 mg) | G1B145 |  |  | $\begin{aligned} & \hline \text { G (01/04) } \\ & \text { F-1 (11/01) } \\ & F(09 / 00) \\ & \hline \end{aligned}$ | [106-51-4] | \$156 |
| 1057507 | Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide) | H0B069 |  |  | G-4 (03/03) | [121-30-2] | \$487 |
| 1059003 | Benzphetamine Hydrochloride CIII ( 200 mg ) (AS) | F-1 |  |  |  | [5411-22-3] | \$207 |
| 1060002 | Benzthiazide (200 mg) | F |  |  |  | [91-33-8] | \$156 |
| 1061005 | Benztropine Mesylate (200 mg) | I0C038 |  |  | H (09/04) | [132-17-2] | \$156 |
| 1061901 | Benzyl Alcohol ( $500 \mathrm{mg} / \mathrm{ampule} \mathrm{)}$ | G0B306 |  |  | FOB106 (10/03) | [100-51-6] | \$156 |
| 1062008 | Benzyl Benzoate (5 g) | J0C060 |  |  | I (05/04) | [120-51-4] | \$156 |
| 1064003 | 1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride ( 25 mg ) | F-1 |  |  |  | n/f | \$487 |
| 1065006 | Bephenium Hydroxynaphthoate ( 500 mg ) | F |  |  |  | [3818-50-6] | \$156 |
| 1065618 | Betahistine Hydrochloride ( 200 mg ) | F0C105 |  |  |  | [5579-84-0] | \$156 |
| 1065709 | Betaine Hydrochloride ( 200 mg ) | F-1 |  |  | F (11/02) | [590-46-5] | \$156 |
| 1066009 | Betamethasone (200 mg) | K2C204 |  |  | $\begin{aligned} & \hline \text { K-1 (10/04) } \\ & \text { K (11/02) } \\ & \hline \end{aligned}$ | [378-44-9] | \$156 |
| 1067001 | Betamethasone Acetate ( 500 mg ) | J0B079 |  |  | I (08/03) | [987-24-6] | \$156 |
| 1067307 | Betamethasone Benzoate ( 200 mg ) | F-1 |  |  |  | [22298-29-9] | \$156 |
| 1067704 | Betamethasone Dipropionate (125 mg) | K0C229 |  |  | $\begin{aligned} & \hline \mathrm{J}(04 / 04) \\ & \mathrm{I}(03 / 99) \\ & \hline \end{aligned}$ | [5593-20-4] | \$124 |
| 1068004 | Betamethasone Sodium Phosphate (500 mg) |  |  |  | $\begin{aligned} & \text { JOB043 (06/05) } \\ & \mathrm{I}-1(02 / 03) \\ & \mathrm{I}(01 / 01) \\ & \hline \end{aligned}$ | [151-73-5] | \$156 |
| 1069007 | Betamethasone Valerate (200 mg) | J |  |  | I (05/00) | [2152-44-5] | \$156 |
| 1069903 | Betaxolol Hydrochloride (200 mg) | G |  |  | F-1 (06/00) | [63659-19-8] | \$156 |
| 1070006 | Betazole Hydrochloride (200 mg) | H |  |  |  | [138-92-1] | \$156 |
| 1071009 | Bethanechol Chloride (200 mg) | G1D088 | $1.00 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{aligned} & \mathrm{G}(03 / 05) \\ & \mathrm{F}-3(07 / 01) \\ & \hline \end{aligned}$ | [590-63-6] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1071304 | Bile Salts (10 g) | 10C003 |  |  | $\begin{aligned} & \mathrm{H}-1(05 / 04) \\ & \mathrm{H} \text { (05/99) } \end{aligned}$ | [145-42-6] | \$124 |
| 1071439 | Positive Bioreaction (3 strips; $10 \mathrm{~cm} \times 1 \mathrm{~cm}$ ) | F0D014 |  |  |  | n/f | \$325 |
| 1071508 | Biotin (200 mg) | H1B019 |  |  | H (04/03) | [58-85-5] | \$156 |
| 1072001 | Biperiden (200 mg) | F2B080 |  |  | F-1 (02/04) | [514-65-8] | \$156 |
| 1073004 | Biperiden Hydrochloride (200 mg) | F-3 |  |  | F-2 (06/99) | [1235-82-1] | \$156 |
| 1074007 | Bisacodyl (125 mg) | 11B162 |  |  | $\begin{aligned} & \hline \text { I (01/04) } \\ & \text { H-1 (02/99) } \end{aligned}$ | [603-50-9] | \$124 |
| 1074700 | 2,5-Bis(D-arabino-1,2,3,4-tetrahydroxybutyl)pyr- azine ( 25 mg ) | F |  |  |  | n/f | \$487 |
| 1075203 | Bis(2-ethylhexyl)maleate ( 250 mg ) | F-2 |  |  | F-1 (01/01) | [142-16-5] | \$487 |
| 1075509 | p-Bis(di-n-propyl)carbamylbenzenesulfonamide ( 50 mg ) | F |  |  |  | n/f | \$487 |
| 1075531 | Bismuth Citrate (100 mg) | F |  |  |  | [813-93-4] | \$156 |
| 1075553 | Bismuth Subsalicylate ( 100 mg ) | F |  |  |  | [14882-18-9] | \$156 |
| 1075757 | Bisoprolol Fumarate ( $200 \mathrm{mg} \mathrm{)}$ | F0B038 |  |  |  | [104344-23-2] | \$156 |
| 1076002 | 4,4'-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimi-dazolinyl)-1-pyridyl]butyrophenone ( 25 mg ) |  |  |  | G (05/03) | n/f | \$487 |
| 1076206 | Powdered Black Cohosh Extract (1.5 g) | F0D086 |  | 1 |  | [84776-26-1] | \$520 |
| 1076308 | Bleomycin Sulfate ( 15 mg ) | J0B213 |  |  | I (01/04) | [9041-93-4] | \$307 |
| 1076341 | Boric Acid (1 g) (AS) | F0D036 | 100.0\% (dr) | 1 |  | [10043-35-3] | \$200 |
| 1076352 | Bretylium Tosylate (200 mg) | F-1 |  |  |  | [61-75-6] | \$156 |
| 1076363 | Brinzolamide (200 mg) | F0C034 |  |  |  | [138890-62-7] | \$156 |
| 1076374 | Brinzolamide Related Compound A ( 50 mg ) ((S)-(-)-4-ethylamino-2,3-dihydro-2-(3-methoxy-propyl)-4H-thieno-[3,2,e]-thiazine-6-sulfona-mide-1,1-dioxide) | F0C033 |  |  |  | n/f | \$487 |
| 1076385 | Brinzolamide Related Compound B ( 50 mg ) ((R)-4-amino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide ethanedioate) | F0C035 |  |  |  | n/f | \$487 |
| 1076501 | Bromocriptine Mesylate ( 150 mg ) | 11C197 |  |  | I (09/04) | [22260-51-1] | \$156 |
| 1077005 | Bromodiphenhydramine Hydrochloride ( 200 mg ) | F-1 |  |  |  | [1808-12-4] | \$156 |
| 1077708 | 8-Bromotheophylline (400 mg) | G |  |  | F (07/02) | [10381-75-6] | \$156 |
| 1078008 | Brompheniramine Maleate ( 125 mg ) | 11A036 |  |  | $\begin{array}{\|l\|} \hline \text { I (01/03) } \\ \text { H-1 (04/99) } \\ \hline \end{array}$ | [980-71-2] | \$124 |
| 1078303 | Bumetanide (250 mg) | 10 C 111 |  |  | $\begin{array}{\|l\|} \hline \text { H0B030 (05/04) } \\ \text { G (03/03) } \\ \hline \end{array}$ | [28395-03-1] | \$156 |
| 1078325 | Bumetanide Related Compound A ( 25 mg ) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid) | F-2 |  |  | F-1 (05/00) | n/f | \$487 |
| 1078336 | Bumetanide Related Compound B ( 25 mg ) (3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid) | F-2 |  |  | F-1 (01/03) | [28328-53-2] | \$487 |
| 1078507 | Bupivacaine Hydrochloride (1 g) | H |  |  | $\begin{aligned} & \hline \text { G-2 (03/03) } \\ & \text { G-1 (08/02) } \end{aligned}$ | [14252-80-3] | \$156 |
| 1078700 | Buprenorphine Hydrochloride CIII ( 50 mg ) | F-1 |  |  | F (02/99) | [53152-21-9] | \$207 |
| 1078711 | Buprenorphine Related Compound A ( 50 mg ) (21-[3-(1-propenyl)]-7-alpha-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine) | F1C076 |  |  | F (04/04) | n/f | \$487 |
| 1078733 | Bupropion Hydrochloride ( 200 mg ) | F0C123 |  |  |  | [31677-93-7] | \$208 |
| 1078802 | Buspirone Hydrochloride (200 mg) | H0B301 |  | 2 | G (05/05) | [33386-08-2] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1079000 | Butabarbital CIII (200 mg) | H0C007 |  |  | G (03/04) | [125-40-6] | \$207 |
| 1080000 | Butacaine Sulfate ( 600 mg ) | F |  |  |  | [149-15-5] | \$156 |
| 1081002 | Butalbital CIII (200 mg) | H0C054 |  |  | $\begin{array}{\|l\|} \hline \text { G2B077 (07/04) } \\ \text { G-2 (06/03) } \\ \text { G (05/02) } \\ \hline \end{array}$ | [77-26-9] | \$207 |
| 1081501 | Butamben (200 mg) | F |  |  |  | [94-25-7] | \$156 |
| 1082300 | Butoconazole Nitrate (200 mg) | F1B097 |  |  | F (03/03) | [64872-77-1] | \$156 |
| 1082504 | Butorphanol Tartrate CIV ( 500 mg ) | J |  |  | I (06/00) | [58786-99-5] | \$207 |
| 1082708 | Butylated Hydroxytoluene ( 500 mg ) (AS) | F0D122 | >99.0\% (ai) | 1 |  | [128-37-0] | \$156 |
| 1082800 | Monotertiary-butyl-p-benzoquinone ( 100 mg ) (FCC) | $F$ |  |  |  | [3602-55-9] | \$156 |
| 1082901 | Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate ( 25 mg ) | F-1 |  |  |  | n/f | \$487 |
| 1083008 | 2-tert-Butyl-4-hydroxyanisole (200 mg) | L0C028 |  |  | K (09/03) | [88-32-4] | \$156 |
| 1083100 | 3-tert-Butyl-4-hydroxyanisole (200 mg) | K0C239 |  |  | $\begin{array}{\|l\|} \hline J(03 / 05) \\ I-1(09 / 01) \\ \hline \end{array}$ | [121-00-6] | \$156 |
| 1084000 | Butylparaben (200 mg) | 10C139 |  |  | $\begin{array}{\|l\|} \hline \text { H-1 (03/04) } \\ \text { H (09/01) } \\ \hline \end{array}$ | [94-26-8] | \$156 |
| 1085003 | Caffeine ( 200 mg ) | $J$ |  |  | I (06/02) | [58-08-2] | \$156 |
| 1086006 | Caffeine Melting Point Standard (1 g) (Approximately 236 degrees) | J0B204 |  |  | I (03/04) | [58-08-2] | \$92 |
| 1086108 | Calcifediol ( 75 mg ) | G |  |  |  | [63283-36-3] | \$156 |
| 1086334 | Calcium Acetate ( 1 g ) (AS) | F0D156 | 100.0\% (an) | 1 |  | [62-54-4] | \$156 |
| 1086356 | Calcium Ascorbate (200 mg) | F-1 |  |  | F (08/01) | [5743-28-2] | \$156 |
| 1086403 | Calcium Carbonate (1 g) (AS) | F0D099 | 99.1\% (dr) | 1 |  | [471-34-1] | \$156 |
| 1086436 | Calcium Chloride ( 1 g ) (AS) | F0D153 | 101.9\% (ai) | 1 |  | [10035-04-8] | \$156 |
| 1086800 | Calcium Gluceptate ( 200 mg ) | F-1 |  |  | F (09/00) | [29039-00-7] | \$156 |
| 1086855 | Calcium Hydroxide ( 1 g ) (AS) | F0D168 | 98.1\% (ai) | 1 |  | [1305-62-0] | \$156 |
| 1086902 | Calcium Lactobionate (200 mg) | G0B138 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (01/04) } \\ \text { F (11/01) } \\ \hline \end{array}$ | [110638-68-1] | \$156 |
| 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) | O0C331 | $0.990 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{array}{\|l\|} \hline \text { N-1 (06/05) } \\ \text { N (06/00) } \\ \hline \end{array}$ | [137-08-6] | \$156 |
| 1087202 | Calcium Saccharate (200 mg) | F |  |  |  | [5793-89-5] | \$156 |
| 1087701 | Candelilla Wax (250 mg) | F0D123 |  | 1 |  | [8006-44-8] | \$156 |
| 1088001 | Candicidin (200 mg) | F |  |  |  | [1403-17-4] | \$156 |
| 1089004 | Cannabidiol CI (25 mg) (AS) | F-2 |  |  |  | [13956-29-1] | \$207 |
| 1090003 | Cannabinol CI (25 mg) (AS) |  |  |  | F-2 (05/02) | [521-35-7] | \$207 |
| 1091006 | Capreomycin Sulfate (200 mg) | G |  |  | F (06/01) | [1405-37-4] | \$156 |
| 1091505 | Caprylocaproyl Polyoxylglycerides (200 mg) | F0C312 |  | 1 |  | n/f | \$175 |
| 1091108 | Capsaicin (100 mg) | G-1 |  |  | $\begin{array}{\|l\|} \hline \text { G (03/02) } \\ \text { F-1 (06/00) } \\ \text { F (03/99) } \\ \hline \end{array}$ | [404-86-4] | \$156 |
| 1091200 | Captopril (200 mg) | H |  |  |  | [62571-86-2] | \$156 |
| 1091221 | Captopril Disulfide ( 100 mg ) | G1B066 |  |  | G (01/04) | [64806-05-9] | \$487 |
| 1092009 | Carbachol (200 mg) | G |  |  |  | [51-83-2] | \$156 |
| 1093001 | Carbamazepine ( 100 mg ) | $J$ |  |  | I-1 (02/00) | [298-46-4] | \$156 |
| 1093205 | Carbarsone ( 200 mg ) | F |  |  |  | [121-59-5] | \$156 |
| 1093500 | Carbenicillin Indanyl Sodium ( 300 mg ) | G |  |  |  | [26605-69-6] | \$156 |
| 1094004 | Carbenicillin Monosodium Monohydrate ( 200 mg ) | G-2 |  |  |  | n/f | \$156 |
| 1095506 | Carbidopa ( 400 mg ) | 1 |  |  | H (10/99) | [38821-49-7] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1095517 | Carbidopa Related Compound A ( 50 mg ) (3-OMethylcarbidopa) | H0B121 |  |  | G (04/03) | n/f | \$487 |
| 1096000 | Carbinoxamine Maleate (200 mg) | H |  |  | G-1 (11/02) | [3505-38-2] | \$156 |
| 1096407 | Carboplatin ( 100 mg ) | H0C240 |  |  | $\begin{aligned} & \text { G (07/04) } \\ & \text { F (03/00) } \end{aligned}$ | [41575-94-4] | \$159 |
| 1096509 | Carboprost Tromethamine ( 25 mg ) | F-1 |  |  | F (02/01) | [58551-69-2] | \$487 |
| 1096600 | Carisoprodol (1 g) | G |  |  | F-2 (05/02) | [78-44-4] | \$156 |
| 1096757 | Carteolol Hydrochloride (200 mg) | F-1 |  |  | F (11/00) | [51781-21-6] | \$156 |
| 1096804 | Cathinone Hydrochloride CI ( 50 mg ) (alphaAminopropiophenone Hydrochloride) | I |  |  |  | [76333-53-4] | \$560 |
| 1096906 | Cefaclor ( 400 mg ) | H |  |  |  | [70356-03-5] | \$156 |
| 1096917 | Cefaclor, Delta-3-Isomer ( 30 mg ) | G |  |  | F-1 (02/00) | n/f | \$156 |
| 1097104 | Cefadroxil ( 125 mg ) | 11B319 | 935 ug/mg (ai) |  | $\begin{array}{\|l\|l\|} \hline I(01 / 05) \\ H \\ \hline \end{array}$ | [66592-87-8] | \$124 |
| 1097308 | Cefamandole Lithium (200 mg) | H |  |  |  | n/f | \$156 |
| 1097400 | Cefamandole Nafate ( 200 mg ) | H |  |  |  | [42540-40-9] | \$156 |
| 1097501 | Cefamandole Sodium ( 250 mg ) | F |  |  |  | [30034-03-8] | \$156 |
| 1097603 | Cefazolin ( 400 mg ) | L0C345 |  |  | $\begin{aligned} & \text { K (04/05) } \\ & \text { J (06/00) } \end{aligned}$ | [25953-19-9] | \$156 |
| 1097636 | Cefepime Hydrochloride ( 500 mg ) |  |  |  | F0C063 (06/05) | [123171-59-5] | \$156 |
| 1097647 | Cefepime Hydrochloride System Suitability ( 25 mg ) | F0C095 |  |  |  | n/f | \$156 |
| 1097658 | Cefixime ( 500 mg ) | F |  |  |  | [79350-37-1] | \$156 |
| 1097771 | Cefmenoxime Hydrochloride ( 350 mg ) | F |  |  |  | [75738-58-8] | \$156 |
| 1097782 | Cefmetazole (200 mg) | F-1 |  |  | F (04/02) | [56796-20-4] | \$156 |
| 1097750 | Cefonicid Sodium (1 g) | H0D105 | 887 ug/mg (an) | 2 | G (06/05) | [61270-78-8] | \$156 |
| 1097705 | Cefoperazone Dihydrate (200 mg) | H |  |  | G (12/99) | [62893-19-0] | \$156 |
| 1097807 | Ceforanide ( 200 mg ) | F-1 |  |  | F (07/00) | [60925-61-3] | \$156 |
| 1097909 | Cefotaxime Sodium ( 250 mg ) | J0C189 | 901 ug/mg (ai) |  | I (11/04) | [64485-93-4] | \$124 |
| 1097975 | Cefotetan ( 500 mg ) | H0C175 |  |  | $\begin{aligned} & \hline \text { G (07/04) } \\ & \text { F (09/00) } \\ & \hline \end{aligned}$ | [69712-56-7] | \$156 |
| 1098005 | Cefotiam Hydrochloride ( 325 mg ) | G0B050 |  |  | F (01/03) | [66309-69-1] | \$156 |
| 1098107 | Cefoxitin ( 500 mg ) | I |  |  | H (05/00) | [35607-66-0] | \$156 |
| 1098118 | Cefpiramide ( 300 mg ) | F0C203 |  |  |  | [70797-11-4] | \$156 |
| 1098027 | Cefpodoxime Proxetil ( 350 mg ) | F0C192 | 736 ug/mg (an) |  |  | [87239-81-4] | \$156 |
| 1098049 | Cefprozil E-Isomer ( 50 mg ) | F2C284 |  |  | $\begin{aligned} & \text { F-1 (10/04) } \\ & \text { F (05/01) } \\ & \hline \end{aligned}$ | [121123-17-9] | \$156 |
| 1098050 | Cefprozil Z-Isomer (200 mg) | G0C037 |  |  | F (12/03) | [121123-17-9] | \$156 |
| 1098129 | Ceftazidime, Delta-3-Isomer ( 25 mg ) | G |  |  | F (03/00) | n/f | \$208 |
| 1098130 | Ceftazidime Pentahydrate ( 300 mg ) | H |  |  | G (12/99) | [78439-06-2] | \$156 |
| 1098173 | Ceftizoxime ( 200 mg ) | H |  |  |  | [68401-81-0] | \$156 |
| 1098184 | Ceftriaxone Sodium ( 350 mg ) | G0B264 |  |  | F (08/03) | [104376-79-6] | \$156 |
| 1098195 | Ceftriaxone Sodium E-Isomer ( 25 mg ) | IOC190 |  |  | $\begin{aligned} & \hline \text { H (07/04) } \\ & G(08 / 01) \\ & \text { F-1 }(02 / 00) \\ & \hline \end{aligned}$ | n/f | \$208 |
| 1098209 | Cefuroxime Sodium ( 200 mg ) | H |  |  | G-1 (05/00) | [56238-63-2] | \$156 |
| 1098220 | Cefuroxime Axetil ( 500 mg ) | G |  |  | F-1 (05/02) | [64544-07-6] | \$156 |
| 1098231 | Cefuroxime Axetil Delta-3-Isomers ( 35 mg ) | H0B160 |  |  | G (03/03) | n/f | \$156 |
| 1098300 | Cellulose Acetate ( 125 mg ) | F-1 |  |  | F (11/99) | [9004-35-7] | \$124 |
| 1098355 | Cellulose Acetate Phthalate ( 125 mg ) | F-1 |  |  | F (03/99) | [9004-38-0] | \$124 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1098708 | Cephaeline Hydrobromide (200 mg) | G-1 |  |  |  | n/f | \$487 |
| 1099008 | Cephalexin (250 mg) | I-2 |  |  | I-1 (03/00) | [23325-78-2] | \$156 |
| 1102000 | Cephalothin Sodium (200 mg) | 1 |  |  |  | [58-71-9] | \$156 |
| 1102408 | Cephapirin Benzathine ( 100 mg ) | F |  |  |  | [97468-37-6] | \$156 |
| 1102500 | Cephapirin Sodium ( 200 mg ) | I-1 |  |  | 1 (07/02) | [24356-60-3] | \$156 |
| 1102805 | Cephradine ( 200 mg ) | J |  |  | 1 (04/00) | [58456-86-3] | \$156 |
| 1103003 | Cetyl Alcohol ( 100 mg ) | I |  |  | H (03/99) | [36653-82-4] | \$156 |
| 1103105 | Cetyl Palmitate ( 50 mg ) | F0B241 |  |  |  | [540-10-3] | \$156 |
| 1104006 | Cetylpyridinium Chloride ( 500 mg ) | I |  |  | $\begin{aligned} & \text { H-1 (06/01) } \\ & \text { H (08/99) } \end{aligned}$ | [6004-24-6] | \$156 |
| 1105009 | Powdered Chaste Tree Extract (1.5 g) | F0C406 |  |  |  | [91722-47-3] | \$520 |
| 1106001 | Chlorambucil ( 125 mg ) (FOR U.S. SALE ONLY) | G |  |  | F-1 (02/99) | [305-03-3] | \$124 |
| 1107004 | Chloramphenicol (200 mg) | N1C074 |  |  | $\begin{aligned} & \hline N(10 / 04) \\ & M(03 / 00) \\ & \hline \end{aligned}$ | [56-75-7] | \$156 |
| 1107300 | Chloramphenicol Palmitate (200 mg) | G-1 |  |  |  | [530-43-8] | \$156 |
| 1107401 | Chloramphenicol Palmitate Nonpolymorph A ( 200 mg ) | F-1 |  |  |  | [530-43-8] | \$487 |
| 1107503 | Chloramphenicol Palmitate Polymorph A ( 200 mg ) | G |  |  | F (08/99) | [530-43-8] | \$487 |
| 1109000 | Chlordiazepoxide CIV (200 mg) | IOB063 |  |  | H-1 (03/03) | [58-25-3] | \$207 |
| 1110009 | Chlordiazepoxide Hydrochloride CIV (200 mg) | G-4 |  |  |  | [438-41-5] | \$207 |
| 1110020 | Chlordiazepoxide Related Compound A (25 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide) | G |  |  |  | [963-39-3] | \$487 |
| 1111001 | Chlorhexidine ( 200 mg ) | F0C306 |  |  |  | [55-56-1] | \$156 |
| 1111103 | Chlorhexidine Acetate ( 500 mg ) | F0C281 |  |  |  | [56-95-1] | \$156 |
| 1111307 | Chlorhexidine Related Compounds ( 50 mg ) | F0D017 |  |  |  | n/f | \$487 |
| 1112503 | Chlorobutanol ( 200 mg ) | G |  |  | F-3 (12/01) | [6001-64-5] | \$156 |
| 1115545 | Chlorogenic Acid ( 50 mg ) | FOC420 | $0.97 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | [327-97-9] | \$156 |
| 1115556 | beta-Chlorogenin (20 mg) | F |  |  |  | n/f | \$156 |
| 1117008 | Chloroprocaine Hydrochloride ( 200 mg ) | G0B285 |  |  | $\begin{aligned} & \text { F-3 (01/04) } \\ & \text { F-2 (03/99) } \\ & \hline \end{aligned}$ | [3858-89-7] | \$156 |
| 1118000 | Chloroquine Phosphate ( 500 mg ) | 1 |  |  | H (10/99) | [50-63-5] | \$156 |
| 1121005 | Chlorothiazide ( 200 mg ) | H0B161 |  |  | G (04/03) | [58-94-6] | \$156 |
| 1122008 | Chlorotrianisene (1 g) | F |  |  |  | [569-57-3] | \$156 |
| 1122700 | Chloroxylenol (125 mg) | F2C259 |  |  | $\begin{aligned} & \hline \text { F-1 (07/04) } \\ & \text { F (10/99) } \\ & \hline \end{aligned}$ | [88-04-0] | \$124 |
| 1122722 | Chloroxylenol Related Compound A ( 25 mg ) (2-chloro-3,5-dimethylphenol) | G0C275 |  |  | F-1 (07/04) | [5538-41-0] | \$487 |
| 1123000 | Chlorpheniramine Maleate (125 mg) | M0B020 |  |  | L-1 (06/03) | [113-92-8] | \$124 |
| 1123102 | Chlorpheniramine Maleate Extended-Release Tablets (Drug Release Calibrator, Single Unit) (60 Tablets) | G0B259 |  |  | F (06/03) | [113-92-8] | \$156 |
| 1124003 | Chlorphenoxamine Hydrochloride (200 mg) | F-1 |  |  |  | [562-09-4] | \$156 |
| 1125006 | Chlorpromazine Hydrochloride ( 200 mg ) | J |  |  | I (04/99) | [69-09-0] | \$156 |
| 1126009 | Chlorpropamide (200 mg) | H |  |  |  | [94-20-2] | \$156 |
| 1127001 | Chlorprothixene (200 mg) | F-1 |  |  |  | [113-59-7] | \$156 |
| 1129007 | Chlortetracycline Hydrochloride (200 mg) | K0C185 | 1008 ug/mg (ai) |  | $\begin{aligned} & \hline \mathrm{J}-1(12 / 04) \\ & \mathrm{J}(02 / 02) \\ & \hline \end{aligned}$ | [64-72-2] | \$156 |
| 1130006 | Chlorthalidone (200 mg) | IOC255 |  |  | $\begin{array}{\|l\|} \hline \mathrm{H}-1(11 / 04) \\ \mathrm{H}(07 / 99) \\ \hline \end{array}$ | [77-36-1] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1119309 | Chlorthalidone Related Compound A ( 25 mg ) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid) | G0C376 |  |  | F-3 (07/04) | n/f | \$487 |
| 1130505 | Chlorzoxazone ( 500 mg ) | 1 |  |  | H (07/01) | [95-25-0] | \$156 |
| 1130527 | Chlorzoxazone Related Compound A (50 mg) (2-Amino-4-chlorophenol) | G-1 |  |  | G (11/00) | [95-85-2] | \$487 |
| 1131009 | Cholecalciferol ( $30 \mathrm{mg} / \mathrm{ampule} ; 5$ ampules) (Vitamin D3) | M0B157 |  |  | $\begin{array}{\|l\|} \hline \text { L (10/03) } \\ \text { K (09/99) } \\ \hline \end{array}$ | [67-97-0] | \$159 |
| 1131803 | Delta-4,6-cholestadienol ( $30 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [14214-69-8] | \$156 |
| 1132001 | Cholesteryl Caprylate (200 mg) | F |  |  |  | [1182-42-9] | \$156 |
| 1133004 | Cholestyramine Resin ( 500 mg ) | 1 |  |  |  | [11041-12-6] | \$124 |
| 1133503 | Cholic Acid (2 g) (AS) | F3B159 |  |  | F-2 (01/03) | [81-25-4] | \$156 |
| 1133536 | Choline Bitartrate ( $200 \mathrm{mg} \mathrm{)}$ | F0C057 |  |  |  | [87-67-2] | \$156 |
| 1133547 | Choline Chloride ( 200 mg ) | F0C058 |  |  |  | [67-48-1] | \$156 |
| 1133570 | Chondroitin Sulfate Sodium ( 300 mg ) | F0B256 |  |  |  | [39455-18-0] | \$156 |
| 1133638 | Chromium Picolinate ( 100 mg ) | F |  |  |  | [14639-25-9] | \$156 |
| 1134007 | Chymotrypsin ( 300 mg ) | 1 |  |  | H (06/01) | [9004-07-3] | \$156 |
| 1134030 | Ciclopirox Olamine ( 125 mg ) | H0C2O7 |  |  | G (05/03) | [41621-49-2] | \$124 |
| 1134051 | Cilastatin Ammonium Salt (100 mg) | G0C334 | 945 ug/mg (ai) |  | $\begin{array}{\|l} \hline \text { F-1 (05/05) } \\ \text { F (07/00) } \\ \hline \end{array}$ | n/f | \$156 |
| 1134062 | Cimetidine ( 200 mg ) | 11C081 |  |  | I (05/04) | [51481-61-9] | \$156 |
| 1134073 | Cimetidine Hydrochloride ( 200 mg ) | F |  |  |  | [70059-30-2] | \$156 |
| 1134109 | Cinoxacin (200 mg) | F |  |  |  | [28657-80-9] | \$156 |
| 1134313 | Ciprofloxacin (125 mg) | G-1 |  |  | G (05/01) | [85721-33-1] | \$124 |
| 1134324 | Ciprofloxacin Ethylenediamine Analog ( 25 mg ) | J0A030 |  |  | $\begin{array}{\|l} \hline \text { I (01/03) } \\ \mathrm{H}-1(02 / 99) \\ \hline \end{array}$ | n/f | \$208 |
| 1134335 | Ciprofloxacin Hydrochloride ( 400 mg ) | 10C265 |  |  | $\begin{aligned} & \mathrm{H}(02 / 05) \\ & \mathrm{G}(04 / 00) \\ & \hline \end{aligned}$ | [86393-32-0] | \$156 |
| 1134357 | Cisplatin (100 mg) | H |  |  | G (03/01) | [15663-27-1] | \$156 |
| 1134368 | Citric Acid (200 mg) | F1B092 |  |  | $\begin{array}{\|l\|l} \hline \text { F-1 (01/04) } \\ \text { F (07/02) } \\ \hline \end{array}$ | [77-92-9] | \$156 |
| 1134379 | Clarithromycin (75 mg) | F4B183 |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-3 (01/04) } \\ \text { F-2 (09/01) } \\ \hline \end{array}$ | [81103-11-9] | \$156 |
| 1134380 | Clarithromycin Related Compound A ( 50 mg ) (6,11-di-O-methylerythromycin A) | G |  |  | F (04/01) | n/f | \$208 |
| 1134404 | Clavam-2-carboxylate Potassium (1 Pellet) | H0C089 |  |  | $\begin{array}{\|l} \hline \text { G0B225 (12/03) } \\ \hline F(10 / 03) \\ \hline \end{array}$ | n/f | \$487 |
| 1134426 | Clavulanate Lithium (200 mg) | 11C270 | $0.952 \mathrm{mg} / \mathrm{mg}$ (ai) |  | $\begin{aligned} & \text { I (02/05) } \\ & \text { H (09/02) } \end{aligned}$ | n/f | \$156 |
| 1134506 | Clemastine Fumarate ( 250 mg ) | 1 |  |  | H (10/00) | [14976-57-9] | \$156 |
| 1135000 | Clidinium Bromide ( 2 g ) | H0B115 |  |  | G (03/05) | [3485-62-9] | \$156 |
| 1135021 | Clidinium Bromide Related Compound A (250 mg) (3-Hydroxy-1-methylquinuclindinium Bromide) | 1 |  |  |  | [76201-95-1] | \$487 |
| 1136002 | Clindamycin Hydrochloride (200 mg) | G4A017 |  |  | $\begin{aligned} & \text { G-3 (07/03) } \\ & \text { G-2 }(05 / 99) \end{aligned}$ | [58207-19-5] | \$428 |
| 1137005 | Clindamycin Palmitate Hydrochloride (200 mg) | F-2 |  |  |  | [25507-04-4] | \$428 |
| 1138008 | Clindamycin Phosphate ( 125 mg ) | 10C165 |  |  | $\begin{aligned} & \mathrm{H}-3(04 / 04) \\ & \mathrm{H}-2(07 / 03) \\ & \mathrm{H}-1(02 / 99) \\ & \hline \end{aligned}$ | [24729-96-2] | \$214 |
| 1138201 | Clioquinol ( 500 mg ) | M |  |  | L-1 (01/03) | [130-26-7] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1138405 | Clobetasol Propionate (200 mg) | F2C309 | $980 \mathrm{ug} / \mathrm{mg}$ (ai) |  | $\begin{aligned} & \text { F-1 (03/05) } \\ & \text { F (10/01) } \end{aligned}$ | [25122-46-7] | \$156 |
| 1138427 | Clobetasol Propionate Related Compound A ( 50 mg ) (9-alpha-fluoro-11-beta-hydroxy-16-beta-methyl-3-oxo-androsta-1,4-diene-17(R)-spiro-2'-[4'-chloro-5'-ethylfuran-3'(2'H)-one]) | F-1 |  |  | F (01/03) | n/f | \$208 |
| 1138507 | Clocortolone Pivalate ( 200 mg ) | G |  |  |  | [34097-16-0] | \$156 |
| 1138904 | Clofazimine ( 200 mg ) | F |  |  |  | [2030-63-9] | \$156 |
| 1139000 | Clofibrate (1 g) | 1 |  |  | H (04/01) | [637-07-0] | \$156 |
| 1140000 | Clomiphene Citrate ( 500 mg ) | H |  |  | G-1 (10/99) | [50-41-9] | \$156 |
| 1140101 | Clomiphene Related Compound A (100 mg) ((E,Z)-2-[4-(1,2-diphenylethenyl)phenoxy]-N,Ndiethylethanamine Hydrochloride) | F1B206 |  |  | F (09/03) | n/f | \$208 |
| 1140247 | Clomipramine Hydrochloride ( 200 mg ) | F0C075 |  |  |  | [17321-77-6] | \$156 |
| 1140305 | Clonazepam CIV (200 mg) | G1B175 |  |  | $\begin{aligned} & \mathrm{G}(01 / 04) \\ & \mathrm{F}-2(01 / 00) \\ & \hline \end{aligned}$ | [1622-61-3] | \$207 |
| 1140327 | Clonazepam Related Compound A ( 25 mg ) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril) | G2B110 |  |  | $\begin{aligned} & \text { G-1 (01/04) } \\ & \text { G }(02 / 99) \end{aligned}$ | n/f | \$487 |
| 1140338 | Clonazepam Related Compound B ( 25 mg ) (2-Amino-2'-chloro-5-nitrobenzophenone) | H |  |  | G (04/01) | [2011-66-7] | \$487 |
| 1140349 | Clonazepam Related Compound C ( 25 mg ) (2-Bromo-2'-(2-chlorobenzoyl)-4'-nitroacetanilide) | F0C340 |  |  |  | n/f | \$487 |
| 1140393 | Clonidine ( 200 mg ) | F0C401 |  |  |  | [4205-90-7] | \$156 |
| 1140407 | Clonidine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H0D106 | $1.000 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | G (05/05) | [4205-91-8] | \$156 |
| 1140418 | Clonidine Related Compound A ( 25 mg ) (Acetylclonidine) | F0C373 |  |  |  | [54707-71-0] | \$487 |
| 1140429 | Clonidine Related Compound B ( 25 mg ) (2-[(E)-2,6-Dichlorophenylimino]-1-(1-\{2-[(E)-2,6-di-chlorophenylimino]-imidazolidin-1-yl\}-ethyl)-imidazolidine) | F0C403 | $0.99 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | n/f | \$487 |
| 1140509 | Clorazepate Dipotassium CIV (125 mg) | G0B027 |  |  | $\begin{aligned} & \text { F-1 (06/03) } \\ & \text { F (12/99) } \\ & \hline \end{aligned}$ | [57109-90-7] | \$207 |
| 1140702 | Clorsulon (200 mg) | F1B084 |  |  | F (01/04) | [60200-06-8] | \$156 |
| 1141002 | Clotrimazole (200 mg) | K0C282 |  |  | $\begin{array}{\|l\|} \hline J(02 / 05) \\ \text { I (05/99) } \end{array}$ | [23593-75-1] | \$124 |
| 1141024 | Clotrimazole Related Compound A (25 mg) ((0chlorophenyl)diphenylmethanol) | I |  |  | $\begin{aligned} & \text { H (10/01) } \\ & \text { G-1 }(02 / 99) \\ & \hline \end{aligned}$ | [66774-02-5] | \$487 |
| 1141909 | Cloxacillin Benzathine ( 200 mg ) | F-1 |  |  | F (03/02) | [23736-58-5] | \$156 |
| 1142005 | Cloxacillin Sodium (200 mg) | LOB086 |  |  | K (01/04) | [7081-44-9] | \$156 |
| 1142107 | Clozapine ( 100 mg ) | F0C032 |  |  |  | [5786-21-0] | \$260 |
| 1143008 | Cocaine Hydrochloride CII (250 mg) | 10B074 |  |  | $\begin{array}{ll} \hline \mathrm{H}-2(01 / 04) \\ \mathrm{H}-1(02 / 99) \end{array}$ | [53-21-4] | \$207 |
| 1143802 | Codeine N-Oxide CI (50 mg) | G0A034 |  |  | F-1 (11/02) | [3688-65-1] | \$207 |
| 1144000 | Codeine Phosphate CII (100 mg) | J0C200 |  |  | $\begin{aligned} & \mathrm{I}-1(10 / 04) \\ & \mathrm{I}(09 / 02) \\ & \mathrm{H}-1(01 / 00) \\ & \hline \end{aligned}$ | [41444-62-6] | \$207 |
| 1145003 | Codeine Sulfate CII (250 mg) | H-2 |  |  | H-1 (01/02) | [6854-40-6] | \$207 |
| 1146006 | Colchicine ( 300 mg ) | J |  |  | I (05/02) | [64-86-8] | \$156 |
| 1146505 | Colestipol Hydrochloride (200 mg) | F-1 |  |  |  | [37296-80-3] | \$156 |
| 1147009 | Colistimethate Sodium ( 200 mg ) | H |  |  |  | [8068-28-8] | \$156 |
| 1148001 | Colistin Sulfate (200 mg) | G-1 |  |  | G (09/99) | [1264-72-8] | \$156 |
| 1148500 | Copovidone ( 100 mg ) | FOC194 |  |  |  | [2586-89-9] | \$156 |
| 1149004 | Corticotropin (5.6 Units/vial; 5 vials) | M |  |  | L (06/99) | [9002-60-2] | \$124 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1150003 | Cortisone Acetate ( 150 mg ) | 1 |  |  |  | [50-04-4] | \$156 |
| 1150353 | Creatinine ( 100 mg ) | F |  |  |  | [60-27-5] | \$156 |
| 1150502 | Cromolyn Sodium ( 500 mg ) | J |  |  | $1(06 / 00)$ | [15826-37-6] | \$156 |
| 1150706 | Crospovidone ( 200 mg ) | G1C273 |  |  | G (12/04) | [9003-39-8] | \$156 |
| 1151006 | Crotamiton ( 200 mg ) | H-1 |  |  | H (07/00) | [483-63-6] | \$156 |
| 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) | N |  |  | M-3 (08/99) | [68-19-9] | \$156 |
| 1152508 | Cyclacillin (200 mg) | G |  |  |  | [3485-14-1] | \$156 |
| 1152701 | Cyclandelate (200 mg) | F0C384 |  |  |  | [456-59-7] | \$156 |
| 1154004 | Cyclizine Hydrochloride (200 mg) | G |  |  |  | [303-25-3] | \$156 |
| 1154503 | Cyclobenzaprine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G0A013 |  |  | F-3 (07/03) | [6202-23-9] | \$156 |
| 1154558 | Alpha Cyclodextrin ( 50 mg ) | F-1 |  |  | F (10/00) | [10016-20-3] | \$156 |
| 1154569 | Beta Cyclodextrin (250 mg) | G |  |  | F-1 (12/02) | [7585-39-9] | \$156 |
| 1154707 | Cyclomethicone 4 (200 mg) | F-2 |  |  | F-1 (06/02) | [69430-24-6] | \$156 |
| 1154809 | Cyclomethicone 5 ( 125 mg ) |  |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 (07/05) } \\ \text { F-1 (09/99) } \\ \hline \end{array}$ | [69430-24-6] | \$124 |
| 1154900 | Cyclomethicone 6 (200 mg) | F2B024 |  |  | F-1 (03/03) | [69430-24-6] | \$156 |
| 1156000 | Cyclopentolate Hydrochloride ( 300 mg ) | 10C424 | $0.999 \mathrm{mg} / \mathrm{mg}$ (dr) |  | $\begin{aligned} & \hline \mathrm{H}(03 / 05) \\ & \mathrm{G}(04 / 00) \\ & \hline \end{aligned}$ | [5870-29-1] | \$156 |
| 1157002 | Cyclophosphamide ( 500 mg ) (FOR U.S. SALE ONLY) | J1B200 |  |  | $J$ (02/05) | [6055-19-2] | \$124 |
| 1157501 | 2-Cyclopropylmethylamino-5-chlorobenzophenone ( 50 mg ) | F |  |  |  | n/f | \$487 |
| 1158005 | Cycloserine (200 mg) | G |  |  |  | [68-41-7] | \$156 |
| 1158504 | Cyclosporine ( 50 mg ) | H-1 |  |  | $\begin{aligned} & \text { H (11/02) } \\ & \text { G-2 }(03 / 00) \\ & \hline \end{aligned}$ | [59865-13-3] | \$479 |
| 1158650 | Cyclosporine Resolution Mixture ( 25 mg ) | F |  |  |  | $\begin{aligned} & {[108027-45-8]} \\ & (\mathrm{U}) \end{aligned}$ | \$412 |
| 1159008 | Cyclothiazide ( 200 mg ) | F-1 |  |  |  | [2259-96-3] | \$156 |
| 1161000 | Cyproheptadine Hydrochloride ( 500 mg ) | G |  |  | F-4 (11/02) | [41354-29-4] | \$156 |
| 1161509 | L-Cysteine Hydrochloride (200 mg) | H |  |  | G (05/00) | [7048-04-6] | \$156 |
| 1162002 | Cytarabine ( 250 mg ) | G-2 |  |  | G-1 (07/00) | [147-94-4] | \$156 |
| 1162308 | Dacarbazine ( 125 mg ) | H |  |  | G (01/99) | [4342-03-4] | \$124 |
| 1162320 | Dacarbazine Related Compound A ( 50 mg ) (5-aminoimidazole-4-carboxamide Hydrochloride) | H0C052 |  |  | $\begin{array}{\|l} \hline G(03 / 04) \\ F(03 / 00) \\ \hline \end{array}$ | [72-40-2] | \$487 |
| 1162330 | Dacarbazine Related Compound B ( 50 mg ) (2azahypoxanthine) | G0C325 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (03/05) } \\ \text { F (12/01) } \\ \hline \end{array}$ | [63907-29-9] | \$600 |
| 1162400 | Dactinomycin ( 50 mg ) | 1 |  |  |  | [50-76-0] | \$427 |
| 1162501 | Danazol ( 200 mg ) | H |  |  | G (10/00) | [17230-88-5] | \$156 |
| 1164008 | Dapsone (125 mg) | G-3 |  |  | G-2 (08/99) | [80-08-0] | \$124 |
| 1164700 | Daunorubicin Hydrochloride ( 200 mg ) | LOB307 |  |  | $\begin{array}{\|l\|} \hline \mathrm{K}(11 / 03) \\ \mathrm{J}(08 / 00) \\ \hline \end{array}$ | [23541-50-6] | \$479 |
| 1165000 | Decamethonium Bromide ( 250 mg ) | F |  |  |  | [541-22-0] | \$156 |
| 1166003 | Deferoxamine Mesylate ( 500 mg ) | 1 |  |  |  | [138-14-7] | \$156 |
| 1166309 | Dehydroacetic Acid (200 mg) | F |  |  |  | [520-45-6] | \$156 |
| 1166400 | Dehydrocarteolol Hydrochloride (100 mg) | F |  |  |  | n/f | \$487 |
| 1166502 | Dehydrocholic Acid (200 mg) | F-1 |  |  | F (03/04) | [81-23-2] | \$156 |
| 1169001 | Demecarium Bromide ( 250 mg ) | F |  |  |  | [56-94-0] | \$156 |
| 1170000 | Demeclocycline Hydrochloride (200 mg) | H1C036 |  |  | $\begin{array}{\|l\|} \hline \mathrm{H} \quad(08 / 04) G-1 \\ (08 / 01) \end{array}$ | [64-73-3] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1171003 | Denatonium Benzoate ( 200 mg ) | IOB129 |  |  | H (09/02) | [86398-53-0] | \$156 |
| 1171706 | Desacetyl Diltiazem Hydrochloride ( 50 mg ) | 1 |  |  | H (08/00) | [23515-45-9] | \$487 |
| 1171900 | Desflurane ( 0.5 mL ) | F0C187 |  |  |  | [57041-67-5] | \$156 |
| 1171910 | Desflurane Related Compound A ( 0.1 mL ) (bis-(1,2,2,2-tetrafluoroethyl) ether) | F0C031 |  |  |  | n/f | \$487 |
| 1172006 | Desipramine Hydrochloride ( 125 mg ) | H-1 |  |  | H (10/99) | [58-28-6] | \$124 |
| 1173009 | Deslanoside ( 100 mg ) | H-1 |  |  |  | [17598-65-1] | \$156 |
| 1173235 | Desogestrel ( 50 mg ) | G0C390 |  |  | FOB282 (11/04) | [54024-22-5] | \$156 |
| 1173246 | Desogestrel Related Compound A ( 15 mg ) (13-Ethyl-11-methylene-18, 19-dinor-5alpha, 17al-pha-preg-3-en-20-yl-17-ol, desogestrel delta-3 isomer) | F0B279 |  |  |  | n/f | \$487 |
| 1173257 | Desogestrel Related Compound B (15 mg) (3-Hydroxy-desogestrel) | F0B284 |  |  |  | n/f | \$487 |
| 1173268 | Desogestrel Related Compound C (25 mg) (3-Keto-desogestrel) | F0B281 |  |  |  | [54048-10-1] | \$487 |
| 1173508 | Desoximetasone ( 200 mg ) | H0B036 |  |  | G (01/04) | [382-67-2] | \$156 |
| 1174001 | Desoxycorticosterone Acetate (200 mg) | J0C014 |  |  | $\begin{aligned} & \text { I (01/04) } \\ & \mathrm{H}(05 / 00) \end{aligned}$ | [56-47-3] | \$156 |
| 1175004 | Desoxycorticosterone Pivalate ( 125 mg ) | H0C276 |  |  | G (01/04) | [808-48-0] | \$124 |
| 1176007 | Dexamethasone ( 125 mg ) | J |  |  |  | [50-02-2] | \$124 |
| 1176506 | Dexamethasone Acetate ( 200 mg ) | G |  |  | F-1 (06/99) | [1177-87-3] | \$156 |
| 1177000 | Dexamethasone Phosphate ( 200 mg ) | J1B070 |  |  | $\begin{array}{\|l\|} \hline J(08 / 03) \\ I(03 / 00) \\ \hline \end{array}$ | [312-93-6] | \$156 |
| 1178002 | Dexbrompheniramine Maleate (200 mg) | $J$ |  |  | $1(03 / 03)$ | [2391-03-9] | \$156 |
| 1179005 | Dexchlorpheniramine Maleate ( 500 mg ) | G1A025 |  |  | G (12/02) | [2438-32-6] | \$156 |
| 1179504 | Dexpanthenol ( 500 mg ) | J0C293 |  |  | $\begin{aligned} & \text { I (08/04) } \\ & \text { H (02/02) } \\ & \hline \end{aligned}$ | [81-13-0] | \$160 |
| 1179708 | Dextran 40 (50 mg) | F0C247 |  |  |  | [9004-54-0] | \$156 |
| 1179741 | Dextran 70 ( 50 mg ) | F0C260 |  |  |  | [9004-54-0] | \$156 |
| 1179854 | Dextran 4 Calibration (100 mg) | F0C002 |  |  |  | [9004-54-0] | \$156 |
| 1179865 | Dextran 10 Calibration ( 100 mg ) | F0C010 |  |  |  | [9004-54-0] | \$156 |
| 1179876 | Dextran 40 Calibration ( 100 mg ) | F0C011 |  |  |  | [9004-54-0] | \$156 |
| 1179720 | Dextran 40 System Suitability ( 200 mg ) | F0B181 |  |  |  | [9004-54-0] | \$156 |
| 1179887 | Dextran 70 Calibration ( 100 mg ) | F0C013 |  |  |  | [9004-54-0] | \$156 |
| 1179763 | Dextran 70 System Suitability ( 200 mg ) | F0B182 |  |  |  | [9004-54-0] | \$156 |
| 1179898 | Dextran 250 Calibration ( 100 mg ) | F0C039 |  |  |  | [9004-54-0] | \$156 |
| 1179800 | Dextran Vo Marker (100 mg) | F0B242 |  |  |  | [9004-54-0] | \$156 |
| 1180004 | Dextroamphetamine Sulfate CII (500 mg) | IOC311 | $1.000 \mathrm{mg} / \mathrm{mg}$ (dr) |  | $\begin{aligned} & \mathrm{H}(05 / 05) \\ & \mathrm{G}(08 / 03) \\ & \mathrm{F}-6(12 / 99) \end{aligned}$ | [51-63-8] | \$216 |
| 1180503 | Dextromethorphan (2 g) | H |  |  | G (06/00) | [125-71-3] | \$487 |
| 1181007 | Dextromethorphan Hydrobromide ( 500 mg ) | J0B167 |  |  | 1 (07/03) | [6700-34-1] | \$156 |
| 1181302 | Dextrose ( 500 mg ) | J-1 |  |  | $\begin{array}{\|l\|} \hline J(11 / 02) \\ I(08 / 99) \\ \hline \end{array}$ | [50-99-7] | \$124 |
| 1181506 | Diacetylated Monoglycerides ( 200 mg ) | G |  |  |  | [68990-54-5] | \$156 |
| 1182000 | Diacetylfluorescein (200 mg) | H |  |  | G (01/02) | [596-09-8] | \$156 |
| 1183002 | Diacetylmorphine Hydrochloride $\mathbf{C l}(25 \mathrm{mg})$ (AS) (Heroin Hydrochloride) | J |  |  | I-1 (10/99) | [1502-95-0] | \$207 |
| 1184005 | Diatrizoic Acid ( 100 mg ) | G |  |  |  | [50978-11-5] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1184027 | Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid) | 1 |  |  | H (02/00) | [1713-07-1] | \$487 |
| 1185008 | Diazepam CIV (100 mg) | 1 |  |  | H (12/01) | [439-14-5] | \$207 |
| 1185020 | Diazepam Related Compound A ( 25 mg ) (2-Methyl-amino-5-chlorobenzophenone) | 1 |  |  | $\begin{array}{\|l\|l} \hline \text { H-1 (11/02) } \\ \text { H (04/00) } \\ \hline \end{array}$ | [1022-13-5] | \$487 |
| 1023403 | Diazepam Related Compound B ( 25 mg ) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril) | 11C102 |  |  | $\begin{aligned} & \hline I(12 / 04) \\ & H(04 / 01) \\ & \hline \end{aligned}$ | [5220-02-0] | \$487 |
| 1186000 | Diazoxide (200 mg) | G1C017 |  |  | G (12/03) | [364-98-7] | \$156 |
| 1187003 | Dibucaine Hydrochloride ( 200 mg ) | 1 |  |  | H-2 (01/03) | [61-12-1] | \$156 |
| 1187080 | Dibutyl Phthalate (200 mg) | FOD125 |  | 1 |  | [84-74-2] | \$156 |
| 1187207 | Dichloralphenazone CIV (200 mg) | F0B010 |  |  |  | [480-30-8] | \$207 |
| 1188006 | Dichlorphenamide (200 mg) | G-1 |  |  |  | [120-97-8] | \$156 |
| 1188800 | Diclofenac Sodium (200 mg) | H0B150 |  |  | $\begin{aligned} & \text { G-1 (03/04) } \\ & \text { G (05/01) } \end{aligned}$ | [15307-79-6] | \$156 |
| 1188811 | Diclofenac Related Compound A (100 mg) (N-(2,6-dichlorophenyl) indolin-2-one) | H |  |  | G (05/02) | [15362-40-0] | \$490 |
| 1189009 | Dicloxacillin Sodium ( 500 mg ) | JOC182 |  |  | $\begin{aligned} & \text { IOB142 (09/04) } \\ & \text { H (05/03) } \end{aligned}$ | [13412-64-1] | \$156 |
| 1190008 | Dicumarol (200 mg) | G |  |  |  | [66-76-2] | \$156 |
| 1191000 | Dicyclomine Hydrochloride ( 125 mg ) | H |  |  | G (03/99) | [67-92-5] | \$124 |
| 1192003 | Dienestrol ( 125 mg ) | 1 |  |  |  | [84-17-3] | \$124 |
| 1193006 | Diethylcarbamazine Citrate ( 200 mg ) | G-1 |  |  |  | [1642-54-2] | \$156 |
| 1193301 | Diethylene Glycol Monoethyl Ether ( $0.5 \mathrm{~mL} /$ ampule) | F0B095 |  |  |  | [111-90-0] | \$156 |
| 1193505 | Diethyl Phthalate (200 mg) | G |  |  | F-1 (03/00) | [84-66-2] | \$156 |
| 1194009 | Diethylpropion Hydrochloride CIV ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  |  | [134-80-5] | \$207 |
| 1195001 | Diethylstilbestrol (200 mg) | K5B291 |  |  | K-4 (05/04) | [56-53-1] | \$156 |
| 1197007 | Diethyltoluamide (3 g) | H |  |  |  | [134-62-3] | \$124 |
| 1197302 | Diflorasone Diacetate (200 mg) | G |  |  | F-1 (03/00) | [33564-31-7] | \$156 |
| 1197506 | Diflunisal ( 200 mg ) | G |  |  |  | [22494-42-4] | \$156 |
| 1198000 | Digitalis (3 g) | F |  |  |  | [8031-42-3] | \$156 |
| 1199002 | Digitoxin (200 mg) | M |  |  |  | [71-63-6] | \$156 |
| 1200000 | Digoxin ( 250 mg ) | O0B096 |  |  | N-1 (04/03) | [20830-75-5] | \$156 |
| 1200600 | Dihydrocapsaicin (25 mg) | G0C071 |  |  | $\begin{array}{\|l} \hline \text { F-1 (12/03) } \\ \text { F (01/00) } \\ \hline \end{array}$ | [19408-84-5] | \$156 |
| 1200804 | Dihydrocodeine Bitartrate CII (200 mg) | H |  |  | G (03/01) | [5965-13-9] | \$207 |
| 1201002 | 17alpha-Dihydroequilin ( 50 mg ) | IOC277 |  |  | H (07/04) | [6639-99-2] | \$208 |
| 1202005 | Dihydroergotamine Mesylate ( 250 mg ) (List Chemical) | JOB085 |  |  | I (03/03) | [6190-39-2] | \$156 |
| 1203008 | Dihydrostreptomycin Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | J |  |  |  | [5490-27-7] | \$156 |
| 1204000 | Dihydrotachysterol (30 mg/ampule; 4 ampules) |  |  |  | I (06/05) | [67-96-9] | \$156 |
| 1204102 | Dihydroxyacetone ( 250 mg ) | F |  |  |  | [96-26-4] | \$156 |
| 1204805 | Diloxanide Furoate ( $200 \mathrm{mg} \mathrm{)}$ | F0C026 |  |  |  | [3736-81-0] | \$156 |
| 1205003 | Diltiazem Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  |  |  | [33286-22-5] | \$156 |
| 1206006 | Dimenhydrinate ( 100 mg ) | JOB055 |  |  | I (06/03) | [523-87-5] | \$156 |
| 1208001 | Dimethisoquin Hydrochloride ( 2 g ) | G |  |  |  | [2773-92-4] | \$156 |
| 1210105 | N -(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8germaspiro [4:5]decane-1,3-dione (AS) | F |  |  |  | [41992-23-8] | \$156 |

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## USP Reference Standards and Authentic Substances

| Cat. <br> No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \text { CAS } \\ \text { No. } \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1211006 | Dimethyl Sulfoxide (3 g) | G0C198 |  |  | $\begin{array}{\|l\|} \hline \text { F-3 (07/04) } \\ \text { F-2 (05/02) } \end{array}$ | [67-68-5] | \$208 |
| 1213001 | Dinoprost Tromethamine ( 50 mg ) | F |  |  |  | [38562-01-5] | \$1,525 |
| 1213103 | Dinoprostone ( 50 mg ) | F0C030 |  |  |  | [363-24-6] | \$1,525 |
| 1214004 | Dioxybenzone ( 150 mg ) | F1B277 |  |  | F (10/03) | [131-53-3] | \$156 |
| 1216000 | Diphemanil Methylsulfate ( 500 mg ) | H |  |  |  | [62-97-5] | \$156 |
| 1217909 | Diphenhydramine Citrate ( 125 mg ) | H0B128 |  |  | G (04/03) | [88637-37-0] | \$124 |
| 1218005 | Diphenhydramine Hydrochloride ( 200 mg ) | J0B013 |  |  | I (07/03) | [147-24-0] | \$156 |
| 1219008 | Diphenoxylate Hydrochloride CII (200 mg) | 1 |  |  | H (03/02) | [3810-80-8] | \$207 |
| 1220302 | Dipivefrin Hydrochloride (200 mg) | 1 |  |  | H (06/99) | [64019-93-8] | \$156 |
| 1220506 | Dipyridamole (200 mg) | H |  |  | G-1 (01/99) | [58-32-2] | \$156 |
| 1220700 | Dirithromycin (200 mg) | F |  |  |  | [62013-04-1] | \$156 |
| 1221000 | Disodium Guanylate ( 300 mg ) (FCC) | F-1 |  |  |  | [5550-12-9] | \$156 |
| 1222002 | Disodium Inosinate (500 mg) (FCC) | F |  |  |  | [4691-65-0] | \$156 |
| 1222501 | Disopyramide Phosphate ( 200 mg ) | H-1 |  |  | H (03/02) | [22059-60-5] | \$156 |
| 1223005 | 2,4-Disulfamyl-5-trifluoromethylaniline ( 125 mg ) | G |  |  |  | [654-62-6] | \$487 |
| 1224008 | Disulfiram (200 mg) | F-3 |  |  | F-2 (07/02) | [97-77-8] | \$156 |
| 1224507 | Dobutamine Hydrochloride ( 600 mg ) | H-1 |  |  | H (01/00) | [49745-95-1] | \$156 |
| 1224700 | Docusate Calcium ( 500 mg ) | H0B044 |  |  | G-1 (07/02) | [128-49-4] | \$156 |
| 1224802 | Docusate Sodium ( 500 mg ) | J |  |  | I-1 (05/02) | [577-11-7] | \$156 |
| 1224904 | Docusate Potassium ( 100 mg ) | F-1 |  |  | F (11/99) | [7491-09-0] | \$156 |
| 1224959 | Dolasetron Mesylate (200 mg) | F0C319 |  |  |  | [115956-13-3] | \$156 |
| 1224960 | Dolasetron Mesylate Related Compound A ( 25 mg ) (Hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3(4H)-one hydrochloride) | F0C321 |  |  |  | n/f | \$487 |
| 1225204 | Dopamine Hydrochloride ( 200 mg ) | G |  |  | F-5 (05/02) | [62-31-7] | \$156 |
| 1225281 | Dorzolamide Hydrochloride ( 500 mg ) | FOC040 |  |  |  | [130693-82-2] | \$156 |
| 1225292 | Dorzolamide Hydrochloride Related Compound A ( 20 mg ) ( $(4 \mathrm{R}, 6 \mathrm{R})$-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide, monohydrochloride) | F0C068 |  |  |  | n/f | \$487 |
| 1225000 | Doxapram Hydrochloride ( 200 mg ) | F4C053 |  |  | F-3 (07/04) | [7081-53-0] | \$156 |
| 1225419 | Doxazosin Mesylate (200 mg) | F0C079 |  |  |  | [77883-43-3] | \$156 |
| 1225500 | Doxepin Hydrochloride ( 500 mg ) | I |  |  |  | [1229-29-4] | \$156 |
| 1225703 | Doxorubicin Hydrochloride ( 50 mg ) | K |  |  | J (06/02) | [25316-40-9] | \$479 |
| 1226003 | Doxycycline Hyclate ( 200 mg ) | I |  |  | H (01/00) | [24390-14-5] | \$156 |
| 1227006 | Doxylamine Succinate ( 300 mg ) | 10B266 |  |  | H (01/04) | [562-10-7] | \$156 |
| 1229001 | Droperidol ( 250 mg ) | 10C029 |  |  | $\begin{array}{\|l\|} \hline \mathrm{H}-1(01 / 05) \\ \mathrm{H}(04 / 99) \\ \hline \end{array}$ | [548-73-2] | \$156 |
| 1230000 | Dyclonine Hydrochloride (200 mg) | G |  |  |  | [536-43-6] | \$156 |
| 1231003 | Dydrogesterone (200 mg) | IOB114 |  |  | H (01/04) | [152-62-5] | \$156 |
| 1231502 | Dyphylline (200 mg) | G-2 |  |  | G-1 (11/02) | [479-18-5] | \$156 |
| 1231728 | Powdered Echinacea Purpurea Extract (1 g) | F0D018 |  |  |  | [90028-20-9] | \$520 |
| 1231706 | Powdered Echinacea Angustifolia Extract (1 g) | F0D019 |  |  |  | [84696-11-7] | \$520 |
| 1231808 | Econazole Nitrate (200 mg) | G |  |  |  | [68797-31-9] | \$156 |
| 1232006 | Edetate Calcium Disodium ( 200 mg ) | H0B272 |  |  | $\begin{aligned} & \text { G-3 (11/04) } \\ & \text { G-2 (11/99) } \end{aligned}$ | [23411-34-9] | \$156 |
| 1233009 | Edetate Disodium (200 mg) | H |  |  | G-2 (04/02) | [6381-92-6] | \$156 |
| 1233508 | Edetic Acid ( 200 mg ) | F-1 |  |  |  | [60-00-4] | \$156 |
| 1234001 | Edrophonium Chloride ( 200 mg ) | H |  |  | G (08/99) | [116-38-1] | \$156 |

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## USP Reference Standards and Authentic Substances

| Cat. <br> No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 |  |  |  | [84696-12-5] | \$520 |
| 1234806 | Emedastine Difumarate ( 100 mg ) | F0C059 |  |  |  | [87233-62-3] | \$156 |
| 1235004 | Emetine Hydrochloride ( $300 \mathrm{mg} \mathrm{)}$ | H0B201 |  |  | G (05/03) | [316-42-7] | \$156 |
| 1235274 | Enalaprilat (300 mg) | J0C268 |  |  | $\begin{aligned} & I(11 / 04) \\ & H(03 / 01) \\ & G(08 / 99) \end{aligned}$ | [84680-54-6] | \$124 |
| 1235300 | Enalapril Maleate (200 mg) | J1C267 | 0.992 mg/mg (ai) | 2 | $\begin{array}{\|l\|} \hline J(05 / 05) \\ \text { I (06/01) } \\ \hline \end{array}$ | [76095-16-4] | \$156 |
| 1235503 | Endotoxin (10,000 USP Endotoxin Units) | G2B274 |  |  | $\begin{aligned} & \text { G-1 (12/03) } \\ & \text { G (06/99) } \\ & \hline \end{aligned}$ | n/f | \$156 |
| 1235809 | Enflurane ( 1 mL ) | G-1 |  |  | G (02/01) | [13838-16-9] | \$156 |
| 1236007 | Ephedrine Sulfate (200 mg) (List Chemical) | H-2 |  |  | $\mathrm{H}-1$ (11/02) | [134-72-5] | \$156 |
| 1236506 | 4-Epianhydrotetracycline Hydrochloride ( 50 mg ) | JOC041 |  |  | $\begin{array}{\|l\|} \hline \text { I-1 (12/03) } \\ \text { I (06/00) } \\ \hline \end{array}$ | [4465-65-0] | \$487 |
| 1236801 | Epilactose ( 200 mg ) | G |  |  | F-1 (06/00) | [103302-12-1] | \$487 |
| 1237000 | Epinephrine Bitartrate (200 mg) | 0 |  |  |  | [51-42-3] | \$156 |
| 1237509 | Epitetracycline Hydrochloride ( 200 mg ) | F |  |  |  | [23313-80-6] | \$487 |
| 1238002 | Equilin ( 25 mg ) | 11B290 |  |  | $\begin{array}{\|l\|l\|l\|l\|l\|} \hline \mathrm{I}(11 / 04) \\ \mathrm{H}-1(05 / 00) \\ \hline \end{array}$ | [474-86-2] | \$208 |
| 1239005 | Ergocalciferol ( $30 \mathrm{mg} /$ ampule; 5 ampules) (Vitamin D2) | P0B275 |  |  | $\begin{aligned} & \mathrm{O}(02 / 04) \\ & \mathrm{N}(12 / 99) \end{aligned}$ | [50-14-6] | \$168 |
| 1239504 | Ergoloid Mesylates ( 300 mg ) | 1 |  |  | H-1 (01/00) | [8067-24-1] | \$156 |
| 1240004 | Ergonovine Maleate ( 100 mg ) (List Chemical) | N |  |  | M-1 (07/02) | [129-51-1] | \$156 |
| 1241007 | Ergosterol ( 50 mg ) | H |  |  |  | [57-87-4] | \$156 |
| 1241506 | Ergotamine Tartrate (150 mg) (List Chemical) | IOB174 |  |  | H (01/04) | [379-79-3] | \$156 |
| 1241550 | Ergotaminine ( 100 mg ) (List Chemical) | G0B177 |  |  | F-1 (06/04) | [639-81-6] | \$156 |
| 1242000 | Erythromycin (250 mg) | M |  |  | L (08/99) | [114-07-8] | \$156 |
| 1242010 | Erythromycin B (150 mg) | G1C080 |  |  | $\begin{array}{\|l\|l} \hline \text { G (11/04) } \\ \text { F-1 (09/01) } \\ \hline F(05 / 01) \\ \hline \end{array}$ | [527-75-3] | \$156 |
| 1242021 | Erythromycin C (50 mg) | F-3 |  |  | $\begin{array}{\|l} \hline \text { F-2 (01/03) } \\ \text { F-1 (02/02) } \\ \hline \\ \hline \end{array}$ | n/f | \$156 |
| 1242032 | Erythromycin Related Compound $\mathrm{N}(50 \mathrm{mg})(\mathrm{N}-$ Demethylerythromycin A) | F2A023 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (06/04) } \\ \text { F (09/99) } \\ \hline \end{array}$ | n/f | \$156 |
| 1243002 | Erythromycin Estolate ( 200 mg ) | H |  |  | G (01/03) | [3521-62-8] | \$156 |
| 1245008 | Erythromycin Ethylsuccinate ( 200 mg ) | H |  |  | G-1 (06/01) | [1264-62-6] | \$156 |
| 1246000 | Erythromycin Gluceptate ( 200 mg ) | H |  |  | G (07/03) | [23067-13-2] | \$156 |
| 1247003 | Erythromycin Lactobionate ( $200 \mathrm{mg} \mathrm{)}$ | H-1 |  |  | H (01/02) | [3847-29-8] | \$156 |
| 1248006 | Erythromycin Stearate ( $200 \mathrm{mg} \mathrm{)}$ | H0B187 |  |  | G-1 (05/03) | [643-22-1] | \$156 |
| 1249009 | Erythrosine Sodium ( 100 mg ) | F |  |  |  | [49746-10-3] | \$156 |
| 1250008 | Estradiol ( 500 mg ) | L0C337 | $0.996 \mathrm{mg} / \mathrm{mg}$ (an) | 2 | $\begin{array}{\|l\|} \hline \text { K1B007 (07/05) } \\ \text { K (04/03) } \\ \hline \end{array}$ | [50-28-2] | \$156 |
| 1251000 | Estradiol Benzoate ( 250 mg ) (AS) | G-1 |  |  |  | [50-50-0] | \$156 |
| 1252003 | Estradiol Cypionate ( 200 mg ) | G-1 |  |  | G (02/00) | [313-06-4] | \$156 |
| 1254009 | Estradiol Valerate ( 100 mg ) | L |  |  | K (05/02) | [979-32-8] | \$156 |
| 1254508 | Estriol ( 100 mg ) | J |  |  | I-1 (06/01) | [50-27-1] | \$156 |
| 1255001 | Estrone ( 200 mg ) | K1B099 |  |  | $\begin{array}{\|l\|} \hline \mathrm{K}(07 / 03) \\ \mathrm{J}-1(07 / 00) \\ \hline \end{array}$ | [53-16-7] | \$156 |
| 1255500 | Estropipate (500 mg) | JOB262 |  |  | $\begin{array}{\|l\|} \hline \text { I (12/03) } \\ \mathrm{H}(09 / 01) \\ \hline \end{array}$ | [7280-37-7] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| Cat. <br> No. | Description | Curr. <br> Lot. | Purity Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1256004 | Ethacrynic Acid (200 mg) | F |  |  |  | [58-54-8] | \$156 |
| 1257007 | Ethambutol Hydrochloride (200 mg) | H |  |  | G (08/02) | [1070-11-7] | \$156 |
| 1258305 | Ethchlorvynol CIV ( 0.7 ml ) | F0B011 |  |  |  | [113-18-8] | \$207 |
| 1260001 | Ethinyl Estradiol ( 150 mg ) | Q0C162 |  |  | $\begin{array}{\|l} \text { P1B193 (11/04) } \\ \text { P0B052 (01/04) } \\ \text { P (03/03) } \\ \text { O (08/99) } \\ \hline \end{array}$ | [57-63-6] | \$156 |
| 1260012 | Ethinyl Estradiol Related Compound A (20 mg) (6-Keto-ethinyl estradiol) | F0B252 |  |  |  | n/f | \$487 |
| 1261004 | Ethionamide ( 200 mg ) | H0B148 |  |  | G (03/03) | [536-33-4] | \$156 |
| 1262801 | Ethopabate ( 125 mg ) | F |  |  |  | [59-06-3] | \$156 |
| 1262823 | Ethopabate Related Compound A ( 25 mg ) (Methyl-4-acetamido-2-hydroxybenzoate) | F |  |  |  | n/f | \$487 |
| 1263000 | Ethopropazine Hydrochloride ( 300 mg ) | G |  |  |  | [1094-08-2] | \$156 |
| 1264002 | Ethosuximide ( 125 mg ) | H |  |  | $\begin{aligned} & \text { G-2 }(11 / 01) \\ & \text { G-1 }(05 / 99) \end{aligned}$ | [77-67-8] | \$124 |
| 1264501 | Ethotoin (200 mg) | F |  |  |  | [86-35-1] | \$156 |
| 1265005 | Ethoxzolamide ( 200 mg ) | F |  |  |  | [452-35-7] | \$156 |
| 1265504 | Ethylcellulose ( 1 g ) | H-1 |  |  | H (06/99) | [9004-57-3] | \$156 |
| 1266008 | Ethyl Maltol (1 g) (FCC) | H |  |  |  | [4940-11-8] | \$156 |
| 1266507 | Ethylnorepinephrine Hydrochloride (200 mg) | F |  |  |  | [3198-07-0] | \$156 |
| 1267000 | Ethylparaben ( 200 mg ) | IOA016 |  |  | H (01/04) | [120-47-8] | \$156 |
| 1267500 | Ethyl Vanillin (200 mg) | F2B134 |  |  | F-1 (04/04) | [121-32-4] | \$156 |
| 1268003 | Ethynodiol Diacetate ( 200 mg ) | 10A033 |  |  | $\begin{aligned} & \mathrm{H}-1(01 / 03) \\ & \mathrm{H}(04 / 01) \\ & \hline \end{aligned}$ | [297-76-7] | \$156 |
| 1268502 | Etidronate Disodium (200 mg) | G |  |  | F-2 (02/03) | [7414-83-7] | \$156 |
| 1268604 | Etidronic Acid Monohydrate (1 g) | G |  |  | F-1 (05/99) | [2809-21-4] | \$156 |
| 1268706 | Etodolac ( 400 mg ) | G |  |  | F (10/01) | [41340-25-4] | \$156 |
| 1268728 | Etodolac Related Compound A (25 mg) ((+/-)-8-ethyl-1-methyl-1,3,4,9-tetrahydropyrano [3,4-b]-indole-1-acetic acid) | F-1 |  |  | F (05/02) | [109518-50-5] | \$208 |
| 1268808 | Etoposide ( 300 mg ) | H0C315 |  |  | G (11/04) | [33419-42-0] | \$124 |
| 1268852 | Etoposide Resolution Mixture ( 30 mg ) | F0B209 |  |  |  | [33419-42-0] | \$208 |
| 1269200 | Famotidine ( 125 mg ) | H-1 |  |  | $\begin{array}{\|l\|} \hline \mathrm{H}(11 / 02) \\ \mathrm{G}(03 / 99) \\ \hline \end{array}$ | [76824-35-6] | \$124 |
| 1269389 | Felodipine (200 mg) | G0D065 | $0.999 \mathrm{mg} / \mathrm{mg}$ (ai) |  | $\begin{aligned} & \hline \text { F-1 (04/05) } \\ & \text { F (09/02) } \\ & \hline \end{aligned}$ | [72509-76-3] | \$156 |
| 1269390 | Felodipine Related Compound A ( 100 mg ) (ethyl methyl 4-(2,3-dichlorophenyl)-2,6-di-methylpyridine-3,5-dicarboxylate) | F0B207 |  |  |  | [96302-71-7] | \$487 |
| 1269403 | Fenbendazole ( 100 mg ) | $F$ |  |  |  | [43210-67-9] | \$487 |
| 1269414 | Fenbendazole Related Compound A ( 30 mg ) (Methyl (1H-benzimidazole-2-yl)carbamate) | F0D009 | $0.99 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | [10605-21-7] | \$487 |
| 1269425 | Fenbendazole Related Compound B ( 30 mg ) (Methyl [5(6)-chlorobenzimidazole-2-yl]carbamate) | F0D008 | $0.99 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | n/f | \$487 |
| 1269458 | Fenoldopam Mesylate ( 200 mg ) | F0C125 |  |  |  | [67227-57-0] | \$156 |
| 1269469 | Fenoldopam Related Compound A (20 mg) (1-Methyl-3-benzazapine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate) | FOC124 |  |  |  | n/f | \$487 |

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| Cat. No. | Description | Curr. Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1269470 | Fenoldopam Related Compound B ( 20 mg ) (1H-3-Benzazapine-7,8-diol, 2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate) | F0C126 |  |  |  | n/f | \$487 |
| 1269505 | Fenoprofen Calcium ( 500 mg ) | G-1 |  |  |  | [53746-45-5] | \$156 |
| 1269550 | Fenoprofen Sodium ( 500 mg ) | G |  |  | F-1 (05/02) | [66424-46-2] | \$156 |
| 1270005 | Fentanyl Citrate CII (100 mg) | K0C264 |  |  | $\begin{aligned} & \text { J2B227 (11/04) } \\ & \mathrm{J}-1(09 / 03) \\ & \mathrm{J}(05 / 02) \\ & \mathrm{I}(06 / 00) \\ & \hline \end{aligned}$ | [990-73-8] | \$207 |
| 1270402 | Finasteride ( 200 mg ) | F |  |  |  | [98319-26-7] | \$156 |
| 1270800 | Flecainide Acetate ( 200 mg ) | F2A022 |  |  | $\begin{aligned} & \hline \text { F-1 (02/05) } \\ & \text { F (06/03) } \\ & \hline \end{aligned}$ | [54143-56-5] | \$156 |
| 1270821 | Flecainide Related Compound A ( 75 mg ) (3-[2,5-bis(2,2,2-trifluoroethoxy)phenyl]-1,5,6,7,8,8a-hexahydroimidazo-[1,5a]pyridine Hydrochloride) | F |  |  |  | n/f | \$487 |
| 1271008 | Floxuridine ( 250 mg ) | F-2 |  |  | F-1 (08/01) | [50-91-9] | \$156 |
| 1272000 | Flucytosine ( 200 mg ) | F |  |  |  | [2022-85-7] | \$156 |
| 1272204 | Fludarabine Phosphate ( 300 mg ) | F0C374 |  |  |  | [75607-67-9] | \$156 |
| 1273003 | Fludrocortisone Acetate ( $250 \mathrm{mg} \mathrm{)}$ | H |  |  | G (08/01) | [514-36-3] | \$156 |
| 1273808 | Flumazenil ( 200 mg ) | F0C305 |  |  |  | [78755-81-4] | \$780 |
| 1274006 | Flumethasone Pivalate ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  |  | H (01/02) | [2002-29-1] | \$156 |
| 1274505 | Flunisolide ( 200 mg ) | 1 |  |  | H (01/01) | [77326-96-6] | \$156 |
| 1274607 | Flunixin Meglumine ( 300 mg ) | G |  |  | $\begin{aligned} & \text { F-1 (04/02) } \\ & \text { F (09/99) } \\ & \hline \end{aligned}$ | [42461-84-7] | \$156 |
| 1275009 | Fluocinolone Acetonide ( 100 mg ) | J |  |  | I (11/99) | [67-73-2] | \$156 |
| 1276001 | Fluocinonide ( 100 mg ) | 1 |  |  |  | [356-12-7] | \$156 |
| 1277004 | Fluorescein (200 mg) | G0B171 |  |  | F-1 (02/03) | [2321-07-5] | \$156 |
| 1277252 | Fluoride Dentifrice: Sodium Fluoride/Silica (4.5 oz) | J0C294 |  |  | $\begin{aligned} & \hline \text { I (08/04) } \\ & \mathrm{H}(04 / 99) \\ & \hline \end{aligned}$ | n/f | \$458 |
| 1277274 | Fluoride Dentifrice: Sodium Fluoride/Sodium Bicarbonate Powder (4 oz) |  |  |  | F (06/05) | n/f | \$487 |
| 1277300 | Fluoride Dentifrice: Sodium Monofluoropho-sphate-Calcium Carbonate (4.6 oz) | G |  |  |  | n/f | \$487 |
| 1277354 | Fluoride Dentifrice: Sodium Monofluorophosphate/Dicalcium Phosphate (4.6 oz) | G |  |  |  | n/f | \$487 |
| 1277401 | Fluoride Dentifrice: Sodium Monofluorophosphate ( 1000 ppm )/Silica ( 5.25 oz ) | G-1 |  |  | G (08/99) | n/f | \$487 |
| 1277423 | Fluoride Dentifrice: Sodium Monofluorophosphate ( 1500 ppm )/Silica ( 5.25 oz ) | F-1 |  |  | F (07/99) | n/f | \$487 |
| 1277456 | Fluoride Dentifrice: Stannous Fluoride-Silica (4 oz) | H0B105 |  |  | G (11/02) | n/f | \$487 |
| 1278007 | Fluorometholone ( $200 \mathrm{mg} \mathrm{)}$ | IOB184 |  |  | H-1 (11/02) | [426-13-1] | \$156 |
| 1278109 | Fluorometholone Acetate ( 200 mg ) | F |  |  |  | [3801-06-7] | \$156 |
| 1278302 | Fluoroquinolonic Acid (50 mg) | H0C140 |  |  | $\begin{array}{\|l\|l} \hline \mathrm{G}(01 / 05) \\ \mathrm{F}-1(12 / 99) \\ \hline \end{array}$ | [86393-33-1] | \$487 |
| 1279000 | Fluorouracil ( 250 mg ) | H-1 |  |  | H (01/02) | [51-21-8] | \$156 |
| 1279804 | Fluoxetine Hydrochloride (200 mg) | F2C132 |  |  | $\begin{aligned} & \text { F-1 }(02 / 05) \\ & \text { F (11/99) } \\ & \hline \end{aligned}$ | [59333-67-4] | \$156 |
| 1279815 | Fluoxetine Related Compound A ( 15 mg ) ( N -methyl-3-phenyl-3-[(alpha,alpha,alpha-(trifluoro-m-tolyl)oxy]propylamine Hydrochloride) | H0C131 |  |  | $\begin{aligned} & \text { G (06/04) } \\ & F-1(05 / 01) \\ & F(06 / 00) \\ & \hline \end{aligned}$ | n/f | \$487 |

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| Cat. <br> No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \hline \text { CAS } \\ \text { No. } \\ \hline \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1279826 | Fluoxetine Related Compound B ( 5 mL of a 0.01 N HCl solution, approx. $2 \mathrm{mg} / \mathrm{mL}$ ) ( N -methyl-3-phenylpropylamine) |  |  |  | $\begin{array}{\|l\|} \hline \text { F3C085 (05/05) } \\ \text { F-2 (06/04) } \\ \text { F-1 (09/02) } \\ \text { F (09/00) } \\ \hline \end{array}$ | [23580-89-4] | \$156 |
| 1279837 | Fluoxetine Related Compound C ( 15 mg ) ( N -Methyl-N-[3-phenyl-3-(4-trifluoromethyl-phe-noxy)-propyl]-succinamic acid) | F0C352 |  |  |  | n/f | \$487 |
| 1280009 | Fluoxymesterone CIII ( 200 mg ) | G-2 |  |  | G-1 (04/00) | [76-43-7] | \$207 |
| 1280803 | Fluphenazine Decanoate Dihydrochloride ( 500 mg ) | G |  |  | F-1 (10/01) | n/f | \$159 |
| 1281001 | Fluphenazine Enanthate Dihydrochloride ( 125 mg ) | H |  |  | G (02/99) | [3105-68-8] | \$124 |
| 1282004 | Fluphenazine Hydrochloride ( 125 mg ) | H |  |  |  | [146-56-5] | \$124 |
| 1284000 | Flurandrenolide ( 100 mg ) | IOB245 |  |  | H (09/03) | [1524-88-5] | \$156 |
| 1285002 | Flurazepam Hydrochloride CIV ( $200 \mathrm{mg} \mathrm{)}$ | J0C365 | $0.996 \mathrm{mg} / \mathrm{mg}$ (ai) |  | I (09/03) | [1172-18-5] | \$207 |
| 1285308 | Flurazepam Related Compound C ( 50 mg ) (5-chloro-2-(2-diethylaminoethyl(amino)-2'-fluorobenzophenone Hydrochloride) | H-1 |  |  |  | n/f | \$487 |
| 1285603 | Flurazepam Related Compound F ( 50 mg ) (7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one) | $10 \mathrm{C092}$ |  |  | H (01/04) | [2886-65-9] | \$487 |
| 1285750 | Flurbiprofen (200 mg) | G |  |  |  | [5104-49-4] | \$156 |
| 1285760 | Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid) | H |  |  | G (03/01) | n/f | \$487 |
| 1285807 | Flurbiprofen Sodium ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [56767-76-1] | \$156 |
| 1285851 | Flutamide (200 mg) | H0B278 |  |  | $\begin{array}{\|l} \hline \text { G (11/04) } \\ \text { F-1 }(06 / 00) \\ \hline \end{array}$ | [13311-84-7] | \$156 |
| 1285862 | o-Flutamide ( 50 mg ) | F-1 |  |  | F (01/00) | n/f | \$156 |
| 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) | P |  |  | O (07/00) | [59-30-3] | \$156 |
| 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) | IOB176 |  |  | $\begin{array}{\|l\|} \hline \mathrm{H}-1(04 / 04) \\ \mathrm{H}(01 / 00) \\ \hline \end{array}$ | [1492-18-8] | \$156 |
| 1286060 | Formononetin ( 50 mg ) | F0C196 |  |  |  | [485-72-3] | \$520 |
| 1286209 | 4-Formylbenzenesulfonamide ( 50 mg ) | F |  |  |  | n/f | \$487 |
| 1286300 | 10-Formylfolic Acid ( 25 mg ) | F2B226 |  |  | F-1 (01/04) | [134-05-4] | \$156 |
| 1286366 | Fosphenytoin Sodium ( 250 mg ) | F0C156 |  |  |  | [92134-98-0] | \$156 |
| 1286504 | Fructose ( 125 mg ) | I-2 |  |  | $\begin{array}{\|l} \hline \text { I-1 (11/02) } \\ \text { I (08/99) } \\ \hline \end{array}$ | [57-48-7] | \$124 |
| 1286708 | Fumaric Acid (200 mg) | G-1 |  |  | G (04/02) | [110-17-8] | \$156 |
| 1286800 | Furazolidone (200 mg) | G-2 |  |  | G-1 (01/01) | [67-45-8] | \$156 |
| 1287008 | Furosemide ( 125 mg ) | J1B131 |  |  | $J(10 / 03)$ | [54-31-9] | \$124 |
| 1287020 | Furosemide Related Compound A ( 50 mg ) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid) | J |  |  | I (08/02) | n/f | \$487 |
| 1287030 | Furosemide Related Compound B ( 100 mg ) (4-Chloro-5-sulfamoylanthranilic Acid) | 10 C 248 |  |  | $\begin{array}{\|l\|} \hline \text { H (08/04) } \\ \text { G-3 }(03 / 01) \\ \hline \end{array}$ | [3086-91-7] | \$487 |
| 1287303 | Gabapentin ( 250 mg ) | F |  |  |  | [60142-96-3] | \$156 |
| 1287325 | Gabapentin Related Compound A ( 100 mg ) (3,3-pentamethylene-5-butyrolactam) | F |  |  |  | [64744-50-9] | \$487 |
| 1287507 | Gadodiamide ( 500 mg ) | F |  |  |  | [131410-48-5] | \$156 |
| 1287518 | Gadodiamide Related Compound A ( 50 mg ) (gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide) | F |  |  |  | n/f | \$487 |

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| Cat. <br> No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1287529 | Gadodiamide Related Compound B ( 50 mg ) (gadolinium disodium diethylenetriamine pentaacetic acid) | F |  |  |  | n/f | \$487 |
| 1287609 | Gadopentetate Monomeglumine ( 500 mg ) | F |  |  |  | [92923-57-4] | \$156 |
| 1287631 | Gadoteridol ( 500 mg ) | F |  |  |  | [120066-54-8] | \$156 |
| 1287642 | Gadoteridol Related Compound A ( 50 mg ) (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclodode-cane-1,4,7-triacetic acid) | F0A002 |  |  |  | [120041-08-9] | \$487 |
| 1287653 | Gadoteridol Related Compound B ( 50 mg ) (1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, monogadolinium salt) | F0B198 |  |  |  | [112188-16-6] | \$487 |
| 1287664 | Gadoteridol Related Compound C (50 mg) (1,4,7,10-Tetraaza-11-oxo-bicyclo[8.2.2]tetrade-cane-4,7-diacetic acid) | FOB199 |  |  |  | [220182-19-4] | \$487 |
| 1287675 | Gadoversetamide ( 200 mg ) | FOC172 |  |  |  | [131069-91-5] | \$156 |
| 1287686 | Gadoversetamide Related Compound A (200 mg) (Hydrogen[8,11,14-tris(carboxy-methyl)-6-oxo-2-oxa-5,8,11,14-tetraazahexade-can-16-oato(4-)]gadolinium) | F0C173 |  |  |  | n/f | \$487 |
| 1287700 | Galactose (200 mg) | F-4 |  |  | F-3 (05/01) | [59-23-4] | \$487 |
| 1288000 | Gallamine Triethiodide ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [65-29-2] | \$156 |
| 1288306 | Ganciclovir ( 200 mg ) | F0C287 |  |  |  | [82410-32-0] | \$364 |
| 1288317 | Ganciclovir Related Compound A ( 15 mg ) ((RS)-2-Amino-9-(2,3-dihydroxy-propoxy-methyl)-1,9-dihydro-purin-6-one) | F0C288 |  |  |  | n/f | \$624 |
| 1288463 | Gemcitabine Hydrochloride (200 mg) | F0D037 | $0.997 \mathrm{mg} / \mathrm{mg}$ (ai) | 1 |  | [122111-03-9] | \$156 |
| 1288500 | Gemfibrozil ( 200 mg ) | H |  |  |  | [25812-30-0] | \$156 |
| 1288510 | Gemfibrozil Related Compound A (20 mg) (2,2-dimethyl-5-[2,5-dimethyl-4-propene-1-yl)phenoxy]valeric acid) | F0C101 |  |  |  | n/f | \$487 |
| 1289003 | Gentamicin Sulfate (200 mg) | L0C279 | 667 ug/mg (dr) |  | $\begin{array}{\|l} \hline \mathrm{K}(12 / 04) \\ \mathrm{J}-1(04 / 00) \\ \hline \end{array}$ | [1405-41-0] | \$156 |
| 1290002 | Gentian Violet (650 mg) | F |  |  |  | [548-62-9] | \$156 |
| 1291005 | Gibberellic Acid (200 mg) (FCC) | G |  |  | F (04/01) | [77-06-5] | \$156 |
| 1291504 | Powdered Ginger ( 500 mg ) | F |  |  |  | n/f | \$156 |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | FOB289 |  |  |  | [50647-08-0] | \$520 |
| 1292008 | Gitoxin ( 50 mg ) | G |  |  | F-3 (07/00) | [4562-36-1] | \$487 |
| 1292507 | Glipizide ( 125 mg ) | G1C174 |  |  | G (07/04) | [29094-61-9] | \$124 |
| 1292609 | Glipizide Related Compound A ( 25 mg ) ( N -\{2-[(4-aminosulfonyl)phenyl]ethyl\}-5-methyl-pyrazinecarboxamide) | G-1 |  |  | G (04/99) | n/f | \$487 |
| 1294003 | Glucagon ( $25 \mathrm{mg}, 0.95 \mathrm{U} / \mathrm{mg}$ ) |  |  |  | H (01/05) | [16941-32-5] | \$156 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 |  |  |  | [66-84-2] | \$156 |
| 1294976 | Glutamic Acid ( 200 mg ) | F0C069 |  |  |  | [56-86-0] | \$156 |
| 1294808 | Glutamine ( 100 mg ) | FOB244 |  |  |  | [56-85-9] | \$156 |
| 1294848 | gamma-Glutamyl-S-allyl-L-cysteine ( 25 mg ) | F |  |  |  | n/f | \$675 |
| 1295006 | Glutethimide CII ( 500 mg ) | F |  |  |  | [77-21-4] | \$207 |
| 1295505 | Glyburide (200 mg) | G |  |  | F-2 (11/02) | [10238-21-8] | \$156 |
| 1295607 | Glycerin ( 2 mL ) | H0C073 |  |  | $\begin{aligned} & \text { G1A001 (04/04) } \\ & \text { G (12/02) } \\ & \text { F (04/99) } \\ & \hline \end{aligned}$ | [56-81-5] | \$156 |
| 1295709 | Glyceryl Behenate (200 mg) | F3B113 |  |  | F-2 (03/03) | [18641-57-1] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1295800 | Glycine (200 mg) | F-3 |  |  | F-2 (02/00) | [56-40-6] | \$156 |
| 1296009 | Glycopyrrolate ( $200 \mathrm{mg} \mathrm{)}$ | H0B304 |  |  | G (05/04) | [596-51-0] | \$156 |
| 1295888 | Glycyrrhizic Acid (25 mg) | F0C006 |  |  |  | [1405-86-3] | \$487 |
| 1297001 | Human Chorionic Gonadotropin (1 vial, 5,760 USP Units per package) | H |  |  | G (07/00) | [9002-61-3] | \$156 |
| 1298004 | Gramicidin ( 200 mg ) | 1 |  |  | H-1 (07/02) | [1405-97-6] | \$156 |
| 1299007 | Griseofulvin (200 mg) | 1 |  |  | H-1 (09/02) | [126-07-8] | \$156 |
| 1299200 | Griseofulvin Permeability Diameter (2 g) | J0C380 |  |  | $\begin{array}{\|l} \text { 10C138 (10/04) } \\ H(08 / 03) \\ \hline \end{array}$ | [126-07-8] | \$156 |
| 1300004 | Guaiacol (1 g) | K |  |  | $\mathrm{J}(04 / 00)$ | [90-05-1] | \$156 |
| 1301007 | Guaifenesin (200 mg) | I |  |  | H (09/02) | [93-14-1] | \$156 |
| 1301404 | Guanabenz Acetate ( 200 mg ) | G |  |  | F-1 (06/00) | [23256-50-0] | \$156 |
| 1301608 | Guanadrel Sulfate (200 mg) | F-1 |  |  |  | [22195-34-2] | \$156 |
| 1301801 | Guanethidine Monosulfate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [645-43-2] | \$156 |
| 1302000 | Guanethidine Sulfate ( 500 mg ) | G-1 |  |  |  | [60-02-6] | \$156 |
| 1302101 | Guanfacine Hydrochloride (125 mg) | G0B123 |  |  | $\begin{array}{\|l\|} \hline F-1(02 / 03) \\ F(11 / 99) \\ \hline \end{array}$ | [29110-48-3] | \$124 |
| 1302305 | Halazepam CIV (200 mg) (AS) | F1C224 |  |  | F (12/04) | [23092-17-3] | \$207 |
| 1302509 | Halcinonide ( 300 mg ) | F |  |  |  | [3093-35-4] | \$156 |
| 1303002 | Haloperidol ( 200 mg ) | 1 |  |  | H-1 (05/02) | [52-86-8] | \$156 |
| 1303013 | Haloperidol Related Compound A (15 mg) (4,4'-Bis[(4-p-chlorophenyl)-4-hydroxy-piperidino]-butyrophenone) | K0C362 |  |  | J (12/04) | [67987-08-0] | \$487 |
| 1303308 | Haloprogin ( 200 mg ) | F |  |  |  | [777-11-7] | \$156 |
| 1303501 | Halothane ( 1 mL ) | G0D068 |  | 2 | F-1 (03/05) | [151-67-7] | \$156 |
| 1304005 | Heparin Sodium ( $10 \times 1 \mathrm{~mL}$ ) | K-5 |  |  | $\begin{aligned} & \hline \text { K-4 (08/03) } \\ & \text { K-3 (02/99) } \end{aligned}$ | [9041-08-1] | \$156 |
| 1305008 | Hexachlorophene ( 500 mg ) | 1 |  |  | H-2 (01/01) | [70-30-4] | \$156 |
| 1305507 | 2E, 4E-Hexadienoic Acid Isobutylamide ( 25 mg ) | F0C353 | $1.00 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | [82240-09-3] | \$540 |
| 1307003 | Hexobarbital CIII ( 500 mg ) | F |  |  |  | [56-29-1] | \$207 |
| 1308006 | Hexylcaine Hydrochloride (1 g) | F-1 |  |  |  | [532-76-3] | \$156 |
| 1308200 | Hexylene Glycol (125 mg) | G |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 }(04 / 02) \\ \text { F-1 } & (04 / 99) \\ \hline \end{array}$ | [107-41-5] | \$156 |
| 1308307 | Hexylresorcinol (200 mg) | F |  |  |  | [136-77-6] | \$156 |
| 1308505 | L-Histidine (200 mg) | G0A018 |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 }(01 / 03) \\ \text { F-1 } & (04 / 00) \\ \hline \end{array}$ | [71-00-1] | \$156 |
| 1309009 | Histamine Dihydrochloride (250 mg) | M0C280 |  |  | L (07/04) | [56-92-8] | \$156 |
| 1310008 | Homatropine Hydrobromide (200 mg) | H2C049 |  |  | $\begin{aligned} & \mathrm{H}-1(02 / 05) \\ & \mathrm{H}(08 / 02) \end{aligned}$ | [51-56-9] | \$156 |
| 1311000 | Homatropine Methylbromide (250 mg) | $J$ |  |  | $\begin{array}{\|l\|} \hline \mathrm{I}-1(06 / 01) \\ \mathrm{H}-1(10 / 01) \\ \hline \end{array}$ | [80-49-9] | \$156 |
| 1311306 | Homopolymer Polypropylene (3 Strips) | F0C096 |  |  |  | [9003-07-0] | \$156 |
| 1311408 | Homosalate ( $500 \mathrm{mg} / \mathrm{ampule}$ ) |  |  |  | F0B102 (04/05) | [118-56-9] | \$156 |
| 1312003 | Hyaluronidase ( 500 mg ) |  |  |  | H (06/05) | [9001-54-1] | \$156 |
| 1313006 | Hydralazine Hydrochloride (200 mg) | K |  |  | J-1 (09/02) | [304-20-1] | \$156 |
| 1314009 | Hydrochlorothiazide ( 200 mg ) | 1 |  |  | H (05/02) | [58-93-5] | \$156 |
| 1315001 | Hydrocodone Bitartrate CII (250 mg) | K0C217 |  |  | $\begin{array}{\|l\|} \hline \text { JOA026 (01/05) } \\ \mathrm{I}-1(12 / 02) \\ \mathrm{I}(07 / 02) \\ \mathrm{H}-2(11 / 99) \\ \hline \end{array}$ | [34195-34-1] | \$207 |

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| Cat. <br> No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII ( 70 mg ) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl) | F0C214 |  |  |  | [847-86-9] | \$513 |
| 1316004 | Hydrocortisone (200 mg) | M1C110 |  |  | $\begin{array}{\|l\|l\|} \hline M(10 / 04) \\ L & (09 / 00) \\ \hline \end{array}$ | [50-23-7] | \$156 |
| 1317007 | Hydrocortisone Acetate ( $200 \mathrm{mg} \mathrm{)}$ | K |  |  | J (10/99) | [50-03-3] | \$156 |
| 1317302 | Hydrocortisone Butyrate (200 mg) | H |  |  |  | [13609-67-1] | \$156 |
| 1318000 | Hydrocortisone Cypionate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [508-99-6] | \$156 |
| 1319002 | Hydrocortisone Hemisuccinate ( 200 mg ) | H |  |  | $\begin{array}{\|l\|l\|} \hline \text { G-3 }(03 / 02) \\ \text { G-2 (08/99) } \\ \hline \end{array}$ | [83784-20-7] | \$156 |
| 1320001 | Hydrocortisone Phosphate Triethylamine ( 200 mg ) | F-1 |  |  |  | n/f | \$156 |
| 1321004 | Hydrocortisone Valerate (200 mg) | F-1 |  |  | F (07/02) | [57524-89-7] | \$156 |
| 1322007 | Hydroflumethiazide ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  |  |  | [135-09-1] | \$156 |
| 1323000 | Hydromorphone Hydrochloride CII (50 mg) | J0C372 |  |  | $\begin{array}{\|l\|} \hline \mathrm{I}(01 / 05) \\ \mathrm{H}-2(03 / 01) \\ \hline \end{array}$ | [71-68-1] | \$207 |
| 1324002 | Hydroquinone ( 500 mg ) | H0C249 |  |  | $\begin{array}{\|l} \hline \text { G-1 }(10 / 04) \\ \text { G (11/01) } \\ \text { F-4 (02/99) } \\ \hline \end{array}$ | [123-31-9] | \$156 |
| 1325005 | Hydroxyamphetamine Hydrobromide ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | F (06/01) | [306-21-8] | \$156 |
| 1327000 | Hydroxychloroquine Sulfate ( $200 \mathrm{mg} \mathrm{)}$ | J0B297 |  |  | I (05/04) | [747-36-4] | \$156 |
| 1329006 | Hydroxyprogesterone Caproate ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  |  | [630-56-8] | \$156 |
| 1329709 | Hydroxypropyl Betadex ( 200 mg ) | F0B295 |  |  |  | [128446-35-5] | \$156 |
| 1329800 | Hydroxypropyl Cellulose (200 mg) | F-1 |  |  |  | [9004-64-2] | \$156 |
| 1332000 | Hydroxyurea (200 mg) | H |  |  | G (01/00) | [127-07-1] | \$156 |
| 1333003 | Hydroxyzine Hydrochloride ( 500 mg ) | I0C385 | $0.998 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | H (05/05) | [2192-20-3] | \$156 |
| 1333058 | Hydroxyzine Related Compound A ( 25 mg ) (pChlorobenzhydrylpiperazine) | H |  |  |  | [303-26-4] | \$208 |
| 1334006 | Hydroxyzine Pamoate ( 500 mg ) | H0C016 |  |  | G-1 (07/03) | [10246-75-0] | \$156 |
| 1335009 | Hyoscyamine Sulfate (125 mg) | H0C193 |  |  | $\begin{array}{\|l\|l\|} \hline \text { G2A007 (09/04) } \\ \text { G-1 (08/02) } \\ \text { G (10/99) } \\ \hline \end{array}$ | [6835-16-1] | \$124 |
| 1335202 | Hyperoside ( 50 mg ) | F |  |  |  | [482-36-0] | \$855 |
| 1330005 | Hypromellose ( 250 mg ) (Hydroxypropyl Methylcellulose) | H0C387 |  |  | $\begin{array}{\|l} \hline \text { G-1 (11/04) } \\ \text { G (02/02) } \\ \hline \end{array}$ | [9004-65-3] | \$156 |
| 1335304 | Hypromellose Phthalate ( 100 mg ) | F-1 |  |  | F (12/00) | [9050-31-1] | \$156 |
| 1335508 | Ibuprofen ( 750 mg ) | J |  |  | I (06/02) | [15687-27-1] | \$156 |
| 1335701 | Idarubicin Hydrochloride ( 50 mg ) | H0C061 |  |  | $\begin{array}{\|l\|} \hline G(11 / 03) \\ F(06 / 00) \\ \hline \end{array}$ | [57852-57-0] | \$479 |
| 1336001 | Idoxuridine ( 250 mg ) | H1B230 |  |  | H (07/04) | [54-42-2] | \$156 |
| 1336205 | Ifosfamide ( 500 mg ) | G |  |  | $\begin{array}{\|l} \hline \text { F-1 (11/00) } \\ \text { F (02/99) } \\ \hline \end{array}$ | [3778-73-2] | \$156 |
| 1336500 | Imidazole (200 mg) | G1B132 |  |  | G (01/04) | [288-32-4] | \$487 |
| 1336806 | Imidurea (200 mg) | H |  |  | G (10/99) | [39236-46-9] | \$156 |
| 1337004 | Iminodibenzyl ( 25 mg ) | 10C253 |  |  | H (11/04) | [494-19-9] | \$487 |
| 1337809 | Imipenem Monohydrate ( 100 mg ) | G1C296 | 930 ug/mg (ai) |  | $\begin{array}{\|l} \hline G(01 / 05) \\ F(01 / 01) \\ \hline \end{array}$ | [74431-23-5] | \$156 |
| 1338007 | Imipramine Hydrochloride ( 200 mg ) | 1 |  |  | H (09/01) | [113-52-0] | \$156 |
| 1338801 | Indapamide (250 mg) | H |  |  | G (07/02) | [26807-65-8] | \$156 |
| 1339000 | Indigotindisulfonate Sodium ( 500 mg ) | H1B153 |  |  | H (06/03) | [860-22-0] | \$156 |
| 1340009 | Indocyanine Green (200 mg) | IOB045 |  |  | H (09/01) | [3599-32-4] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1341001 | Indomethacin (200 mg) | J0B165 |  |  | $\begin{array}{\|l\|} \hline \text { I (01/04) } \\ H(05 / 99) \\ \hline \end{array}$ | [53-86-1] | \$156 |
| 1342004 | Insulin (100 mg) | H |  |  |  | [9004-10-8] | \$156 |
| 1342106 | Insulin Human (100 mg) | H1A031 |  |  | $\begin{aligned} & \mathrm{H}(11 / 02) \\ & \mathrm{G}(04 / 00) \end{aligned}$ | [11061-68-0] | \$156 |
| 1342208 | Insulin (Beef) (100 mg) | F |  |  |  | [11070-73-8] | \$156 |
| 1342300 | Insulin (Pork) (100 mg) | F |  |  |  | [12584-58-6] | \$156 |
| 1342503 | locetamic Acid (200 mg) | F |  |  |  | [16034-77-8] | \$156 |
| 1343007 | lodipamide ( 200 mg ) | G |  |  |  | [606-17-7] | \$156 |
| 1343517 | Iodixanol (200 mg) | FOB240 |  |  |  | [92339-11-2] | \$156 |
| 1343540 | Iodixanol Related Compound C ( 25 mg ) (5-Acetyl[3-[[3,5-bis[[(2,3-dihydroxypropyl)amino]-carbonyl]-2,4,6-triiodophenyl]amino]-2-hydroxy-propyl]amino]-N,N'-bis-(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B236 |  |  |  | n/f | \$487 |
| 1343550 | lodixanol Related Compound D ( 50 mg ) ( $5-$ [Acetyl(2-hydroxy-3-methylpropyl)amino]-N,N'-bis(2,3-dihydroxypropyl)2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B231 |  |  |  | [89797-00-2] | \$487 |
| 1343561 | Iodixanol Related Compound E ( 25 mg ) (5-[[3-[[3-[[(2,3-Dihydoxypropyl)amino]carbonyl]-5-[[amino]carbonyl]-2,4,6-triiodophenyl](acetylimi-no)]-2-hydroxypropyl]-(acetylimino)]-N,N'-bis(2,3-dihydoxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F0B229 |  |  |  | n/f | \$487 |
| 1344305 | o-lodohippuric Acid (100 mg) | F |  |  |  | [147-58-0] | \$156 |
| 1344509 | lodoquinol ( 100 mg ) | H |  |  | G (07/02) | [83-73-8] | \$156 |
| 1344600 | lohexol ( 100 mg ) | F-1 |  |  | F (01/99) | [66108-95-0] | \$124 |
| 1344622 | lohexol Related Compound A ( 100 mg ) ( $5-$ (acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide) | F-1 |  |  | F (10/01) | n/f | \$487 |
| 1344644 | Iohexol Related Compound B (50 mg) (5-amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triio-do-1,3-benzenedicarboxamide) | F-1 |  |  | F (01/04) | [76801-93-9] | \$487 |
| 1344666 | lohexol Related Compound C ( 100 mg ) ( $\mathrm{N}, \mathrm{N}$ '-bis(2,3-dihydroxypropyl)-5-nitro-1,3-benzenedicarboxamide) | F-1 |  |  | F (09/03) | n/f | \$156 |
| 1344702 | lopamidol (200 mg) | G |  |  |  | [60166-93-0] | \$156 |
| 1344724 | lopamidol Related Compound A ( 50 mg ) ( $\mathrm{N}, \mathrm{N}$ '-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triio-doiso-phthalamide) | G |  |  |  | [60166-98-5] | \$487 |
| 1344735 | lopamidol Related Compound B (100 mg) (5-Glycolamido-N,N'-bis[2-hydroxy-1-(hydroxy-methyl)ethyl]-2,4,6-triiodoisophthalamide) | F |  |  |  | n/f | \$487 |
| 1344804 | lopromide ( 400 mg ) | F |  |  |  | [73334-07-3] | \$156 |
| 1344826 | lopromide Related Compound A ( 50 mg ) ( $5-$ Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triio-do-N-methyl-1,3-benzenedicarboxamide) | F |  |  |  | n/f | \$487 |
| 1344837 | lopromide Related Compound B ( 50 mg ) ( $5-$ (Acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide) | F |  |  |  | n/f | \$487 |
| 1345002 | Iothalamic Acid (200 mg) | G |  |  |  | [2276-90-6] | \$156 |
| 1345104 | loversol (200 mg) | F |  |  |  | [87771-40-2] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1345115 | loversol Related Compound A (50 mg) (5-Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide) | F |  |  |  | [76801-93-9] | \$487 |
| 1345126 | loversol Related Compound B ( 50 mg ) ( $\mathrm{N}, \mathrm{N}$ '-bis(2,3-dihydroxypropyl)-5-[(N-(2-hydroxyethyl)-carbonyl)methoxy]-2,4,6-triiodoisophthalamide) | F |  |  |  | n/f | \$487 |
| 1345159 | loxaglic Acid (100 mg) | F |  |  |  | [59017-64-0] | \$156 |
| 1345206 | loxilan ( 400 mg ) | F |  |  |  | [107793-72-6] | \$156 |
| 1345228 | Ioxilan Related Compound A (100 mg) (5-amino-2,4,6-triiodo-3 N-(2-hydroxyethyl)carbamoyl benzoic acid) | F |  |  |  | [22871-58-5] | \$487 |
| 1346005 | Ipodate Calcium ( 200 mg ) | F |  |  |  | [1151-11-7] | \$156 |
| 1347008 | Ipodate Sodium (200 mg) | F-1 |  |  |  | [1221-56-3] | \$156 |
| 1347755 | Isoamyl Methoxycinnamate ( $750 \mathrm{mg} / \mathrm{ampule} \mathrm{)}$ | F0B017 |  |  |  | [71617-10-2] | \$156 |
| 1348000 | Isocarboxazid ( 200 mg ) | F-1 |  |  |  | [59-63-2] | \$156 |
| 1348500 | Isoetharine Hydrochloride ( 250 mg ) | F-2 |  |  |  | [2576-92-3] | \$156 |
| 1348907 | Isoflupredone Acetate ( 200 mg ) | F0C109 |  |  |  | [338-98-7] | \$156 |
| 1349003 | Isoflurane ( 1 mL ) | H1C199 |  |  | H (12/04) | [26675-46-7] | \$156 |
| 1349014 | Isoflurane Related Compound A ( 0.1 mL ) (1-Chloro-2,2,2-trifluoroethyl chlorodifluoromethyl ether) | F0C232 |  |  |  | n/f | \$487 |
| 1349025 | Isoflurane Related Compound B ( 0.1 mL ) (2,2,2Trifluoroethyldifluoromethyl ether) | F0C233 |  |  |  | n/f | \$487 |
| 1349502 | L-Isoleucine ( 200 mg ) | F-2 |  |  | F-1 (09/02) | [73-32-5] | \$156 |
| 1349604 | Isomalathion ( 50 mg ) | F1B107 |  |  | F (01/03) | [3344-12-5] | \$487 |
| 1349659 | Isometheptene Mucate ( 200 mg ) | F |  |  |  | [7492-31-1] | \$156 |
| 1349706 | Isoniazid (200 mg) | H |  |  |  | [54-85-3] | \$156 |
| 1350002 | Isopropamide lodide (200 mg) | F-2 |  |  |  | [71-81-8] | \$156 |
| 1350400 | Isopropyl Myristate ( 500 mg ) | I1C183 |  |  | 1 (01/05) | [110-27-0] | \$156 |
| 1350603 | Isopropyl Palmitate ( 500 mg ) | 1 |  |  | H (10/99) | [142-91-6] | \$156 |
| 1351005 | Isoproterenol Hydrochloride ( 125 mg ) | K |  |  |  | [51-30-9] | \$124 |
| 1352008 | Isosorbide ( $75 \%$ solution, 1 g ) | 1 |  |  | H-2 (10/00) | [652-67-5] | \$156 |
| 1353000 | Diluted Isosorbide Dinitrate ( 500 mg of $25 \%$ mixture with mannitol) | I-1 |  |  | I (10/99) | [87-33-2] | \$156 |
| 1353500 | Isotretinoin (200 mg) | 1 |  |  | H (10/00) | [4759-48-2] | \$156 |
| 1354003 | Isoxsuprine Hydrochloride (200 mg) | F-3 |  |  |  | [579-56-6] | \$156 |
| 1354207 | Isradipine (200 mg) | G0B054 |  |  | F (05/03) | [75695-93-1] | \$156 |
| 1354218 | Isradipine Related Compound A ( 25 mg ) (Isopropyl methyl 4-(4-benzofurazanyl)-2,6-di-methyl-3,5-pyridinedicarboxylate) | F |  |  |  | n/f | \$487 |
| 1354309 | Ivermectin (200 mg) | FOB196 |  |  |  | [70288-86-7] | \$156 |
| 1355006 | Kanamycin Sulfate (200 mg) | J |  |  | I (06/99) | [25389-94-0] | \$156 |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 |  |  |  | n/f | \$260 |
| 1355753 | Kawain (200 mg) | F0C160 |  |  |  | [500-64-1] | \$208 |
| 1356009 | Ketamine Hydrochloride CIII (250 mg) | G-2 |  |  | G-1 (07/00) | [1867-66-9] | \$207 |
| 1356020 | Ketamine Related Compound A (50 mg) (1-[(2-Chlorophenyl)(methylimino)methyl]cylcopentanol) | F0C118 |  |  |  | [6740-87-0] | \$487 |
| 1356508 | Ketoconazole (200 mg) | G4B179 |  |  | $\begin{aligned} & \text { G-3 }(01 / 04) \\ & \text { G-2 }(06 / 01) \\ & \text { G-1 }(01 / 99) \end{aligned}$ | [65277-42-1] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1356632 | Ketoprofen ( 200 mg ) | H0B216 |  |  | $\begin{aligned} & \hline \text { G (07/04) } \\ & \text { F-2 (05/99) } \\ & \hline \end{aligned}$ | [22071-15-4] | \$156 |
| 1356643 | Ketoprofen Related Compound A ( 25 mg ) (al-pha-Methyl-3-(4-methylbenzoyl) benzeneacetic acid) | G |  |  |  | [107257-20-5] | \$487 |
| 1356665 | Ketorolac Tromethamine (200 mg) | G |  |  | F-2 (04/99) | [74103-07-4] | \$156 |
| 1356654 | Labetalol Hydrochloride (200 mg) | G |  |  | $\begin{aligned} & \text { F-2 (01/02) } \\ & \text { F-1 (03/01) } \\ & \hline \end{aligned}$ | [32780-64-6] | \$156 |
| 1356676 | Anhydrous Lactose (100 mg) | G1C004 |  |  | $\begin{aligned} & \hline G(12 / 04) \\ & F(06 / 01) \\ & \hline \end{aligned}$ | [63-42-3] | \$156 |
| 1356687 | Lactitol ( 500 mg ) | F0B005 |  |  |  | [81025-04-9] | \$156 |
| 1356701 | Lactose Monohydrate ( 500 mg ) | G-1 |  |  | G (08/02) | [5989-81-1] | \$156 |
| 1356803 | Lactulose (1 g) | H |  |  | G-1 (08/00) | [4618-18-2] | \$156 |
| 1356836 | Lamivudine ( 200 mg ) | F0C361 |  |  |  | [134678-17-4] | \$156 |
| 1356847 | Lamivudine Resolution Mixture A (10 mg) | F0D024 |  |  |  | [134678-17-4] | \$487 |
| 1356880 | Lanolin (20 g) | F |  |  |  | [8006-54-0] | \$156 |
| 1356905 | Lanolin Alcohols (5 g) | F |  |  |  | [8027-33-6] | \$156 |
| 1356916 | Lansoprazole (200 mg) | F0B310 |  |  |  | [103577-45-3] | \$156 |
| 1356927 | Lansoprazole Related Compound A ( 25 mg ) (2-[[[3-methyl-4-(2,2,2-triflouroethoxy)-2-pyridyl]methyl]sulfonyl]benzimidazole) | F0B311 |  |  |  | n/f | \$487 |
| 1356950 | Lauroyl Polyoxylglycerides (500 mg) (AS) | FOD020 |  | 1 |  | n/f | \$156 |
| 1356971 | Letrozole (200 mg) | F0B170 |  |  |  | [112809-51-5] | \$156 |
| 1356982 | Letrozole Related Compound A ( 15 mg ) (4,4'-(1H-1,3,4-triazol-1-ylmethylene)dibenzonitrile) | F0B168 |  |  |  | n/f | \$487 |
| 1357001 | L-Leucine (200 mg) | H0B237 |  |  | $\begin{aligned} & \mathrm{G}-1(04 / 04) \\ & \mathrm{G}(08 / 00) \\ & \hline \end{aligned}$ | [61-90-5] | \$156 |
| 1358004 | Leucovorin Calcium (500 mg) | J2B219 |  |  | $\begin{aligned} & \hline J-1(07 / 04) \\ & J(05 / 02) \\ & \hline \end{aligned}$ | [1492-18-8] | \$160 |
| 1358503 | Leuprolide Acetate (200 mg) | F0C430 | $0.907 \mathrm{mg} / \mathrm{mg}(\mathrm{an}, \mathrm{fb})$ |  |  | [74381-53-6] | \$1,525 |
| 1359007 | Levallorphan Tartrate ( 200 mg ) DISCONTINUED |  |  |  | $\begin{aligned} & \text { G-1 (09/04) } \\ & \text { G (11/02) } \\ & \hline \end{aligned}$ | [71-82-9] | \$156 |
| 1359302 | Levamisole Hydrochloride ( 125 mg ) | F2C122 |  |  | F-1 (05/04) | [16595-80-5] | \$124 |
| 1359506 | Levmetamfetamine CII (75 mg) | F |  |  |  | [33817-09-3] | \$207 |
| 1359801 | Levobunolol Hydrochloride ( 200 mg ) | G |  |  |  | [27912-14-7] | \$156 |
| 1359903 | Levocarnitine (400 mg) | G0B197 |  |  | $\begin{aligned} & \hline \text { F-2 }(06 / 03) \\ & \text { F-1 }(12 / 00) \\ & \hline \end{aligned}$ | [541-15-1] | \$156 |
| 1359925 | Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride) | F-1 |  |  | F (08/01) | [6538-82-5] | \$208 |
| 1361009 | Levodopa (200 mg) | 1 |  |  | H (09/00) | [59-92-7] | \$156 |
| 1361010 | Levodopa Related Compound A ( 50 mg ) (3-(3,4,6-Trihydroxyphenyl)-alanine) | K |  |  | $\begin{array}{\|l} \hline J(01 / 03) \\ I(06 / 00) \\ \hline \end{array}$ | [27244-64-0] | \$487 |
| 1420006 | Levodopa Related Compound B ( 50 mg ) (3Methoxytyrosine) | 10 C 300 |  |  | H (07/04) |  | \$487 |
| 1362500 | Levonordefrin ( 200 mg ) | F-1 |  |  |  | [829-74-3] | \$156 |
| 1363004 | Levopropoxyphene Napsylate ( 300 mg ) | G |  |  |  | [55557-30-7] | \$156 |
| 1364007 | Levorphanol Tartrate CII (500 mg) | H |  |  | G (03/01) | [5985-38-6] | \$207 |
| 1365000 | Levothyroxine ( 500 mg ) | K |  |  | $J(10 / 00)$ | [51-48-9] | \$156 |
| 1366002 | Lidocaine ( 250 mg ) | L |  |  |  | [137-58-6] | \$156 |
| 1367005 | Lincomycin Hydrochloride ( 200 mg ) | H2B130 |  |  | H-1 (01/04) | [7179-49-9] | \$156 |
| 1367504 | Lindane ( 200 mg ) | F-2 |  |  |  | [58-89-9] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1367708 | Linoleoyl Polyoxylglycerides ( 100 mg ) | F0C283 |  |  |  | n/f | \$156 |
| 1368008 | Liothyronine ( 250 mg ) | L1C262 |  |  | $\begin{array}{\|l\|} \hline \text { L (08/04) } \\ \mathrm{K}(08 / 01) \\ \hline \end{array}$ | [6893-02-3] | \$156 |
| 1368609 | Lisinopril (300 mg) | 11C045 |  |  | $\begin{aligned} & \hline \text { (11/04) } \\ & H(09 / 01) \\ & G(10 / 99) \\ & \hline \end{aligned}$ | [83915-83-7] | \$156 |
| 1369000 | Lithium Carbonate (300 mg) | G0B031 |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 (01/03) } \\ \text { F-1 (01/01) } \\ \hline \end{array}$ | [554-13-2] | \$156 |
| 1370000 | Loperamide Hydrochloride (200 mg) | H0C202 |  |  | $\begin{aligned} & \text { G-2 }(09 / 04) \\ & \text { G-1 }(02 / 03) \\ & \hline \end{aligned}$ | [34552-83-5] | \$156 |
| 1370203 | Loracarbef (200 mg) | F |  |  |  | [121961-22-6] | \$156 |
| 1370225 | Loracarbef L-Isomer (25 mg) | F |  |  |  | n/f | \$156 |
| 1370270 | Loratadine (200 mg) | F0C414 |  |  |  | [79794-75-5] | \$260 |
| 1370305 | Lorazepam CIV (200 mg) | 10 C 048 |  |  | H0B023 (06/04) | [846-49-1] | \$207 |
| 1370327 | Lorazepam Related Compound A ( 25 mg ) (7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-3-acet-oxy-2H-1,4-benzodiazepin-2-one) | G |  |  | F-1 (06/01) | [2848-96-6] | \$487 |
| 1370338 | Lorazepam Related Compound B ( 25 mg ) (2-Amino-2',5-dichlorobenzophenone) | G |  |  | F-2 (01/04) | [2958-36-3] | \$487 |
| 1370349 | Lorazepam Related Compound C ( 25 mg ) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde) | H |  |  | $\begin{array}{\|l\|} \hline \mathrm{G}(01 / 03) \\ \mathrm{F}-3(01 / 02) \end{array}$ | n/f | \$487 |
| 1370350 | Lorazepam Related Compound D (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid) | G0A014 |  |  | F-2 (01/04) | [54643-79-7] | \$487 |
| 1370360 | Lorazepam Related Compound E ( 25 mg ) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol) | G |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-3 (07/02) } \\ \text { F-2 (04/99) } \end{array}$ | n/f | \$487 |
| 1370600 | Lovastatin (125 mg) | H2C012 |  |  | $\begin{aligned} & \mathrm{H} 1 \mathrm{B067}(01 / 04) \\ & \mathrm{H}(08 / 03) \end{aligned}$ | [75330-75-5] | \$124 |
| 1370611 | Lovastatin Related Compound A (20 mg) (Butanoic acid, 2-methyl-, 1,2,3,4,4a,7,8,8a-octahy-dro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl es-ter,[1S-[alpha(R*), 3alpha,7beta,8beta( $2 \mathrm{~S}^{*}, 4 \mathrm{~S}^{*}$ ), 8alpha beta]]-) | G0C326 |  |  | F0B235 (09/04) | n/f | \$487 |
| 1370702 | Loxapine Succinate (125 mg) | G0B026 |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-2 (06/03) } \\ \text { F-1 (07/01) } \\ \text { F (03/99) } \\ \hline \end{array}$ | [27833-64-3] | \$124 |
| 1370906 | Lynestrenol (20 mg) | FOB314 |  |  |  | [52-76-6] | \$203 |
| 1371002 | Lysergic Acid Diethylamide Tartrate Cl (10 mg) (AS) (LSD) | 1 |  |  |  | [50-37-3] | \$207 |
| 1371501 | L-Lysine Acetate ( 200 mg ) | F1C027 |  |  | F (11/04) | [57282-49-2] | \$156 |
| 1372005 | L-Lysine Hydrochloride (200 mg) | H |  |  | G (07/00) | [657-27-2] | \$156 |
| 1373008 | Mafenide Acetate (200 mg) | F |  |  |  | [13009-99-9] | \$156 |
| 1374000 | Magaldrate ( 200 mg ) | F-1 |  |  |  | [74978-16-8] | \$156 |
| 1374260 | Magnesium Hydroxide (1 g) (AS) | F0D158 | 98.5\% (dr) | 1 |  | [1309-42-8] | \$156 |
| 1374306 | Magnesium Salicylate (200 mg) | F2B081 |  |  | F-1 (01/04) | [18917-95-8] | \$156 |
| 1374408 | Malathion ( 500 mg ) | F-1 |  |  | F (08/01) | [121-75-5] | \$156 |
| 1374500 | Maleic Acid ( 300 mg ) | G |  |  | F-2 (12/00) | [110-16-7] | \$487 |
| 1374601 | Malic Acid (200 mg) | G0B158 |  |  | F-1 (04/03) | [617-48-1] | \$156 |
| 1374907 | Maltitol (200 mg) | G |  |  | F-1 (12/99) | [585-88-6] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

## USP Reference Standards and Authentic Substances

| Cat. No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1375003 | Maltol (4 g) (FCC) | G |  |  | F-1 (12/99) | [118-71-8] | \$156 |
| 1375058 | Mandelic Acid ( 500 mg ) | F |  |  |  | [90-64-2] | \$156 |
| 1375127 | Manganese Chloride (1 g) (AS) | F0D150 | 99.6\% (dr) | 1 |  | [13446-34-9] | \$156 |
| 1375149 | Manganese Sulfate (1 g) (AS) | F0D151 | 99.8\% (ai) | 1 |  | [10034-96-5] | \$156 |
| 1375105 | Mannitol ( 200 mg ) | IOB212 |  |  | H (03/04) | [69-65-8] | \$156 |
| 1375207 | Maprotiline Hydrochloride ( 200 mg ) | H |  |  | G (07/02) | [10347-81-6] | \$156 |
| 1375309 | Mazindol CIV ( 350 mg ) | H |  |  | G (02/03) | [22232-71-9] | \$207 |
| 1375502 | Mebendazole ( 200 mg ) | G1C195 |  |  | G (11/04) | [31431-39-7] | \$156 |
| 1375706 | Mebrofenin ( 100 mg ) | F |  |  |  | [78266-06-5] | \$156 |
| 1376006 | Mecamylamine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | F-2 |  |  |  | [826-39-1] | \$156 |
| 1376505 | Mechlorethamine Hydrochloride ( 100 mg ) (FOR U.S. SALE ONLY) | F-1 |  |  | F (09/00) | [55-86-7] | \$156 |
| 1377009 | Meclizine Hydrochloride ( 500 mg ) | I-1 |  |  |  | [31884-77-2] | \$156 |
| 1377508 | Meclocycline Sulfosalicylate ( 300 mg ) | G |  |  |  | [73816-42-9] | \$156 |
| 1377803 | Meclofenamate Sodium ( 500 mg ) | H |  |  |  | [6385-02-0] | \$156 |
| 1378001 | Medroxyprogesterone Acetate (200 mg) | H-2 |  |  | H-1 (04/03) | [71-58-9] | \$156 |
| 1378012 | Medroxyprogesterone Acetate Related Compound A ( 25 mg ) (4,5-beta-Dihydromedroxyprogesterone acetate) | FOC427 | 1.00 mg/mg (ai) |  |  | n/f | \$500 |
| 1379004 | Medrysone ( 500 mg ) | F |  |  |  | [2668-66-8] | \$156 |
| 1379605 | Mefenamic Acid (200 mg) | G0C025 |  |  | $\begin{array}{\|l\|} \hline \text { F3A032 (08/04) } \\ \text { F-2 (01/03) } \\ \hline \end{array}$ | [61-68-7] | \$156 |
| 1379106 | Megestrol Acetate ( 500 mg ) | 1 |  |  | H (05/00) | [595-33-5] | \$156 |
| 1379300 | Melphalan Hydrochloride ( 100 mg ) (FOR U.S. SALE ONLY) | H0B296 | $0.975 \mathrm{mg} / \mathrm{mg}$ (ai) |  | G (01/05) | [3223-07-2] | \$156 |
| 1381006 | Menadione (200 mg) (Vitamin K3) | H-3 |  |  | H-2 (02/00) | [58-27-5] | \$156 |
| 1381709 | Menthol ( 250 mg ) | IOB049 |  |  | H (04/03) | [2216-51-5] | \$156 |
| 1381742 | Menthyl Anthranilate ( $500 \mathrm{mg} / \mathrm{ampule}$ ) | F0B103 |  |  |  | [134-09-8] | \$156 |
| 1382009 | Mepenzolate Bromide ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [76-90-4] | \$156 |
| 1383001 | Meperidine Hydrochloride CII (200 mg) | I |  |  | H-1 (12/99) | [50-13-5] | \$207 |
| 1384004 | Mephentermine Sulfate ( $250 \mathrm{mg} \mathrm{)}$ |  |  |  | F-1 (04/05) | [1212-72-2] | \$156 |
| 1385007 | Mephenytoin ( 250 mg ) | G |  |  |  | [50-12-4] | \$156 |
| 1386000 | Mephobarbital CIV (250 mg) | G |  |  | F (01/01) | [115-38-8] | \$207 |
| 1387002 | Mepivacaine Hydrochloride (200 mg) | H |  |  | G-4 (02/99) | [1722-62-9] | \$156 |
| 1388005 | Meprednisone ( 200 mg ) | G |  |  |  | [1247-42-3] | \$156 |
| 1389008 | Meprobamate CIV (200 mg) | G-1 |  |  | G (03/02) | [57-53-4] | \$207 |
| 1390007 | Meprylcaine Hydrochloride (200 mg) | F |  |  |  | [956-03-6] | \$156 |
| 1391000 | 3-Mercapto-2-methylpropanoic Acid 1,2-Diphenylethylamine Salt ( 75 mg ) | G |  |  |  | n/f | \$487 |
| 1392002 | Mercaptopurine ( 500 mg ) | 12C263 |  |  | $\begin{array}{\|l\|} \hline \text { I-1 (10/04) } \\ \text { I (07/02) } \\ H(12 / 99) \\ \hline \end{array}$ | [6112-76-1] | \$156 |
| 1392454 | Meropenem ( 300 mg ) | F0C201 |  |  |  | [119478-56-7] | \$182 |
| 1392705 | Mesalamine ( 200 mg ) | H0C341 |  | 2 | $\begin{array}{\|l} \hline \text { G1B001 (06/05) } \\ \text { G (01/03) } \\ \text { F-1 (03/00) } \\ \hline \end{array}$ | [89-57-6] | \$156 |
| 1393005 | Mesoridazine Besylate (250 mg) | J0C117 |  |  | I-1 (12/04) | [32672-69-8] | \$156 |
| 1394008 | Mestranol (200 mg) | K0C065 |  |  | $\begin{array}{\|l\|} \hline J \text { (07/04) } \\ \text { I-1 (09/99) } \\ \hline \end{array}$ | [72-33-3] | \$156 |
| 1395500 | Metaproterenol Sulfate ( 200 mg ) | F-3 |  |  |  | [5874-97-5] | \$156 |
| 1396003 | Metaraminol Bitartrate ( 200 mg ) | F-3 |  |  |  | [33402-03-8] | \$156 |

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| Cat. <br> No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \text { CAS } \\ \text { No. } \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1396309 | Metformin Hydrochloride (200 mg) | F0C209 |  |  |  | [1115-70-4] | \$182 |
| 1396310 | Metformin Related Compound A ( 50 mg ) (1Cyanoguanidine) | F0C210 |  |  |  | [461-58-5] | \$487 |
| 1396400 | Methacrylic Acid Copolymer Type A (200 mg) | G0B140 |  |  | F-2 (04/03) | n/f | \$156 |
| 1396502 | Methacrylic Acid Copolymer Type B (200 mg) | G0B141 |  |  | F-2 (04/03) | n/f | \$156 |
| 1396604 | Methacrylic Acid Copolymer Type C (100 mg) | G1B088 |  |  | G (08/03) | n/f | \$124 |
| 1397006 | Methacycline Hydrochloride ( 200 mg ) | H |  |  | G (04/01) | [3963-95-9] | \$156 |
| 1398009 | Methadone Hydrochloride CII (200 mg) | IOB163 |  |  | H-1 (08/03) | [1095-90-5] | \$207 |
| 1399001 | Methamphetamine Hydrochloride CII (125 mg) | I |  |  |  | [51-57-0] | \$207 |
| 1401001 | Methantheline Bromide ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  |  | [53-46-3] | \$156 |
| 1402004 | Methapyrilene Fumarate (200 mg) | F-1 |  |  |  | [33032-12-1] | \$156 |
| 1404000 | Methaqualone Cl ( 500 mg ) | F-1 |  |  |  | [72-44-6] | \$207 |
| 1405002 | Metharbital CIII (200 mg) | F-2 |  |  | F-1 (07/99) | [50-11-3] | \$207 |
| 1406005 | Methazolamide ( 500 mg ) | H0B239 |  |  | G-1 (05/04) | [554-57-4] | \$156 |
| 1407008 | Methdilazine (200 mg) | F-1 |  |  |  | [1982-37-2] | \$156 |
| 1408000 | Methdilazine Hydrochloride ( 200 mg ) | G |  |  |  | [1229-35-2] | \$156 |
| 1409003 | Methenamine ( 500 mg ) | H0C047 |  |  | G (05/04) | [100-97-0] | \$156 |
| 1409502 | Methenamine Hippurate (200 mg) | F |  |  |  | [5714-73-8] | \$156 |
| 1409604 | Methenamine Mandelate ( 200 mg ) | G0C304 |  |  | $\begin{array}{\|l\|} \hline \text { F-2 (01/05) } \\ \text { F-1 }(11 / 00) \\ \hline \end{array}$ | [587-23-5] | \$156 |
| 1410002 | Methicillin Sodium (500 mg) (AS) | J0C333 |  | 3 | $\begin{array}{\|l} \text { I1B186 (11/04) } \\ \text { I (03/03) } \\ \text { H (03/00) } \\ \hline \end{array}$ | [7246-14-2] | \$156 |
| 1411005 | Methimazole (200 mg) | G |  |  | F (02/01) | [60-56-0] | \$156 |
| 1411504 | L-Methionine (200 mg) | G |  |  | F-2 (11/99) | [63-68-3] | \$156 |
| 1412008 | Methocarbamol (200 mg) | H2B029 |  |  | H-1 (03/04) | [532-03-6] | \$156 |
| 1413000 | Methohexital CIV (500 mg) | F-2 |  |  |  | [18652-93-2] | \$207 |
| 1414003 | Methotrexate ( 500 mg ) | I |  |  |  | [59-05-2] | \$156 |
| 1415006 | Methotrimeprazine ( 125 mg ) | F-2 |  |  | F-1 (05/99) | [60-99-1] | \$124 |
| 1416009 | Methoxamine Hydrochloride ( 200 mg ) | F |  |  |  | [61-16-5] | \$156 |
| 1417001 | Methoxsalen ( 500 mg ) | H |  |  |  | [298-81-7] | \$156 |
| 1418004 | Methoxyflurane (1 mL) | G |  |  |  | [76-38-0] | \$156 |
| 1419007 | Methoxyphenamine Hydrochloride ( $250 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [5588-10-3] | \$156 |
| 1421009 | Methscopolamine Bromide ( $200 \mathrm{mg} \mathrm{)}$ | G1D004 | $0.999 \mathrm{mg} / \mathrm{mg}$ (dr) |  | G (02/05) | [155-41-9] | \$156 |
| 1422001 | Methsuximide ( 500 mg ) | F-2 |  |  | F-1 (08/99) | [77-41-8] | \$156 |
| 1424007 | Methyclothiazide ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  |  | [135-07-9] | \$156 |
| 1424018 | Methyclothiazide Related Compound A ( 100 mg ) ( 4 -amino-6-chloro-N-3-methyl-m-benzenedisulfonamide) | G |  |  | F-2 (12/00) | n/f | \$487 |
| 1424222 | Methyl Benzylidene Camphor (200 mg) | F0B118 |  |  |  | [36861-47-9] | \$156 |
| 1424233 | Methyl Caprate ( 300 mg ) | F |  |  |  | [110-42-9] | \$156 |
| 1424244 | Methyl Caproate ( 300 mg ) | F |  |  |  | [106-70-7] | \$156 |
| 1424255 | Methyl Caprylate ( 300 mg ) | F |  |  |  | [111-11-5] | \$156 |
| 1424506 | Methylcellulose (1 g) (AS) | G0B222 |  |  | F-2 (05/03) | [9004-67-5] | \$156 |
| 1425000 | 4-Methyl-2,5-dimethoxyamphetamine Hydrochloride $\mathbf{C l}(25 \mathrm{mg})$ (AS) (STP) | F |  |  |  | [15589-00-1] | \$207 |
| 1426002 | Methyldopa ( 500 mg ) | 1 |  |  |  | [41372-08-1] | \$156 |
| 1427005 | Methyldopate Hydrochloride ( 200 mg ) | G-2 |  |  |  | [2508-79-4] | \$156 |
| 1428008 | Methylene Blue (250 mg) | G |  |  |  | [7220-79-3] | \$156 |

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| Cat. No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1429000 | Methylenedioxy-3,4-amphetamine Hydrochloride $\mathbf{C l}(25 \mathrm{mg})$ (AS) (MDA) | F-1 |  |  |  | [6292-91-7] | \$207 |
| 1430000 | Methylergonovine Maleate ( 50 mg ) (List Chemical) | $J$ |  |  | I (05/02) | [57432-61-8] | \$156 |
| 1430305 | Methyl Laurate ( 500 mg ) | G0C356 | $0.998 \mathrm{mg} / \mathrm{mg}$ (ai) |  | F (03/05) | [111-82-0] | \$156 |
| 1430327 | Methyl Linoleate ( $5 \times 50 \mathrm{mg}$ ) | F |  |  |  | [112-63-0] | \$156 |
| 1430349 | Methyl Linolenate ( $5 \times 50 \mathrm{mg}$ ) | F |  |  |  | [301-00-8] | \$156 |
| 1430509 | $3-\mathrm{O}-\mathrm{Methylmethyldopa} \mathrm{( } 50 \mathrm{mg}$ ) | G-1 |  |  |  | n/f | \$487 |
| 1431002 | Methyl 5-methyl-3-isoxazolecarboxylate ( 25 mg ) | F-1 |  |  | F (01/01) | n/f | \$487 |
| 1431501 | Methyl Myristate ( 300 mg ) | G0C357 | 0.998 mg/mg (ai) |  | F (03/05) | [124-10-7] | \$156 |
| 1431556 | Methyl Oleate ( 500 mg ) | G0C148 |  |  | F (04/04) | [112-62-9] | \$156 |
| 1431603 | Methyl Palmitate ( 300 mg ) | F |  |  |  | [112-39-0] | \$156 |
| 1431625 | Methyl Palmitoleate ( 300 mg ) | F |  |  |  | n/f | \$156 |
| 1432005 | Methylparaben ( 125 mg ) | J-1 |  |  | $J$ (03/03)) | [99-76-3] | \$124 |
| 1433008 | Methylphenidate Hydrochloride CII (125 mg) | I1C241 |  |  | $\begin{aligned} & \text { I (04/05) } \\ & \text { H (05/01) } \end{aligned}$ | [298-59-9] | \$165 |
| 1434000 | Methylphenidate Hydrochloride Erythro Isomer CII $(25 \mathrm{mg})$ DISCONTINUED; please order 1434011 |  |  |  | $\begin{aligned} & \text { JOB294 (04/05) } \\ & \text { IOAO06 (09/03) } \\ & \text { H-1 (01/03) } \\ & \text { H (06/01) } \\ & \hline \end{aligned}$ | [298-59-9] | \$560 |
| 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution CII ( 0.5 mL ) | F0C368 | $0.5 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$560 |
| 1434022 | Methylphenidate Related Compound A ( 50 mg ) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride) | G |  |  | F-2 (10/99) | n/f | \$487 |
| 1435003 | Methylprednisolone ( 200 mg ) | H |  |  |  | [83-43-2] | \$156 |
| 1436006 | Methylprednisolone Acetate ( 200 mg ) | H0D148 | 0.995 mg/mg (ai) | 2 | $\begin{aligned} & \text { G-2 (05/05) } \\ & \text { G-1 }(02 / 00) \end{aligned}$ | [53-36-1] | \$156 |
| 1437009 | Methylprednisolone Hemisuccinate ( 200 mg ) | I0C146 |  |  | H (07/04) | [2921-57-5] | \$156 |
| 1437508 | Methyl Stearate ( 300 mg ) | F |  |  |  | [112-61-8] | \$156 |
| 1438001 | Methyltestosterone CIII (200 mg) | J |  |  | I (11/01) | [58-18-4] | \$207 |
| 1440003 | Methysergide Maleate ( 200 mg ) | H |  |  |  | [129-49-7] | \$156 |
| 1440808 | Metoclopramide Hydrochloride ( 500 mg ) | H0D121 | $0.999 \mathrm{mg} / \mathrm{mg}$ (an) | 2 | $\begin{aligned} & \mathrm{G}(06 / 05) \\ & \mathrm{F}-2(06 / 99) \\ & \hline \end{aligned}$ | [54143-57-6] | \$156 |
| 1441006 | Metocurine lodide ( 300 mg ) | G |  |  |  | [7601-55-0] | \$156 |
| 1441200 | Metolazone ( 200 mg ) | G0B246 |  |  | F-1 (05/03) | [17560-51-9] | \$156 |
| 1441287 | Metoprolol Fumarate ( $200 \mathrm{mg} \mathrm{)}$ | F |  |  |  | [119637-66-0] | \$156 |
| 1441232 | Metoprolol Related Compound A (20 mg) ((+/-)1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol) | F0C343 |  |  |  | n/f | \$520 |
| 1441243 | Metoprolol Related Compound B ( 50 mg ) ( $(+/-$ )1-chloro-2-hydroxy-3-[4-(2-methoxyethyl)phe-noxy]-propane) | F0C377 |  |  |  | n/f | \$520 |
| 1441254 | Metoprolol Related Compound C (20 mg) ((+/-)4-[2-Hydroxy-3-(1-methylethyl)aminopropoxy]benzaldehyde) | F0C344 |  |  |  | n/f | \$520 |
| 1441265 | Metoprolol Related Compound D (50 mg) ( (+/-)N,N-bis-[2-hydroxy-3-[4-(2-methoxyethyl)phe-noxy]propyl](1-methylethyl)amine) | F0C378 |  |  |  | n/f | \$520 |
| 1441298 | Metoprolol Succinate ( $200 \mathrm{mg} \mathrm{)}$ | F0C415 | 0.998 mg/mg (ai) |  |  | [98418-47-4] | \$156 |
| 1441301 | Metoprolol Tarrrate (200 mg) | H1B059 |  |  | $\begin{aligned} & \mathrm{H}(01 / 04) \\ & \mathrm{G}-1(11 / 99) \\ & \hline \end{aligned}$ | [56392-17-7] | \$156 |

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| Cat. No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1441505 | Metrizamide ( 500 mg ) | F |  |  |  | [31112-62-6] | \$156 |
| 1442009 | Metronidazole ( 100 mg ) | 1 |  |  |  | [443-48-1] | \$156 |
| 1443001 | Metyrapone ( 200 mg ) | H |  |  | G (06/01) | [54-36-4] | \$156 |
| 1443205 | Metyrosine ( 200 mg ) | F |  |  |  | [672-87-7] | \$156 |
| 1443250 | Mexiletine Hydrochloride (200 mg) | F-2 |  |  | F-1 (09/02) | [5370-01-4] | \$156 |
| 1443307 | Mezlocillin Sodium ( 350 mg ) | G |  |  |  | [59798-30-0] | \$156 |
| 1443409 | Miconazole ( 200 mg ) | G-1 |  |  | G (07/02) | [22916-47-8] | \$156 |
| 1443500 | Miconazole Nitrate (200 mg) | JoD011 | 0.997 mg/mg (dr) | 2 | $\begin{aligned} & \text { I (06/06) } \\ & \text { H (06/99) } \end{aligned}$ | [22832-87-7] | \$156 |
| 1443850 | Powdered Milk Thistle Extract (250 mg) | FOB321 |  |  |  | [84604-20-6] | \$260 |
| 1443908 | Milrinone ( 500 mg ) | F0C050 |  |  |  | [78415-72-2] | \$260 |
| 1443919 | Milrinone Related Compound A ( 50 mg ) ( $1,6-$ Dihydro-2-methyl-6-oxo(3,4'-bipyridine)-5-carboxamide) | F0C051 |  |  |  | [80047-24-1] | \$487 |
| 1444004 | Minocycline Hydrochloride (200 mg) | 10C178 |  |  | $\begin{array}{\|l} \hline \mathrm{H}-3(04 / 04) \\ \mathrm{H}-2(07 / 02) \\ \hline \end{array}$ | [13614-98-7] | \$156 |
| 1444208 | Minoxidil (125 mg) | H1C168 |  |  | $\begin{aligned} & \mathrm{H}(03 / 04) \\ & \mathrm{G}(05 / 99) \end{aligned}$ | [38304-91-5] | \$124 |
| 1444279 | Mirtazapine ( 350 mg ) | F0D155 | $0.999 \mathrm{mg} / \mathrm{mg}$ (an) | 1 |  | [61337-67-5] | \$800 |
| 1444707 | Mitomycin ( 50 mg ) | K |  |  | J (07/01) | [50-07-7] | \$479 |
| 1445007 | Mitotane ( 500 mg ) | GOC044 |  |  | F (07/04) | [53-19-0] | \$156 |
| 1445200 | Mitoxantrone Hydrochloride ( 400 mg ) |  |  |  | $\begin{aligned} & \mathrm{H}(05 / 05) \\ & \mathrm{G}(03 / 01) \end{aligned}$ | [70476-82-3] | \$498 |
| 1445211 | Mitoxantrone System Suitability Mixture ( 0.3 mg ) | F0D010 |  |  |  | n/f | \$500 |
| 1445459 | Molindone Hydrochloride ( 500 mg ) | F |  |  |  | [15622-65-8] | \$156 |
| 1445470 | Mometasone Furoate (200 mg) | G0B073 |  |  | $\begin{array}{\|l} \hline \text { F-1 (04/03) } \\ \text { F (02/01) } \\ \hline \end{array}$ | [83919-23-7] | \$156 |
| 1445481 | Monensin Sodium (200 mg) | F0B293 |  |  |  | [22373-78-0] | \$156 |
| 1445506 | Monobenzone ( 200 mg ) | F |  |  |  | [103-16-2] | \$156 |
| 1445801 | Mono- and Di-acetylated Monoglycerides ( 200 mg ) | F |  |  |  | [68990-54-5] | \$156 |
| 1446000 | Monoglycerides (125 mg) | H |  |  |  | [68990-53-4] | \$124 |
| 1446804 | Monostearyl Maleate ( 100 mg ) | G |  |  | F-2 (04/00) | [2424-62-6] | \$487 |
| 1446950 | Moricizine Hydrochloride ( $250 \mathrm{mg} \mathrm{)}$ | F1D057 | $0.999 \mathrm{mg} / \mathrm{mg}$ (an) | 2,3 | F (03/05) | [29560-58-5] | \$390 |
| 1447002 | Morphine Monohydrate CII (50 mg) (AS) | G |  |  |  | [6009-81-0] | \$207 |
| 1448005 | Morphine Sulfate CII (500 mg) | M0D016 | $0.999 \mathrm{mg} / \mathrm{mg}$ (an) |  | $\begin{array}{\|l\|} \hline \text { LOB056 (04/05) } \\ \text { K (06/03) } \\ \mathrm{J}-1(07 / 00) \\ \hline \end{array}$ | [6211-15-0] | \$332 |
| 1448504 | Moxalactam Disodium ( 500 mg ) | F-1 |  |  |  | [64953-12-4] | \$156 |
| 1448901 | Mupirocin ( 50 mg ) | F2C158 |  |  | $\begin{array}{\|l} \hline \text { F-1 (12/04) } \\ \text { F (03/02) } \\ \hline \end{array}$ | [12650-69-0] | \$156 |
| 1448923 | Mupirocin Lithium (100 mg) | H0C176 | 926 ug/mg (ai) |  | $\begin{array}{\|l\|} \hline G(03 / 05) \\ F(02 / 01) \\ \hline \end{array}$ | [73346-79-9] | \$156 |
| 1449008 | Myristyl Alcohol (1 g) | G |  |  | F (02/02) | [112-72-1] | \$156 |
| 1449518 | Nabumetone (200 mg) | F0C072 |  |  |  | [42924-53-8] | \$156 |
| 1449530 | Nabumetone Related Compound A (15 mg) (1-(6-Methoxy-2-naphthyl)-but-1-en-3-one) | F0D165 |  | 1 |  | n/f | \$487 |
| 1449700 | Nadolol (200 mg) | G0C308 | $0.995 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | $\begin{aligned} & \text { F-3 (04/05) } \\ & \text { F-2 (04/02) } \end{aligned}$ | [42200-33-9] | \$156 |
| 1450007 | Nafcillin Sodium (200 mg) | H |  |  |  | [7177-50-6] | \$156 |
| 1450404 | Naftifine Hydrochloride ( 200 mg ) | F |  |  |  | [65473-14-5] | \$156 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1451000 | Nalidixic Acid (200 mg) | G |  |  |  | [389-08-2] | \$156 |
| 1452002 | Nalorphine Hydrochloride CIII (250 mg) | 1 |  |  |  | [57-29-4] | \$207 |
| 1453005 | Naloxone (125 mg) | LOB124 |  |  | $\begin{aligned} & \hline \text { K-1 (12/02) } \\ & \text { K (07/01) } \\ & \hline \end{aligned}$ | [465-65-6] | \$124 |
| 1453504 | Naltrexone (200 mg) | H0C150 |  |  | $\begin{array}{\|l} \text { G1B039 (03/04) } \\ \text { G (02/03) } \\ \hline \end{array}$ | [16590-41-3] | \$156 |
| 1453526 | Naltrexone Related Compound A CII (30 mg) (N-(3-butenyl)-noroxymorphone Hydrochloride) | F |  |  |  | n/f | \$207 |
| 1454008 | Nandrolone CIII ( 50 mg ) | F4D144 | $1.00 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | F-3 (04/05) | [434-22-0] | \$560 |
| 1455000 | Nandrolone Decanoate CIII ( $250 \mathrm{mg} \mathrm{)}$ | 1 |  |  |  | [360-70-3] | \$207 |
| 1456003 | Nandrolone Phenpropionate CIII (250 mg) | H |  |  |  | [62-90-8] | \$207 |
| 1457006 | Naphazoline Hydrochloride (200 mg) | K |  |  |  | [550-99-2] | \$156 |
| 1457301 | Naproxen (200 mg) | $\mathrm{I}-1$ |  |  | $\begin{aligned} & \text { I (03/03) } \\ & \text { H-1 (01/01) } \end{aligned}$ | [22204-53-1] | \$156 |
| 1457403 | Naproxen Sodium (200 mg) | I |  |  |  | [26159-34-2] | \$156 |
| 1457469 | Naratriptan Hydrochloride ( 125 mg ) | F0C360 | $0.998 \mathrm{mg} / \mathrm{mg}$ (ai) |  |  | [143388-64-1] | \$208 |
| 1457505 | Natamycin (200 mg) |  |  |  | $\begin{array}{\|l\|} \hline I \text { (06/05) } \\ H(11 / 99) \\ \hline \end{array}$ | [7681-93-8] | \$156 |
| 1458009 | Neomycin Sulfate (200 mg) | L-2 |  |  | $\begin{array}{\|l\|} \hline \text { L-1 (09/01) } \\ \text { L (02/99) } \\ \hline \end{array}$ | [1405-10-3] | \$156 |
| 1459001 | Neostigmine Bromide (200 mg) | G |  |  |  | [114-80-7] | \$156 |
| 1460000 | Neostigmine Methylsulfate ( 200 mg ) | I |  |  | H (07/00) | [51-60-5] | \$156 |
| 1460500 | Netilmicin Sulfate ( 500 mg ) | $10 C 388$ | $653 \mathrm{ug} / \mathrm{mg}$ (dr) |  | $\begin{aligned} & \mathrm{H}(01 / 05) \\ & \mathrm{G}(05 / 02) \\ & \hline \end{aligned}$ | [56391-57-2] | \$156 |
| 1460703 | Nevirapine Anhydrous (100 mg) | FOD159 | $0.997 \mathrm{mg} / \mathrm{mg}$ (ai) | 1 |  | [129618-40-2] | \$156 |
| 1460714 | Nevirapine Hemihydrate ( 100 mg ) | F0D034 |  |  |  | n/f | \$156 |
| 1460725 | Nevirapine Related Compound A ( 15 mg ) (5,11-Dihydro-6H-11-ethyl-4-methyl-dipyrido[3,2-b2',3'-e][1,4]diazepin-6-one) | F0D035 |  |  |  | n/f | \$487 |
| 1460736 | Nevirapine Related Compound B ( 15 mg ) (5,11-Dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one) | F0D033 |  |  |  | n/f | \$487 |
| 1461003 | Niacin (200 mg) | H2C121 |  |  | H-1 (01/05) | [59-67-6] | \$156 |
| 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) | M-1 |  |  | M (02/01) | [98-92-0] | \$156 |
| 1463304 | Nicotine Bitartrate Dihydrate ( 500 mg ) | G1C070 |  | 2 | $\begin{array}{\|l} \hline G(05 / 05) \\ F(05 / 99) \\ \hline \end{array}$ | [6019-06-3] | \$156 |
| 1463508 | Nifedipine ( 125 mg ) | J0B243 |  |  | I-1 (04/04) | [21829-25-4] | \$124 |
| 1463600 | Nifedipine Nitrophenylpyridine Analog ( 25 mg ) | K |  |  | $J$ (04/01) | n/f | \$487 |
| 1463701 | Nifedipine Nitrosophenylpyridine Analog ( 25 mg ) | K |  |  | J (07/02) | n/f | \$487 |
| 1464001 | Nitrofurantoin ( 500 mg ) | $J$ |  |  | I-1 (11/02) | [67-20-9] | \$156 |
| 1465004 | Nitrofurazone ( 200 mg ) | H-1 |  |  | H (09/01) | [59-87-0] | \$156 |
| 1465503 | Nitrofurfural Diacetate ( 100 mg ) | GOD066 | $0.99 \mathrm{mg} / \mathrm{mg}$ (ai) |  | F-1 (12/04) | [92-55-7] | \$487 |
| 1466007 | Nitrofurazone Related Compound A ( 500 mg ) (5-Nitro-2-furfuraldazine) | H0B100 |  |  | G (07/03) | n/f | \$487 |
| 1466506 | Diluted Nitroglycerin (5 ampules, approx. 200 mg of a $0.948 \%$ solution in propylene glycol each) | G |  |  |  | [55-63-0] | \$156 |
| 1467804 | Nizatidine (200 mg) | G |  |  | F-1 (06/00) | [76963-41-2] | \$156 |
| 1467950 | Nonoxynol 9 ( 0.5 mL ) | H-1 |  |  | H (03/02) | [26027-38-3] | \$156 |
| 1468002 | Nonoxynol 10 (200 mg) | F |  |  |  | [26027-38-3] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1468400 | Nordazepam CIV ( 50 mg ) (7-Chloro-1,3-dihy-dro-5-phenyl-2H-1,4-benzodiazepin-2-one) | H1B035 |  |  | $\begin{aligned} & \mathrm{H}(03 / 03) \\ & \mathrm{G}(03 / 00) \end{aligned}$ | [1088-11-5] | \$560 |
| 1468501 | Norepinephrine Bitartrate ( 125 mg ) | I0C381 |  |  | H (04/05) | [69815-49-2] | \$124 |
| 1469005 | Norethindrone ( 200 mg ) | J1B065 |  |  | $\begin{array}{\|l} \hline \mathrm{J}-1(05 / 03) \\ \mathrm{J}(07 / 02) \\ \mathrm{I}-1(03 / 01) \\ \hline \end{array}$ | [68-22-4] | \$156 |
| 1470004 | Norethindrone Acetate (100 mg) | JOB072 |  |  | $\begin{aligned} & \text { I (04/03) } \\ & \mathrm{H}(06 / 99) \end{aligned}$ | [51-98-9] | \$156 |
| 1471007 | Norethynodrel ( 200 mg ) | G |  |  |  | [68-23-5] | \$156 |
| 1471506 | Norfloxacin (200 mg) | H |  |  | G (04/01) | [70458-96-7] | \$156 |
| 1471914 | Norgestimate (200 mg) | F0C086 |  |  |  | [35189-28-7] | \$156 |
| 1472000 | Norgestrel (125 mg) | J0C269 |  |  | $\begin{array}{\|l} \hline \mathrm{I}(07 / 04) \\ \mathrm{H}(05 / 99) \\ \hline \end{array}$ | [6533-00-2] | \$124 |
| 1473002 | Noroxymorphone Hydrochloride CII (50 mg) | H1C177 |  |  | H (11/04) | n/f | \$560 |
| 1474005 | Nortriptyline Hydrochloride ( 200 mg ) | 11D054 | $1.000 \mathrm{mg} / \mathrm{mg}$ (dr) | 2 | $\begin{aligned} & \mathrm{I}(05 / 052) \mathrm{H}(04 / \\ & 00) \\ & \hline \end{aligned}$ | [894-71-3] | \$156 |
| 1474504 | Noscapine ( 500 mg ) | G |  |  |  | [128-62-1] | \$156 |
| 1475008 | Novobiocin ( 200 mg ) |  |  |  | G-2 (05/05) | [303-81-1] | \$156 |
| 1476000 | Nylidrin Hydrochloride ( 200 mg ) | F-2 |  |  |  | [849-55-8] | \$156 |
| 1477003 | Nystatin ( 200 mg ) | N1B004 |  |  | N (01/03) | [1400-61-9] | \$156 |
| 1477900 | Octinoxate ( 500 mg ) (Octyl Methoxycinnamate) | G0C024 |  |  | FOB032 (12/03) | [5466-77-3] | \$156 |
| 1477411 | Octocrylene ( 500 mg ) | G0C211 |  |  | FOB104 (05/04) | [6197-30-4] | \$156 |
| 1477502 | Octoxynol 9 (200 mg) | G |  |  | F-2 (07/00) | [9002-93-1] | \$156 |
| 1477808 | Octyldodecanol (200 mg) | G |  |  | F-1 (07/99) | [5333-42-6] | \$156 |
| 1477943 | Octyl Salicylate (400 mg) | F0B091 |  |  |  | [118-60-5] | \$156 |
| 1478108 | Ofloxacin (200 mg) | F-2 |  |  | F-1 (08/02) | [82419-36-1] | \$156 |
| 1478152 | Oleoyl Polyoxylglycerides (100 mg) | F0C313 |  |  |  | n/f | \$156 |
| 1478505 | Omeprazole (200 mg) | H1B211 |  |  | $\begin{array}{\|l\|} \hline \text { H (05/04) } \\ \text { G-1 (04/02) } \\ \text { G (09/01) } \\ \hline \end{array}$ | [73590-58-6] | \$156 |
| 1478582 | Ondansetron Hydrochloride ( 300 mg ) | G0D154 | $0.993 \mathrm{mg} / \mathrm{mg}(\mathrm{an})$ | 2 | F0C222 (05/05) | [103639-04-9] | \$208 |
| 1478593 | Ondansetron Related Compound A (50 mg) (3[(Dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride) | F0C191 |  |  |  | [119812-29-2] | \$487 |
| 1478618 | Ondansetron Related Compound C ( 50 mg ) (1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4one) | F0C251 |  |  |  | [27397-31-1] | \$487 |
| 1478629 | Ondansetron Related Compound D (50 mg) (1,2,3,9-Tetrahydro-9-methyl-3-methylene-4H-carbazol-4-one) | F0C226 |  |  |  | n/f | \$487 |
| 1479009 | Orphenadrine Citrate (200 mg) | G |  |  | F-4 (05/02) | [4682-36-4] | \$156 |
| 1481000 | Oxacillin Sodium (200 mg) | $J$ |  |  | I (03/02) | [7240-38-2] | \$156 |
| 1481500 | Oxamniquine ( 200 mg ) | F |  |  |  | [21738-42-1] | \$156 |
| 1481703 | Oxamniquine Related Compound A ( 25 mg ) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolinemethyl methanesulfonate) | F |  |  |  | n/f | \$487 |
| 1481805 | Oxamniquine Related Compound B ( 25 mg ) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-5-nitro-6-quinolinemethanol) | F |  |  |  | n/f | \$487 |
| 1482003 | Oxandrolone CIII ( 50 mg ) | G0B220 |  |  | F-4 (07/03) | [53-39-4] | \$207 |
| 1482207 | Oxaprozin (200 mg) | F0C115 |  |  |  | [21256-18-8] | \$156 |
| 1483006 | Oxazepam CIV (200 mg) | G-1 |  |  | G (12/00) | [604-75-1] | \$207 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1483301 | Oxfendazole (200 mg) | F0C128 |  |  |  | [53716-50-0] | \$156 |
| 1483505 | Oxprenolol Hydrochloride ( 200 mg ) | IOC344 |  |  | H (02/05) | [6452-73-9] | \$156 |
| 1484009 | Oxtriphylline ( 500 mg ) | G |  |  |  | [4499-40-5] | \$156 |
| 1485001 | Oxybenzone ( 150 mg ) | H0B263 |  |  | $\begin{aligned} & \text { G (11/03) } \\ & \text { F-2 }(12 / 99) \\ & \hline \end{aligned}$ | [131-57-7] | \$156 |
| 1485103 | Oxybutynin Chloride (200 mg) | G-1 |  |  | G (11/02) | [1508-65-2] | \$156 |
| 1485114 | Oxybutynin Related Compound A ( 100 mg ) (Phenylcyclohexylglycolic Acid) | G |  |  | F-2 (01/00) | [4335-77-7] | \$487 |
| 1485125 | Oxybutynin Related Compound B ( 20 mg ) (Cyclohexyl mandelic acid methyl ester) | F0D061 |  |  |  | [10399-13-0] | \$487 |
| 1485136 | Oxybutynin Related Compound C (20 mg) (4-(Ethylmethylamino)but-2-ynyl(+/-)-2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride) | F0D062 |  |  |  | n/f | \$487 |
| 1485191 | Oxycodone CII (200 mg) | IOB046 |  |  | $\begin{aligned} & \mathrm{H}(01 / 03) \\ & \mathrm{G}-1(01 / 01) \end{aligned}$ | [76-42-6] | \$207 |
| 1486004 | Oxymetazoline Hydrochloride (200 mg) | J0C206 |  |  | I (03/05) | [2315-02-8] | \$156 |
| 1487007 | Oxymetholone CIII (200 mg) | G1B247 |  |  | G (10/03) | [434-07-1] | \$207 |
| 1488000 | Oxymorphone CII ( 500 mg ) | H0B214 |  |  | G (03/03) | [76-41-5] | \$207 |
| 1489002 | Oxyphenbutazone (1 g) | H |  |  |  | [7081-38-1] | \$156 |
| 1490103 | Oxyquinoline Sulfate (200 mg) | F-1 |  |  | F (07/02) | [134-31-6] | \$156 |
| 1491004 | Oxytetracycline (200 mg) | J0C084 | 913 ug/mg (ai) |  | I-1 (10/04) | [6153-64-6] | \$156 |
| 1491300 | Oxytocin (5 vials, 46 USP units per vial) | F |  |  |  | [50-56-6] | \$156 |
| 1491332 | Paclitaxel ( 200 mg ) | F0C180 |  |  |  | [33069-62-4] | \$1,508 |
| 1491343 | Paclitaxel Related Compound A (20 mg) (Cephalomannine) | F0C179 |  |  |  | [71610-00-9] | \$754 |
| 1491354 | Paclitaxel Related Compound B (20 mg) (10-Deacetyl-7-epipaclitaxel) | F0C181 |  |  |  | nf | \$754 |
| 1491503 | Padimate O ( 300 mg ) | H0B154 |  |  | G (04/03) | [21245-02-3] | \$156 |
| 1492007 | Palmitic Acid ( 500 mg ) | 1 |  |  |  | [57-10-3] | \$156 |
| 1493000 | Pamoic Acid (250 mg) | G-4 |  |  | G-3 (01/03) | [130-85-8] | \$156 |
| 1494057 | Pancreatin Amylase and Protease (2 g) | I |  |  | H (10/00) | [8049-47-6] | \$156 |
| 1494079 | Pancreatin Lipase (2 g) | 1 |  |  | H-1 (03/01) | [8049-47-6] | \$156 |
| 1494501 | Panthenol, Racemic ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | F-1 (02/00) | [16485-10-2] | \$156 |
| 1494807 | Pantolactone ( 500 mg ) | F |  |  |  | [599-04-2] | \$487 |
| 1495005 | Papain (1 g) | I0C389 | 6700 USP units/ <br> mg (ai) | 2,6 | $\begin{aligned} & \mathrm{H}(06 / 04) \\ & \mathrm{G}(12 / 01) \\ & \hline \end{aligned}$ | [9001-73-4] | \$156 |
| 1496008 | Papaverine Hydrochloride (200 mg) | H |  |  |  | [61-25-6] | \$156 |
| 1497000 | Paramethadione ( 500 mg ) | G |  |  |  | [115-67-3] | \$156 |
| 1498003 | Paramethasone Acetate (200 mg) | G |  |  | F-1 (05/01) | [1597-82-6] | \$156 |
| 1498706 | Parbendazole (200 mg) | F |  |  |  | [14255-87-9] | \$156 |
| 1499006 | Pargyline Hydrochloride (200 mg) | F-1 |  |  |  | [306-07-0] | \$156 |
| 1500003 | Paromomycin Sulfate ( 125 mg ) | G |  |  | F-3 (01/01) | [1263-89-4] | \$156 |
| 1500218 | Paroxetine Hydrochloride ( 350 mg ) | G0D003 | $0.972 \mathrm{mg} / \mathrm{mg}$ (ai) |  | FOB288 (09/04) | [110429-35-1] | \$156 |
| 1500229 | Paroxetine Related Compound A ( 20 mg ) (trans-4-(p-methoxyphenyl)-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine Hydrochloride) | F0B172 |  |  |  | n/f | \$487 |
| 1500230 | Paroxetine Related Compound B ( 20 mg ) (trans-4-phenyl-3-([(3,4-methylenedioxy)phenoxy]methylpiperidine acetate) | F0B189 |  |  |  | n/f | \$487 |
| 1500240 | Paroxetine Related Compound C (15 mg) ((+)-trans-Paroxetine hydrochloride) | G0D053 | $0.96 \mathrm{mg} / \mathrm{mg}$ (ai) |  | FOB192 (05/05) | [130855-30-0] | \$487 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1500251 | Paroxetine Related Compound D (15 mg) ((-)-cis-Paroxetine hydrochloride) | F0C228 |  |  |  | n/f | \$487 |
| 1500400 | Parthenolide ( 25 mg ) | F |  |  |  | [20554-84-1] | \$156 |
| 1500502 | Particle Count Set (2 blanks and 2 suspensions) | 1 |  |  | H (09/02) | n/f | \$487 |
| 1500808 | Penbutolol Sulfate (200 mg) | F |  |  |  | [38363-32-5] | \$156 |
| 1501006 | Penicillamine (200 mg) | H1B164 |  |  | H (01/04) | [52-67-5] | \$156 |
| 1501108 | Penicillamine Disulfide ( 100 mg ) | H |  |  | G (07/00) | [20902-45-8] | \$487 |
| 1502009 | Penicillin G Benzathine (200 mg) | J |  |  |  | [41372-02-5] | \$156 |
| 1502508 | Penicillin G Potassium ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  |  | H (02/99) | [113-98-4] | \$156 |
| 1502552 | Penicillin G Procaine ( $200 \mathrm{mg} \mathrm{)}$ | G0C271 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (08/04) } \\ \text { F (03/99) } \\ \hline \end{array}$ | [6130-64-9] | \$156 |
| 1502701 | Penicillin G Sodium ( 200 mg ) | L-3 |  |  | L-2 (09/01) | [69-57-8] | \$156 |
| 1504489 | Penicillin V ( 200 mg ) | F |  |  |  | [87-08-1] | \$156 |
| 1504503 | Penicillin V Potassium ( 200 mg ) | H0C213 |  |  | $\begin{aligned} & \text { G-1 (06/04) } \\ & \text { G }(06 / 00) \\ & \hline \end{aligned}$ | [132-98-9] | \$156 |
| 1505007 | Pentazocine CIV (500 mg) | 10 C 418 | $0.998 \mathrm{mg} / \mathrm{mg}$ (dr) |  | $\begin{aligned} & \mathrm{H}(01 / 05) \\ & \mathrm{G}-1(11 / 00) \end{aligned}$ | [359-83-1] | \$207 |
| 1505506 | Pentetic Acid (100 mg) | F-1 |  |  | F (09/01) | [67-43-6] | \$156 |
| 1507002 | Pentobarbital CII (200 mg) | H3C144 |  |  | $\begin{aligned} & \mathrm{H}-2(07 / 04) \\ & \mathrm{H}-1(08 / 02) \\ & \hline \end{aligned}$ | [76-74-4] | \$207 |
| 1508901 | Pentoxifylline (200 mg) | F0B202 |  |  |  | [6493-05-6] | \$156 |
| 1510007 | Pepsin (5 g) | F-2 |  |  |  | [9001-75-6] | \$156 |
| 1510801 | Perflubron ( 0.5 mL ) | G0C103 |  |  | F (04/04) | [423-55-2] | \$156 |
| 1510845 | Pergolide Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | F1C225 |  |  | F (07/04) | [66104-23-2] | \$194 |
| 1510867 | Pergolide Sulfoxide ( 50 mg ) | F0B014 |  |  |  | [72822-01-6] | \$194 |
| 1511000 | Perphenazine ( 200 mg ) | JOB249 |  |  | 1 (10/03) | [58-39-9] | \$156 |
| 1511203 | Perphenazine Sulfoxide ( 100 mg ) | G-1 |  |  | G (07/02) | [10078-25-8] | \$487 |
| 1512002 | Phenacemide ( 250 mg ) | F |  |  |  | [63-98-9] | \$156 |
| 1513005 | Phenacetin ( 500 mg ) | H-1 |  |  | H (09/00) | [62-44-2] | \$156 |
| 1514008 | Phenacetin Melting Point Standard ( 500 mg ) (Approximately 135 degrees) | H3A009 |  |  | $\begin{array}{\|l\|l} \hline \mathrm{H}-2(02 / 03) \\ \mathrm{H}-1(06 / 01) \\ \hline \end{array}$ | [62-44-2] | \$92 |
| 1515000 | Phenazopyridine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H0C426 | $0.998 \mathrm{mg} / \mathrm{mg}$ (dr) |  | G-4 (12/04) | [136-40-3] | \$156 |
| 1516003 | Phencyclidine Hydrochloride CII ( 25 mg ) (AS) | G1B025 |  |  | G (12/02) | [956-90-1] | \$207 |
| 1516502 | Phendimetrazine Tartrate CIII ( 350 mg ) | G |  |  | F (01/01) | [50-58-8] | \$207 |
| 1517006 | Phenelzine Sulfate (200 mg) | G |  |  | F-1 (04/02) | [156-51-4] | \$156 |
| 1517301 | D-Phenethicillin Potassium (200 mg) | F |  |  |  | n/f | \$487 |
| 1517607 | L-Phenethicillin Potassium (200 mg) | F |  |  |  | n/f | \$156 |
| 1520000 | Phenformin Hydrochloride (200 mg) | G |  |  |  | [834-28-6] | \$156 |
| 1522006 | Phenindione ( 250 mg ) | F |  |  |  | [83-12-5] | \$156 |
| 1522301 | Pheniramine Maleate ( 100 mg ) | F1C342 |  |  | F (08/04) | [132-20-7] | \$156 |
| 1523009 | Phenmetrazine Hydrochloride CII (200 mg) | F-2 |  |  |  | [1707-14-8] | \$207 |
| 1524001 | Phenobarbital CIV (200 mg) | J |  |  |  | [50-06-6] | \$207 |
| 1524908 | Phenolphthalein ( $250 \mathrm{mg} \mathrm{)}$ | F-3 |  |  |  | [77-09-8] | \$156 |
| 1525004 | Phenolsulfonphthalein ( 100 mg ) | F-2 |  |  |  | [143-74-8] | \$156 |
| 1526007 | Phenoxybenzamine Hydrochloride ( $250 \mathrm{mg} \mathrm{)}$ | G |  |  |  | [63-92-3] | \$156 |
| 1528002 | Phensuximide ( 500 mg ) | G |  |  | F-1 (03/01) | [86-34-0] | \$156 |
| 1528501 | Phentermine Hydrochloride CIV (200 mg) | H0B309 |  |  | G (08/03) | [1197-21-3] | \$207 |
| 1529005 | Phentolamine Hydrochloride ( 300 mg ) | F |  |  |  | [73-05-2] | \$156 |
| 1530004 | Phentolamine Mesylate ( $200 \mathrm{mg} \mathrm{)}$ | 1 |  |  |  | [65-28-1] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1530503 | L-Phenylalanine (200 mg) | H |  |  | G (02/02) | [63-91-2] | \$156 |
| 1530809 | Phenylbenzimidazole Sulfonic Acid (200 mg) | F |  |  |  | [27503-81-7] | \$156 |
| 1531007 | Phenylbutazone (250 mg) | J0A008 |  |  | I-1 (02/03) | [50-33-9] | \$156 |
| 1533002 | Phenylephrine Hydrochloride (125 mg) | K1C290 |  |  | $\begin{aligned} & \hline \mathrm{K}(03 / 05) \\ & \mathrm{J}(02 / 99) \\ & \hline \end{aligned}$ | [61-76-7] | \$124 |
| 1533308 | 5-Phenylhydantoin ( 100 mg ) | F |  |  |  | [89-24-7] | \$487 |
| 1533851 | Phenylpropanediol ( 100 mg ) | F |  |  |  | n/f | \$487 |
| 1533909 | Phenylpropanolamine Bitartrate ( 100 mg ) (List Chemical) | F |  |  |  | [67244-90-0] | \$156 |
| 1534005 | Phenylpropanolamine Hydrochloride ( 250 mg ) (List Chemical) | J |  |  | I (02/02) | [154-41-6] | \$156 |
| 1535008 | Phenytoin (200 mg) | 12B233 |  |  | $\begin{array}{\|l\|} \hline \text { I-1 (03/04) } \\ \text { I (04/01) } \\ \hline \end{array}$ | [57-41-0] | \$156 |
| 1535507 | Phenytoin Sodium (200 mg) | H |  |  | G (05/99) | [630-93-3] | \$156 |
| 1535019 | Phenytoin Related Compound A (50 mg) (2,2Diphenylglycine) | F0C155 |  |  |  | [3060-50-2] | \$487 |
| 1535020 | Phenytoin Related Compound B ( 50 mg ) (al-pha-((aminocarbonyl)amino)-alpha-phenyl benzeneacetic acid) | FOC157 |  |  |  | [6802-95-5] | \$487 |
| 1535700 | Phosphated Riboflavin ( 100 mg ) | G1B286 |  |  | G (07/04) | [6184-17-4] | \$124 |
| 1537003 | Physostigmine Salicylate ( 200 mg ) | H-1 |  |  | H (06/00) | [57-64-7] | \$156 |
| 1538006 | Phytonadione (500 mg) (Vitamin K1) | N0B303 |  |  | $\begin{aligned} & \text { M-1 (07/04) } \\ & \mathrm{M}(09 / 01) \\ & \hline \end{aligned}$ | [84-80-0] | \$156 |
| 1538505 | Pilocarpine ( 300 mg ) | F |  |  |  | [92-13-7] | \$156 |
| 1538902 | Pilocarpine Hydrochloride ( 200 mg ) | H |  |  |  | [54-71-7] | \$156 |
| 1539009 | Pilocarpine Nitrate (200 mg) | 1 |  |  |  | [148-72-1] | \$156 |
| 1539508 | Pimozide ( 200 mg ) | G |  |  |  | [2062-78-4] | \$156 |
| 1539701 | Pindolol ( 200 mg ) | IOB210 |  |  | H-1 (12/04) | [13523-86-9] | \$156 |
| 1541000 | Piperacetazine ( 250 mg ) | F |  |  |  | [3819-00-9] | \$156 |
| 1541500 | Piperacillin ( 500 mg ) | H |  |  |  | [66258-76-2] | \$156 |
| 1541703 | Piperazine Adipate ( 200 mg ) | F |  |  |  | [142-88-1] | \$156 |
| 1541805 | Piperazine Citrate ( 200 mg ) | F |  |  |  | [144-29-6] | \$156 |
| 1541907 | Piperazine Dihydrochloride ( 200 mg ) | F |  |  |  | [142-64-3] | \$156 |
| 1542003 | Piperazine Phosphate ( 200 mg ) | F |  |  |  | [14538-56-8] | \$156 |
| 1543006 | Piperidolate Hydrochloride ( 200 mg ) | F |  |  |  | [129-77-1] | \$156 |
| 1544508 | Piroxicam (200 mg) | H |  |  | G (01/99) | [36322-90-4] | \$156 |
| 1545205 | Plicamycin ( 50 mg ) | H |  |  | G (04/00) | [18378-89-7] | \$479 |
| 1545409 | Polacrilex Resin (100 mg) | F |  |  |  | n/f | \$156 |
| 1545500 | Polacrilin Potassium (200 mg) | F-2 |  |  | F-1 (09/00) | n/f | \$156 |
| 1546106 | Poloxalene ( 500 mg ) | F0C009 |  |  |  | [9003-11-6] | \$156 |
| 1546300 | Polydimethylsiloxane ( 500 mg ) | H0CO2O |  |  | $\begin{array}{ll} \text { G-5 }(05 / 04) \\ \text { G-4 }(06 / 01) \\ \hline \end{array}$ | [9016-00-6] | \$156 |
| 1546707 | Polyethylene, High Density (3 strips) | G1D115 |  | 2 | $\begin{array}{\|l\|} \hline \text { G (06/05) } \\ \text { F-1 (04/01) } \\ \hline \end{array}$ | [9002-88-4] | \$156 |
| 1546809 | Polyethylene, Low Density (3 strips) | G1B166 |  |  | $\begin{array}{\|l} \hline \text { G (06/04) } \\ \text { F-2 (12/99) } \\ \hline \end{array}$ | [9002-88-4] | \$156 |
| 1546853 | Polyethylene Oxide ( 100 mg ) | F-1 |  |  |  | [25322-68-3] | \$156 |
| 1546900 | Polyethylene Terephthalate (PET) (3 Strips) | F |  |  |  | [25038-59-9] | \$156 |
| 1546922 | Polyethylene Terephthalate G (PETG) (3 Strips) | F |  |  |  | [25640-14-6] | \$156 |
| 1547007 | Polymyxin B Sulfate (200 mg) | K |  |  | J-1 (09/99) | [1405-20-5] | \$156 |
| 1547404 | Polyoxyl 50 Stearate ( 200 mg ) | F |  |  |  | [9004-99-3] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1547903 | Polyoxyl 40 Stearate (200 mg) | F-2 |  |  | F-1 (05/00) | [9004-99-3] | \$156 |
| 1547925 | Polysorbate 20 (2 g) (AS) | FOD130 |  | 1 |  | [9005-64-5] | \$156 |
| 1547947 | Polysorbate 60 (2 g) (AS) | F0D131 |  | 1 |  | [9005-67-8] | \$156 |
| 1547969 | Polysorbate 80 (2 g) (AS) | F0D132 |  | 1 |  | [9005-65-6] | \$156 |
| 1548000 | Polythiazide (200 mg) | F-1 |  |  |  | [346-18-9] | \$156 |
| 1548101 | Potassium Benzoate (1 g) (AS) | F0D161 | $0.999 \mathrm{mg} / \mathrm{mg}$ (an) | 1 |  | [582-25-2] | \$156 |
| 1548134 | Potassium Bicarbonate (1 g) (AS) | F0D074 | 99.9\% (dr) |  |  | [298-14-6] | \$156 |
| 1548167 | Potassium Carbonate (1 g) (AS) | F0D075 | 99.8\% (dr) | 1 |  | [584-08-7] | \$156 |
| 1548190 | Potassium Chloride (1 g) (AS) | F0D127 | 100.0\% (dr) | 1 |  | [7447-40-7] | \$156 |
| 1550001 | Potassium Gluconate (200 mg) | H0C064 |  |  | G (06/04) | [299-27-4] | \$156 |
| 1551004 | Potassium Guaiacolsulfonate ( 500 mg ) | J0B292 |  |  | $\begin{array}{\|l\|l} \hline \text { I-1 (07/03) } \\ \text { I (11/00) } \\ \hline \end{array}$ | [78247-49-1] | \$156 |
| 1548280 | Potassium lodide (1 g) (AS) | F0D078 | 100.0\% (dr) | 1 |  | [7681-11-0] | \$156 |
| 1551150 | Potassium Sucrose Octasulfate ( 300 mg ) | IOB283 |  |  | $\begin{array}{\|l\|} \hline \text { H0B119 (04/04) } \\ \text { G-1 (04/03) } \\ \text { G (02/01) } \\ \hline \end{array}$ | [76578-81-9] | \$156 |
| 1551300 | Potassium Trichloroammineplatinate ( $20 \mathrm{mg} \mathrm{)}$ | IOD022 | $0.84 \mathrm{mg} / \mathrm{mg}$ (dr) |  | $\begin{aligned} & \hline \text { H0B149 (12/04) } \\ & \text { G-1 (01/03) } \\ & \text { G (07/99) } \\ & \hline \end{aligned}$ | [13820-91-2] | \$487 |
| 1551503 | Povidone ( 100 mg ) | F-1 |  |  | F (11/01) | [9003-39-8] | \$156 |
| 1553000 | Pralidoxime Chloride (200 mg) | G-2 |  |  | $\begin{aligned} & \text { G-1 (03/01) } \\ & \text { G (08/99) } \\ & \hline \end{aligned}$ | [51-15-0] | \$156 |
| 1554002 | Pramoxine Hydrochloride ( 500 mg ) | 1 |  |  | H (11/02) | [637-58-1] | \$156 |
| 1554501 | Prazepam CIV ( 500 mg ) | G0C066 |  |  | F-1 (11/02) | [2955-38-6] | \$207 |
| 1554603 | Praziquantel ( 200 mg ) | G |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-3 }(07 / 02) \\ \text { F-2 }(09 / 00) \\ \hline \end{array}$ | [55268-74-1] | \$156 |
| 1554658 | Praziquantel Related Compound A (50 mg) (2-benzoyl-1,2,3,6,7,11b-hexahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one) | F-1 |  |  |  | n/f | \$487 |
| 1554669 | Praziquantel Related Compound B ( 50 mg ) (2-(cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one) | F-2 |  |  | F-1 (06/00) | n/f | \$487 |
| 1554670 | Praziquantel Related Compound C (50 mg) (2-(N-formylhexahydrohippuroyl)-1,2,3,4-tetrahy-droisoquinolin-1-one) | F-2 |  |  | F-1 (06/00) | n/f | \$487 |
| 1554705 | Prazosin Hydrochloride ( 500 mg ) | H0B254 |  |  | $\begin{aligned} & \text { G-1 (02/05) } \\ & G(02 / 01) \end{aligned}$ | [19237-84-4] | \$156 |
| 1555005 | Prednisolone (200 mg) | M |  |  | L-1 (04/02) | [50-24-8] | \$156 |
| 1556008 | Prednisolone Acetate (200 mg) | $J$ |  |  | I-1 (02/02) | [52-21-1] | \$156 |
| 1556507 | Prednisolone Hemisuccinate ( 125 mg ) | H-1 |  |  | H (02/99) | [2920-86-7] | \$124 |
| 1558003 | Prednisolone Tebutate ( 200 mg ) | F |  |  |  | [7681-14-3] | \$156 |
| 1559006 | Prednisone ( 250 mg ) | L1B251 |  |  | $\begin{array}{\|l\|} \hline \text { L (11/04) } \\ \text { K-1 (01/02) } \\ \text { K (02/00) } \\ \hline \end{array}$ | [53-03-2] | \$156 |
| 1559505 | Prednisone Tablets (Dissolution Calibrator, Disintegrating) (30 tablets) | O0C056 |  |  | $\begin{array}{\|l\|l\|} \hline N(06 / 04) \\ M(09 / 02) \\ L(11 / 00) \\ \hline \end{array}$ | [53-03-2] | \$180 |
| 1561008 | Prilocaine Hydrochloride (200 mg) | F3B215 |  |  | F-2 (03/04) | [1786-81-8] | \$156 |
| 1561507 | Primaquine Phosphate ( $200 \mathrm{mg} \mathrm{)}$ | F-1 |  |  |  | [63-45-6] | \$156 |
| 1562000 | Primidone ( 200 mg ) | G |  |  | F-6 (04/99) | [125-33-7] | \$156 |
| 1563003 | Probenecid ( 200 mg ) | IOA011 |  |  | H-1 (03/03) | [57-66-9] | \$156 |
| 1563309 | Probucol ( 200 mg ) | G |  |  | F-1 (01/02) | [23288-49-5] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1563320 | Probucol Related Compound A ( 25 mg ) (2,2',6,6'-tetra-tert-butyldiphenoquinone) | F-2 |  |  | F-1 (11/04) | n/f | \$487 |
| 1563331 | Probucol Related Compound B ( 25 mg ) (4,4'-dithio-bis(2,6-di-tert-butylphenol)) | F-2 |  |  | F-1 (08/03) | n/f | \$487 |
| 1563342 | Probucol Related Compound C ( 25 mg ) (4-[(3,5-di-tert-butyl-2-hydroxyphenylthio)isopropy-lidenethio]-2,6-di-tert-butylphenol) | F-2 |  |  | F-1 (05/00) | n/f | \$487 |
| 1563502 | Procainamide Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H1B117 |  |  | H (04/03) | [614-39-1] | \$156 |
| 1564006 | Procaine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  |  | [51-05-8] | \$156 |
| 1565009 | Procarbazine Hydrochloride ( 200 mg ) | F |  |  |  | [366-70-1] | \$156 |
| 1566001 | Prochlorperazine Maleate ( 200 mg ) | H-1 |  |  |  | [84-02-6] | \$156 |
| 1567004 | Procyclidine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  |  | [1508-76-5] | \$156 |
| 1568007 | Progesterone (200 mg) | H6C088 |  |  | $\begin{array}{\|l\|l} \hline \text { H-5 }(11 / 04) \\ \text { H-4 (07/02) } \\ \hline \end{array}$ | [57-83-0] | \$124 |
| 1568506 | L-Proline (200 mg) | F-2 |  |  | F-1 (01/02) | [147-85-3] | \$156 |
| 1569000 | Promazine Hydrochloride ( 200 mg ) | H0B261 |  |  | G (10/03) | [53-60-1] | \$156 |
| 1570009 | Promethazine Hydrochloride ( 500 mg ) | K |  |  | J-1 (10/00) | [58-33-3] | \$156 |
| 1570304 | Propafenone Hydrochloride ( 200 mg ) | G1C184 |  |  | $\begin{aligned} & \hline \text { G (12/04) } \\ & \text { F-1 }(01 / 01) \\ & \hline \end{aligned}$ | [34183-22-7] | \$156 |
| 1570508 | Propantheline Bromide ( $200 \mathrm{mg} \mathrm{)}$ | IOA019 |  |  | H (11/02) | [50-34-0] | \$156 |
| 1329505 | Propantheline Bromide Related Compound A ( 50 mg ) (9-Hydroxypropantheline bromide) | G0B258 |  |  | F-1 (12/03) | n/f | \$487 |
| 1571001 | Proparacaine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  |  | [5875-06-9] | \$156 |
| 1572208 | Propionic Acid ( $1.5 \mathrm{~mL} /$ ampule; 3 ampules) (AS) | F0D029 | 99.8 \% w/w (ai) | 1 |  | [79-09-4] | \$156 |
| 1573007 | Propoxycaine Hydrochloride (200 mg) | F |  |  |  | [550-83-4] | \$156 |
| 1574000 | Propoxyphene Hydrochloride CII (1 g) | LOC285 |  |  | K (09/04) | [1639-60-7] | \$207 |
| 1575002 | Propoxyphene Napsylate CII (1 g) | H1C323 | $0.993 \mathrm{mg} / \mathrm{mg}$ (an) | 2 | H (05/05) | [26570-10-5] | \$207 |
| 1575206 | Propoxyphene Related Compound A ( 50 mg ) (alpha-d-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride) | G-5 |  |  |  | n/f | \$487 |
| 1008002 | Propoxyphene Related Compound B ( 50 mg ) (alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphe-nyl-3-methylbutane) | H0D012 | $0.94 \mathrm{mg} / \mathrm{mg}$ (ai) | 2,8 | G-3 (05/05) | n/f | \$487 |
| 1576005 | Propranolol Hydrochloride ( 200 mg ) | 10 C 170 |  |  | $\begin{aligned} & \mathrm{H}-1(12 / 04) \\ & \mathrm{H}(09 / 01) \end{aligned}$ | [318-98-9] | \$156 |
| 1576504 | Propylene Carbonate (200 mg) | F |  |  |  | [108-32-7] | \$156 |
| 1576708 | Propylene Glycol (1 mL) | $10 \mathrm{C022}$ |  |  | $\begin{aligned} & \mathrm{H}(03 / 04) \\ & \mathrm{G}(02 / 99) \\ & \hline \end{aligned}$ | [57-55-6] | \$156 |
| 1576720 | Propylene Glycol Diacetate ( 250 mg ) | F |  |  |  | [623-84-7] | \$156 |
| 1576800 | Propyl Gallate ( 200 mg ) | G-1 |  |  | G (01/03) | [121-79-9] | \$156 |
| 1577008 | Propylparaben ( $200 \mathrm{mg} \mathrm{)}$ | I |  |  | H (02/00) | [94-13-3] | \$156 |
| 1578000 | Propylthiouracil (200 mg) | G |  |  | F-1 (01/00) | [51-52-5] | \$156 |
| 1578500 | Prostaglandin A1 ( 25 mg ) | H0B108 |  |  | G (04/03) | [14152-28-4] | \$529 |
| 1580002 | Protriptyline Hydrochloride (200 mg) | F-1 |  |  |  | [1225-55-4] | \$156 |
| 1581005 | Pseudoephedrine Hydrochloride ( 125 mg ) (List Chemical) | J1B203 |  |  | $\begin{array}{\|l\|l} \hline J(01 / 04) \\ I(05 / 02) \\ \hline \end{array}$ | [345-78-8] | \$124 |
| 1581504 | Pseudoephedrine Sulfate ( 200 mg ) (List Chemical) | G1C135 |  |  | $\begin{aligned} & \hline \mathrm{G}(06 / 04) \\ & \mathrm{F}-2(05 / 02) \\ & \hline \end{aligned}$ | [7460-12-0] | \$156 |
| 1584003 | Pyrantel Pamoate (1 g) | 1 |  |  | H-1 (04/00) | [22204-24-6] | \$156 |
| 1585006 | Pyrazinamide ( 200 mg ) | G |  |  | F-2 (02/00) | [98-96-4] | \$156 |
| 1586009 | Pyridostigmine Bromide (200 mg) | I0C324 | $0.999 \mathrm{mg} / \mathrm{mg}$ (dr) |  | H (01/05) | [101-26-8] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) | P |  |  | O-1 (04/00) | [58-56-0] | \$156 |
| 1588004 | Pyrilamine Maleate ( $200 \mathrm{mg} \mathrm{)}$ | IOB276 |  |  | H (12/03) | [59-33-6] | \$156 |
| 1589007 | Pyrimethamine ( $200 \mathrm{mg} \mathrm{)}$ | H |  |  | G (07/02) | [58-14-0] | \$156 |
| 1592001 | Pyrvinium Pamoate ( 500 mg ) | G |  |  |  | [3546-41-6] | \$156 |
| 1592205 | Quazepam CIV (200 mg) | F |  |  |  | [36735-22-5] | \$207 |
| 1592227 | Quazepam Related Compound A ( 30 mg ) (7-Chloro-1-(2,2,2-trifluoroethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one) | F |  |  |  | n/f | \$487 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 |  |  |  | [6151-25-3] | \$156 |
| 1593004 | Quinacrine Hydrochloride ( 200 mg ) | F-1 |  |  |  | [6151-30-0] | \$156 |
| 1593412 | Quinapril Related Compound A ( 50 mg ) (Ethyl[3S-[2(R*),3a,11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-pheny-lethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate) | F0C114 |  |  |  | [103733-49-9] | \$487 |
| 1593423 | Quinapril Related Compound B ( 50 mg ) (3Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetra-hydro-,[3S-[2[R*( $\left.\left.\left.\left.\left.\mathrm{R}^{*}\right)\right], 3 \mathrm{R}^{*}\right]\right]-\right)$ | F0C116 |  |  |  | [85441-60-7] | \$487 |
| 1594007 | Quinethazone ( 1.5 g ) | G |  |  |  | [73-49-4] | \$156 |
| 1594506 | Quinic Acid ( 200 mg ) | F |  |  |  | [77-95-2] | \$156 |
| 1595000 | Quinidine Gluconate (200 mg) | H1A028 |  |  | H (04/03) | [7054-25-3] | \$156 |
| 1595509 | Quinidine Sulfate ( 500 mg ) | H-1 |  |  | H (12/99) | [6591-63-5] | \$156 |
| 1596807 | Quinine Hydrochloride Dihydrate (1 g) | FOC108 |  |  |  | [6119-47-7] | \$156 |
| 1597005 | Quinine Sulfate (200 mg) | H |  |  |  | [6119-70-6] | \$156 |
| 1597504 | Quininone ( 50 mg ) | H0B034 |  |  | G-1 (03/04) | [84-31-1] | \$487 |
| 1598008 | 3-Quinuclidinyl Benzilate ( 25 mg ) (FOR U.S. SALE ONLY) | H |  |  | G (11/01) | [6581-06-2] | \$515 |
| 1598303 | Ramipril ( 200 mg ) | F0C099 |  |  |  | [87333-19-5] | \$156 |
| 1598314 | Ramipril Related Compound A ( 20 mg ) ((2S,3aS,6aS)-1-[(S)2-[[(S)1-(methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydro-cyclopenta[b]pyrrole-2-carboxylic acid) | F0C100 |  |  |  | [91224-69-0] | \$487 |
| 1598405 | Ranitidine Hydrochloride (200 mg) | H0B268 |  |  | G (01/04) | [66357-59-3] | \$156 |
| 1598507 | Ranitidine Related Compound A (50 mg) (5-[[( $2-$ aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine hemifumarate) | H1B137 |  |  | $\begin{aligned} & \mathrm{H}(01 / 04) \\ & \mathrm{G}(01 / 01) \end{aligned}$ | [91224-69-0] | \$487 |
| 1598609 | Ranitidine Related Compound B $(50 \mathrm{mg})\left(\mathrm{N}, \mathrm{N}^{\prime}-\right.$ bis[2-[[[5-[(dimethylamino)methyl]-2-furanyl]-methyl]thio]ethyl]-2-nitro-1,1-ethenediamine) | G |  |  | F-4 (04/02) | [72126-78-4] | \$487 |
| 1598700 | Ranitidine Related Compound C $(50 \mathrm{mg})(\mathrm{N}-[2-$ [[[5-[(dimethylamino)methyl]-2-furanyl]methyl]-sulfinyl]ethyl]-N-methyl-2-nitro-1,1-ethenediamine) | 11B136 |  |  | $\begin{aligned} & \hline \text { I (01/04) } \\ & \text { H (05/01) } \end{aligned}$ | [73851-70-4] | \$487 |
| 1599000 | Rauwolfia Serpentina (15 g) | G |  |  |  | [8063-17-0] | \$156 |
| 1599500 | Powdered Red Clover Extract ( 500 mg ) | F0C188 |  |  |  | n/f | \$260 |
| 1600813 | Repaglinide (200 mg) | FOB265 |  |  |  | [135062-02-1] | \$156 |
| 1600824 | Repaglinide Related Compound A (50 mg) ((S)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butylamine, N -acetyl-L-glutamate salt) | F0B267 |  |  |  | n/f | \$487 |
| 1600835 | Repaglinide Related Compound B ( 50 mg ) ( $3-$ Ethoxy-4-ethoxycarbonyl-phenylacetic acid) | F0B269 |  |  |  | [99469-99-5] | \$487 |

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## USP Reference Standards and Authentic Substances

| Cat. No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | $\begin{array}{\|l} \text { CAS } \\ \text { No. } \end{array}$ | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1600846 | Repaglinide Related Compound C (25 mg) ((S)-2-Ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)phe-nyl]ethyl]aminoj-2-oxoethyl] benzoic acid) | FOB271 |  |  |  | [107362-12-9] | \$487 |
| 1601000 | Reserpine (200 mg) | O0C106 |  |  | N (06/03) | [50-55-5] | \$156 |
| 1601102 | Residual Solvents Mixture - Class 1 ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C407 |  |  |  | n/f | \$156 |
| 1601146 | Residual Solvent Class 1 - Benzene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C408 | $10.1 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601168 | Residual Solvent Class 1 - Carbon Tetrachloride ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C409 | 19.7 mg/mL (ai) |  |  | n/f | \$156 |
| 1601180 | Residual Solvent Class 1-1,2-Dichloroethane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C412 | 25.1 mg/mL (ai) |  |  | n/f | \$156 |
| 1601204 | Residual Solvent Class 1-1,1-Dichloroethene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C411 | $37.9 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601226 | Residual Solvent Class 1-1,1,1-Trichloroethane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | FOC410 | $49.1 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601340 | Residual Solvent Class 2 - Acetonitrile ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D049 | $2.00 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601361 | Residual Solvent Class 2 - Chlorobenzene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D048 | $1.81 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601420 | Residual Solvent Class 2-1,2-Dichloroethene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D040 | 9.2 mg/mL (ai) |  |  | n/f | \$156 |
| 1601521 | Residual Solvent Class 2-1,4-Dioxane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D050 | $1.89 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601623 | Residual Solvent Class 2 - Methanol ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D045 | $14.8 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601689 | Residual Solvent Class 2 - Methylcyclohexane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | FOD044 | $5.46 \mathrm{mg} / \mathrm{mL}$ (ai) | 1 |  | n/f | \$156 |
| 1601441 | Residual Solvent Class 2 - Methylene Chloride ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D046 | $2.90 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601770 | Residual Solvent Class 2 - Tetrahydrofuran ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D043 | $3.49 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601805 | Residual Solvent Class 2 - Toluene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | FOD042 | $4.39 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1601849 | Residual Solvent Class 2 - Xylenes ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D041 | $10.7 \mathrm{mg} / \mathrm{mL}$ (ai) |  |  | n/f | \$156 |
| 1602003 | Resorcinol ( 200 mg ) | H-1 |  |  | H (04/01) | [108-46-3] | \$156 |
| 1602706 | Ribavirin (200 mg) | H1C335 |  |  | $\begin{array}{\|l\|} \hline \mathrm{H}(03 / 05) \\ \mathrm{G}(08 / 01) \\ \hline \end{array}$ | [36791-04-5] | \$289 |
| 1603006 | Riboflavin (500 mg) (Vitamin B2) | N0C021 |  |  | $\begin{array}{\|l\|} \hline \text { M-1 (09/04) } \\ M(11 / 00) \\ \hline \end{array}$ | [83-88-5] | \$156 |
| 1603800 | Rifabutin ( 50 mg ) | G0B040 |  |  | F (11/02) | [72559-06-9] | \$156 |
| 1604009 | Rifampin ( $300 \mathrm{mg} \mathrm{)}$ | $J$ |  |  | 1 (09/00) | [13292-46-1] | \$156 |
| 1604202 | Rifampin Quinone ( 50 mg ) | H |  |  | G (12/01) | [13983-13-6] | \$156 |
| 1604508 | Rimantadine Hydrochloride ( 300 mg ) | F0C266 |  |  |  | [1501-84-4] | \$156 |
| 1604600 | Rimexolone ( 100 mg ) | F |  |  |  | [49697-38-3] | \$156 |
| 1604701 | Ritodrine Hydrochloride (200 mg) | G-1 |  |  |  | [23239-51-2] | \$156 |
| 1606208 | Roxarsone (200 mg) | F |  |  |  | [121-19-7] | \$156 |
| 1606503 | Rutin ( 100 mg ) | F |  |  |  | [153-18-4] | \$156 |
| 1607007 | Saccharin (200 mg) | G-3 |  |  | G-2 (12/01) | [81-07-2] | \$156 |
| 1608000 | Salicylamide (200 mg) | F-4 |  |  | F-3 (05/03) | [65-45-2] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1609002 | Salicylic Acid (125 mg) | J2B147 |  |  | $\begin{array}{\|l} \hline \mathrm{J}-1(10 / 03) \\ \mathrm{J}(10 / 02) \\ \mathrm{I}(07 / 99) \\ \hline \end{array}$ | [69-72-7] | \$124 |
| 1609501 | Salicylic Acid Tablets (Dissolution Calibrator, Non-disintegrating) (33 tablets) | 0 |  |  | N (02/02) | [69-72-7] | \$156 |
| 1609807 | Salsalate ( 125 mg ) | G |  |  |  | [552-94-3] | \$124 |
| 1609829 | Saquinavir Mesylate ( 200 mg ) | F0B008 |  |  |  | [149845-06-7] | \$156 |
| 1609831 | Saquinavir Related Compound A ( 25 mg ) ( N -tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-D-asparaginyl]ami-no]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide) | F0B009 |  |  |  | n/f | \$487 |
| 1610001 | Scopolamine Hydrobromide ( 250 mg ) | J0B051 |  |  | I-1 (01/03) | [6533-68-2] | \$156 |
| 1610090 | Scopoletin (20 mg) | F0C329 |  |  |  | [92-61-5] | \$156 |
| 1611004 | Secobarbital CII (200 mg) | H |  |  |  | [76-73-3] | \$207 |
| 1611900 | Selegiline Hydrochloride (200 mg) | G |  |  |  | [14611-52-0] | \$156 |
| 1611955 | Selenomethionine ( 100 mg ) | F0B006 |  |  |  | [1464-42-2] | \$156 |
| 1612007 | Sennosides ( 250 mg ) | H1B223 |  |  | H (04/04) | $\begin{aligned} & {[81-27-6]} \\ & {[128-57-4]} \\ & \hline \end{aligned}$ | \$156 |
| 1612506 | L-Serine ( 200 mg ) | G |  |  | F-3 (11/00) | [56-45-1] | \$156 |
| 1612540 | Sevoflurane ( 1 mL ) | FOC219 |  |  |  | [28523-86-6] | \$156 |
| 1612550 | Sevoflurane Related Compound A ( 0.2 mL ) (1,1,3,3,3-Pentafluoroisopropenyl fluoromethyl ether) | F0C261 |  |  |  | [58109-34-5] | \$487 |
| 1612608 | Silver Sulfadiazine (200 mg) | 1 |  |  | H (04/01) | [22199-08-2] | \$156 |
| 1612630 | Silybin ( 50 mg ) | F |  |  |  | [22888-70-6] | \$156 |
| 1612641 | Silydianin (20 mg) | F |  |  |  | [29782-68-1] | \$156 |
| 1612652 | Simethicone (50 g) |  |  |  | $\begin{array}{\|l} \hline G(01 / 05) \\ F(07 / 00) \\ \hline \end{array}$ | [8050-81-5] | \$156 |
| 1612700 | Simvastatin (200 mg) | H1B093 |  |  | $\begin{array}{\|l\|} \hline \mathrm{H}(07 / 03) \\ \mathrm{G}(02 / 02) \\ \mathrm{F}-1(05 / 99) \\ \hline \end{array}$ | [79902-63-9] | \$156 |
| 1612801 | Sisomicin Sulfate (500 mg) | 10 C 238 |  |  | $\begin{aligned} & \text { H (04/04) } \\ & \text { G (10/00) } \\ & \hline \end{aligned}$ | [53179-09-2] | \$156 |
| 1613407 | Sodium Acetate (1 g) (AS) | F0D083 | 99.8\% (dr) | 1 |  | [127-09-3] | \$156 |
| 1613509 | Sodium Ascorbate (200 mg) | G2C067 |  |  | G-1 (03/05) | [134-03-2] | \$156 |
| 1613600 | Sodium Butyrate ( 25 mg ) | F |  |  |  | [156-54-7] | \$156 |
| 1613757 | Sodium Carbonate Anhydrous (1 g) (AS) | FOD100 | 100.0\% (dr) | 1 |  | [497-19-8] | \$156 |
| 1614002 | Sodium Fluoride (1 g) (FOR U.S. SALE ONLY) | H-1 |  | 3 | H (05/01) | [7681-49-4] | \$156 |
| 1614308 | Sodium Lactate (200 mg) | 10C299 |  |  | $\begin{aligned} & \mathrm{H}(04 / 05) \\ & \mathrm{G}(06 / 00) \end{aligned}$ | [867-56-1] | \$156 |
| 1614396 | Sodium Metabisulfite (1 g) (AS) | F0D111 | 98.6\% (ai) | 1 |  | [7681-57-4] | \$156 |
| 1614454 | Sodium Nitrite (1 g) (AS) | F0D117 | 99.6\% (dr) | 1 |  | [7632-00-0] | \$156 |
| 1614501 | Sodium Nitroprusside ( 500 mg ) | H |  |  | G (11/99) | [13755-38-9] | \$156 |
| 1614603 | Sodium Propionate (200 mg) | F-1 |  |  | F (03/02) | [6700-17-0] | \$156 |
| 1614669 | Sodium Starch Glycolate ( 400 mg ) | F0C087 |  |  |  | [9063-38-1] | \$156 |
| 1614705 | Sodium Stearyl Fumarate ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | F-2 (05/01) | [4070-80-8] | \$156 |
| 1614807 | Sodium Sulfate Anhydrous (1 g) (AS) | F0D112 | 99.8\% (dr) | 1 |  | [7757-82-6] | \$156 |
| 1616008 | 1,4-Sorbitan (200 mg) | 10A003 |  |  | $\begin{array}{\|l} \mathrm{H}(04 / 03) \\ \mathrm{G}(02 / 00) \\ \hline \end{array}$ | [27299-12-3] | \$156 |
| 1617000 | Sorbitol (125 mg) | H1B139 |  |  | H (01/04) | [50-70-4] | \$124 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1617408 | Sotalol Hydrochloride ( 300 mg ) | F0C234 |  |  |  | [959-24-0] | \$182 |
| 1617419 | Sotalol Related Compound A (50 mg) (N-[4-[[(1-Methylethyl)amino]acetyl]phenyl]methanesulfonamide monohydrochloride) | F0C235 |  |  |  | n/f | \$487 |
| 1617420 | Sotalol Related Compound B ( 50 mg ) ( N -(4Formylphenyl)methanesulfonamide) | F0C236 |  |  |  | n/f | \$487 |
| 1617430 | Sotalol Related Compound C ( 50 mg ) ( N -[4-[2-[(1-Methylethyl)amino]ethyl]phenyl]methanesulfonamide hydrochloride) | F0C237 |  |  |  | n/f | \$487 |
| 1618003 | Spectinomycin Hydrochloride (200 mg) | G0C310 | $650 \mathrm{ug} / \mathrm{mg}$ (ai) |  | F-2 (01/05) | [22189-32-8] | \$156 |
| 1619006 | Spironolactone ( 125 mg ) | J-1 |  |  |  | [52-01-7] | \$124 |
| 1619505 | Squalane ( 500 mg ) | G-1 |  |  |  | [111-01-3] | \$156 |
| 1620005 | Stanozolol CIII (200 mg) | F-3 |  |  | F-2 (02/01) | [10418-03-8] | \$207 |
| 1621008 | Stearic Acid ( 500 mg ) | J |  |  | 1 (10/01) | [57-11-4] | \$156 |
| 1621507 | Stearoyl Polyoxyglycerides (100 mg) | F0C286 |  |  |  | n/f | \$156 |
| 1622000 | Stearyl Alcohol (125 mg) | H2B217 |  |  | $\begin{aligned} & \hline \mathrm{H}-1(12 / 04) \\ & \mathrm{H}(09 / 99) \\ & \hline \end{aligned}$ | [112-92-5] | \$124 |
| 1623003 | Streptomycin Sulfate (200 mg) | J0B195 |  |  | I (04/03) | [3810-74-0] | \$156 |
| 1623502 | Succinylcholine Chloride ( 500 mg ) | H |  |  |  | [71-27-2] | \$156 |
| 1623604 | Succinylmonocholine Chloride ( 150 mg ) | G |  |  | F-1 (02/01) | n/f | \$487 |
| 1623626 | Sucralose ( 400 mg ) | G0B028 |  |  | F (04/03) | [56038-13-2] | \$156 |
| 1623637 | Sucrose ( 100 mg ) | H1C223 |  |  | $\begin{aligned} & \text { HOB002 (11/04) } \\ & \text { G-1 (03/03) } \\ & \text { G }(05 / 99) \end{aligned}$ | [57-50-1] | \$156 |
| 1623648 | Sufentanil Citrate ClI (25 mg) | H0B208 |  |  | $\begin{aligned} & \hline \text { G (05/03) } \\ & \text { F-1 (04/02) } \\ & \text { F (09/99) } \\ & \hline \end{aligned}$ | [60561-17-3] | \$207 |
| 1623670 | Sulbactam (250 mg) | H0C396 | 0.976 mg/mg (ai) | 2 | $\begin{aligned} & \mathrm{G}(05 / 05) \\ & \mathrm{F}-1(05 / 00) \\ & \hline \end{aligned}$ | [68373-14-8] | \$156 |
| 1623681 | Sulconazole Nitrate ( 200 mg ) | F-1 |  |  | F (05/02) | [61318-91-0] | \$156 |
| 1623706 | Sulfabenzamide ( 200 mg ) | G |  |  |  | [127-71-9] | \$156 |
| 1623808 | Sulfacetamide ( 300 mg ) | G-1 |  |  |  | [144-80-9] | \$156 |
| 1624006 | Sulfacetamide Sodium ( 500 mg ) | 11B318 |  |  | $\begin{aligned} & \text { I (09/04) } \\ & H(08 / 01) \end{aligned}$ | [6209-17-2] | \$156 |
| 1624505 | Sulfachlorpyridazine (200 mg) | F |  |  |  | [80-32-0] | \$156 |
| 1625009 | Sulfadiazine (200 mg) | J |  |  | 1 (03/04) | [68-35-9] | \$156 |
| 1626001 | Sulfadimethoxine ( 200 mg ) | F4C298 |  |  | $\begin{aligned} & \hline \text { F-3 (11/04) } \\ & \text { F-2 (03/99) } \\ & \hline \end{aligned}$ | [122-11-2] | \$156 |
| 1626500 | Sulfadoxine (200 mg) | F-2 |  |  | F-1 (07/02) | [2447-57-6] | \$156 |
| 1628007 | Sulfamerazine ( 500 mg ) | H1C171 |  |  | H (12/04) | [127-79-7] | \$156 |
| 1629000 | Sulfamethazine (1 g) | G-3 |  |  |  | [57-68-1] | \$156 |
| 1630009 | Sulfamethizole (200 mg) | F-3 |  |  | F-2 (01/03) | [144-82-1] | \$156 |
| 1631001 | Sulfamethoxazole ( $200 \mathrm{mg} \mathrm{)}$ | I-1 |  |  | I (04/02) | [723-46-6] | \$156 |
| 1631500 | Sulfamethoxazole N4-glucoside ( 25 mg ) | H |  |  | G (11/01) | n/f | \$487 |
| 1632004 | Sulfanilamide (5 g) | O0B047 |  |  | N (01/04) | [63-74-1] | \$156 |
| 1633007 | Sulfanilamide Melting Point Standard ( 500 mg ) (Approximately 165 degrees) | K0B133 |  |  | $\begin{aligned} & \hline \mathrm{J}-1(03 / 04) \\ & \mathrm{J}(09 / 99) \\ & \hline \end{aligned}$ | [63-74-1] | \$75 |
| 1633506 | Sulfanilic Acid ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | F-2 (09/00) | [121-57-3] | \$487 |
| 1634000 | Sulfapyridine (200 mg) | IOB298 |  |  | H (07/04) | [144-83-2] | \$156 |
| 1635002 | Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees) | J |  |  | I (07/00) | [144-83-2] | \$92 |
| 1635206 | Sulfaquinoxaline ( 200 mg ) | F0A005 |  |  |  | [59-40-5] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1636005 | Sulfasalazine ( 125 mg ) | G-2 |  |  | G-1 (06/99) | [599-79-1] | \$124 |
| 1636504 | Sulfathiazole ( 350 mg ) | H |  |  | G (08/00) | [72-14-0] | \$156 |
| 1637008 | Sulfinpyrazone (200 mg) | H0C416 | $0.992 \mathrm{mg} / \mathrm{mg}$ (ai) |  | G (03/05) | [57-96-5] | \$156 |
| 1638000 | Sulfisoxazole (200 mg) | J |  |  | I-1 (06/99) | [127-69-5] | \$156 |
| 1639003 | Sulfisoxazole Acetyl ( 200 mg ) | H-1 |  |  |  | [80-74-0] | \$156 |
| 1640002 | Sulfisoxazole Diolamine ( 500 mg ) | F |  |  |  | [4299-60-9] | \$156 |
| 1642008 | Sulindac (200 mg) | H |  |  | G-1 (12/01) | [38194-50-2] | \$156 |
| 1642154 | Sumatriptan ( 50 mg ) | F0C220 |  |  |  | [103628-46-2] | \$208 |
| 1642201 | Sumatriptan Succinate ( 200 mg ) | F0C231 |  |  |  | [103628-48-4] | \$208 |
| 1642212 | Sumatriptan Succinate Related Compound A ( 15 mg ) ([33-[2-(dimethylamino)ethyl]-2-[[3-[2-(di-methylamino)ethyl]-1 H-indol-5-yl]methyl]-1H-in-dol-5-yl]-N-methylmethansulfonamide, succinate salt) | F0C221 |  |  |  | n/f | \$624 |
| 1642223 | Sumatriptan Succinate Related Compound C ( 50 mg ) ([3-[2-(dimethylamino)ethyl]-1-(hydro-xymethyl)-1H-indol-5-yl]-N-methylmethanesulfonamide succinate salt) | F0C230 |  |  |  | n/f | \$624 |
| 1642507 | Suprofen ( 200 mg ) | F |  |  |  | [40828-46-4] | \$156 |
| 1642700 | Tacrine Hydrochloride ( 500 mg ) | F0C119 |  |  |  | [1684-40-8] | \$156 |
| 1643000 | Talbutal CIII (250 mg) | F |  |  |  | [115-44-6] | \$207 |
| 1643306 | Tamoxifen Citrate (200 mg) | H |  |  | $\begin{aligned} & \text { G-2 }(09 / 01) \\ & \text { G-1 }(05 / 00) \\ & \hline \end{aligned}$ | [54965-24-1] | \$156 |
| 1643361 | Taurine ( 100 mg ) | F0C104 |  |  |  | [107-35-7] | \$156 |
| 1643408 | Temazepam CIV (200 mg) | H0C205 |  |  | $\begin{aligned} & \hline \text { G (06/04) } \\ & \text { F (12/99) } \end{aligned}$ | [846-50-4] | \$207 |
| 1643452 | Terazosin Hydrochloride ( 200 mg ) | F0C244 |  |  |  | [70024-40-7] | \$156 |
| 1643463 | Terazosin Related Compound A (50 mg) (1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)piperazine dihydrochloride) | F0C245 |  |  |  | n/f | \$487 |
| 1643474 | Terazosin Related Compound B (50 mg) (1-(4-hydroxy-6,7-dimethoxy-2-quinazolinyl)-4-[(tetra-hydro-2-furanyl)carbonyl]piperazine) | F0C218 |  |  |  | n/f | \$487 |
| 1643485 | Terazosin Related Compound C ( 25 mg ) (1,4-bis(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine dihydrochloride) | F0C257 |  |  |  | n/f | \$487 |
| 1643500 | Terbutaline Sulfate ( 125 mg ) | H |  |  | G (04/99) | [23031-32-5] | \$124 |
| 1643703 | Terconazole (200 mg) | G-2 |  |  | $\begin{aligned} & \text { G-1(04/01) } \\ & \text { G (03/99) } \\ & \hline \end{aligned}$ | [67915-31-5] | \$156 |
| 1643805 | Terfenadine ( 200 mg ) | H |  |  | G (12/99) | [50679-08-8] | \$156 |
| 1643907 | Terfenadine Related Compound A (100 mg) (1-[4-(1,1-dimethylethyl)phenyl]-4-[4-(hydroxydi-phenylmethyl)-1-piperidinyl]-1-butanone) | G |  |  |  | n/f | \$487 |
| 1643929 | Terfenadine Related Compound B ( 50 mg ) (Terfenadine-N-oxide) | F |  |  |  | n/f | \$487 |
| 1644003 | Terpin Hydrate ( 750 mg ) | G |  |  |  | [2451-01-6] | \$156 |
| 1645006 | Testolactone CIII ( 125 mg ) | F-1 |  |  |  | [968-93-4] | \$165 |
| 1646009 | Testosterone CIII ( 125 mg ) | 11B253 |  |  | 1 (08/04) | [58-22-0] | \$165 |
| 1647001 | Testosterone Cypionate CIII ( 200 mg ) | H0D162 | $1.000 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | $\begin{aligned} & \text { G-1 (03/05) } \\ & \text { G (08/01) } \end{aligned}$ | [58-20-8] | \$207 |
| 1648004 | Testosterone Enanthate CIII ( 200 mg ) | J |  |  |  | [315-37-7] | \$207 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| Cat. No. | Description | Curr. <br> Lot. | Purity <br> Value/Conc. | Change Code* | Previous Lot/Valid Use Date | CAS <br> No. | Price |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1649007 | Testosterone Propionate CIII (200 mg) | L1C005 |  |  | $\begin{aligned} & \hline \text { L (08/04) } \\ & \text { K-1 }(11 / 01) \\ & \hline \end{aligned}$ | [57-85-2] | \$207 |
| 1650006 | Tetracaine Hydrochloride ( 200 mg ) | J |  |  |  | [136-47-0] | \$156 |
| 1651009 | Tetracycline Hydrochloride ( 200 mg ) | L0C216 | 976 ug/mg (ai) |  | K (12/04) | [64-75-5] | \$156 |
| 1652001 | Tetrahydrozoline Hydrochloride ( 200 mg ) | G1A015 |  |  | G (03/03) | [522-48-5] | \$156 |
| 1652500 | Thalidomide ( $200 \mathrm{mg} \mathrm{)}$ | F0C107 |  |  |  | [50-35-1] | \$182 |
| 1653004 | Theophylline ( 200 mg ) | J0B180 |  |  | I (01/04) | [58-55-9] | \$156 |
| 1653106 | Theophylline Extended-Release Beads (Drug Release Calibrator, Multiple Unit) (20 g) DISCONTINUED |  |  | 9 | F-1 (11/04) | [58-55-9] | \$156 |
| 1655000 | Thiabendazole (100 mg) | G0A027 |  |  | $\begin{aligned} & \hline \text { F-1 (04/03) } \\ & \text { F (04/01) } \\ & \hline \end{aligned}$ | [148-79-8] | \$156 |
| 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) | 0 |  |  | $\begin{aligned} & \hline N(11 / 02) \\ & M-1(04 / 99) \\ & \hline \end{aligned}$ | [67-03-8] | \$156 |
| 1656308 | Thiamylal CIII ( 200 mg ) | F |  |  |  | [77-27-0] | \$207 |
| 1657005 | Thiethylperazine Malate ( $200 \mathrm{mg} \mathrm{)}$ | G |  |  | F-1 (09/00) | [52239-63-1] | \$156 |
| 1658008 | Thiethylperazine Maleate ( 200 mg ) | F-1 |  |  |  | [1179-69-7] | \$156 |
| 1659000 | Thimerosal ( 500 mg ) | H1B205 |  |  | $\begin{aligned} & \text { H (09/04) } \\ & \text { G (12/99) } \end{aligned}$ | [54-64-8] | \$156 |
| 1660000 | Thioguanine (200 mg) | F-1 |  |  |  | [154-42-7] | \$156 |
| 1661002 | Thiopental CIII ( 250 mg ) | 1 |  |  |  | [76-75-5] | \$207 |
| 1662504 | Thioridazine ( 200 mg ) | H |  |  |  | [50-52-2] | \$156 |
| 1663008 | Thioridazine Hydrochloride (200 mg) | H |  |  |  | [130-61-0] | \$156 |
| 1663700 | Thiostrepton (200 mg) | F1B022 |  |  | F (11/02) | [1393-48-2] | \$156 |
| 1664000 | Thiotepa ( 500 mg ) | 1 |  |  | H (01/99) | [52-24-4] | \$156 |
| 1665003 | Thiothixene ( 250 mg ) | G |  |  |  | [3313-26-6] | \$156 |
| 1666006 | (E)-Thiothixene (100 mg) | H |  |  | G-1 (05/00) | [3313-27-7] | \$487 |
| 1667100 | Thonzonium Bromide (200 mg) | F |  |  |  | [553-08-2] | \$156 |
| 1667202 | L-Threonine ( 200 mg ) | G |  |  | F-3 (12/00) | [72-19-5] | \$156 |
| 1667279 | Thromboplastin, Human Recombinant (set) ( 1 vial Thromboplastin and 1 vial Diluent) DISCONTINUED |  |  |  | F (10/04) | [9002-05-5] | \$156 |
| 1667290 | Tiamulin Fumarate ( 250 mg ) | F0C327 |  |  |  | [55297-96-6] | \$156 |
| 1667337 | Tiamulin Related Compound A ( 50 mg ) (Tosyl pleuromutilin) | F0C328 |  |  |  | n/f | \$494 |
| 1667304 | Ticarcillin Monosodium Monohydrate ( 200 mg ) | H |  |  | G-1 (03/99) | [74682-62-5] | \$156 |
| 1667359 | Tiletamine Hydrochloride ( 200 mg ) | F0C019 |  |  |  | [14176-50-2] | \$156 |
| 1667406 | Timolol Maleate (200 mg) | G-1 |  |  |  | [26921-17-5] | \$156 |
| 1667520 | Tinidazole (200 mg) | F0C093 |  |  |  | [19387-91-8] | \$156 |
| 1667530 | Tinidazole Related Compound A (100 mg) (2-methyl-5-nitroimidazole) | F0C091 |  |  |  | [696-23-1] | \$487 |
| 1667439 | Tioconazole ( 200 mg ) | H |  |  | G (04/02) | [65899-73-2] | \$156 |
| 1667450 | Tioconazole Related Compound A (25 mg) (1-[2,4-Dichloro-beta-[(3-thenyl)-oxy]phenethyl]imidazole Hydrochloride) | G |  |  |  | n/f | \$487 |
| 1667461 | Tioconazole Related Compound B ( 25 mg ) (1-[2,4-Dichloro-beta-[(2,5-dichloro-3-thenyl)oxy]phenethyl]imidazole Hydrochloride) | G |  |  |  | n/f | \$487 |
| 1667472 | Tioconazole Related Compound C ( 25 mg ) (1-[2,4-Dichloro-beta-[(5-bromo-2-chloro-3-thenyl)-oxy]-phenethyl]imidazole Hydrochloride) | G |  |  |  | n/f | \$487 |
| 1667585 | Titanium Dioxide (1 g) (AS) | F0D079 | 99.6\% (dr) | 1 |  | [13463-67-7] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1667508 | Tobramycin (250 mg) | K0B248 |  |  | J (08/03) | [32986-56-4] | \$156 |
| 1667552 | Tocainide Hydrochloride ( 125 mg ) | F-1 |  |  | F (04/99) | [35891-93-1] | \$124 |
| 1667600 | Alpha Tocopherol (250 mg) (Vitamin E Alcohol) | M |  |  | L-1 (01/00) | [10191-41-0] | \$156 |
| 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) | K |  |  | J (06/99) | [7695-91-2] | \$156 |
| 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) |  |  |  | $\begin{array}{\|l\|} \hline \text { F-5 (05/05) } \\ \text { F-4 (01/02) } \\ \hline \end{array}$ | [4345-03-3] | \$156 |
| 1668001 | Tolazamide (200 mg) | G-2 |  |  | G-1 (06/00) | [1156-19-0] | \$156 |
| 1669004 | Tolazoline Hydrochloride ( 300 mg ) | F |  |  |  | [59-97-2] | \$156 |
| 1670003 | Tolbutamide ( 200 mg ) | 1 |  |  | H (06/00) | [64-77-7] | \$156 |
| 1670502 | Tolmetin Sodium ( 500 mg ) | IOB064 |  |  | H (09/03) | [64490-92-2] | \$156 |
| 1671006 | Tolnaftate (200 mg) | J0C405 | $1.000 \mathrm{mg} / \mathrm{mg}$ (dr) |  | I (02/05) | [2398-96-1] | \$156 |
| 1672009 | Toluenesulfonamides, ortho and para ( 200 mg of each supplied in a set) | F-4 |  |  | F-3 (11/99) | $\begin{aligned} & {[88-19-7](0)} \\ & {[70-55-3] \text { (p) }} \end{aligned}$ | \$487 |
| 1672304 | Torsemide ( 200 mg ) | F0B090 |  |  |  | [56211-40-6] | \$156 |
| 1672315 | Torsemide Related Compound A (75 mg) (4-[(3-methylphenyl)amino]-3-pyridinesulfonamide) | F0B071 |  |  |  | n/f | \$487 |
| 1672326 | Torsemide Related Compound B ( 75 mg ) ( N -[(n-butylamino)carbonyl]-4-[(3-methylphenyl)a-minoj-3-pyridinesulfonamide) | F0B083 |  |  |  | n/f | \$487 |
| 1672337 | Torsemide Related Compound C ( 75 mg ) ( N -[(ethylamino)carbonyl]-4-[(3-methylphenyl)ami-noj-3-pyridinesulfonamide) | F0B078 |  |  |  | n/f | \$487 |
| 1672803 | Transplatin ( 25 mg ) | H0B287 |  |  | G (03/04) | [14913-33-8] | \$487 |
| 1673500 | Trazodone Hydrochloride ( 200 mg ) | F-2 |  |  |  | [25332-39-2] | \$156 |
| 1674004 | Tretinoin ( $30 \mathrm{mg} /$ ampule; 5 ampules) | I2B185 |  |  | $\begin{array}{\|l\|} \hline \text { I-1 (01/04) } \\ \text { I (01/02) } \\ \text { H (06/01) } \\ \hline \end{array}$ | [302-79-4] | \$156 |
| 1675007 | Triacetin (1 g) | H0C413 |  |  | $\begin{aligned} & \text { G-1 (02/05) } \\ & \text { G (06/01) } \\ & \hline \end{aligned}$ | [102-76-1] | \$156 |
| 1676000 | Triamcinolone (250 mg) | H-1 |  |  |  | [124-94-7] | \$156 |
| 1677002 | Triamcinolone Acetonide ( 500 mg ) | K |  |  | J (03/99) | [76-25-5] | \$156 |
| 1678005 | Triamcinolone Diacetate (200 mg) | G |  |  |  | [67-78-7] | \$156 |
| 1679008 | Triamcinolone Hexacetonide ( 125 mg ) | G |  |  |  | [5611-51-8] | \$124 |
| 1680007 | Triamterene ( 200 mg ) | 1 |  |  |  | [396-01-0] | \$156 |
| 1680506 | Triazolam CIV (200 mg) | H0B041 |  |  | G-1 (03/03) | [28911-01-5] | \$207 |
| 1680608 | Tributyl Citrate ( 500 mg ) | G0C227 |  |  | F (01/05) | [77-94-1] | \$156 |
| 1680801 | Trichlorfon ( 200 mg ) | F |  |  |  | [52-68-6] | \$156 |
| 1681000 | Trichlormethiazide ( 200 mg ) | H |  |  |  | [133-67-5] | \$156 |
| 1682206 | Triclosan ( 200 mg ) | G0D001 | $0.997 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | F0B135 (05/05) | [3380-34-5] | \$156 |
| 1683005 | Tridihexethyl Chloride (200 mg) | F-1 |  |  |  | [4310-35-4] | \$156 |
| 1683504 | Trientine Hydrochloride (125 mg) | F2B257 |  |  | $\begin{array}{\|l\|l\|} \hline \text { F-1 (09/03) } \\ \text { F (08/96) } \\ \hline \end{array}$ | [38260-01-4] | \$124 |
| 1683606 | Triethyl Citrate ( 500 mg ) | F-1 |  |  | F (03/02) | [77-93-0] | \$156 |
| 1685000 | Trifluoperazine Hydrochloride ( $200 \mathrm{mg} \mathrm{)}$ | H0A010 |  |  | G (03/03) | [440-17-5] | \$156 |
| 1685500 | 2-[N-(2,2,2-Trifluoro-ethyl)amino-5]-chlorobenzophenone ( 25 mg ) | F |  |  |  | n/f | \$487 |
| 1686003 | Triflupromazine Hydrochloride (200 mg) | F-2 |  |  | F-1 (03/04) | [1098-60-8] | \$156 |
| 1686309 | Trifluridine (200 mg) | F |  |  |  | [70-00-8] | \$156 |
| 1686310 | Trifluridine Related Compound A (20 mg) (5-Carboxy-2'-deoxyuridine) | F |  |  |  | [14599-46-3] | \$487 |

*See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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| 1687006 | Trihexyphenidyl Hydrochloride (200 mg) | J |  |  | 1 (07/01) | [52-49-3] | \$156 |
| 1689001 | Trimeprazine Tartrate (200 mg) | F-3 |  |  | F-2 (08/01) | [4330-99-8] | \$156 |
| 1690000 | Trimethadione ( 200 mg ) | G |  |  |  | [127-48-0] | \$156 |
| 1692006 | Trimethobenzamide Hydrochloride ( 500 mg ) | H-2 |  |  | H-1 (06/02) | [554-92-7] | \$156 |
| 1692505 | Trimethoprim ( 300 mg ) | J0B228 |  |  | $1(01 / 04)$ | [738-70-5] | \$156 |
| 1693009 | Trioxsalen (200 mg) | H0C278 |  |  | G (04/04) | [3902-71-4] | \$156 |
| 1694001 | Tripelennamine Citrate ( 200 mg ) | G |  |  | F (02/03) | [6138-56-3] | \$156 |
| 1695004 | Tripelennamine Hydrochloride (200 mg) | J |  |  |  | [154-69-8] | \$156 |
| 1696007 | Triprolidine Hydrochloride ( 500 mg ) | 1 |  |  | H-1 (02/02) | [6138-79-0] | \$156 |
| 1696109 | Triprolidine Hydrochloride Z-Isomer (100 mg) | G |  |  | F-1 (02/02) | n/f | \$487 |
| 1696200 | Trisalicylic Acid (100 mg) | G |  |  | F-1 (10/99) | n/f | \$487 |
| 1697000 | Troleandomycin (250 mg) | F-1 |  |  |  | [2751-09-9] | \$156 |
| 1698002 | Tromethamine ( 125 mg ) | G |  |  | F-3 (07/99) | [77-86-1] | \$124 |
| 1699005 | Tropicamide ( 125 mg ) | G-1 |  |  | G (02/99) | [1508-75-4] | \$124 |
| 1700002 | Trypsin Crystallized ( 300 mg ) | H |  |  | G (12/99) | [9002-07-7] | \$156 |
| 1700501 | L-Tryptophan (200 mg) | G-1 |  |  | G (09/00) | [73-22-3] | \$156 |
| 1702008 | Tubocurarine Chloride ( 250 mg ) | K-1 |  |  |  | [6989-98-6] | \$156 |
| 1703805 | Tylosin (250 mg) | F0C008 |  |  |  | [1401-69-0] | \$156 |
| 1704003 | Tyloxapol (600 mg) | H |  |  | G (02/00) | [25301-02-4] | \$156 |
| 1704502 | Tyropanoate Sodium ( 500 mg ) | F |  |  |  | [7246-21-1] | \$156 |
| 1705006 | L-Tyrosine ( 500 mg ) | K0C141 | $1.00 \mathrm{mg} / \mathrm{mg}$ (ai) | 2 | J (05/05) | [60-18-4] | \$156 |
| 1705301 | Ubidecarenone ( 200 mg ) | F0B191 |  |  |  | [303-98-0] | \$156 |
| 1705312 | Ubidecarenone for System Suitability ( 25 mg ) | FOB194 |  |  |  | [303-98-0] | \$156 |
| 1705505 | Undecylenic Acid (200 mg) | G2C018 |  |  | $\begin{aligned} & \text { G-1 (11/04) } \\ & \text { G }(01 / 02) \end{aligned}$ | [112-38-9] | \$156 |
| 1705800 | Uracil Arabinoside ( 50 mg ) | G |  |  | F-1 (06/99) | [3083-77-0] | \$156 |
| 1706009 | Uracil Mustard ( 500 mg ) (FOR U.S. SALE ONLY) | F |  | 3 |  | [66-75-1] | \$156 |
| 1706701 | Urea C 13 (100 mg) | F0C078 |  | 4 |  | [58069-82-2] | \$182 |
| 1707806 | Ursodiol ( 125 mg ) | G |  |  | $\begin{aligned} & \hline \text { F-1 (11/01) } \\ & \text { F (09/99) } \\ & \hline \end{aligned}$ | [128-13-2] | \$124 |
| 1707908 | Valerenic Acid (15 mg) | H0D126 | $1.00 \mathrm{mg} / \mathrm{mg}$ (ai) | 2,3 | $\begin{aligned} & \text { GOB146 (05/05) } \\ & \text { F (01/04) } \end{aligned}$ | [3569-10-6] | \$696 |
| 1708503 | L-Valine ( 200 mg ) | F-2 |  |  | F-1 (05/02) | [72-18-4] | \$156 |
| 1708707 | Valproic Acid (500 mg) | J1B127 |  |  | $\begin{array}{\|l\|} \hline J \text { (01/04) } \\ \text { I-1 }(11 / 00) \\ \hline \end{array}$ | [99-66-1] | \$156 |
| 1708729 | Valproic Acid Related Compound A ( 0.25 mL ) (diallylacetic acid) | F2C386 |  | 2 | $\begin{aligned} & \text { F1B156 (05/05) } \\ & \text { F (01/03) } \end{aligned}$ | [99-67-2] | \$208 |
| 1708762 | Valsartan ( 350 mg ) | F0C147 | $0.995 \mathrm{mg} / \mathrm{mg}$ (an) |  |  | [137862-53-4] | \$156 |
| 1708773 | Valsartan Related Compound A (20 mg) ((R)-N-Valeryl-N-([2'-(1-H-tetrazole-5-yl)-biphenyl-4-yl]-methyl)-valine) | F0C215 |  |  |  | n/f | \$624 |
| 1708795 | Valsartan Related Compound C (10 mg) ((S)-N-Valeryl-N-([2'-(1-H-tetrazole-5-yl)biphenyl-4-yl]methyl)valine benzyl ester) | F0C208 |  |  |  | n/f | \$624 |
| 1709007 | Vancomycin Hydrochloride (4 vials, each vial contains $100,500 \mathrm{mcg}$ of vancomycin activity) | L |  |  | K (08/01) | [1404-93-9] | \$156 |
| 1710006 | Vanillin (200 mg) | J0A021 |  |  | $\begin{aligned} & \text { I (03/05) } \\ & \mathrm{H}(04 / 99) \end{aligned}$ | [121-33-5] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1711009 | Vanillin Melting Point Standard (1 g) (Approximately 82 degrees) | J1C303 |  | 2 | $\begin{array}{\|l\|} \hline J(06 / 05) \\ I-1(03 / 03) \\ I(11 / 00) \\ \hline \end{array}$ | [121-33-5] | \$92 |
| 1711155 | Vecuronium Bromide ( 50 mg ) | F0C367 |  | 4 |  | [50700-72-6] | \$156 |
| 1711166 | Vecuronium Bromide Related Compound A ( 25 mg ) (3alpha, 17beta-diacetyl-oxy-2beta, 16beta-bispiperidinyl-5alpha-androstan) | F0B178 |  |  |  | n/f | \$487 |
| 1711202 | Verapamil Hydrochloride (200 mg) | G |  |  | F-4 (06/00) | [152-11-4] | \$156 |
| 1711304 | Verapamil Related Compound A ( 50 mg ) (3,4-Dimethoxy-alpha-[3-(methylamino)propyl]-al-pha-(1-methylethyl)-benzeneacetonitrile monoHydrochloride) | H |  |  | G (01/01) | n/f | \$487 |
| 1711406 | Verapamil Related Compound B ( 50 mg ) (al-pha-[2-[[2-(3,4-dimethoxyphenyl)-ethyl]methyla-mino]ethyl]-3,4-dimethoxy-alpha-(1-methy-lethyl)-benzeneacetonitrile monoHydrochloride) | G |  |  |  | [1794-55-4] | \$487 |
| 1711461 | Verteporfin ( 200 mg ) | F0C166 |  |  |  | [129497-78-5] | \$156 |
| 1711472 | Verteporfin Related Compound A ( 50 mg ) ( $(+/-$ )18-Ethenyl-4,4a-dihydro-3,4-bis(methoxycarbo-nyl)-4a,8,14,19-tetramethyl-23H,25H-benzo[b]-prophine-9,13-dipropanoic acid) | F0C167 |  |  |  | n/f | \$487 |
| 1711508 | Vidarabine ( 200 mg ) | G-1 |  |  |  | [24356-66-9] | \$156 |
| 1713004 | Vinblastine Sulfate ( 50 mg ) | M0B308 |  |  | $\begin{array}{\|l\|} \hline \mathrm{L}(12 / 04) \\ \mathrm{K}(05 / 99) \\ \hline \end{array}$ | [143-67-9] | \$354 |
| 1714007 | Vincristine Sulfate ( $50 \mathrm{mg} /$ ampule) | O0B062 |  |  | $\begin{aligned} & \mathrm{N}(01 / 03) \\ & \mathrm{M}(04 / 99) \\ & \hline \end{aligned}$ | [2068-78-2] | \$479 |
| 1714506 | Vinorelbine Tartrate ( 200 mg ) | F0C243 |  |  |  | [125317-39-7] | \$156 |
| 1714528 | Vinorelbine Related Compound A ( 25 mg ) (4-ODeacetylvinorelbine tartrate) | F0C242 |  |  |  | n/f | \$487 |
| 1715000 | Viomycin Sulfate (200 mg) | F |  |  |  | [37883-00-4] | \$156 |
| 1716002 | Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil) | V0C258 |  |  | U (04/04) | [127-47-9] | \$156 |
| 1717504 | Vitamin D Assay System Suitability (1.5 g) | F |  |  |  | [67-97-0] | \$156 |
| 1717708 | Vitexin ( 30 mg ) | F0C142 |  |  |  | [3681-93-4] | \$520 |
| 1719000 | Warfarin (200 mg) | IOB305 |  |  | $\begin{array}{ll} \hline \mathrm{H}-2(08 / 04) \\ \mathrm{H}-1(11 / 01) \\ \hline \end{array}$ | [81-81-2] | \$156 |
| 1719102 | Warfarin Related Compound A (50 mg) (3-(0-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one) | G1B111 |  |  | G (01/04) | [37209-23-7] | \$156 |
| 1720000 | Xanthanoic Acid (100 mg) | G-1 |  |  | G (12/00) | [82-07-5] | \$487 |
| 1720203 | Xanthone ( 100 mg ) | F-1 |  |  |  | [90-47-1] | \$487 |
| 1720407 | Xylazine ( 200 mg ) | F1C001 |  |  | F (02/05) | [7361-61-7] | \$156 |
| 1720429 | Xylazine Hydrochloride (200 mg) | F |  |  |  | [23076-35-9] | \$156 |
| 1720600 | Xylitol (1 g) | G0B037 |  |  | $\begin{aligned} & \hline \text { F-3 (11/02) } \\ & \text { F-2 (05/00) } \\ & \hline \end{aligned}$ | [87-99-0] | \$156 |
| 1721002 | Xylometazoline Hydrochloride (125 mg) | IOB101 |  |  | H-1 (05/03) | [1218-35-5] | \$124 |
| 1722005 | Xylose (1 g) | F |  |  |  | [58-86-6] | \$156 |
| 1724000 | Yohimbine Hydrochloride ( 200 mg ) | F |  |  |  | [65-19-0] | \$156 |
| 1724306 | Zalcitabine ( 200 mg ) | F |  |  |  | [7481-89-2] | \$156 |
| 1724317 | Zalcitabine Related Compound A ( 50 mg ) (2',3'-Didehydro-2',3'-dideoxycytidine) | F0B234 |  |  |  | [7481-88-1] | \$487 |
| 1724500 | Zidovudine ( 400 mg ) | G |  |  | F (09/01) | [30516-87-1] | \$156 |

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| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1724521 | Zidovudine Related Compound B ( 25 mg ) ( 3 '-chloro-3'-deoxythymidine) | G0B116 |  |  | $\begin{array}{\|l\|} \hline \text { F-1 (03/03) } \\ \text { F (06/01) } \\ \hline \end{array}$ | [25526-94-7] | \$487 |
| 1724532 | Zidovudine Related Compound C (100 mg) (thymine) | F-1 |  |  | F (09/01) | [65-71-4] | \$487 |
| 1724656 | Zileuton ( 150 mg ) | F0C062 |  |  |  | [111406-87-2] | \$156 |
| 1724667 | Zileuton Related Compound A (50 mg) (N-(1-Benzo[b]thien-2-ylethyl) urea) | F0B316 |  |  |  | n/f | \$487 |
| 1724678 | Zileuton Related Compound B ( 50 mg ) (2-(Benzo[b]thien-2-oyl)benzo[b]thiophene) | F0B313 |  |  |  | n/f | \$487 |
| 1724689 | Zileuton Related Compound C ( 50 mg ) (1-Benzo[b]thien-2-ylethanone) | F0B299 |  |  |  | n/f | \$487 |
| 1724769 | Zinc Sulfate (1 g) (AS) | F0D133 | 56.4\% (ai) | 1 |  | [7446-20-2] | \$156 |
| 1724805 | Zolazepam Hydrochloride ( 500 mg ) | G0C023 |  |  | $\begin{aligned} & \text { F-1 (03/04) } \\ & \text { F (05/02) } \end{aligned}$ | [33754-49-3] | \$156 |

## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. <br> No. | New Description |
| :---: | :---: | :---: | :---: |
| 00200-6 | 5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid ( 50 mg ) (Limit Test) | 1184027 | Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid) |
| 1008002 | alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane | 1008002 | Propoxyphene Related Compound B ( 50 mg ) (alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane) |
| 02200-3 | 3-Amino-4-carboxamidopyrazole Hemisulfate ( 50 mg ) (Limit Test) | 1013024 | Allopurinol Related Compound A ( 50 mg ) (3-Amino-4-carboxamidopyrazole Hemisulfate) |
| 02250-2 | 4-Amino-6-chloro-1,3-benzenedisulfonamide ( 100 mg ) (Lim- <br> it Test) | 1057507 | Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide) |
| 1023403 | 3-Amino-6-chloro-1-methyl-4-phenylcarbostyril (25 mg) | 1023403 | Diazepam Related Compound B ( 25 mg ) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril) |
| 02380-0 | 2-Amino-2'-chloro-5-nitrobenzophenone ( 25 mg ) (Limit Test) | 1140338 | Clonazepam Related Compound B ( 25 mg ) (2-Amino-2'-chloro-5-nitrobenzophenone) |
| 02420-2 | 4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide ( 100 mg ) (Limit Test) | 1424018 | Methyclothiazide Related Compound A (100 mg) (4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide) |
| 02240-6 | 2-Amino-4-chlorophenol (50 mg) (Limit Test) | 1130527 | Chlorzoxazone Related Compound A (25 mg) ( 2-Amino-4chlorophenol) |
| 02460-0 | 3-Amino-4-(2-chloro-phenyl)-6-nitrocarbostyril ( 25 mg ) (Lim- it Test) | 1140327 | Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril) |
| 02490-5 | 2-Amino-2',5-dichlorobenzophenone ( 25 mg ) (Limit Test) | 1370338 | Lorazepam Related Compound B ( 25 mg ) (2-Amino-2',5dichlorobenzophenone) |
| 02610-6 | 3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid (25 mg) (Limit Test) | 1078325 | Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid) |
| 02620-8 | alpha-Aminopropiophenone Hydrochloride ( 50 mg ) (Limit Test) | 1096804 | Cathinone Hydrochloride CI (50 mg) (alpha-Aminopropiophenone Hydrochloride) |
| 06300-0 | 5-Benzyl-3,6-dioxo-2-piperazineacetic Acid ( 250 mg ) (Limit Test) | 1043728 | Aspartame Related Compound A ( 75 mg ) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid) |
| 07350-3 | 2-(4-Biphenylyl)propionic Acid (100 mg) (Limit Test) | 1285760 | Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid) |
| 07480-1 | N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide ( 50 mg ) (Limit Test) | 1344724 | lopamidol Related Compound A ( 50 mg ) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide) |
| 07500-4 | 4,4'-Bis[4-(p-chlorophenyl)-4-hydroxypiperidino]-butyrophenone ( 25 mg ) (Limit Test) | 1303013 | Haloperidol Related Compound A ( 25 mg ) ( $4,4-\operatorname{Bis}[4-\mathrm{p}-$ chlorophenyl)-4-hydroxypiperidino]-butyrophenone |
| 08650-5 | Calcium Formyltetrahydrofolate ( 50 mg ) (AS) (For Qualitiative Use Only) | 1286027 | Folic Acid Related Compound A ( 50 mg ) (Calcium Formyltetrahydrofolate) |
| 11230-0 | p -Chlorobenzhydrylpiperazine ( 25 mg ) | 1333058 | Hydroxyzine Related Compound A ( 25 mg ) (p-Chlorobenzhydrylpiperazine) |
| 11310-9 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxaldehyde ( 25 mg ) (Limit Test) | 1370349 | Lorazepam Related Compound C (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde) |
| 11320-0 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxylic Acid ( 25 mg ) (Limit Test) | 1370350 | Lorazepam Related Compound D (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid) |
| 11330-2 | 6-Chloro-4-(o-chloro-phenyl)-2-quinazoline Methanol ( 25 mg ) (Limit Test) | 1370360 | Lorazepam Related Compound E ( 25 mg ) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol) |
| 11400-0 | 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one ( 50 mg ) (Limit Test) | 1468400 | Nordazepam CIV (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) |
| 11500-2 | 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4 -oxide ( 25 mg ) (Limit Test) | 1110020 | Chlordiazepoxide Related Compound A ( 25 mg ) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide) |
| 11510-4 | 2-Chloro-4-N-furfuryl-amino-5-sulfamolybenzoic acid ( 50 mg ) (Limit Test) | 1287020 | Furosemide Related Compound A ( 50 mg ) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid) |
| 11550-1 | 2-Chloro-3,5-dimethyl-phenol ( 50 mg ) (Limit Test) | 1122722 | Chloroxylenol Related Compound A (50 mg) (2-Chloro-3,5-dimethyl-phenol) |
| 11650-4 | (o-Chlorophenyl)diphenyl-methanol (25 mg) (Limit Test) | 1141024 | Clotrimazole Related Compound A ( 25 mg ) ((o-Chlorophe-nyl)diphenyl-methanol ) |
| 11670-8 | 4-(4-Chlorophenyl)-2-pyrrolidinone (75 mg) (Limit Test) | 1048222 | Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone) |

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## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. <br> No. | New Description |
| :---: | :---: | :---: | :---: |
| 11900-3 | 4-Chloro-5-sulfamoylanthranilic Acid (100 mg) (Limit Test) | 1287030 | Furosemide Related Compound B (100 mg) (4-Chloro-5sulfamoylanthranilic Acid) |
| 1119309 | 4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid ( 100 mg ) | 1119309 | Chlorthalidone Related Compound A (25 mg) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid) |
| 1153001 | Cyclizine ( 1 g ) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F (04/04) |
| 15870-8 | Cyclosporine U (25 mg) DISCONTINUED | 1158650 | Cyclosporine Resolution Mixture ( 25 mg ) (Replaces Cat. No. 15870-8 Cyclosporine U ( 25 mg )) |
| 21000-3 | alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride ( 125 mg ) (Limit Test) | 1575206 | Propoxyphene Related Compound A ( 50 mg ) (alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride) |
| 1268820 | Etoposide Related Compound A ( 25 mg ) (4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-alpha-D-glucopyranoside) DISCONTINUED | 1268852 | Etoposide Resolution Mixture ( 30 mg ) |
| 1269006 | Evans Blue (200 mg) | N/A | DISCONTINUED, Last Lot/Valid Use Date: G (04/04) |
| 1277208 | Fluoride Dentifrice: Sodium Fluoride-Calcium Pyrophosphate (high beta-phase) ( 180 g ) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F (01/04) |
| 32720-4 | 3-Hydroxy-1-methylquinuclidinium Bromide ( 250 mg ) (Limit Test) | 1135021 | Clidinium Bromide Related Compound A (250 mg) (3-Hydro-xy-1-methylquinuclindinium Bromide) |
| 1329505 | 9-Hydroxypropantheline Bromide ( 50 mg ) | 1329505 | Propantheline Bromide Related Compound A ( 50 mg ) (9Hydroxypropantheline bromide) |
| 1330005 | Hydroxypropyl Methylcellulose ( 250 mg ) | 1330005 | Hypromellose (250 mg) (Hydroxypropyl Methylcellulose) |
| 33010-7 | Hydroxypropyl Methylcellulose Phthalate ( 100 mg ) | 1335304 | Hypromellose Phthalate ( 100 mg ) |
| 1362001 | Levo-alpha-acetylmethadol Hydrochloride CII (25 mg) (AS) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F-1 (08/03) |
|  | Melting Point Standard - Acetanilide ( 500 mg ; approximately 114 degrees) | 1004001 | Acetanilide Melting Point Standard ( 500 mg ) (Approximately 114 degrees) |
|  | Melting Point Standard - Caffeine (1 g; approximately 236 degrees) | 1086006 | Caffeine Melting Point Standard (1 g) (Approximately 236 degrees) |
|  | Melting Point Standard - Phenacetin (500 mg; approximately 135 degrees) | 1514008 | Phenacetin Melting Point Standard ( 500 mg ) (Approximately 135 degrees) |
|  | Melting Point Standard - Sulfanilamide ( 1 g ; approximately 165 degrees) | 1633007 | Sulfanilamide Melting Point Standard ( 500 mg ) (Approximately 165 degrees) |
|  | Melting Point Standard - Sulfapyridine ( 2 g ; approximately 191 degrees) | 1635002 | Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees) |
|  | Melting Point Standard - Vanillin (1 g; approximately 82 degrees) | 1711009 | Vanillin Melting Point Standard (1 g) (Approximately 82 degrees) |
| 1420006 | 3-Methoxytyrosine ( 50 mg ) | 1420006 | Levodopa Related Compound B (50 mg) (3-Methoxytyrosine) |
| 42420-0 | 2-Methylamino-5-chlorobenzophenone (25 mg) (Limit Test) | 1185020 | Diazepam Related Compound A ( 25 mg ) (2-Methylamino-5chlorobenzophenone) |
| 42430-2 | 3-O-Methylcarbidopa (50 mg) | 1095517 | Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa) |
| 1434000 | Methylphenidate Hydrochloride Erythro Isomer CII (25 mg) DISCONTINUED; please order 1434011 | 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution CII ( 0.5 mL ) |
| 1445222 | Mitoxantrone Related Compound A Hydrochloride ( 30 mg ) (8-amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]a-minol-9,10-anthracenedione Hydrochloride) DISCONTINUED; Please order 1445211 | 1445211 | Mitoxantrone System Suitability Mixture ( 0.3 mg ) |
| 46600-7 | 5-Nitro-2-furfuraldazine (500mg) | 1466007 | Nitrofurazone Related Compound A (500mg) (5-Nitro-2furfuraldazine) |
| 46660-8 | 3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid ( 25 mg ) (Limit Test) | 1078336 | Bumetanide Related Compound B ( 25 mg ) (3-Nitro-4-phe-noxy-5-sulfamoylbenzoic Acid) |
| 1477900 | Octyl Methoxycinnamate ( 500 mg ) | 1477900 | Octinoxate ( 500 mg ) (Octyl Methoxycinnamate) |
| 49400-2 | Pancreatin (2 g) | $\begin{array}{\|l} \hline 1494057 \\ \text { and/or } \\ 1494079 \end{array}$ | Pancreatin Amylase and Protease (2 g) and/or Pancreatin Lipase (2 g) |

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## Cross Reference List

| Former Cat. No. | Former Description/Cross Reference | Cat. No. | New Description |
| :---: | :---: | :---: | :---: |
| 1527000 | Phenprocoumon (200 mg) DISCONTINUED | N/A | DISCONTINUED, Last Lot/Valid Use Date: F-1 (02/04) |
| 53180-1 | Phenylcyclohexylglycolic Acid (100 mg) (Limit Test) | 1485114 | Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid) |
| 53350-1 | alpha-Phenyl-2-piperidineacetic Acid Hydrochloride ( 50 mg ) (Limit Test) | 1434022 | Methylphenidate Related Compound A (50 mg) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride) |
| 54500-1 | Plastic, Negative Control | 1546707 | Polyethylene, High Density (3 strips) |
| 61500-5 | Sodium Taurocholate (20 g) | 1071304 | Bile Salts (10 g) (Sodium Taurocholate) |
| 68800-9 | 3 -(3,4,6-Trihydroxyphenyl)-alanine (50 mg) (Limit Test) | 1361010 | Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydrox-yphenyl)-alanine) |
|  | Vitamin B1 Hydrochloride | 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) |
|  | Vitamin B2 | 1603006 | Riboflavin ( 500 mg ) (Vitamin B2) |
|  | Vitamin B3 | 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) |
|  | Vitamin B5 | 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) |
|  | Vitamin B6 | 1587001 | Pyridoxine Hydrochloride ( 200 mg ) (Vitamin B6) |
|  | Vitamin B12 | 1152009 | Cyanocobalamin ( 1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) |
|  | Vitamim Bc | 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) |
|  | Vitamin C | 1043003 | Ascorbic Acid (1 g) (Vitamin C) |
|  | Vitamin D2 | 1239005 | Ergocalciferol ( $150 \mathrm{mg} ; 30 \mathrm{mg} /$ ampule; 5 ampules) (Vitamin D2) |
|  | Vitamin D3 | 1131009 | Cholecalciferol ( $30 \mathrm{mg} / \mathrm{ampul}$; 5 ampuls) (Vitamin D3) |
|  | Vitamin E Alcohol | 1667600 | Alpha Tocopherol ( 250 mg ) (Vitamin E Alcohol) |
|  | Vitamin E Acetate | 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) |
|  | Vitamin E Acid Succinate | 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) |
|  | Vitamin K1 | 1538006 | Phytonadione ( 500 mg ) (Vitamin K1) |
|  | Vitamin K3 | 1381006 | Menadione ( 200 mg ) (Vitamin K3) |
|  | Vitamin M | 1286005 | Folic Acid (500 mg) (Vitamin M or Vitamin Bc) |

USP Authentic Substances

| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| Catalog Number | Description | Current Lot | Price |
| 1005706 | Glacial Acetic Acid (1.5 mL/ampule; 3 ampules) (AS) | F0D002 | \$156 |
| 1042000 | Aprobarbital CIII (200 mg) (AS) | F-1 | \$207 |
| 1059003 | Benzphetamine Hydrochloride CIII (200 mg) (AS) | F-1 | \$207 |
| 1076341 | Boric Acid (1 g) (AS) | F0D036 | \$200 |
| 1082708 | Butylated Hydroxytoluene (500 mg) (AS) | F0D122 | \$156 |
| 1086334 | Calcium Acetate (1 g) (AS) | F0D156 | \$156 |
| 1086403 | Calcium Carbonate (1 g ) (AS) | F0D099 | \$156 |
| 1086436 | Calcium Chloride (1 g) (AS) | F0D153 | \$156 |
| 1086855 | Calcium Hydroxide (1 g) (AS) | F0D168 | \$156 |
| 1089004 | Cannabidiol CI (25 mg) (AS) | F-2 | \$207 |
| 1090003 | Cannabinol CI (25 mg) (AS) |  | \$207 |
| 1133503 | Cholic Acid (2 g) (AS) | F3B159 | \$156 |
| 1183002 | Diacetylmorphine Hydrochloride CI (25 mg) (AS) (Heroin Hydrochloride) | $J$ | \$207 |
| 1210105 | N -(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8-germaspiro [4:5]decane-1,3-dione (AS) | F | \$156 |
| 1251000 | Estradiol Benzoate ( 250 mg ) (AS) | G-1 | \$156 |
| 1302305 | Halazepam CIV (200 mg) (AS) | F1C224 | \$207 |
| 1356950 | Lauroyl Polyoxylglycerides ( 500 mg ) (AS) | F0D020 | \$156 |
| 1371002 | Lysergic Acid Diethylamide Tartrate CI (10 mg) (AS) (LSD) | 1 | \$207 |
| 1374260 | Magnesium Hydroxide (1 g) (AS) | F0D158 | \$156 |
| 1375127 | Manganese Chloride (1 g) (AS) | F0D150 | \$156 |
| 1375149 | Manganese Sulfate (1 g) (AS) | F0D151 | \$156 |
| 1410002 | Methicillin Sodium ( 500 mg ) (AS) | J0C333 | \$156 |
| 1424506 | Methylcellulose (1 g) (AS) | G0B222 | \$156 |
| 1425000 | 4-Methyl-2,5-dimethoxyamphetamine Hydrochloride Cl (25 mg) (AS) (STP) | F | \$207 |
| 1429000 | Methylenedioxy-3,4-amphetamine Hydrochloride Cl (25 mg) (AS) (MDA) | F-1 | \$207 |
| 1447002 | Morphine Monohydrate CII (50 mg) (AS) | G | \$207 |
| 1516003 | Phencyclidine Hydrochloride CII (25 mg) (AS) | G1B025 | \$207 |
| 1547925 | Polysorbate 20 (2 g) (AS) | F0D130 | \$156 |
| 1547947 | Polysorbate 60 (2 g) (AS) | F0D131 | \$156 |
| 1547969 | Polysorbate 80 (2 g) (AS) | F0D132 | \$156 |
| 1548101 | Potassium Benzoate (1 g) (AS) | F0D161 | \$156 |
| 1548134 | Potassium Bicarbonate (1 g) (AS) | F0D074 | \$156 |
| 1548167 | Potassium Carbonate (1 g) (AS) | F0D075 | \$156 |
| 1548190 | Potassium Chloride (1 g) (AS) | F0D127 | \$156 |
| 1548280 | Potassium lodide (1 g) (AS) | F0D078 | \$156 |
| 1572208 | Propionic Acid ( 1.5 mL /ampule; 3 ampules) (AS) | F0D029 | \$156 |
| 1613407 | Sodium Acetate (1 g) (AS) | F0D083 | \$156 |
| 1613757 | Sodium Carbonate Anhydrous (1 g) (AS) | F0D100 | \$156 |
| 1614396 | Sodium Metabisulfite (1 g) (AS) | F0D111 | \$156 |
| 1614454 | Sodium Nitrite (1 g) (AS) | F0D117 | \$156 |
| 1614807 | Sodium Sulfate Anhydrous (1 g) (AS) | F0D112 | \$156 |
| 1667585 | Titanium Dioxide (1 g) (AS) | F0D079 | \$156 |
| 1724769 | Zinc Sulfate (1 g) (AS) | F0D133 | \$156 |

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## Dietary Supplement Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| AMINO ACIDS |  |  |  |
| 1012509 | L-Alanine (200 mg) | F-2 | \$156 |
| 1021000 | Aminocaproic Acid (200 mg) | F-4 | \$156 |
| 1042500 | L-Arginine (200 mg) | G-1 | \$156 |
| 1042601 | Arginine Hydrochloride ( 125 mg ) | G0B060 | \$124 |
| 1161509 | L-Cysteine Hydrochloride ( 200 mg ) | H | \$156 |
| 1294976 | Glutamic Acid ( 200 mg ) | F0C069 | \$156 |
| 1294808 | Glutamine ( 100 mg ) | FOB244 | \$156 |
| 1295800 | Glycine ( 200 mg ) | F-3 | \$156 |
| 1308505 | L-Histidine ( 200 mg ) | G0A018 | \$156 |
| 1349502 | L-Isoleucine ( 200 mg ) | F-2 | \$156 |
| 1357001 | L-Leucine (200 mg) | H0B237 | \$156 |
| 1359903 | Levocarnitine ( 400 mg ) | G0B197 | \$156 |
| 1359925 | Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride) | F-1 | \$208 |
| 1371501 | L-Lysine Acetate ( 200 mg ) | F1C027 | \$156 |
| 1372005 | L-Lysine Hydrochloride (200 mg) | H | \$156 |
| 1411504 | L-Methionine ( 200 mg ) | G | \$156 |
| 1530503 | L-Phenylalanine ( 200 mg ) | H | \$156 |
| 1568506 | L-Proline (200 mg) | F-2 | \$156 |
| 1612506 | L-Serine (200 mg) | G | \$156 |
| 1667202 | L-Threonine ( 200 mg ) | G | \$156 |
| 1700501 | L-Tryptophan (200 mg) | G-1 | \$156 |
| 1705006 | L-Tyrosine ( 500 mg ) | K0C141 | \$156 |
| 1708503 | L-Valine ( 200 mg ) | F-2 | \$156 |
| BOTANICALS |  |  |  |
| BLACK COHOSH |  |  |  |
| 1076206 | Powdered Black Cohosh Extract (1.5 g) | F0D086 | \$520 |
| CAPSAICIN/CAPSICUM |  |  |  |
| 1091108 | Capsaicin (100 mg) | G-1 | \$156 |
| 1200600 | Dihydrocapsaicin (25 mg) | G0C071 | \$156 |
| CHAMOMILE |  |  |  |
| 1040708 | Apigenin-7-Glucoside ( 30 mg ) | F | \$487 |
| CHASTE TREE |  |  |  |
| 1105009 | Powdered Chaste Tree Extract (1.5 g) | FOC406 | \$520 |
| CRANBERRY LIQUID |  |  |  |
| 1134368 | Citric Acid (200 mg) | F1B092 | \$156 |
| 1181302 | Dextrose ( 500 mg ) | J-1 | \$124 |
| 1286504 | Fructose (125 mg) | I-2 | \$124 |
| 1374601 | Malic Acid (200 mg) | G0B158 | \$156 |
| 1594506 | Quinic Acid ( 200 mg ) | F | \$156 |
| 1617000 | Sorbitol (125 mg) | H1B139 | \$124 |
| 1623637 | Sucrose ( 100 mg ) | H1C223 | \$156 |
| ELEUTHERO |  |  |  |
| 1234704 | Powdered Eleuthero Extract (1.5 g) | F0C291 | \$520 |
| ECHINACEA |  |  |  |
| 1115545 | Chlorogenic Acid ( 50 mg ) | FOC420 | \$156 |
| 1231728 | Powdered Echinacea Purpurea Extract (1 g) | F0D018 | \$520 |
| 1231706 | Powdered Echinacea Angustifolia Extract (1 g) | F0D019 | \$520 |
| 1305507 | 2E, 4E-Hexadienoic Acid Isobutylamide ( 25 mg ) | F0C353 | \$540 |

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## Dietary Supplement Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| FEVERFEW |  |  |  |
| 1500400 | Parthenolide ( 25 mg ) | F | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| GARLIC |  |  |  |
| 1012145 | Agigenin (25 mg) | F | \$156 |
| 1012950 | Alliin (25 mg) | F | \$1,525 |
| 1115556 | beta-Chlorogenin ( $20 \mathrm{mg} \mathrm{)}$ | F | \$156 |
| 1294848 | gamma-Glutamyl-S-allyl-L-cysteine ( 25 mg ) | F | \$675 |
| 1411504 | L-Methionine (200 mg) | G | \$156 |
| GARLIC FLUID EXTRACT |  |  |  |
| 1013057 | S-Allyl-L-Cysteine (25 mg) | F | \$487 |
| GINGER |  |  |  |
| 1091108 | Capsaicin (100 mg) | G-1 | \$156 |
| 1291504 | Powdered Ginger (500 mg) | F | \$156 |
| GINKGO |  |  |  |
| 1115545 | Chlorogenic Acid ( 50 mg ) | FOC420 | \$156 |
| 1592409 | Quercetin ( 500 mg ) | F0B015 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| AMERICAN GINSENG |  |  |  |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | FOB289 | \$520 |
| ASIAN GINSENG |  |  |  |
| 1291708 | Powdered Asian Ginseng Extract (1.5 g) | FOB289 | \$520 |
| HAWTHORN LEAF WITH FLOWER |  |  |  |
| 1115545 | Chlorogenic Acid ( 50 mg ) | FOC420 | \$156 |
| 1335202 | Hyperoside ( 50 mg ) | F | \$855 |
| 1592409 | Quercetin (500 mg) | F0B015 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| 1717708 | Vitexin ( 30 mg ) | F0C142 | \$520 |
| KAVA |  |  |  |
| 1355709 | Powdered Kava Extract (1 g) | F0C161 | \$260 |
| KAWAIN |  |  |  |
| 1355753 | Kawain (200 mg) | F0C160 | \$208 |
| LICORICE |  |  |  |
| 1295888 | Glycyrrhizic Acid (25 mg) | F0C006 | \$487 |
| MILK THISTLE |  |  |  |
| 1443850 | Powdered Milk Thistle Extract (250 mg) | F0B321 | \$260 |
| 1612630 | Silybin ( 50 mg ) | F | \$156 |
| 1612641 | Silydianin ( 20 mg ) | F | \$156 |
| RED CLOVER |  |  |  |
| 1286060 | Formononetin ( 50 mg ) | F0C196 | \$520 |
| 1599500 | Powdered Red Clover Extract (500 mg) | FOC188 | \$260 |
| SAW PALMETTO |  |  |  |
| 1424233 | Methyl Caprate ( 300 mg ) | F | \$156 |
| 1424244 | Methyl Caproate ( 300 mg ) | F | \$156 |
| 1424255 | Methyl Caprylate ( 300 mg ) | F | \$156 |
| 1430305 | Methyl Laurate ( 500 mg ) | G0C356 | \$156 |
| 1430327 | Methyl Linoleate ( $5 \times 50 \mathrm{mg}$ ) | F | \$156 |
| 1430349 | Methyl Linolenate ( $5 \times 50 \mathrm{mg}$ ) | F | \$156 |
| 1431501 | Methyl Myristate ( 300 mg ) | G0C357 | \$156 |

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| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1431556 | Methyl Oleate ( 500 mg ) | G0C148 | \$156 |
| 1431603 | Methyl Palmitate ( 300 mg ) | F | \$156 |
| 1431625 | Methyl Palmitoleate ( 300 mg ) | F | \$156 |
| 1437508 | Methyl Stearate ( 300 mg ) | F | \$156 |
| ST. JOHN S WORT |  |  |  |
| 1115545 | Chlorogenic Acid (50 mg) | F0C420 | \$156 |
| 1335202 | Hyperoside ( 50 mg ) | F | \$855 |
| 1485001 | Oxybenzone ( 150 mg ) | H0B263 | \$156 |
| 1606503 | Rutin ( 100 mg ) | F | \$156 |
| VALERIAN |  |  |  |
| 1707908 | Valerenic Acid (15 mg) | H0D126 | \$696 |
| MISCELLANEOUS DIETARY SUPPLEMENTS |  |  |  |
| 1133570 | Chondroitin Sulfate Sodium ( 300 mg ) | F0B256 | \$156 |
| 1133638 | Chromium Picolinate ( 100 mg ) | F | \$156 |
| 1150353 | Creatinine ( 100 mg ) | F | \$156 |
| 1294207 | Glucosamine Hydrochloride ( 200 mg ) | F0C363 | \$156 |
| 1611955 | Selenomethionine ( 100 mg ) | FOB006 | \$156 |
| VITAMINS-MINERALS |  |  |  |
| 1043003 | Ascorbic Acid (1 g) (Vitamin C) | Q0B012 | \$156 |
| 1071508 | Biotin ( 200 mg ) | H1B019 | \$156 |
| 1086356 | Calcium Ascorbate (200 mg) | F-1 | \$156 |
| 1087009 | Calcium Pantothenate (200 mg) (Vitamin B5) | O0C331 | \$156 |
| 1131009 | Cholecalciferol ( $30 \mathrm{mg} / \mathrm{ampule}$; 5 ampules) (Vitamin D3) | M0B157 | \$159 |
| 1131803 | Delta-4,6-cholestadienol ( 30 mg ) | F | \$156 |
| 1152009 | Cyanocobalamin (1.5 g of mixture with mannitol; $10.7 \mathrm{mcg} / \mathrm{mg}$ of mixture) (Vitamin B12) | N | \$156 |
| 1179504 | Dexpanthenol ( 500 mg ) | J0C293 | \$160 |
| 1239005 | Ergocalciferol ( $30 \mathrm{mg} / \mathrm{ampule;} 5$ ampules) (Vitamin D2) | P0B275 | \$168 |
| 1241007 | Ergosterol ( 50 mg ) | H | \$156 |
| 1286005 | Folic Acid ( 500 mg ) (Vitamin M or Vitamin Bc) | P | \$156 |
| 1286027 | Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate) | IOB176 | \$156 |
| 1381006 | Menadione (200 mg) (Vitamin K3) | H-3 | \$156 |
| 1461003 | Niacin (200 mg) | H2C121 | \$156 |
| 1462006 | Niacinamide ( 500 mg ) (Vitamin B3) | M-1 | \$156 |
| 1494501 | Panthenol, Racemic ( $200 \mathrm{mg} \mathrm{)}$ | G | \$156 |
| 1494807 | Pantolactone ( 500 mg ) | F | \$487 |
| 1538006 | Phytonadione ( 500 mg ) (Vitamin K1) | N0B303 | \$156 |
| 1550001 | Potassium Gluconate (200 mg) | H0C064 | \$156 |
| 1587001 | Pyridoxine Hydrochloride (200 mg) (Vitamin B6) | P | \$156 |
| 1603006 | Riboflavin ( 500 mg ) (Vitamin B2) | N0C021 | \$156 |
| 1613509 | Sodium Ascorbate ( $200 \mathrm{mg} \mathrm{)}$ | G2C067 | \$156 |
| 1614002 | Sodium Fluoride (1 g) | H-1 | \$156 |
| 1656002 | Thiamine Hydrochloride ( 500 mg ) (Vitamin B1 Hydrochloride) | $\bigcirc$ | \$156 |
| 1667600 | Alpha Tocopherol (250 mg) (Vitamin E Alcohol) | M | \$156 |
| 1667701 | Alpha Tocopheryl Acetate ( 250 mg ) (Vitamin E Acetate) | K | \$156 |
| 1667803 | Alpha Tocopheryl Acid Succinate ( 250 mg ) (Vitamin E Succinate) |  | \$156 |
| 1716002 | Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil) | V0C258 | \$156 |
| 1717504 | Vitamin D Assay System Suitability (1.5 g) | F | \$156 |

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## Controlled Substances Reference Standards Available from USP

| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1012906 | Alfentanil Hydrochloride CII (500 mg) | F0B016 | \$207 |
| 1014005 | Alphaprodine Hydrochloride CII (250 mg) | F | \$207 |
| 1015008 | Alprazolam CIV (200 mg) | H1C133 | \$207 |
| 1030001 | Amobarbital CII (200 mg) | F-2 | \$207 |
| 1036008 | Anileridine Hydrochloride CII ( $250 \mathrm{mg} \mathrm{)}$ | F | \$207 |
| 1042000 | Aprobarbital CIII (200 mg) (AS) | F-1 | \$207 |
| 1059003 | Benzphetamine Hydrochloride CIII (200 mg) (AS) | F-1 | \$207 |
| 1078700 | Buprenorphine Hydrochloride CIII ( 50 mg ) | F-1 | \$207 |
| 1079000 | Butabarbital CIII (200 mg) | H0C007 | \$207 |
| 1081002 | Butalbital CIII (200 mg) | H0C054 | \$207 |
| 1082504 | Butorphanol Tartrate CIV (500 mg) | $J$ | \$207 |
| 1089004 | Cannabidiol CI (25 mg) (AS) | F-2 | \$207 |
| 1090003 | Cannabinol CI (25 mg) (AS) |  | \$207 |
| 1096804 | Cathinone Hydrochloride CI (50 mg) (alpha-Aminopropiophenone Hydrochloride) | I | \$560 |
| 1109000 | Chlordiazepoxide CIV (200 mg) | IOB063 | \$207 |
| 1110009 | Chlordiazepoxide Hydrochloride CIV (200 mg) | G-4 | \$207 |
| 1140305 | Clonazepam CIV (200 mg) | G1B175 | \$207 |
| 1140509 | Clorazepate Dipotassium CIV (125 mg) | G0B027 | \$207 |
| 1143008 | Cocaine Hydrochloride CII (250 mg) | IOB074 | \$207 |
| 1143802 | Codeine N-Oxide CI (50 mg) | G0A034 | \$207 |
| 1144000 | Codeine Phosphate CII (100 mg) | JOC200 | \$207 |
| 1145003 | Codeine Sulfate CII (250 mg) | H-2 | \$207 |
| 1180004 | Dextroamphetamine Sulfate CII (500 mg) | IOC311 | \$216 |
| 1183002 | Diacetylmorphine Hydrochloride (Heroin Hydrochloride) CI (25 mg) (AS) | J | \$207 |
| 1185008 | Diazepam CIV (100 mg) | 1 | \$207 |
| 1187207 | Dichloralphenazone CIV (200 mg) | F0B010 | \$207 |
| 1194009 | Diethylpropion Hydrochloride CIV (200 mg) | H | \$207 |
| 1200804 | Dihydrocodeine Bitartrate CII (200 mg) | H | \$207 |
| 1219008 | Diphenoxylate Hydrochloride CII (200 mg) | I | \$207 |
| 1258305 | Ethchlorvynol CIV ( 0.7 ml ) | F0B011 | \$207 |
| 1270005 | Fentanyl Citrate CII (100 mg) | K0C264 | \$207 |
| 1280009 | Fluoxymesterone CIII (200 mg) | G-2 | \$207 |
| 1285002 | Flurazepam Hydrochloride CIV (200 mg) | J0C365 | \$207 |
| 1295006 | Glutethimide CII ( 500 mg ) | F | \$207 |
| 1302305 | Halazepam CIV (200 mg) (AS) | F1C224 | \$207 |
| 1307003 | Hexobarbital CIII ( 500 mg ) | F | \$207 |
| 1315001 | Hydrocodone Bitartrate CII (250 mg) | K0C217 | \$207 |
| 1315012 | Hydrocodone Bitartrate Related Compound A CII (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl) | F0C214 | \$513 |
| 1323000 | Hydromorphone Hydrochloride CII (50 mg) | J0C372 | \$207 |
| 1356009 | Ketamine Hydrochloride CIII ( $250 \mathrm{mg} \mathrm{)}$ | G-2 | \$207 |
| 1359506 | Levmetamfetamine Cll ( 75 mg ) | F | \$207 |
| 1364007 | Levorphanol Tartrate CII (500 mg) | H | \$207 |
| 1370305 | Lorazepam CIV (200 mg) | $10 \mathrm{CO48}$ | \$207 |
| 1371002 | Lysergic Acid Diethylamide Tartrate (LSD) Cl (10 mg) (AS) | 1 | \$207 |
| 1375309 | Mazindol CIV ( 350 mg ) | H | \$207 |
| 1383001 | Meperidine Hydrochloride CII (200 mg) | 1 | \$207 |
| 1386000 | Mephobarbital CIV (250 mg) | G | \$207 |
| 1389008 | Meprobamate CIV (200 mg) | G-1 | \$207 |
| 1398009 | Methadone Hydrochloride CII (200 mg) | IOB163 | \$207 |

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| Cat. <br> No. | Description | Curr. <br> Lot | Price |
| :---: | :---: | :---: | :---: |
| 1399001 | Methamphetamine Hydrochloride CII (125 mg) | I | \$207 |
| 1404000 | Methaqualone $\mathbf{C l}(500 \mathrm{mg}$ ) | F-1 | \$207 |
| 1405002 | Metharbital CIII ( 200 mg ) | F-2 | \$207 |
| 1413000 | Methohexital CIV ( 500 mg ) | F-2 | \$207 |
| 1425000 | 4-Methyl-2,5-dimethoxyamphetamine Hydrochloride (STP) CI (25 mg) (AS) | F | \$207 |
| 1429000 | Methylenedioxy-3,4-amphetamine Hydrochloride (MDA) CI (25 mg) (AS) | F-1 | \$207 |
| 1433008 | Methylphenidate Hydrochloride CII (125 mg) | I1C241 | \$165 |
| 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution CII ( 0.5 mL ) | F0C368 | \$560 |
| 1438001 | Methyltestosterone CIII ( 200 mg ) | $J$ | \$207 |
| 1447002 | Morphine Monohydrate CII (50 mg) (AS) | G | \$207 |
| 1448005 | Morphine Sulfate CII ( 500 mg ) | M0D016 | \$332 |
| 1452002 | Nalorphine Hydrochloride CIII (250 mg) | 1 | \$207 |
| 1453526 | Naltrexone Related Compound A CII (30 mg) ( N -(3-butenyl)-noroxymorphone hydrochloride) | F | \$207 |
| 1454008 | Nandrolone CIII ( 50 mg ) | F4D144 | \$560 |
| 1455000 | Nandrolone Decanoate CIII (250 mg) | I | \$207 |
| 1456003 | Nandrolone Phenpropionate CIII (250 mg) | H | \$207 |
| 1468400 | Nordazepam CIV (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) | H1B035 | \$560 |
| 1473002 | Noroxymorphone Hydrochloride CII ( 50 mg ) | H1C177 | \$560 |
| 1482003 | Oxandrolone CIII (50 mg) | G0B220 | \$207 |
| 1483006 | Oxazepam CIV (200 mg) | G-1 | \$207 |
| 1485191 | Oxycodone CII (200 mg) | IOB046 | \$207 |
| 1487007 | Oxymetholone CIII (200 mg) | G1B247 | \$207 |
| 1488000 | Oxymorphone CII ( 500 mg ) | H0B214 | \$207 |
| 1505007 | Pentazocine CIV ( 500 mg ) | 10 C 418 | \$207 |
| 1507002 | Pentobarbital CII ( 200 mg ) | H3C144 | \$207 |
| 1516003 | Phencyclidine Hydrochloride CII (25 mg) (AS) | G1B025 | \$207 |
| 1516502 | Phendimetrazine Tartrate CIII ( 350 mg ) | G | \$207 |
| 1523009 | Phenmetrazine Hydrochloride CII (200 mg) | F-2 | \$207 |
| 1524001 | Phenobarbital CIV (200 mg) | J | \$207 |
| 1528501 | Phentermine Hydrochloride CIV (200 mg) | H0B309 | \$207 |
| 1554501 | Prazepam CIV (500 mg) | G0C066 | \$207 |
| 1574000 | Propoxyphene Hydrochloride CII (1 g) | L0C285 | \$207 |
| 1575002 | Propoxyphene Napsylate CII (1 g) | H1C323 | \$207 |
| 1592205 | Quazepam CIV (200 mg) | F | \$207 |
| 1611004 | Secobarbital CII (200 mg) | H | \$207 |
| 1620005 | Stanozolol CIII ( 200 mg ) | F-3 | \$207 |
| 1623648 | Sufentanil Citrate Cll ( 25 mg ) | H0B208 | \$207 |
| 1643000 | Talbutal CIII ( 250 mg ) | F | \$207 |
| 1643408 | Temazepam CIV ( 200 mg ) | H0C205 | \$207 |
| 1645006 | Testolactone CIII ( 125 mg ) | F-1 | \$165 |
| 1646009 | Testosterone CIII ( 125 mg ) | 11B253 | \$165 |
| 1647001 | Testosterone Cypionate CIII ( 200 mg ) | H0D162 | \$207 |
| 1648004 | Testosterone Enanthate CIII ( 200 mg ) | $J$ | \$207 |
| 1649007 | Testosterone Propionate CIII ( $200 \mathrm{mg} \mathrm{)}$ | L1C005 | \$207 |
| 1656308 | Thiamylal CIII ( 200 mg ) | F | \$207 |
| 1661002 | Thiopental CIII ( 250 mg ) | 1 | \$207 |
| 1680506 | Triazolam CIV (200 mg) | H0B041 | \$207 |

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# CHROMATOGRAPHIC REAGENTS USED IN $\boldsymbol{U S P} \boldsymbol{- N F}$ AND PHARMACOPEIAL FORUM 

This is an update based on the proposals published in this issue of $P F$.

## CHROMATOGRAPHIC REAGENTS

## Chromatographic Reagents Used in USP-NF and Pharmacopeial Forum

September-October 2004

| ACYCLOVIR |  |  |  | DSD Mgh \#890 |
| :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(5) | L1 | MicroBondapak C18 | Assay and Limit of . | Assay and limit of guanine. $25 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 10$ $\mu \mathrm{m}$, manufacturer Waters Corp. |
|  | BUPIVACAINE HYDROCHLORIDE |  |  | DSD Mgh \#10490 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(5) | S3 | Porapak Q | Residual solvents | $2 \mathrm{~m} \times 4 \mathrm{~mm}$. Manufacturer Waters Corp. |
|  | DALTEPARIN SODIUM |  |  | DSD Mgh \#21930 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(5) | L\#\# | Dowex 1X8 | Molar ratio of sulfate to carboxylate | $1.5 \mathrm{~cm} \times 2.5 \mathrm{~cm}$ 200-400 mesh. Fluka P/N 44462 |
| 30(5) | L\#\# | Dowex 50W2 | Molar ratio of sulfate to carboxylate | $1.5 \mathrm{~cm} \times 7.5 \mathrm{~cm} 100-200$ mesh. Fluka Cat $\# 44339$ |
|  | ETIDRONATE DISODIUM |  |  | DSD Mgh \#32350 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(5) | L23 | IC-Pak Anion | Assay | $15 \mathrm{~cm} \times 4.6 \mathrm{~mm}$, manufacturer Waters Corp. |
| 30(5) | L46 | Ion Pac AS11 | Phosphite | $25 \mathrm{~cm} \times 4.6 \mathrm{~mm}$, manufacturer Dionex. |
|  | FINASTERIDE TABLETS |  |  | DSD Mgh \#33182 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(5) | L11 | Zorbax SB Phenyl | Dissolution | $15 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer Agilent Technologies. |
|  | INSULIN |  | Type of Test | DSD Mgh \#40520 |
| 30(5) | L20 | Zorbax GF250 | Limit of . . . . . . . . | Limit of high molecular weight proteins, $25 \mathrm{~cm} \times$ 9.4 mm . Manufacturer Agilent technologies. |
|  | MODAFINIL |  |  | DSD Mgh \#54521 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(5) | L1 | Inertsil ODS-2 | Assay and Related Compounds | $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}, 5$ : m, <br> $15 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer GL Science. |
|  | MODAFINIL TABLETS |  |  | DSD Mgh \#54523 |
| 30(5) | L1 | Inertsil ODS-2 | Assay and Related Compounds | $15 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer GL |
|  | PRILOCAINE |  |  | DSD Mgh \#68980 |
| 30(5) | L1 | Symmetry C-18 | Related compounds | $15 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer Waters Corp. |
| 30(5) | L1 | Symmetry C-18 | Limit of . | Limit of prilocaine related compound A. $15 \mathrm{~cm} x$ $4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer Waters Corp. |
|  |  |  | 1 |  |

## CHROMATOGRAPHIC REAGENTS

|  | TAGATOSE |  |  | DSD Mgh \#937 |
| :---: | :---: | :---: | :---: | :---: |
| 30(5) | L19 | Aminex HPX-87C | Assay | $30 \mathrm{~cm} \times 7.8 \mathrm{~mm}, 9 \mu \mathrm{~m}$, manufacturer BIO RAD Laboratories. |

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[^336]
## STANDARDS DEVELOPMENT

This section presents an overview of the public review and comment process, conducted through Pharmacopeial Forum $(P F)$, for the development of official pharmaceutical standards.

USP publishes Pharmacopeial Forum (PF) bimonthly as the working vehicle of the USP Council of Experts. PF provides interested parties an opportunity to review and comment as the Council of Experts develops or revises standards for the United States Pharmacopeia and the National Formulary (USP-NF).
$P F$ includes the following:

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USP welcomes comments and data on potential, proposed, or official standards. ${ }^{*}$ Comments, along with USP's responses, will be published either in PF Briefings, the Commentary section of $P F$, the Commentary section of Supplements to USP-NF, or the Commentary section of $U S P-N F$.
[^337]The chart below shows the public review and comment process and its relationship to standards development.

# Public Review and Comment Process for Standards Development 



Questions on the process should be addressed to John W. Gasper, M.A., J.D., Director, Office of the Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: jg@usp.org).

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## HOW TO USE PF

This section provides descriptions of the various parts of $P F$. It also includes Committee Designations and the Staff Directory.

The contents of the different sections of $P F$ are briefly described below. Readers will get an idea of how each section is relevant to their job functions. They may contact USP scientific staff liaisons or staff members of the Executive Secretariat (listed in the Staff Directory) if they have any questions. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a Request for Revision is available on the USP website (www.usp.org/standards/revisionguideline/).

Proposed and Adopted Revisions

| Section | Content | How Readers Can Respond |
| :---: | :---: | :---: |
| Pharmacopeial <br> Previews <br> Early ideas for revisions | -Briefing: Scientific rationale for potential inclusion or change. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -Potential revisions not yet targeted for official adoption that require a longer public review and comment process because of issues such as: <br> - the controversial nature of an item; <br> - the application of new technologies that require further study; and <br> - articles produced by multiple sources. | Review drafts and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview. |
| In-Process Revision Revisions targeted for adoption | -BriEfing: Scientific rationale for proposed changes. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. <br> -New and revised standards that have been approved for publication by the appropriate USP Committee when it is considering whether to advance standards to official status (see Standards Development). New or revised text is marked with symbols ( ${ }^{\square}$ or ) to specify the tentative earliest date on which the revision would be officially adopted. | Review material and send comments promptly to USP staff liaison (see the Staff Directory). Guidelines on how to comment are found at the end of the Policies and Announcements section. |
| Harmonization <br> Items the Pharmacopeial Discussion Group (PDG) is trying to harmonize internationally | -Briefing: Scientific rationale for the potential inclusion or change or for the proposed change. The designated stage of harmonization. The stage determines whether an item appears under Pharmacopeial Previews or under In-Process Revision, both separate sections of Harmonization. <br> -For In-Process Revision, new or revised text is marked with symbols (■) to specify the tentative, earliest date on which the revision would be officially adopted. | Review material and provide comments to the appropriate staff liaison cited in the Briefing preceding each Preview or In-Process Revision. |
| Interim Revision Announcement Adopted standards | Standards that have been adopted and will become officially binding on the specified date. Effective date is specified in the section's introductory page or within parentheses following a particular item. New or revised text is set off by the symbols ${ }^{\circ}$. | Review to see if affected by any of the changes. Note effective date when standards become official and ensure compliance. |

## Other Sections

## Committee Designations

Names of the committees (composed of volunteer scientific experts) that USP staff work with on the development of standards.

## Staff Directory

Names of all USP scientific staff liaisons with contact information.

## Policies and Announcements

- General scientific and policy issues affecting $U S P-N F$ standards and processes
- Update on standards-related issues being considered by USP
- Summaries of meetings of the Council of Experts
- Guidelines on how to comment
- Publication and comment schedules


## Stimuli to the Revision Process

- Articles on standards development issues authored by the USP Council of Experts, USP staff, or other interested parties
- Discussions of issues on which USP desires public input prior to further development


## Nomenclature

- Latest adopted United States Adopted Names (USAN) and International Nonproprietary Names (INN) for drugs
- Revisions to existing names as a supplement to the USP Dictionary of USAN and International Drug Names
- Suggested, proposed, and recommended USAN and INN
- Information on how nonproprietary drug names are devised
- Articles relevant to compendial nomenclature issues


## Index

Cumulative directory for the content of all issues of $P F$ beginning with $P F 30(1)$.

## Reference Standards Catalog

List of official USP Reference Standards specified in $U S P-N F$, along with availability and ordering information.

## Chromatographic Reagents Used in USP-NF and Pharmacopeial Forum

Update of chromatographic reagents based on the proposals published in this issue of $P F$.

## EXPERT COMMITTEE DESIGNATIONS*

The names of the Committees and their abbreviations are as follows:

| AER | Aerosols |
| :---: | :---: |
| AMB | Analytical Microbiology |
| BBP | Blood and Blood Products |
| BNA | Bioavailability and Nutrient Absorption |
| BNT | Biotechnology and Natural Therapeutics and Diagnostics |
| BPC | Biopharmaceutics |
| BST | Biostatistics |
| CRX | Compounding Pharmacy |
| DSB | Dietary Supplements-Botanicals |
| DSI | Dietary Supplements-Information |
| DSN | Dietary Supplements-Non-Botanicals |
| EMC | Excipient Monograph Content |
| ETM | Excipients-Test Methods |
| GCT | Gene Therapy, Cell Therapy, and Tissue Engineering |
| GTB | General Toxicity and Biocompatibility |
| NL | Nomenclature and Labeling |
| PA1 | Pharmaceutical Analysis 1 |
| PA2 | Pharmaceutical Analysis 2 |
| PA3 | Pharmaceutical Analysis 3 |
| PA4 | Pharmaceutical Analysis 4 |
| PA5 | Pharmaceutical Analysis 5 |
| PA6 | Pharmaceutical Analysis 6 |
| PA7 | Pharmaceutical Analysis 7-Antibiotics |
| PDF | Pharmaceutical Dosage Forms |
| PPC | Parenteral Products-Compounding and Preparation |
| PPI | Parenteral Products-Industrial |
| PSD | Packaging, Storage, and Distribution |
| PW | Pharmaceutical Waters |
| RMI | Radiopharmaceuticals and Medical Imaging |
| SMU | Safe Medication Use |
| VET | Veterinary Drugs |
| VVI | Vaccines, Virology, and Immunology |

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## STAFF DIRECTORY

This is an updated directory that reflects assignment changes based on the reorganization of USP. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Committee is not identified. The Fax number is (301) 816-8373.

| STAFF | E-MAIL | PHONE | ASSIGNMENT |
| :--- | :--- | :--- | :--- |
| Clydewyn M. Anthony, <br> Senior Scientific Associate | cma@usp.org | $(301) 816-8139$ | Pharmaceutical Analysis 1 <br> (PA1) |
| Frank P. Barletta, Consultant <br> Charles H. Barnstein, Consultant | fpb@usp.org <br> chbarnstein@ <br> email.msn.com | $(301) 816-8328$ | Pharmaceutical Waters (PW) |
| Daniel K. Bempong, <br> Scientist | dkb@usp.org | $(301) 774-9457$ | Nomenclature and Labeling <br> (NL) |
| Lokesh Bhattacharyya, Director, <br> Non-Complex Actives and <br> Excipients | Ib@usp.org | $(301) 816-8143$ | Excipient Monograph <br> Content (EMC) |
| Barbara A. Bowman, <br> Manager, Administrative <br> Services | bab@usp.org | $(301) 816-8201$ |  |
| William E. Brown, <br> Senior Scientist | web@usp.org | $(301) 816-8278$ | USP Correspondence |

STAFF DIRECTORY (continued)
\(\left.$$
\begin{array}{llll}\hline \text { STAFF } & \text { E-MAIL } & \text { PHONE } & \text { ASSIGNMENT } \\
\hline \begin{array}{c}\text { Gabriel I. Giancaspro, } \\
\text { Associate Director and } \\
\text { Latin American Liaison }\end{array} & \text { gig@usp.org } & (301) 816-8343 & \begin{array}{c}\text { Dietary Supplements-Botani- } \\
\text { cals (DSB); Dietary } \\
\text { Supplements-Bioavail- }\end{array}
$$ <br>

ability and Nutrient\end{array}\right]\)| Absorption (BNA) |
| :---: |

STAFF DIRECTORY (continued)

| STAFF | E-MAIL | PHONE | ASSIGNMENT |
| :---: | :---: | :---: | :---: |
| Salvador Salado, Scientist and Latin American Liaison | ss@usp.org | (301) 816-8165 | Pharmaceutical Analysis 3 (PA3) |
| Stefan P. Schuber, Director, Standards Development and Administration | sps@usp.org | (301) 816-8551 |  |
| Catherine M. Sheehan, Senior Scientific Associate | cxs@usp.org | (301) 816-8262 | Excipient Monograph Content (EMC) |
| Eric B. Sheinin, Vice President, Department of Standards Development | es@usp.org | (301) 816-8103 |  |
| Radhakrishna S. Tirumalai, Scientist | rst@usp.org | (301) 816-8339 | Blood \& Blood Products (BBP); General Toxicology and Biocompatibility (GTB) |
| Andrzej Wilk, Scientist | aw@usp.org | (301) 816-8305 | Pharmaceutical Analysis 5 (PA5); Radiopharmaceuticals and Medical Imaging (RMI) |
| William W. Wright, Scientific Fellow | www@usp.org | (301) 816-8335 | Pharmaceutical Analysis 7Antibiotics (PA7a) |
| Kahkashan Zaidi, Scientist | kxz@usp.org | (301) 816-8269 | Aerosols (AER) |

## POLICIES AND ANNOUNCEMENTS

In this section, readers may find statements about general scientific and policy issues that may have an impact on $U S P-N F$ standards and processes, announcements about issues being considered by USP, and summaries of Council of Experts meetings. This section also includes publication and comment schedules.

## In Memoriam

## Leonard C. Bailey, Ph.D.

Last summer the United States Pharmacopeia lost a strong contributor and friend-for 15 years Leonard C. Bailey, Ph.D., brought to USP both his considerable energy and commitment as a member of the Committee of Revision/Expert Committees.

Dr. Bailey was foremost an educator, but he had experience in the pharmaceutical industry and a strong background as a pharmacist. The latter experience stood him well in focusing the need for standards that were meaningful in the physician/pharmacist/patient interface.

Most distinctive were Dr. Bailey's commitment to objective science, his insistence on data in support of arguments, and his discounting of merely institutional arguments. His areas of service to USP were the Packaging and Stability and Chemistry Subcommittees and later the Packaging, Storage, and Distribution Expert Committee. He also chaired a USP Advisory Panel on Compendial Items Storage, Shipment, and Distribution and was a member of an NF XIV Special Advisory Panel on Nuclear Magnetic Resonance Spectroscopy.
He provided motivation for and contributed to Stimuli articles and new general chapters that recognized the changing scientific basis of pharmaceutical packaging and distribution. A notable contribution was his work helping establish the concept of mean kinetic temperature (MKT) and the method of calculating it, which are now part of the USP definition for General Chapter Controlled Room Temperature and Pharmaceutical Stability $\langle 1150\rangle$.
Dr. Bailey was widely published in the area of pharmaceutical analysis and control, and he also served as a referee for a number of well-known journals in the field. Dr. Bailey was a popular speaker and was frequently invited to make presentations at conferences and seminars. As an educator, he was regularly recognized for his contributions. As a major advisor or co-advisor to many students, he played a key role in their development, and as a testament to his influence, they are found throughout the pharmaceutical industry.

Leonard Bailey was both liked and respected by his coworkers, students, and other USP volunteers. Our memory of him is warm, and we are grateful for the opportunity to have known and worked with him.

## Some memories of Dr. Bailey by colleagues-

"Dr. Leonard Bailey, a colleague of mine for over 40 years, was an intelligent, kind, and empathetic man. As a professor, he set high standards and was respected by students. As a research scientist, he was innovative and thorough. In his work on the USP Expert Committee on Packaging, Storage, and Distribution, he was insightful and energetic, dealing with all issues in a manner designed to protect the public. I valued his thoughts and counsel always.

I am grateful for the privilege of knowing Leonard Bailey. I, like many others, miss him very much."
—Thomas Medwick

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"As the liaison of the Committee, I have known and worked for Len for almost 10 years. He worked very hard on any project given to him, and he always made time to tackle difficult issues. When he wasn't sure, he took time to study the issue before dealing with it. He always stood by his conviction especially when data were involved. I remember his energy and desire to design a study approach for the shipping studies USP performed and to defend USP's position on MKT calculations. He was a nice, kind man, always willing to help, and easy going. I will miss him."
-Claudia Okeke
"I will miss Len Bailey. He not only was knowledgeable, clever and intelligent, but a good person, with a good heart and a great sense of humor. I remember him fondly, not only from my association with him from USP but also from my many years of working with him on various projects (along with Tom Medwick) from the New Jersey Pharmaceutical Quality Control Association while he was still active at Rutgers University."
-Herbert Letterman
"What I will always remember is Len's passion to see that the right things were done for the patient. He never forgot that it is the patient who ultimately matters, and I appreciated the enthusiasm he brought to our work. I will miss him."
-Robert H. Seevers
"USP lost a highly productive and reliable volunteer. Len was a true scientist who followed where the data and facts led. He had a large impact on the content of USP."
—Lee T. Grady
"It was a pleasure to work with Dr. Bailey and to have met him. USP and many, many others will miss his warm personality and competence."

> - Barry Coleman
"I worked with Len for many years and always appreciated his knowledge and his concern about doing the right things for the patient. I will miss him."
-Larry Paul
"Very sad news. I liked Len and respected his science a lot. I always thought of Len as the 'Father of MKT' at USP."
-David Newton
"Len was the epitome of what a professional pharmaceutical scientist should be. He brought to the workplace a perfect combination of good science, common sense, and professional concern for the ultimate beneficiary of the USP, the public. This is a great loss, and he will be missed by many."
-Edward M. Cohen

USAN COUNCIL SECRETARIAT REVISES USAN FEE-FOR-SERVICE CHARGES. A revised schedule of fee-for-service charges has been placed in effect as of January 1, 2004. The increased fees appear on the USAN submission forms that are provided under Appendix XI of the 2004 edition of the USP Dictionary of USAN and International Drug Names. This announcement will be important to inform those who are not yet using the revised 2004 edition of the changes in the USP Dictionary.

For further information please contact:
United States Adopted Names (USAN) Program
American Medical Association
515 North State Street
Chicago, IL 60610
Phone: 312-464-4046
Fax: 312-464-4028
Web site: http://www.ama-assn.org/go/usan

USP GUIDELINE FOR SUBMITTING REQUESTS FOR REVISION TO THE USP-NF. We are pleased to announce the availability of the USP Guideline for Submitting Requests for Revision to the $U S P-N F$. This document was developed in conjunction with the USP Council of Experts and its Expert Committees, USP Staff, and the Drug Substance, Complex Actives, and Excipients Project Teams of the Prescription/Nonprescription Stakeholders Forum. This document includes information
to aid submission of new monographs and revisions to existing monographs for Noncomplex Active Substances and Products, Biological and Biotech Substances and Products, Excipients, and Vaccines. It incorporates many of the concepts and suggestions included in the ICH Q3A, Q3B, Q3C, Q6A, and Q6B guidelines. These include the definition of a specification and incorporate much of the terminology of Q3A for the control of impurities. The guideline clearly defines the information needed for the USP's Council of Experts and its Expert Committees to evaluate a request for revision. The document is approximately 75 pages in length with about 25 pages of addenda and is available in PDF format from the USP website at www.usp.org. Hard copies will be provided upon request.

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education series has been developed to enhance the knowledge, skills, and expertise of pharmaceutical industry personnel.

The following list indicates tentatively scheduled course dates. For further information, contact Laura A. McCurry, Manager, Pharmacopeial Education, lam@usp.org, 301-816-8285; Diana Lenahan, Program Associate, dpl@ usp.org, 301-816-8530; or visit the website at www.usp. org/education to register. Call 301-816-8530 to get information on customized courses offered at USP or at your site.

Calendar of Pharmacopeial Education Courses, 2004

| Date | Name of course | Location |
| :--- | :--- | :--- |
| November 11 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| November 11 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| November 12 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |
| November 12 | Fundamentals of Dissolution (Lecture) | USP Headquarters, Rockville, MD |
| December 2 | Analytical Method Validation | USP Headquarters, Rockville, MD |
| December 8 | Standards 100: Fundamentals of the Use of $U S P-$ <br> $N F$ and the Standards Development Process | USP Headquarters, Rockville, MD |
| December 9 | Standards 101: Advanced Use of $U S P-N F$, General <br> Notices, and Monograph Chapters | USP Headquarters, Rockville, MD |

VISIT THE USP WEB SITE AT 〈http://www.usp.org〉. Various resources related to Pharmacopeial standards are presented, including highlights from $P F$.

## USP-NF AVAILABLE IN THREE ELECTRONIC

FORMATS. The trusted reference for official pharmaceutical standards is available in three convenient electronic formats- $C D$, intranet, and online. The $C D$ is ideal for single users who prefer to have $U S P-N F$ on their
hard drives. The intranet format allows Web browser-based access to multiple users within a company, through their own intranet server. The online format can be accessed by individual registered users through the World Wide Web. All three electronic formats provide fast and easy access to official $U S P-N F$ content. More information can be obtained by visiting www.usp.org/products or by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

CHROMATOGRAPHIC REAGENTS NOW AVAILABLE. Chromatographic Reagents lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic test methods that has been published in Pharmacopeial Forum ( $P F$ ) since 1980. Chromatographic Reagents also helps to track which column reagents were used to validate methods that have become official and are included in $U S P-N F$. The branded column reagents list is updated bimonthly through Pharmacopeial Forum. Chromatographic Reagents can be ordered by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

INTERNATIONAL CORRESPONDENCE. Individuals who wish to correspond with the European and Japanese Pharmacopoeias concerning monographs in the Official Inquiry and Consensus stages of international harmonization should address their comments to the coordinating pharmacopeia for a given article. The addresses for the European and Japanese Pharmacopoeias are as follows:

Technical Secretariat of the European Pharmacopoeia Commission B.P. 907

F 67029 Strasbourg Cedex 1
France

## NAKASHIMA Nobumasa

Evaluation and Licensing Division
Pharmaceutical and Medical Safety Bureau
Ministry of Health, Labour and Welfare, Japan
Tel. +81-3-3595-2431, Fax. +81-3-3597-9535
E-mail: nakashima-nobumasa@mhlw.go.jp

HOW TO SUBMIT COMMENTS. The USP welcomes and encourages interested parties to submit comments and data regarding potential, proposed, or adopted (official) standards. Submissions concerning a particular item that has appeared in a $P F$ should be submitted to the appropriate USP scientific staff liaison identified at the end of the Briefing accompanying each item. To submit comments and data to a liaison, use the e-mail address and telephone numbers listed in the Staff Directory included in every $P F$.

Please note that $U S P-N F$ is being published in an annual edition with one main book and two Supplements a year. In addition, the following schedule will repeat every year so that users will know what to expect and become familiar with the deadlines.

The publication and comment schedule for USP 27-NF 22 is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2003 | November 2003 | January 2004 |
| Supplement One | October 15,2003 | February 2004 | April 2004 |
| Supplement Two | February 17,2004 | June 2004 | August 2004 |

The publication and comment schedule for USP $28-N F 23$ is as follows:

|  | Comment Deadline | Publication Date | Official Date |
| :--- | :--- | :--- | :--- |
| Main Book | May 15, 2004 | November 2004 | January 2005 |
| Supplement One | October 15, 2004 | February 2005 | April 2005 |
| Supplement Two | February 17,2005 | June 2005 | August 2005 |

In the future, USP anticipates including the comment submission deadline in each briefing of every revision proposal when it is published for public review and comment.

For general inquiries or in cases where a particular liaison is not identified, use the general USP telephone number 301-881-0666 or FAX number 301-816-8373.

All official revisions are published in Supplements to USP-NF (twice yearly). Between Supplements, official revisions are published in PF in the Interim Revision Announcement; these revisions are also incorporated in the upcoming Supplement. The electronic version of $U S P-N F$ is updated as each Supplement becomes available and, therefore, contains all official text up to and including the contents of the latest Supplement.

Publication Schedules

| Publication | Publication Date | Official Date |
| :---: | :---: | :---: |
| $1^{\text {st }}$ Supplement | Feb. 2004 | Apr. 1, 2004 |
| $P F 30(2)$ [Mar.-Apr. 2004] | Mar. 2004 | Not Applicable |
| $2^{\text {nd }} I R A$ [published in $\left.P F 30(2)\right]$ | Mar. 2004 | Apr. 1, 2004 |
| $P F 30(3)[$ May-June 2004] | May 2004 | Not Applicable |
| $3^{\text {rd }} I R A$ [published in $\left.P F 30(3)\right]$ | May 2004 | June 1, 2004 |
| $2^{\text {nd }}$ Supplement | June 2004 | Aug. 1, 2004 |
| $P F 30(4)[$ July-Aug. 2004] | July 2004 | Not Applicable |
| $4^{\text {th }} I R A$ [published in $\left.P F 30(4)\right]$ | July 2004 | Aug. 1, 2004 |
| $P F 30(5)$ [Sept.-Oct. 2004] | Sept. 2004 | Not Applicable |
| $5^{\text {th }} I R A$ [published in $\left.P F 30(5)\right]$ | Sept. 2004 | Oct. 1, 2004 |
| $P F 30(6)[$ Nov.-Dec. 2004] | Nov. 2004 | Not Applicable |
| $6^{\text {th }} I R A[$ published in $P F 30(6)]$ | Nov. 2004 | Dec. 1, 2004 |

## INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

- The list of new USP Reference Standards that have become available
- The list of assays or tests that are adopted but held in abeyance pending availability of required USP Reference Standards
- New adopted (official) revisions to the $U S P-N F$ that become effective before the effective date of the next Supplement or that were not ready for adoption by the closing date for the upcoming Supplement. (The effective date for these revisions is stated on the next page.)

Readers should review this section to determine if they are affected by any of the changes.
Symbols-Interim revisions are shown with new text (if any) enclosed in circles, ${ }^{\bullet}$ new text ${ }_{\mathbf{0}}$. Text enclosed in squares, $\mathbf{■}^{\text {new }}$ text $\mathbf{n}$, has already been adopted in a Supplement. Where the symbols appear together with no enclosed text, such as $\bullet \bullet$ or $■$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the IRA or Supplement in which the revision first appeared. For example, $\bullet 2$ indicates that
 officially adopted in the Second Supplement to USP 27.

Errata-At the end of the Interim Revision Announcement section is a list of errata and corrections to USP 27-NF 22. The page number indicates where the item is found in $U S P-N F$. If necessary, this list will be updated with every issue of $P F$. This information will also be cumulative in the next available Supplement, and will appear in its corrected form in the next annual edition of $U S P-N F$. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.
SIXTH INTERIM REVISION ANNOUNCEMENT ..... 1965
MONOGRAPHS (USP) ..... 1969
NOTICE OF LIFTING OF POSTPONEMENT—Doxorubicin Hydrochloride ..... 1968
Loratadine Oral Solution ..... 1969
GENERAL CHAPTERS ..... 1969
$\langle 11\rangle$ USP Reference Standards ..... 1969

# SIXTH INTERIM REVISION ANNOUNCEMENT <br> to USP 27 and to NF 22 

# By authority of the United States Pharmacopeial Convention, Inc. Prepared by the Council of Experts and published by the Board of Trustees 

Larry L. Braden, Chair
USP Board of Trustees
Roger L. Williams, Executive Vice President and Chairman, USP Council of Experts

John W. Gasper, Director, Executive Secretariat

Official December 1, 2004.
Released November 1, 2004.

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## New USP Reference Standards

The following USP Reference Standards, which were indicated in past Supplements to $U S P-N F$ as being not yet available, have since become available. Thus, the official date of each USP 27 or NF 22 standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list. (AS) indicates Authentic Substances, which are materials that have no specified use in monographs or General Chapters and are offered for the convenience of $U S F-N F$ users

USP Alcohol RS (May 1, 2005)
USP Alcohol Determination-Acetonitrile RS (March 1, 2005)
USP Alcohol Determination-Alcohol RS (March 1, 2005)
USP Amlodipine Besylate RS (May 1, 2005)
USP Ammonium Carbonate (AS)
USP Benazepril Related Compound C RS (January 1, 2005)
USP Positive Bioreaction RS (November 1, 2004)
USP Powdered Black Cohosh Extract RS (March 1, 2005)
USP Boric Acid (AS)
USP Butylated Hydroxytoluene RS (March 1, 2005)
USP Calcium Acetate (AS)
USP Calcium Carbonate (AS)
USP Calcium Choride (AS)
USP Calcium Hydroxide (AS)
USP Calcium Sulfate (AS)
USP Candelilla Wax RS (March 1, 2005)
USP Caprylocaproyl Polyoxylglycerides RS (March 1, 2005)
USP Cefpodoxime Proxetil RS (January 1, 2005)
USP Cellaburate (cellulose acetate butyrate) RS (May, 1, 2005)
USP Powdered Chaste Tree Extract RS (November 1, 2004)
USP Chlorhexidine Related Compounds RS (November 1, 2004)
USP Chlorogenic Acid RS (November 1, 2004)
USP Clonidine Related Compound B RS (November 1, 2004)
USP Corn Oil (AS)
USP Cottonseed Oil (AS)
USP Dehydrated Alcohol RS (May 1, 2005)
USP Dibutyl Phthalate RS (March 1, 2005)
USP Powdered Echinacea purpurea Extract RS (November 1, 2004)

USP Fenbendazole Related Compound A RS (January 1, 2005)
USP Fenbendazole Related Compound B RS (January 1, 2005)
USP Ferrous Sulfate (AS)
USP Gemcitabine Hydrochloride RS (March 1, 2005)
USP Glacial Acetic Acid (AS)
USP $2 E, 4 E$-Hexadienoic Acid Isobutylamide RS (November 1, 2004)

USP Homopolymer Polypropylene RS (January 1, 2005)
USP Lactase RS (May 1, 2005)
USP Lamivudine Resolution Mixture A RS (November 1, 2004)
USP Lauroyl Polyoxylglycerides (AS)
USP Leuprolide Acetate RS (January 1, 2005)
USP Linoleoyl Polyoxylglycerides RS (January 1, 2005)
USP Loratadine Related Compound A RS (May 1, 2005)
USP Loratadine Related Compound B RS (May1, 2005)
USP Magnesium Chloride (AS)
USP Magnesium Hydroxide (AS)
USP Magnesium Sulfate (AS)
USP Manganese Chloride (AS)
USP Manganese Sulfate (AS)
USP Medroxyprogesterone Acetate Related Compound A RS (November 1, 2004)
USP Methylphenidate Hydrochloride Erythro Isomer Solution CII RS (November 1, 2004)
USP Metoprolol Succinate RS (November 1, 2004)
USP Mirtazapine RS (March 1, 2005)

USP Mitoxantrone System Suitability Mixture RS (November 1, 2004)

USP Nabumetone Related Compound A RS (May 1, 2005)
USP Naratriptan Hydrochloride RS (November 1, 2004)
USP Nevirapine Anhydrous RS (March 1, 2005)
USP Nevirapine Hemihydrate RS (January 1, 2005)
USP Nevirapine Related Compound A RS (January 1, 2005)
USP Nevirapine Related Compound B RS (January 1, 2005)
USP Ondansetron Resolution Mixture RS (May 1, 2005)
USP Oxybutynin Related Compound B RS (January 1, 2005)
USP Oxybutynin Related Compound C RS (January 1, 2005)
USP Oleoyl Polyoxylglycerides RS (January 1, 2005)
USP Palm Oil (AS)
USP Paroxetine Related Compound F RS (May 1, 2005)
USP Paroxetine Related Compound G RS (May 1, 2005)
USP Phenothiazine (AS)
USP Polysorbate 20 (AS)
USP Polysorbate 40 (AS)
USP Polysorbate 60 (AS)
USP Polysorbate 80 (AS)
USP Potassium Benzoate (AS)
USP Potassium Bicarbonate RS (January 1, 2005)
USP Potassium Carbonate (AS)
USP Potassium Chloride (AS)
USP Potassium Iodide (AS)
USP Propionic Acid (AS)
USP Residual Solvent Class 1—Benzene RS (November 1, 2004)
USP Residual Solvent Class 1-1,2 Dichloroethane RS (November 1, 2004)
USP Residual Solvent Class 1-1,2 Dichloroethene RS (November 1, 2004)
USP Residual Solvent Class 1-Carbon Tetrachloride RS (November 1, 2004)
USP Residual Solvent Class 1-1,1,1-Trichloroethane RS (November 1, 2004)
USP Residual Solvent Class 2-Chlorobenzene RS (January 1, 2005)

USP Residual Solvent Class 2-Chloroform RS (May 1, 2005)
USP Residual Solvent Class 2-Cyclohexane RS (May 1, 2005)
USP Residual Solvent Class 2-1,2-Dichoroethene RS (March 1, 2005)

USP Residual Solvent Class 2-1,2-Dimethoxyethane RS (May 1, 2005)

USP Residual Solvent Class 2— $N$, $N$-Dimethylacetamide RS (May 1, 2005)
USP Residual Solvent Class 2- $N$, $N$-Dimethylformamide RS (May 1, 2005)
USP Residual Solvent Class 2-1,4-Dioxane RS (January 1, 2005)
USP Residual Solvent Class 2-2-Ethoxyethanol RS (May 1, 2005)

USP Residual Solvent Class 2—Formamide RS (May 1, 2005)
USP Residual Solvent Class 2-Methanol RS (January 1, 2005)
USP Residual Solvent Class 2-Methylbutylketone RS (May 1, 2005)

USP Residual Solvent Class 2-Methylcyclohexane RS (March 1, 2005)

USP Residual Solvent Class 2-Methylene Chloride RS (January 1, 2005)
USP Residual Solvent Class 2— $N$-Methylpyrrolidone RS (May 1, 2005)

USP Residual Solvent Class 2-2-Methoxyethanol RS (May 1, 2005)

USP Residual Solvent Class 2-Mixture A RS (May 1, 2005)
USP Residual Solvent Class 2-Mixture C RS (May 1, 2005)
USP Residual Solvent Class 2-Nitromethane RS (May 1, 2005)
USP Residual Solvent Class 2-Pyridine RS (May 1, 2005)
USP Residual Solvent Class 2-Sulfolane RS (May 1, 2005)
USP Residual Solvent Class 2-Tetrahydrofuran RS (January 1, 2005)

USP Residual Solvent Class 2-Tetralin RS (May 1, 2005)
USP Residual Solvent Class 2-Toluene RS (January 1, 2005)

USP Residual Solvent Class 2-Trichloroethylene RS (May 1, 2005)

USP Residual Solvent Class 2-Xylenes RS (January 1, 2005)
USP Residual Solvent Mixture-Class 1 RS (November 1, 2004)
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USP Sodium Carbonate Anhydrous (AS)
USP Sodium Citrate (AS)
USP Sodium Metabisulfite (AS)
USP Sodium Nitrite (AS)
USP Sodium Sulfate Anhydrous (AS)
USP Sodium Thiosulfate (AS)
USP Titanium Dioxide (AS)
USP Valsartan RS (November 1, 2004)
USP Zinc Oxide (AS)
USP Zinc Sulfate (AS)
The official dates of any USP 27 or NF 22 standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards.

USP Alteplase RS
USP Amiloxate RS
USP Bupropion Hydrochloride Related Compound A RS
USP Bupropion Hydrochloride Related Compound B RS
USP Bupropion Hydrochloride Related Compound C RS
USP Bupropion Hydrochloride Related Compound D RS
USP Bupropion Hydrochloride Related Compound E RS
USP Bupropion Hydrochloride Related Compound F RS
USP Cinoxate RS
USP Decoquinate RS
USP Diethylstilbestrol Diphosphate RS

USP Enalapril Related Compound B RS
USP Enzacamene RS
USP Fludeoxyglucose RS
USP Ginseng Extract RS
USP Gonadorelin Hydrochloride RS
USP Hypericin RS
USP Lactase RS
USP Maltose Monohydrate RS
USP Menotropins RS
USP Methyldopa-Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Ondansetron Related Compound B RS
USP Potassium Perchlorate RS
USP Propofol RS
USP Propofol Related Compound A RS
USP Propofol Related Compound B RS
USP Propofol Resolution RS
USP Propofol for System Suitability RS
USP Pyrethrum Extract RS
USP Sargramostim RS
USP Sulisobenzone RS
USP Terbutaline Related Compound A RS
USP $\Delta^{8}$-tetrahydrocannabinol RS
USP $\Delta^{9}$-tetrahydrocannabinol RS
USP Thiacetarsamide RS
USP Tilmicosin RS
USP Tinidazole Related Compound B RS
USP Trenbolone RS
USP Trenbolone Acetate RS
USP Powdered Valerian RS
USP Vasopressin RS

## NOTICE OF LIFTING OF POSTPONEMENT

In response to the request that USP reconsider the decision to postpone the official date of the revision to the Doxorubicin Hydrochloride monograph published in the First Supplement to USP-NF, the Noncomplex Actives and Excipients Executive Committee has considered this request and subsequently voted to lift the postponement. This action makes the revision to the Doxorubicin Hydrochloride monograph official as of September 7, 2004.

## Doxorubicin Hydrochloride

## Change to read:

Packaging and storage-Preserve in tight containers, ${ }^{\bullet}$ and store at controlled room temperature, except where it is labeled as amorphous, in which case it should be stored in the freezer. $\bullet_{6}$
${ }^{\bullet}$ (Official September 7, 2004) ${ }^{6}$

## Add the following:

${ }^{\bullet}$ Labeling-The amorphous form is so labeled. $\bullet_{6}$
${ }^{\bullet}$ (Official September 7, 2004) ${ }^{\bullet 6}$

## Change to read:

Crystallinity $\langle 695\rangle$ : meets the requirements, ${ }^{\bullet}$ except that where it is labeled as amorphous, most of the particles do not exhibit birefringence and extinction positions. $\bullet 6$
${ }^{\bullet}$ (Official September 7, 2004) ${ }^{\bullet} 6$

## MONOGRAPHS（USP）

## Loratadine Oral Solution

## Change to read：

Assay－
0．05 M Monobasic potassium phosphate solution－Transfer about 6.8 g of monobasic potassium phosphate，accurately weighed，to a 1－L volumetric flask，dissolve in and dilute with wa－ ter to volume，and mix．Adjust with phosphoric acid to a pH of $3.0 \pm 0.1$ ．

Mobile phase－Prepare a filtered and degassed mixture of 0．05 M Monobasic potassium phosphate solution and acetonitrile （7：3）．Make adjustments if necessary（see System Suitability under Chromatography $\langle 621\rangle$ ）．

Internal standard preparation－Dissolve an accurately weighed quantity of butylparaben in a mixture of water and acetonitrile （ $7: 3$ ），and dilute quantitatively，and stepwise if necessary，with a mixture of water and acetonitrile $(7: 3)$ to obtain a solution having a concentration of about 0.3 mg per mL ．

Standard stock preparation－Dissolve an accurately weighed quantity of USP Loratadine RS in acetonitrile，and dilute quantita－ tively，and stepwise if necessary，with acetonitrile to obtain a solu－ tion having a known concentration of about 1.0 mg per mL ．

Standard preparation－Transfer 5.0 mL of Internal standard preparation， 5.0 mL of Standard stock preparation，and 12 mL of water into a $50-\mathrm{mL}$ volumetric flask．Dilute with a mixture of water and acetonitrile $(7: 3)$ ，and mix．

Assay preparation－Transfer an accurately measured quantity of Oral Solution，equivalent to 5 mg of loratadine，into a $50-\mathrm{mL}$ vol－ umetric flask．Pipet 5.0 mL of Internal standard preparation into the flask，dilute with a mixture of water and acetonitrile $(7: 3)$ to volume，and mix．

Chromatographic system（see Chromatography $\langle 621\rangle$ ）－The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains ${ }^{\bullet} 10-\mu \mathrm{m}_{\bullet 6}$ packing L11． The flow rate is about 2 mL per minute．The column temperature is maintained between $20^{\circ}$ and $30^{\circ}$ ．Chromatograph the Standard preparation，and record the peak responses as directed for Proce－ dure：the relative retention times are about 0.78 for butylparaben and 1.0 for loratadine；the resolution，$R$ ，between loratadine and butylparaben is not less than 1．9；the tailing factor is not more than 1.6 for the loratadine and butylparaben peaks；and the relative stan－ dard deviation for replicate injections is not more than $2 \%$ ．

Procedure－Separately inject equal volumes（about $10 \mu \mathrm{~L}$ ）of the Standard preparation and the Assay preparation into the chro－ matograph，record the chromatograms，and measure the responses for the major peaks．Calculate the quantity，in mg of loratadine $\left(\mathrm{C}_{22} \mathrm{H}_{23} \mathrm{ClN}_{2} \mathrm{O}_{2}\right)$ in the portion of Oral Solution taken by the formu－ la：

$$
50 C\left(R_{U} / R_{S}\right)
$$

in which $C$ is the concentration，in mg per mL ，of USP Loratadine RS in the Standard preparation；and $R_{U}$ and $R_{S}$ are the ratios of loratadine to the internal standard peak responses obtained from the Assay preparation and the Standard preparation，respectively．

## GENERAL CHAPTERS

## General Tests and Assays

## General Requirements for Tests and Assays

## 〈11〉 USP REFERENCE STANDARDS

## Change to read：

USP Bendroflumethiazide RS－－Do not dry．Keep container tightly closed．Store in a refrigerator．Protect from moisture．$\bullet 6$

## Change to read：

USP Bismuth Subsalicylate RS－－Do not dry．e6 Keep container tightly closed．

## Change to read：

USP Dihydrocodeine Bitartrate RS－Dry portion at $105^{\circ}$ for 4 hours before using．Keep container tightly closed．${ }^{\bullet}$ Protect from light．e6

## Change to read：

USP Lactase RS－Do not dry before using．${ }^{\bullet}$ Keep container tight－ ly closed．Store in a refrigerator．Before opening，allow to attain room temperature．Protect from air and humidity after opening．$\bullet 6$

## Change to read：

USP Mafenide Acetate RS－${ }^{\bullet}$ Determine the water content titri－ metrically at the time of use．$\bullet 6$ Keep container tightly closed．Pro－ tect from light．${ }^{\bullet}$ 。

## Change to read：

■USP Paroxetine Related Compound E RS－－（NAME CHANGE） See USP Paroxetine Related Compound E Mixture RS．$\bullet$ ■ $\mathbf{L S}^{\text {S（USP27）}}$

## Add the following:

${ }^{\bullet}$ USP Paroxetine Related Compound E Mixture RS (paroxetine hydrochloride spiked with 1-methyl-4-( $p$-fluorophenyl)-1,2,3,6-tetrahydropyridine)-Do not dry. Keep container tightly closed. Protect from light. $\bullet 6$

## Change to read:

■USP Paroxetine Related Compound F RS [trans(-)-1-methyl-3-[1,3-benzodioxol-5-yloxy)methyl]-4-(fluorophenyl)piperidine] $\left(\mathrm{C}_{20} \mathrm{H}_{22} \mathrm{FNO}_{3} \triangleleft 343.39\right)-$ Do not dry. Keep container tightly closed. Protect from light. $\bullet_{6}\lfloor 2$ S (USP27)

## Change to read:

■USP Paroxetine Related Compound G RS [( $\pm$ )trans-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4"-fluorophenyl-4'-phenyl)piperidine hydrochloride] $\left(\mathrm{C}_{25} \mathrm{H}_{24} \mathrm{FNO}_{3} \diamond 405.46\right)-$ Do not dry. Keep container tightly closed. Protect from light. $\bullet \square \mathbf{\square}$ 2S (USP27)

## Change to read:

USP Resorcinol RS-- Do not dry. ${ }^{6}$ Keep container tightly closed. Protect from light. Avoid contact with metals.

## Change to read:

USP Salicylic Acid RS-- Do not dry.e ${ }^{\circ}$ Keep container tightly closed.

## Change to read:

USP Alpha Tocopheryl Acid Succinate RS- ${ }^{\bullet}$ Do not dry. Keep container tightly closed. Protect from light.

## Change to read:

USP Valproic Acid RS-Do not dry. ${ }^{\bullet}$ After opening ampul, store in a tightly closed container. $\bullet 6$

## IN-PROCESS REVISION

This section contains proposals for adoption as official $U S P$ or $N F$ standards (either proposed new standards or proposed revisions of current $U S P$ or $N F$ standards). These may be any of the following: (1) items that previously appeared under Pharmacopeial Previews and are now formally proposed as revisions, (2) proposed revisions placed directly under In-Process Revision, or (3) modifications of revisions previously proposed under In-Process Revision. Readers should review material in this section and provide comments to the staff liaison (use the Staff Directory to find the contact information). Information on how to comment is found in the Policies and Announcements section. It is important to send comments promptly so that the Committee members can consider readers' input as they are deciding whether to advance standards to official status.

Briefings Each Proposal is preceded by a Briefing in the following format:

## BRIEFING

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being proposed, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see How to Use PF), the name of the scientific staff liaison who handled the particular issue, and the USP tracking correspondence number, as shown in the example below:
(PA5: K. Russo) RTS-55678-1

Symbols Proposed revisions are shown with language proposed for deletion or replacement crossed off. New text (if any) follows, and is enclosed in symbols and set off from the current official text by a paragraph break and by larger type, as shown in the examples below:
${ }^{\bullet}$ new text.
if slated for an Interim Revision Announcement to USP 27-NF 22 (IRA);
$\Delta_{\text {new text }}^{\Delta U S P 28}{ }$
if slated for $U S P 28-N F 23$; and
$\square_{\text {new text }}$
if slated for a Supplement to $U S P-N F$. The same symbols not set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as ${ }^{\bullet}$ 。 or $\boldsymbol{\bullet}^{\boldsymbol{n}}{ }^{\boldsymbol{\wedge}}$, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular IRA or Supplement or indicates the USP or NF as the publication where the revision will appear if approved. For example, $\bullet 2$ indicates that the revision is proposed for the Second Interim Revision Announcement, $\boldsymbol{\square} 2 \mathrm{~S}$ (USP 27) indicates that the proposed revision is slated for the Second Supplement to USP 27, and $\boldsymbol{\Delta U S P 2 8}$ and $\boldsymbol{\Delta N F 2 3}$ indicate that the revisions are proposed for USP 28 and $N F 23$, respectively.

Official Title Changes Where the specification "Monograph title change" is found, it indicates that the official title stated after that specification will be substituted for the former title in the appropriate places throughout that monograph once this revision becomes official.
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Amoxicillin Tablets ( $2^{\text {nd }}$ Supp to USP 28) ..... 1977
Brompheniramine Maleate Tablets ( $2^{\text {nd }}$ Supp to USP 28) ..... 1978
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Megestrol Acetate Oral Suspension (Proposal for $2^{\text {nd }}$ IRA) ..... 2015
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Nystatin, Neomycin Sulfate, Thiostrepton, and Triamcinolone Acetonide Ointment (2 ${ }^{\text {nd }}$ Supp to USP 28) ..... 2020
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## MONOGRAPHS (USP)

## Briefing


#### Abstract

Amifostine, USP 27 page 109 and page 52 of $P F 30(1)$ [Jan.Feb. 2004]; Amifostine for Injection, USP 27 page 110. On the basis of comments received, a new HPLC method is proposed for the Related compounds test and the Assay. Improved peak shape and resolution were observed. The tests were validated using the Ultrasphere C18 5- $\mu \mathrm{m}$ (Beckman-Coulter) brand of L1 column. Typical retention times in the Related compounds test are about 4.8 minutes for amifostine thiol and about 14 minutes for amifostine disulfide. The typical retention time for amifostine in the Assay is about 10 minutes.


(PA5: A. Wilk) RTS-41217-1

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. ${ }^{15}$ (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Amifostine RS. USP Amifostine Thiol RS.

- USP Endotoxin RS. $\mathbf{I S ~}_{1 S}$ (USP28)


## Change to read:

Related compounds-
Mobile phase-Prepare-as-directed in the-Assat:

- Dissolve 1.0 mL of nonafluorobutane sulfonic acid in 1200 mL of HPLC grade water, add $400 \mu \mathrm{~L}$ of trifluoroacetic acid, and adjust with triethylamine to a pH of 2.5 . Prepare a degassed mixture of this solution and acetonitrile (68:32). $\mathbf{n}^{2 S}$ (USP28)

Blank solution-Transfer 12.5 mL of water to - 25 mL volumet rie flack, dilute with methaneltovelume, and mix.
-Use water. ${ }^{\text {n2S }}$ (USP28)
Standard thiol solution-Transfer about 7-mg
$-12.4 \mathrm{mg}_{\text {. }} 2 \mathrm{~S}$ (USP28
of USP Amifostine Thiol RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with hobile phase
$\square_{\text {water }}{ }^{2 S}$ (USP28)
to volume, and mix. [NOTE-Inject immediately after preparation, or refrigerate until use.
-The solution is stable for 48 hours if maintained at about $5^{\circ}$.]

System suitability solution-Dissolve about 5.0 mg of USP Amifostine RS, accurately weighed, in 1 mL of Standard thiol solution, and mix. [NOTE-Inject immediately after preparation, or refrigerate until use. The solution is stable
for 12 hours if maintained at about $5^{\circ}$.] ${ }_{\text {USS }}$ (USP28)
Test solution-Transfer about 150 mg
$-50 \mathrm{mg}_{\text {2S }}$ (USP28)
of Amifostine, accurately weighed, to a 10 mL

- $1-\mathrm{mL}_{\mathbf{2 S}}$ (USP28)
volumetric flask. Dissolve in 5.0 mL of water, dilute with methanet
$\square_{\text {and }}$ dilute with water ${ }_{\text {2S }}$ (USP28)
to volume, and mix. [NOTE-Inject immediately after preparation, or refrigerate until use.
-The solution is stable for 48 hours if maintained at about $5^{\circ}$. $]_{\text {■ }}$ (USP28)

Chromatographic system (see Chromatography $\langle 621\rangle$ )-Prepare direeted in the Assay.
-The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The column temperature is maintained at $30^{\circ}$, and the temperature of the solutions to be injected is maintained at $2^{\circ}-8^{\circ}$. The flow rate is about 1.0 mL per minute. ${ }^{2 S}$ (USP28) Chromatograph the
-System suitability solution and the $\mathbf{N 2 S}^{\text {(USP28) }}$
Standard thiol solution, and record the peak responses as directed for Procedure:
-the resolution between the amifostine and amifostine thiol peaks is not less than 2.0 ; the column efficiency calculated for the amifostine thiol peak is not less than 2300 theoretical plates; the tailing factor is not more than 4.0; the capacity
factor, $k^{\prime}$, is more than 0.5 ; and ${ }_{\text {2S }}$ (USP28)
the relative standard deviation for replicate injections is not more than $4.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard thiol solution, the Test solution, and the Blank solution into the chromatograph, record the chromatograms, and mea-
sure the responses of all the peaks, excluding the peaks corresponding to those obtained from the Blank solution. Calculate the percentage of amifostine thiol in the portion of Amifostine taken by the formula:

$$
(134.24 / 207.17) 1000(C / W)\left(r_{U} / r_{S}\right)
$$

in which 134.24 and 207.17 are the molecular weights of amifostine thiol and amifostine thiol dihydrochloride, respectively; $C$ is the concentration, in mg per mL , of amifostine thiol dihydrochloride in the Standard thiol solution; $W$ is the weight, in mg , of Amifostine taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the amifostine thiol peak responses obtained from the Test solution and the Standard thiol solution, respectively. Calculate the percentage of each of the other impurities in the portion of Amifostine taken by the formula:

$$
100\left(r_{i} / r_{A}\right),
$$

in which $r_{i}$ and $r_{A}$ are the peak responses for each impurity and amifostine, respectively, obtained from the Test solution: not more than $0.1 \%$ of any individual impurity, excluding amifostine thiol, is found; and not more than $0.3 \%$ of total impurities, including amifostine thiol, is found.

## Add the following:

-Other requirements-Where the label states that Amifostine is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Amifostine for Injection. Where the label states that Amifostine must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Am-
ifostine for Injection.■1S (USP28)

## Change to read:

```
Assay-
    Mobile phase Dissolve-0.54%
P
of sodilum-1-0ctanesulfenate in 500-mL
曐1-hexamesulfenate-in 1000-mEn1s (USP28)
of water. Adjust with phespheric acidto a pH Of 2.5.
##.0.■1S (USP28)
Prepare a fltered and degassed mixtureof this-solution and meth-
anol(1:1).
튜ᄂ(72:28):п1S (USP28)
Make adjustments if necessaty (see-System-Suitability under Chre-
matography (624)).
```

- Dissolve 1.0 mL of nonafluorobutane sulfonic acid in 1200 mL of HPLC grade water. Prepare a degassed mixture of this solution and acetonitrile ( $90: 10$ ). $\quad$ 2S (USP28)

Standard preparation-Transfer about 30 mg of USP Amifostine RS, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask. Dissolve in 5 mL of water, dilute with methanel
$\square_{\text {and dilute with water }}^{\mathbf{m}_{2 S} \text { (USP28) }}$
to volume, and mix. [NOTE-Inject immediately after preparation, or refrigerate until use.
-The solution is stable for 48 hours if maintained at about $\left.5^{\circ}.\right]_{\text {п2S }}$ (USP28)

Assay preparation-Transfer about 30 mg of Amifostine, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask. Dissolve in 5 mt of water, dilute with methanel
$\bullet_{\text {and dilute with water }}^{\mathbf{m}_{2 S} \text { (USP28) }}$
to volume, and mix. [NOTE-Inject immediately after preparation, or refrigerate until use.
-The solution is stable for 48 hours if maintained at about $5^{\circ}$.] ${ }_{\text {2S }}$ (USP28)

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1.

- L7.■1S (USP28)

The column temperature is maintained at $30^{\circ}$, and the temperature of the solutions to be injected is maintained at $2^{\circ}-$ $8^{\circ}$.The flow rate is about 1.0 mL per minute. Chromatograph the Standard preparation and the Assay preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 1000
-7500 $\quad$ 2S (USP28)
theoretical plates; the tailing factor is not more than 2 ; and the relative standard deviation for replicate injections is not more than 2.0\%.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{5} \mathrm{H}_{15} \mathrm{~N}_{2} \mathrm{O}_{3} \mathrm{PS}$ in the portion of Amifostine taken by the formula:

$$
10 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Amifostine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Amifostine for Injection, USP 27 page 110—See briefing under Amifostine.
(PA5: A. Wilk) RTS-41217-2

## Change to read:

## Related compounds-

## TEST 1-

Mebile phase Prepare as directed in the Assay under Amifos tine.

Standard thiol solution and Chromatographic system
-Mobile phase, Blank solution, and Test solution-■2S (USP28) Prepare as directed in the test for Related compounds under Amifostine.

■Standard thiol solution-Transfer about 40.1 mg of USP
Amifostine Thiol RS, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE-Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about $5^{\circ}$.]

Standard disulfide solution-Transfer about 18.6 mg of USP Amifostine Disulfide RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE-Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about $5^{\circ}$.]

System suitability solution-Dissolve about 5.0 mg of USP Amifostine RS, accurately weighed, in 1 mL of Standard thiol solution, and mix. [NOTE-Inject immediately after preparation, or refrigerate until use. The solution is stable for 12 hours if maintained at about $5^{\circ}$.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a detector capable of recording at both 220 nm and 247 nm , and a $4.6-\mathrm{mm}$ $\times 25-\mathrm{cm}$ column that contains packing L1. The column temperature is maintained at $30^{\circ}$, and the temperature of so-
lutions to be injected is maintained at $2^{\circ}-8^{\circ}$. The flow rate is about 1.0 mL per minute. Chromatograph the System suitability solution, the Standard disulfide solution, and the Standard thiol solution, and record the peak responses as directed for Procedure: the column efficiency calculated for the amifostine thiol peak is not less than 2300 theoretical plates; the tailing factor is not more than 4.0 ; the capacity factor, $k^{\prime}$, is more than 0.5 ; and the relative standard deviation for replicate injections is not more than $4.0 \%$. The column efficiency calculated for the amifostine disulfide peak is not less than 2000 theoretical plates; the tailing factor is not more than 4.5 ; the capacity factor, $k^{\prime}$, is more than 2.2 ; and the relative standard deviation for replicate injections is not more than $4.0 \%$. ${ }^{2 S}$ (USP28)
Procedure-Proceed as dirieeted in the for Related pounds under Amififostine.
-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard thiol solution, the Standard disulfide solution, the Test solution, and the Blank solution into the chromatograph, record the chromatograms, and measure the responses of all the peaks except the peaks corresponding to those obtained from the Blank solution. $\quad 2$ (USP28) Calculate the percentage of amifostine thiol in the portion of Amifostine for Injection taken by the formula:
$(134.24 / 207.17)(41.67 C)(\not+\downarrow+5)$,

$$
\boldsymbol{\bullet}(134.24 / 207.17) 1000(C / W)\left(r_{U} / r_{S}\right), \amalg 2 S(U S P 28)
$$

in which the-terms are as defmed therein.
-134.24 and 207.17 are the molecular weights of amifostine thiol and amifostine thiol dihydrochloride, respectively; $C$ is the concentration, in mg per mL , of amifostine thiol dihydrochloride in the Standard thiol solution; $W$ is the weight, in mg , of amifostine taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the amifostine thiol peak responses recorded at 220 nm , obtained from the Test solution and the Standard
thiol solution, respectively. Calculate the percentage of amifostine disulfide in the portion of Amifostine for Injection taken by the formula:
$(266.47 / 412.31)(10 C)\left(r_{U} / r_{S}\right)$,
in which 266.47 and 412.31 are the molecular weights of amifostine disulfide and amifostine disulfide tetrahydrochloride, respectively; $C$ is the concentration, in mg per mL, of USP Amifostine Disulfide RS in the Standard disulfide solution; and $r_{U}$ and $r_{S}$ are the peak responses recorded at 247 nm , obtained from the Test solution and the
Standard disulfide solution, respectively: not more than
$2.0 \%$ of total impurities, including amifostine thiol and am-
ifostine disulfide, is found. ${ }^{2 S}$ (USP28)
Calculate the percentage of each of the other impurities in the portion of Amifostine for Injection taken by the formula:

$$
100\left(r_{i} / r_{A}\right)
$$

in which $r_{i}$ and $r_{A}$ are the peak responses for each impurity and amifostine, respectively, obtained from the Test solution: not more than $0.1 \%$ of any individual impurity except amifostine thiol is found.

TEST 2
Mobile phase Dissolve 0.28 g of sodium 1 octanesulfenate in 700 mL of water. Adjust with trifluroracetic aeid to a pH-of 2.5 . Prepare a filtered and degassed mix ture of this solution and acetemitrile (7:3). Make adjustments if necessary (see-System-Sutabit ity under Chromatography $\langle 621\rangle$ ).

Standard disulfide seltion Transfer about 4.6 mg of USP Am ifestine-Disulfide RS, qeeurately weighed, to a 100 mL volumetrie flask. Dissolve in 70 mE of water, dilate-with acetenitrile to vol ume, and mix.

Test solution Transfer an aceurately weighed quantity of Am ifestine for Injection, equivalent to about 500 me of amifestine, to a -50 mL volumetric flask, dissolve-in-9 mL of water, dilute with water to veltame, and mix.

Chromatogituphie system (see-Chromatography $\langle 624\rangle$ ) The liquid chrematograph is equipped with a 247 nm detector and a $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}$ coltam that contains 5 Hm packing L1. The flow rate is about 1 mL per minute. Chromategraph the Standard disulfite solution, and record the peak respenses as directed for Procedure: the coltamnefficieney is not less than 1000 theoretical plates; the tailing factor for the amifestine disulfle peak is not more than 2.5; and the relative-standard deviation-for replieate-injections is net mere than $4.0 \%$.

Proedure Separately injeet equal volumes (about $10 \mu \mathrm{~L}$ ) -f the Standard disulfide selution and the Test solution into the chromatograph, record the ehromategrams, and measure the respenses for the amifestine disulfide peaks. Caleulate the pereentage of amt ifestine disulfide in the pertion of Amifostine for Injection taken by the formala:

$$
(266.47 / 412.31)(10 C)\left(r_{4}+r_{s}\right)
$$

in whieh 266.47 and 412.31 are the molecular weights of amifes-tine-disulfide and amifestine-disulfide-tetrahydrechleride, respee
tively; $C$ is the concentration, in mg per mL, of USP Amifortine Pisulfide RS in the Standetd disulfite solution; and $r_{t}$-and $r_{s}$-are the peak response obtained from the Test solution and the Stat dard disulfide solution, respectively: net more than $2.0 \%$ of totat impurities, ineluding amifostine thiol and amifostine disulfide, is fount.

■- ${ }^{\text {2S }}$ (USP28)

## Briefing

Amoxicillin Tablets, USP 27 page 141. It is proposed to revise the Dissolution test to modify the Times and Tolerances in accordance with those approved by FDA.
(BPC: M. Marques) RTS-40246-1

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: water, 900 mL .
Apparatus 2: 75 rpm
Time: 9

- $30_{\text {■2S (USP28) }}$
minutes.
Determine the amount of $\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{5} \mathrm{~S}$ dissolved by employing the following method.
pH 5.0 Buffer-Dissolve 27.2 g of monobasic potassium phosphate in 3 L of water, adjust with a $45 \%(\mathrm{w} / \mathrm{w})$ solution of potassium hydroxide to a pH of $5.0 \pm 0.1$, dilute with water to obtain 4 L of solution, and mix.

Mobile phase-Prepare a mixture of pH 5.0 Buffer and acetonitrile ( $3900: 100$ ), and pass through a filter having a $0.5-\mu \mathrm{m}$ or finer porosity. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard solution-Dissolve an accurately weighed quantity of USP Amoxicillin RS in $p H$ 5.0 Buffer to obtain a solution having a known concentration of about 0.05 mg per mL . Use this solution within 6 hours.

Test solution-Pass a portion of the solution under test through a filter having a $0.5-\mu \mathrm{m}$ or finer porosity. Quantitatively dilute an accurately measured volume of the filtrate with water to obtain a solution having an estimated concentration of about 0.045 mg of amoxicillin per mL . Use this solution within 6 hours.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $230-\mathrm{nm}$ detector, a 3.9 $\mathrm{mm} \times 30-\mathrm{cm}$ analytical column that contains packing L1, and a $2-\mathrm{mm} \times 2-\mathrm{cm}$ guard column that contains packing L2. The analytical column is maintained at a constant temperature of about $40 \pm 1^{\circ}$. The flow rate is about 0.7 mL per minute. Chromatograph the $\overline{S t a n d a r d}$ solution, and record the peak responses as directed for Procedure: the capacity factor, $k^{\prime}$, is between 1.1 and 2.8 ; the column efficiency is not less than 1700 theoretical plates; the tailing factor is not more than 2.5 ; and the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of amoxicillin $\left(\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{5} \mathrm{~S}\right)$ dissolved by the formula:

$$
0.9 D C P\left(r_{U} / r_{S}\right)
$$

in which $D$ is the dilution factor used in preparing the Test solution; $C$ is the concentration, in mg per mL, of USP Amoxicillin RS in the Standard solution; $P$ is the stated content, in $\mu \mathrm{g}$ of amoxicillin $\left(\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{5} \mathrm{~S}\right)$ per mg, of USP Amoxicillin RS; and $r_{U}$ and $r_{S}$ are the amoxicillin peak responses obtained from the Test solution and the Standard solution, respectively.

Tolerances-Not less than $80 \%$
-75\% ${ }^{\text {■ } 2 S}$ (USP28)
(Q) of the labeled amount of $\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{5} \mathrm{~S}$ is dissolved in $9 \theta$
-30 $\mathbf{n}_{2 S}$ (USP28)
minutes.
FOR PRODUCTS LABELED AS CHEWABLE TABLETS-Proceed as directed above.
-Time: 20 minutes.п2S (USP28)
Tolerances-Not less than $70 \%(Q)$ of the labeled amount of $\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}_{5} \mathrm{~S}$ is dissolved in 90
-20!2S (USP28) minutes.

■FOR VETERINARY PRODUCTS——Proceed as directed above, except to use Apparatus 2 at 100 rpm .п2S (USP28)

## Briefing

Brompheniramine Maleate Tablets, USP 27 page 272. It is proposed to specify the path length of the cuvette used in the Dissolution test.
(BPC: M. Marques) RTS-41779-1

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: water; 500 mL .
Apparatus 1: 100 rpm .
Time: 45 minutes.
Procedure-Determine the amount of $\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{BrN}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 264 nm on filtered portions of the solution under test, suitably diluted with 3 N hydrochloric acid,

■using 5-cm cuvettes, $\boldsymbol{m}_{2 S}$ (USP28)
in comparison with a Standard solution having a known concentration of USP Brompheniramine Maleate RS in the same medium. Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{16} \mathrm{H}_{19} \mathrm{BrN}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$ is dissolved in 45 minutes.

## Briefing

Budesonide. Because there is no existing USP monograph for this drug substance, a new monograph is being proposed. The liquid chromatographic procedure in the Assay is based on analyses performed with the Symmetry brand of L1 column. The typical retention times are about 15.0 for the first eluted epimer of budesonide (epimer B) and about 16.0 for the second eluted epimer of budesonide (epimer A).
(PA1: C. Anthony) RTS-38281-1

## Add the following:

## - Budesonide

$\mathrm{C}_{25} \mathrm{H}_{34} \mathrm{O}_{6} \quad 430.53$
Pregna-1,4-diene-3,20-dione, 16,17-butylidenebis(oxy)-
11,21-dihydroxy-, [11 $\beta, 16 \alpha(R)]$;
16 $\alpha, 17-[(S)$-Butylidenebis(oxy)]-11 $\beta, 21$-dihydroxypregna-1,4-diene-3,20-dione;
(RS)-11 $\beta, 16 \alpha, 17,21-T e t r a h y d r o x y p r e g n a-1,4-d i e n e-3,20-$ dione cyclic 16,17-acetal with butyraldehyde
[51372-29-3; 51372-28-2; 51333-22-3].
» Budesonide is a mixture of two epimeric forms, epimer A and epimer B. It contains not less than 44.0 percent and not more than 51.0 percent of epimer A, and the sum of both epimers is not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{25} \mathrm{H}_{34} \mathrm{O}_{6}$, calculated on the dried basis.

Packaging and storage-Preserve in tight, light-resistant containers. Store at controlled room temperature.

USP Reference standards $\langle 11\rangle — U S P$ Budesonide RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle-$
Solution: $\quad 50 \mu \mathrm{~g}$ per mL .
Medium: methanol.
Microbial limits $\langle 61\rangle$-The total aerobic microbial count does not exceed 1000 cfu per g , and the total combined molds and yeast count does not exceed 100 cfu per g .

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ to constant weight. It loses not more than $0.3 \%$ of its weight.

Organic volatile impurities, Method $I\langle 467\rangle$ : meets the requirements.

## Limit of methanol-

Standard stock solution 1-Prepare a solution of about 50 mg per mL and 25 mg per mL , respectively, of methanol and methylene chloride in $\mathrm{N}, \mathrm{N}$-dimethylacetamide.

Standard stock solution 2-Transfer 10.0 mL of Standard stock solution 1 into a $100-\mathrm{mL}$ volumetric flask, and dilute with $N, N$-dimethylacetamide to volume.

Standard solution 1-Transfer 1.0 mL of Standard stock solution 2 into a $100-\mathrm{mL}$ volumetric flask, and dilute with $\mathrm{N}, \mathrm{N}$-dimethylacetamide to volume.

Standard solution 2-Transfer 2.0 mL of Standard stock solution 2 into a $100-\mathrm{mL}$ volumetric flask, and dilute with $\mathrm{N}, \mathrm{N}$-dimethylacetamide to volume.

Resolution solution-Transfer 1 mL of Standard stock solution 1 and 4 mL of $\mathrm{N}, \mathrm{N}$-dimethylacetamide into a $10-\mathrm{mL}$ headspace vial.

Test solution 1-Transfer about 0.5 g of Budesonide, accurately weighed, into a $10-\mathrm{mL}$ headspace vial, add 5.0 ml of $N, N$-dimethylacetamide, and seal.

Test solution 2-Transfer about 0.5 g of Budesonide, accurately weighed, into a $10-\mathrm{mL}$ headspace vial, add 5.0 ml of Standard solution 1, and seal.

Test solution 3-Transfer about 0.5 g of Budesonide, accurately weighed, into a $10-\mathrm{mL}$ headspace vial, add 5.0 ml of Standard solution 2, and seal.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a headspace injector, a flame-ionization detector, a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ fused silica column bonded with a $0.5 \mu \mathrm{~m}$ layer of phase G43, and a split injection system. The carrier gas is helium; the linear flow velocity is about 30 cm per second; the equilibration time is 10 minutes; and the bath and valve/loop temperatures are maintained at $80^{\circ}$ and $85^{\circ}$, respectively. The chromatograph is programmed as follows. Initially the column temperature is equilibrated at $50^{\circ}$ for 6 minutes, then the temperature is increased at a rate of $30^{\circ}$ per minute to $220^{\circ}$, and is maintained at $220^{\circ}$ for 2 minutes. The injection port temperature is maintained at $250^{\circ}$, and the detector is maintained at $300^{\circ}$. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between methanol and methylene chloride is not less than 5.0.

Procedure-Separately inject equal volumes (about 1 mL ) of the headspace of Test solution 1, 2, and 3 into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Plot the response for methanol in each test solution versus the quantity, in mg , of methanol in each test solution. Draw the straight line best fitting the three points, and extrapolate the line until it intersects the quantity-of-methanol axis. From the intercept, determine the quantity, in mg, of methanol in Test solution 1; not more than $0.1 \%$ is found.

## Limit of 21-acetate of budesonide-

Buffer solution-Proceed as directed in the Assay.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (55:45). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Standard solution-Prepare as directed for Standard preparation in the Assay.

Test solution-Prepare as directed for Assay preparation in the Assay.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 3.1 for the first eluted epimer of 21-acetate of budesonide, about 3.2 for the second eluted epimer of 21acetate of budesonide, 1.0 for the first eluted epimer of budesonide (epimer B), and about 1.1 for the second eluted epimer of budesonide (epimer A); and the column efficiency is not less than 5500 theoretical plates, determined from the budesonide epimer B peak.

Procedure-Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of the 21-acetate of budesonide in the portion of Budesonide taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the sum of the peak areas for the two epimers of 21-acetate of budesonide; and $r_{s}$ is the sum of the areas of the two budesonide peaks; not more than $0.1 \%$ of the $21-\mathrm{ac}-$ etate of budesonide is found.

## Limit of 11-ketobudesonide-

Buffer solution-Proceed as directed in the Assay.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution, acetonitrile, and isopropanol (65:26:9). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Prepare as directed for Standard preparation in the Assay.

Test solution-Proceed as directed for Assay preparation in the Assay.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $3.5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.73 and 0.78 , respectively, for the two epimers of 11-ketobudesonide, about 0.68 for 21-dehydrobudesonide, about 0.84 for 14,15-dehydrobudesonide, and 1.0 for the first eluted epimer of budesonide (epimer B); the resolution, $R$, between the first epimer of 11-ketobudesonide and 21-dehydrobudesonide is not less than 1.0 and between the second epimer of 11-ketobudesonide and 14,15 -dehydrobudesonide is not less than 1.2 ; and the column efficiency is not less than 5500 theoretical plates, determined from the budesonide epimer B peak.

Procedure-Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of 11-ketobudesonide in the portion of Budesonide taken by the formula:

$$
100\left(r_{i} / r_{U}\right)
$$

in which $r_{i}$ is the sum of the areas of the two ketobudesonide peaks; and $r_{U}$ is the sum of the areas of the two budesonide peaks; not more than $0.2 \%$ of 11 -ketobudesonide is found.

## Related compounds-

Buffer solution and Mobile phase-Proceed as directed in the Assay.

Standard solution-Prepare as directed for Standard preparation in the Assay.

Test solution-Proceed as directed for Assay preparation in the Assay.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $3.5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency
is not less than 5500 theoretical plates, determined from the budesonide epimer B peak.

Procedure—Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Budesonide taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak area response for each impurity; and $r_{s}$ is the sum of the responses of all the peaks: the impurities meet the requirements listed in the table below.

| Compound Name | Relative <br> Retention Time | Limit $\%$ |
| :--- | :---: | :---: |
| $16 \alpha$-hydroxylprednoislone | 0.11 | 0.2 |
| D-homobudesonide | 0.36 | 0.1 |
| 21-dehydrobudesonide | 0.61 | 0.07 |
| 14,15 -dehydrobudesonide | 0.86 | 0.1 |
| Total specified impurities | - | 0.4 |
| Any other individual impurity | - | $<0.1$ |
| Total unspecified impurities | - | 0.4 |

## Assay-

Buffer solution-Dissolve 3.17 g of sodium dihydrogen phosphate in water, add 0.23 g of phosphoric acid, dilute with water to 1000 mL , and mix. The pH should be $3.2 \pm 0.1$.
Mobile phase—Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $68: 32$ ). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Standard preparation-Dissolve an accurately weighed quantity of USP Budesonide RS in acetonitrile, and dilute quantitatively and stepwise, if necessary, with Buffer solution to obtain a solution having a known concentration of about 0.5 mg per mL . [NOTE-The solution should be protected from light].

Assay preparation-Transfer about 25 mg of Budesonide, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in 15 mL of acetonitrile, dilute with Buffer solution to volume, and mix. [NOTE-The solution should be protected from light.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )_
The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention time for epimer A is 1.1 with respect to epimer B ; the resolution, $R$, between the two budesonide epimer peaks is greater than 1.5 ; and the column efficiency is not less than 5500 theoretical plates, determined from the budesonide epimer B peak.

Procedure—Separately inject equal volumes (about 20 $\mu \mathrm{L})$ of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak area responses for the major peaks. Calculate the quantity, in mg , of epimer $\mathrm{A}\left(\mathrm{C}_{25} \mathrm{H}_{34} \mathrm{O}_{6}\right)$ in the portion of Budesonide taken by the formula:

$$
50 C\left[r_{U A} /\left(r_{S A}+r_{S B}\right)\right]
$$

in which $C$ is the concentration, in mg per mL , of USP Budesonide RS in the Standard preparation; $r_{U A}$ and $r_{S A}$ are the peak area responses for epimer A obtained from the Assay preparation and the Standard preparation, respectively; and $r_{S B}$ is the peak area response for epimer B obtained from the Assay preparation and the Standard preparation, respectively. Calculate the quantity, in mg , of budesonide $\left(\mathrm{C}_{25} \mathrm{H}_{34} \mathrm{O}_{6}\right)$ in the portion of Budesonide taken by the formula:

$$
50 C\left[\left(r_{U A}+r_{U B}\right) /\left(r_{S A}+r_{S B}\right)\right]
$$

in which $r_{U B}$ is the peak area response of the epimer B obtained from the Assay preparation, and the other terms are as defined above.■2S (USP28)

## BRIEFING

Clorazepate Dipotassium, USP 27 page 489. It is proposed to replace the TLC Related compounds test with two HPLC procedures, that, according to the validation data received, are more sensitive and specific. The validation of the procedures was based on analyses performed with a $\mu$ Bondapak C18 brand of L1 column. For Test 1 , the typicl retention time of the internal standard is about 8 minutes and about 11 minutes for 7-chloro-1,3-dihydro-5-phe-nyl-2H-1,4-benzodiazepin-2-one. For Test 2, the typical retention time of 2-amino-5-chlorobenzophenone is about 11 minutes. In both methods, clorazepate dipotassium elutes in the solvent front.
(PA3: S. Salado) RTS-40998-1

## Change to read:

USP Reference standards $\langle 11\rangle-U S P$ 2-Amino-5-chlorobenzophenone RS.
-USP 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiaze-
pin-2-one RS.■2S (USP28)
USP Clorazepate Dipotassium RS.

## Change to read:

Related compounds-[NOTE-Onee the selutions are prepared, they are unstable and should be used immediately.]

Piltting soldtion- Prepare a solution by dissolving 4 g of potassitm carbenate in 100 mL of water.
Standed solution - . Dissolve an aceurately weighed quantity ef USP Clerazepate Dipetassium-PS and dilute stepwise with $D i$ tuting solution to obtain a solution having a concentration of 0.1 mepermb.
Standard solution B. Transfer an aceurately weighed quantity of about 10 mg of USP 2 Amine- 5 chlorobenzophenene RS to a 100 mL volumetric flask, dissolve in acetone, dilute with ace to volume, and mix. Dilute 10.0 mL of this solution with ace tone to 50.0 mL .

Test solution Dissolve an aceurately weighed quantity of about 100 mg of Clorazepate Dipotassimm in 5.0 mL of $P$ ilhting solution.

Proeedure- Apply separately $5 \mu \mathrm{~L}$ of the Test solution and $5 \mu \mathrm{~L}$ of each Standed solution to a suitable thin layer chrematographie plate (see Chromagrap $\langle 624$ ) ) eoated with a- 0.25 mm layer of ehrematographic silie gel mixture. Allow the spets dry, and develop the chromatograms in a solvent system consisting of a mix tre of chloroform and acetone ( $85: 15$ ) until the solvent front has moved about three fourths of the length of the plate. Remove the plate from the developing chamber, matk the solvent fromt, and at fow the solvent to evaporate. Examine the plate under short wavelength UV light, and compare the intensities of any secondary spets observed in the chromatogram of the Test solution with these of the prineipal spets in the chromatograms of Staded solution A. No secendary spet frem the chremategram of the Test solution is larger or more intense than the principal spot obtained from-Standatd solution $4(0.5 \%)$. Suecessively spray the plate with a freshly prepared $1 \%$ solution of soditm nitrite in 1 N hydrochloric acid. Bry the plate in a current of air and spray with a $0.4 \%$ (w/v) solution of N ( 1 naphthyl) ethylenediamine dihyydrochloride in aleohol. Any violet colored spot present in the chromatogram of the Test solution is not greater in size or intensity than the principal spet
obtained from Standard solution $B(0.1 \%)$, and the sum of the in tensities of all secendary spets obtained by both vistalization tech niques from the Test solution correspends to not more than-1\%.
-TEST 1—
Phosphate buffer solution-Dissolve about 13.8 g of monobasic sodium phosphate in 500 mL of water, adjust with 2.5 N sodium hydroxide to a pH of 8.0 , and mix.

Mobile phase-Prepare a filtered and degassed mixture of water, acetonitrile, and Phosphate buffer solution (5:4:1). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Internal standard solution-Dissolve about 5 mL of 2,6dimethylaniline in 50 mL of hexane, and carefully add dropwise hydrochloric acid to precipitate the amine hydrochloride. Filter through a sintered-glass funnel, wash the solid precipitate with hexane, and allow the precipitate to dry. Transfer about 50 mg of the dried precipitate of 2,6-dimethylaniline hydrochloride to a $100-\mathrm{mL}$ volumetric flask, add 10.0 mL of Phosphate buffer solution and 40 mL of water, and dilute with acetonitrile to volume.

Standard solution-Dissolve an accurately weighed quantity of USP 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about $75 \mu \mathrm{~g}$ per mL . Transfer 4.0 mL of this solution to a $50-\mathrm{mL}$ conical flask, add 4.0 mL of 0.7 M potassium carbonate, 2.0 mL of Internal standard solution, and 15.0 mL of water. Insert a stopper, and mix.

Test solution-Transfer an accurately weighed quantity of about 50 mg of Clorazepate Dipotassium to a $50-\mathrm{mL}$ conical flask. Add 4.0 mL of 0.7 M potassium carbonate, and start stirring the solution. Add 2 mL of Internal standard solution and 19.0 mL of water. Stop stirring about 5 minutes after the addition of the 0.7 M potassium carbonate solution. [NOTEPrepare fresh immediately before each injection.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a 232 -nm detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention time for 2,6dimethylaniline is about 0.8 and 1.0 for 7-chloro-1,3-dihy-dro-5-phenyl-2H-1,4-benzodiazepin-2-one; the relative standard deviation of the peak area ratio of 7-chloro-1,3-di-hydro-5-phenyl-2 H -1,4-benzodiazepin-2-one to 2,6-dimethylaniline for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of 7-chloro-1,3-dihy-dro-5-phenyl-2H-1,4-benzodiazepin-2-one in the portion of Clorazepate Dipotassium taken by the formula:

$$
2500(C / W)\left(R_{i} / R_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one RS in the Standard solution; $W$ is the weight, in mg , of Clorazepate Dipotassium taken to prepare the Test solution; $R_{i}$ is the peak area ratio of any impurity to 2,6-dimethylaniline obtained from the Test solution; and $R_{s}$ is the peak area ratio of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2one to 2,6-dimethylaniline obtained from the Standard solution: not more than $0.5 \%$ of 7 -chloro-1,3-dihydro-5-phenyl$2 \mathrm{H}-1,4$-benzodiazepin-2-one is found, and not more than $0.1 \%$ of any individual impurity is found.

TEST 2-
Diluent-Prepare a mixture of 0.001 N sodium hydroxide and acetonitrile $(1: 1)$.

Mobile phase-Prepare a filtered and degassed mixture of water, acetonitrile, and a 1 M solution of tetrabutylammonium hydroxide in methanol (110:90:1), adjust with phosphoric acid to a pH of 7.7, and mix. Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Standard solution-Dissolve an accurately weighed quantity of USP 2-Amino-5-chlorobenzophenone RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent, to obtain a solution having a known concentration of about 0.0026 mg per mL .
Test solution-Transfer about 300 mg of Clorazepate Dipotassium, accurately weighed, to a glass test tube. Add 10.0 mL of Diluent, and vigorously mix on a vortex mixer for about 90 seconds.[NOTE-Prepare fresh immediately before each injection.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $238-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation of the peak height for replicate injections is not more than $3.0 \%$.
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Clorazepate Dipotassium taken formula:

$$
1000(C / W)\left(r_{i} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP 2-Amino-5-chlorobenzophenone RS in the Standard solution; $W$ is the weight, in mg, of sample taken; $r_{i}$ is the peak height of each impurity obtained from the Test solution; and $r_{s}$ is the peak height of 2-amino-5-chlorobenzophenone obtained
from the Standard solution: not more than $0.1 \%$ of 7 -chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one is found, not more than $0.1 \%$ of any other individual impurity is found, and not more than $1.0 \%$ of total impurities in Test 1 and Test 2 is found. $\mathbf{Q S S}^{\text {S }}$ (USP28)

## BRIEFING

Clozapine, USP 27 page 498 and page 3053 of the First Supplement. It is proposed to revise the test for Chromatographic purity to include the chemical name corresponding to each approximate $R_{F}$ value specified in the Procedure.
(PA3: S. Salado) RTS-41679-1

## Change to read:

## Chromatographic purity-

Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic silica gel mixture.

Test solution-Dissolve an accurately weighed quantity of Clozapine in chloroform to obtain a solution containing 10.0 mg per mL .
Standard solutions-Dissolve an accurately weighed quantity of USP Clozapine RS in chloroform, and mix to obtain a solution having a known concentration of 0.1 mg per mL . Quantitatively dilute portions of this solution with chloroform to obtain the following solutions.

| Standard <br> solution | Dilution | Concentration <br> ( $\mu$ g of RS <br> per mL) | Percentage <br> $(\%$, for <br> comparison with <br> test specimen) |
| :---: | :---: | :---: | :---: |
| $A$ | 3 in 10 | 30 | 0.3 |
| $B$ | 1 in 5 | 20 | 0.2 |
| $C$ | 1 in 10 | 10 | 0.1 |
| $D$ | 1 in 20 | 5 | 0.05 |

Application volume: $20 \mu \mathrm{~L}$.
Developing solvent system: a mixture of chloroform and methanol (3:1).

Procedure-Proceed as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$. Examine the plate under short-wavelength UV light, and compare the intensities of any secondary spots observed in the chromatogram of the Test solution with those of the principal spots in the chromatograms of the Standard solutions: no spot from the chromatogram of the Test solution with an $R_{F}$ value of about $0.82,0.67$, or 0.10 .

■about 0.82 , corresponding to 1,4 -bis( 8 -chloro- $5 H$-diben-zo[b,e][1,4]diazepin-11-yl)piperazine; about 0.67 , corresponding to 8 -chloro-5,10-dihydro-11H-dibenzo[b, e][1,4]-diazepin-11-one; or about 0.10 , corresponding to 8 -chloro-
11-(1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, $■ 25$ (USP28) is larger or more intense than that obtained from Standard solution B, Standard solution C, or Standard solution A, respectively; no other secondary spot from the chromatogram of the Test solution is larger or more intense than the principal spot obtained from Standard solution $C(0.1 \%)$; and the sum of the intensities of all secondary spots obtained from the Test solution corresponds to not more than $0.6 \%$.

## BRIEFING

Cyclandelate, page 1023 of $P F$ 29(4) [July-Aug. 2003]. On the basis of comments received, it is proposed to revise Identification test $A$ to make corrections in the Solution and the Medium.
(PA5: A. Wilk) RTS-41810-1

## Add the following:

## ©Cyclandelate


$\mathrm{C}_{17} \mathrm{H}_{24} \mathrm{O}_{3} \quad 276.38$

## 3,3,5-Trimethylcyclohexanol $\alpha$-phenyl- $\alpha$-hydroxyacetate.

1,5-cis-3,3,5-Trimethylcyclohexyl 2-hydroxy-2-phenyl acetate [456-59-7].
» Cyclandelate contains not less than 98.0 percent of $\mathrm{C}_{17} \mathrm{H}_{24} \mathrm{O}_{3}$, calculated on the dried basis.

Packaging and storage-Preserve in tight, light-resistant containers, and store below $40^{\circ}$, preferably between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle — U S P$ Cyclandelate $R S$.

## Identification-

A: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle-$
Solution: $0.5 \mu \mathrm{mg}$ per mL .
Medium: 95 percent alcohol. The solution exhibits absorption maxima between 250 and 254 nm , between 256 and 260 nm , and between 262 and 266 nm .
B: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -

Test solution-Dissolve 10 mg of Cyclandelate in 1 mL of alcohol.

Application volume: $5 \mu \mathrm{~L}$.
Developing solvent system: a mixture of hexane, ethyl acetate, and glacial acetic acid ( $8: 2: 1$ ).

Loss on drying $\langle 731\rangle$ —Dry 1 g over silica gel for 24 hours: it loses not more than $0.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $0.002 \%$.

## Chromatographic purity-

Mobile phase and Chromatographic system-Prepare as directed in the Assay.

Test solution-Transfer about 100 mg of Cyclandelate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Standard solution-Pipet 3.0 mL of the Test solution into a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Test solution and the Standard solution into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Allow the chromatogram of the Test solution to run for a period of time that is about 3 times the
retention time of cyclandelate. The total area of all the peaks from the Test solution, other than the peak obtained from cyclandelate, is not greater than the peak area of cyclandelate obtained from the Standard solution: not more than $3.0 \%$ of total impurities is found.

## Assay-

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and water ( $4: 1$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Resolution solution-Dissolve accurately weighed quantities of USP Cyclandelate RS and dicyclohexyl phthalate in Mobile phase to obtain a solution having known concentrations of about 0.2 mg per mL and 0.08 mg per mL , respectively.

Standard preparation-Dissolve an accurately weighed quantity of USP Cyclandelate RS in Mobile phase to obtain a solution having a known concentration of about 1.0 mg per mL . Pipet 10.0 mL of this solution into a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix. Assay preparation-Transfer about 100 mg of Cyclandelate, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix. Pipet 10.0 mL of this solution into a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $228-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between cyclandelate and dicyclohexyl phthalate is not less than 7. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{17} \mathrm{H}_{24} \mathrm{O}_{3}$ in the portion of Cyclandelate taken by the formula:

$$
500 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Cyclandelate RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP28)

## BRIEFING

Diclofenac Sodium Delayed-Release Tablets, USP 27 page 596. It is proposed to make a correction in the Procedure in the test for Drug release to be in accordance with the validation report.
(BPC: M. Marques) RTS-40477-4

## Change to read:

Drug release, Method $B\langle 724\rangle$ -
ACID STAGE-
Medium: $\quad 0.1 \mathrm{~N}$ hydrochloric acid; 900 mL .
Apparatus 2 (paddles constructed of, or coated with, polytef being used): 50 rpm .

Procedure-At the end of 2 hours, remove each Tablet, or the major portion thereof if the Tablet is not intact, from the individual vessels, and subject them to the test in the Buffer stage. To the 0.1 N hydrochloric acid remaining in each vessel, add 20.0 mL of 5 N sodium hydroxide, and stir for 5 minutes. Determine the amount of $\mathrm{C}_{14} \mathrm{H}_{10} \mathrm{Cl}_{2} \mathrm{NNaO}_{2}$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solution under test in comparison with a Standard solution prepared as follows. Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 2.0 mL

- $3.0 \mathrm{~mL}_{\mathbf{■} 2 \mathrm{~S}}$ (USP28)
of this solution to a second $100-\mathrm{mL}$ volumetric flask, dilute with a mixture of 0.1 N hydrochloric acid and 5 N sodium hydroxide ( $900: 20$ ) to volume, and mix. This Standard solution contains about $13.6 \mu \mathrm{~g}$ of USP Diclofenac Sodium RS per mL.
buffer stage-
pH 6.8 Phosphate buffer-Dissolve 76 g of tribasic sodium phosphate in water to obtain 1000 mL of solution. Mix 250 mL of this solution with 750 mL of 0.1 N hydrochloric acid, and, if necessary, adjust with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of $6.8 \pm 0.05$.
Medium: pH 6.8 Phosphate buffer; 900 mL .
Apparatus 2: 50 rpm .
Procedure-At the end of 45 minutes, determine the amount of $\mathrm{C}_{14} \mathrm{H}_{10} \mathrm{Cl}_{2} \mathrm{NNaO}_{2}$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 276 nm on filtered portions of the solutions under test, suitably diluted with Medium, in comparison with a Standard solution prepared as follows. Transfer about 68 mg of USP Diclofenac Sodium RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, add 10.0 mL of 0.1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 3.0 mL of this solution to a second $100-\mathrm{mL}$ volumetric flask, dilute with Medium, as obtained in the Buffer stage, to volume, and mix. This Standard solution contains about 0.02 mg of USP Diclofenac Sodium RS per mL .

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{14} \mathrm{H}_{10} \mathrm{Cl}_{2} \mathrm{NNaO}_{2}$ is dissolved.

Dimercaprol Injection, USP 27 page 632. It is proposed to add a test for Bacterial endotoxins to this monograph.
(PA4: E. Gonikberg; AMB: D. Porter) RTS-41570-1

## Add the following:

■USP Reference standards $\langle 11\rangle-U S P$ Endotoxin $R S_{\square}$ ■ (USP28)

## Add the following:

■Bacterial endotoxins $\langle 85\rangle$-It contains not more than 1 USP Endotoxin Unit per mg of dimercaprol.■2S (USP28)

BRIEFING
Diphenoxylate Hydrochloride and Atropine Sulfate Oral So-
ution, USP 27 page 641 and page 3251 of the Second Supplement.
It is proposed to clarify that the test for Uniformity of dosage units
should be performed with respect to diphenoxylate hydrochloride
BRIEFING
Diphenoxylate Hydrochloride and Atropine Sulfate Oral So-
ution, USP 27 page 641 and page 3251 of the Second Supplement.
It is proposed to clarify that the test for Uniformity of dosage units
should be performed with respect to diphenoxylate hydrochloride
BRIEFING
Diphenoxylate Hydrochloride and Atropine Sulfate Oral So-
lution, USP 27 page 641 and page 3251 of the Second Supplement.
It is proposed to clarify that the test for Uniformity of dosage units
should be performed with respect to diphenoxylate hydrochloride
BRIEFING
Diphenoxylate Hydrochloride and Atropine Sulfate Oral So-
lution, USP 27 page 641 and page 3251 of the Second Supplement.
It is proposed to clarify that the test for Uniformity of dosage units
should be performed with respect to diphenoxylate hydrochloride should be performed with respect to diphenoxylate hydrochloride only.
(PA4: E. Gonikberg) RTS-41786-1

## Change to read:

- Uniformity of dosage units $\langle 905\rangle$ -

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements $\mathbf{m}^{2 S}$ (USP27)
$\boldsymbol{\square}_{\text {with }}$ respect to diphenoxylate hydrochloride.■2S (USP28)

Doxepin Hydrochloride Capsules, USP 27 page 664. It is proposed to revise the Identification test, changing the GC system (which has a packed column that is difficult to find on the market) for the HPLC system described in the Assay.
(PA3: S. Salado) RTS-41586-01

## Change to read:

Identification-Transfer the contents of 2 Capsules to a suitable flask. Add about 30 mL of chloroform, and shake by mechanieal means for 30 minttes. Dilute with chlereform 1050 mL , and mix. Quickly flter a pertion of the solution threugh Whatman No. 4 fit ter paper, rejecting the first 15 mL of the filtrate. Pipet an aliquot of the filtered solution containing about 10 mg of doxepin into a-se parator. Add, if necessary, additional chloroform to bring the vol ume to 25 mL . Extract with 50 mL of 1 N sodium hydroxide, and drain the chloroform into another separator. Discard the sodium hydroxide washing. Wash the chloreform solution with $20-\mathrm{mL}$ of 1 N sodium hydroxide. Filter the chloroform layer through eotton into a 100 mL volumetric flack, extract the aqueous layer with 25 mL of chloreform, and add the chloreform layer to the volumetrie flask. Dilute with chloroform to volume, and mix. Inject a portion of the chloroform solution, equivalent to 0.5 Hg of doxepin, dilut ing the chloroform solution, if necessary, into a gas chromatograph equipped with a flame-ionization detector and a $-3.1 \mathrm{~m} \times 2 \mathrm{~mm}$
eolumn packed with 3\% eymmomethylphenyl silieone liquid phase en 80-10-110 mesh acid washed, silanized diatemaceous earth. The carrier gas is helium flowing at a rate of 30 mL per minute. The coltumn temperature is $220^{\circ}$, and the temperattre of the injec tion pert and the detector is $250^{\circ}$. The retention times obtained for the ( $Z$ ) and (E) isomer peaks in the chrematogram of the solution from the Capsules are the same as these obtained for a 20 mg spec imen of USP Doxepin Hydrochloride PS treat and chromatgraphed in a similar manner.
-The retention times for the major peaks for (E)- and (Z)isomers in the chromatogram of the Assay preparation correspond to those in the chromatogram of the Standard preparation, as obtained in the Assay.■2S (USP28)

## Briefing

Enalapril Maleate and Hydrochlorothiazide Tablets, USP 27 page 703. It is proposed to make a correction in the procedure in the Dissolution test.
(BPC: M. Marques) RTS-41753-1

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
Determine the amount of $\mathrm{C}_{20} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{O}_{5} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$ dissolved, using filtered portions of the solution under test and following the Procedure for content uniformity of enalapril maleate, making any necessary volumetric adjustments, in comparison with a Standard solution of USP Enalapril Maleate RS having similar concentrations in the same medium.

Determine the amount of $\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{ClN}_{3} \mathrm{O}_{4} \mathrm{~S}_{2}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 320 nm and at 360 nm

- $\quad$ 2S (USP28)
in 1-cm cells, on filtered portions of the solution under test, suitably diluted with Medium, in comparison with a Standard solution having a known concentration of USP Hydrochlorothiazide RS dissolved in 20 mL of methanol and diluted with Medium.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of enalapril maleate $\left(\mathrm{C}_{20} \mathrm{H}_{28} \mathrm{~N}_{2} \mathrm{O}_{5} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}\right)$ and not less than $60 \%$ $(Q)$ of the labeled amount of hydrochlorothiazide $\left(\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{ClN}_{3} \mathrm{O}_{4} \mathrm{~S}_{2}\right)$ are dissolved in 30 minutes.

BRIEFING

Ergotamine Tartrate and Caffeine Suppositories, USP 27 page 726; Ergotamine Tartrate and Caffeine Tablets, USP 27 page 727. It is proposed to replace the undefined term "fixed alkali" in Identification test $B$ with the name of the actual reagent used.
(PA3: S. Salado) RTS-41195-2

## Change to read:

Identification-Melt 1 Suppository in 10 mL of hot tartaric acid solution (1 in 100), and mix. Chill the mixture until the layer of oil has hardened, then filter, divide the filtrate into two parts, and use this filtrate for the following tests.

A: To one part of the filtrate add 10 mL of $p$-dimethylaminobenzaldehyde TS: a blue color develops (presence of ergotamine).

B: Transfer the remaining part of the filtrate to a small evaporating dish, evaporate on a steam bath to dryness, add 1 mL of hydrochloric acid and 100 mg of potassium chlorate, and evaporate. Invert the dish over a vessel containing ammonium hydroxide: the residue acquires a purple color, which disappears upon the addition of a solution of fixed alkali
$\mathbf{- 1 ~}_{1} \mathrm{~N}$ sodium hydroxide ${ }_{\square 2 S}$ (USP28) (presence of caffeine).

## BRIEFING

Estradiol and Norethindrone Acetate Tablets. Because there is no existing USP monograph for this dosage form, a new monograph is being proposed. The liquid chromatographic procedure is based on analyses performed with the Waters Symmetry C18 brand of L1 column.
(PA1: C. Anthony) RTS—39932-1

## Add the following:

## Estradiol and Norethindrone Acetate Tablets

» Estradiol and Norethindrone Acetate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of estradiol $\left(\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{O}_{2}\right)$ and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of norethindrone acetate $\left(\mathrm{C}_{22} \mathrm{H}_{28} \mathrm{O}_{3}\right)$.

Packaging and storage-Preserve in well-closed containers.

USP Reference standards $\langle 11\rangle$ —USP Estradiol RS. USP
Estrone RS. USP Norethindrone Acetate RS.

## Identification-

A: Thin-Layer Chromatographic Identification Test $\langle 201\rangle$ -

Test solution-Place 2 Tablets into a $10-\mathrm{mL}$ vial, and add 0.2 mL of water. When the Tablets are partially disintegrated, add a few glass beads, and shake vigorously to disintegration. Add 4.0 mL of dehydrated alcohol, and shake. Centrifuge until the supernatant is clear before application to the plate.

Standard solution-Dissolve accurately weighed quantities, of USP Estradiol RS and USP Norethindrone Acetate RS in dehydrated alcohol to obtain a solution having known concentrations of 0.5 mg per mL and 0.25 mg per mL , respectively.

Application volume: $2 \mu \mathrm{~L}$.
Developing solvent solution: a mixture of chloroform and acetone ( $9: 1$ ).
Procedure-Proceed as directed in the chapter, using the Developing solvent system. After removal of the plate, mark the solvent front, and allow the solvent to evaporate. Place the plate on a heating plate at $100^{\circ}$ for 15 minutes. Allow the plate to cool, and then immerse it in a mixture of dehydrated alcohol and concentrated sulfuric acid (95:5). Place the plate on a piece of thick horizontal paper until it is almost dry. Heat the plate at $100^{\circ}$ until it has fully developed. Examine under UV light at 365 nm . The color and $R_{F}$ value of the principal spots obtained from the Test solution correspond to those obtained from the Standard solution.

B: The retention time and UV spectrum of the major peaks in the chromatogram of the Assay preparation correspond to those in the chromatogram of the Standard preparation, as obtained in the Assay.

Microbial limits $\langle 61\rangle$ —The total aerobic microbial count does not exceed 1000 cfu per g , and the total combined molds and yeasts count does not exceed 100 cfu per g . The Tablets meet the requirements of the tests for the absence of Salmonella species and Escherichia coli.

Dissolution-[To come.]
Loss on drying $\langle 731\rangle$ —Dry about 1200 mg of finely powdered Tablets in a tared evaporating dish at a pressure not exceeding 25 mm of mercury at $60^{\circ}$ for 3 hours: it loses not more than $7.5 \%$ of its weight.

## Chromatographic purity-

Solution $A$-Prepare a mixture of water and tetrahydrofuran (200:1).

Solution $B$-Prepare a degassed solution of acetonitrile, water, and tetrahydrofuran ( $160: 40: 1$ ).

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments, if necessary (see System Suitability under Chromatography (621〉).

Diluent-Prepare a mixture of water and dehydrated alcohol (1:1).

System suitability solution-Dissolve accurately weighed quantities of USP Estradiol RS, USP Norethindrone Acetate RS, and USP Estrone RS in Diluent to obtain a solution having known concentrations of about $240 \mu \mathrm{~g}$ per $\mathrm{mL}, 60 \mu \mathrm{~g}$ per mL , and $1 \mu \mathrm{~g}$ per mL , respectively.

Test solution-Accurately weigh and finely powder 20 Tablets. Transfer the equivalent of 12 Tablets to an appropriate flask, and dissolve in a known volume of Diluent to obtain a solution having known concentrations of estradiol and norethindrone acetate of about $240 \mu \mathrm{~g}$ per mL and $120 \mu \mathrm{~g}$ per mL , respectively. Filter the solution, if necessary.

Estradiol standard stock solution-Dissolve an accurately weighed quantity of USP Estradiol RS in alcohol to obtain a solution having a known concentration of estradiol of about $250 \mu \mathrm{~g}$ per mL .
Norethindrone acetate standard stock solution-Dissolve an accurately weighed quantity of USP Norethindrone Acetate RS in alcohol to obtain a solution having a known concentration of norethindrone acetate of about $150 \mu \mathrm{~g}$ per mL .

Standard solution-Combine $250 \mu \mathrm{~L}$ of Estradiol standard stock solution and $100 \mu \mathrm{~L}$ of Norethindrone acetate standard stock solution, and dilute with 50.0 mL of Diluent.

Chromatographic system-The liquid chromatograph is equipped with a dual wavelength detector ( 235 nm and 254 nm ) and a $3.9-\times 30-\mathrm{cm}$ column that contains $4-\mu \mathrm{m}$ packing L1. The flow rate is about 0.8 mL per minute. Program the chromatogram as follows.

| Time | Solution $A$ <br> (minutes) | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 80 | 20 | equilibration |
| $0-2$ | $80 \rightarrow 65$ | $20 \rightarrow 35$ | linear gradient |
| $2-35$ | $65 \rightarrow 20$ | $35 \rightarrow 80$ | linear gradient |
| $35-49$ | 20 | 80 | isocratic |
| $49-50$ | $20 \rightarrow 80$ | $80 \rightarrow 20$ | linear gradient |
| $50-60$ | 80 | 20 | isocratic |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.4 for estrone, about 3.0 for norethindrone acetate, and 1.0 for estradiol. The resolution, $R$, between estrone and estradiol is not less than 1.3, measured at 254 nm .

Procedure-Separately inject equal volumes (about 100 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of any estradiol impurity in the portion of Tablets taken by the formula:

$$
100 F\left(C_{S} / C_{T}\right)\left(r_{i} / r_{s}\right)
$$

in which $F$ is the relative response factor of any estradiol impurity relative to estradiol; $C_{S}$ and $C_{T}$ are the concentrations of the Standard solution and the Test solution, respectively; $r_{i}$ is the peak area at 235 nm for each impurity obtained from the Test solution; and $r_{s}$ is the peak area at 235 nm obtained from the Standard solution. The Tablets meet the requirements given in Table 1.

Table 1

|  | Compound | Relative <br> retention time | Relative <br> response factor |
| :--- | :---: | :---: | :---: |
| 6- $\alpha$ Hydroxyl estradiol | about 0.47 | 1.0 | $(\%)$ |
| 6- $\beta$ Hydroxyl estradiol | about 0.51 | 1.0 | 0.1 |
| 6-Keto estradiol | about 0.62 | 1.0 | 0.1 |
| 16-Keto estradiol | about 0.65 | 1.0 | 0.1 |
| 6-Keto estrone | about 0.75 | 1.0 | 0.1 |
| $\beta$-Equilenol | about 0.88 | 0.04 | 0.1 |
| 6-Dehydro estradiol | about 0.95 | 1.0 | 0.1 |
| Estradiol | 1.0 | 1.0 | 0.1 |
| $\alpha$-Estradiol | about 1.06 | 1.0 | 0.1 |
| Estrone | about 1.17 | 1.0 | 0.1 |
| 4-Methyl estradiol | about 1.24 | 1.0 | 0.1 |

Not more than $0.1 \%$ of any other impurity is found, and not more than $1.0 \%$ of total impurities is found. Calculate the percentage of any norethindrone acetate related impurities in the portion of Tablets taken by the formula:

$$
100 F\left(C_{S} / C_{T}\right)\left(r_{i} / r_{S}\right),
$$

in which $F$ is the relative response factor of any norethindrone acetate related impurity relative to norethindrone acetate; $C_{S}$ and $C_{T}$ are the concentrations of the Standard solution and the Test solution, respectively; $r_{i}$ is the peak area at 254 nm for each impurity obtained from the Test solution; and $r_{s}$ is the peak area at 254 nm obtained from the Standard solution. The Tablets meet the requirements given in Table 2.

Table 2

| Compound | Relative <br> retention time | Relative <br> response factor | Limit <br> $(\%)$ |
| :--- | :---: | :---: | :---: |
| 6- $\beta$ Hydroxy-norethindrone acetate | about 0.58 | 1.0 | 0.05 |
| Norethindrone | about 0.66 | 1.0 | 0.05 |
| 6-Keto-norethindrone acetate | about 0.79 | 1.8 | 0.05 |
| 19-Nor-17-alpha-preg-4-ene-3,20-dione | about 0.90 | 1.0 | 0.05 |
| 6-Dehydro-norethindrone acetate | about 0.97 | 2.2 | 0.05 |
| Norethindrone acetate | about 1.0 | 1.0 | 0.05 |

Not more than $0.5 \%$ of any other impurity is found, and not more than $1.0 \%$ of total impurities is found.

Assay-
Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and water ( $55: 45$ ) (see Chromatography $\langle 621\rangle$ ).
Diluent-Prepare a mixture of water and dehydrated alcohol (1:1).

Estrone standard stock solution-Transfer about 6.00 mg of USP Estrone RS, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, and dissolve in 10 mL of dehydrated alcohol. Dilute with dehydrated alcohol to volume, and mix.

Estradiol standard stock solution-Prepare a solution of USP Estradiol RS in dehydrated alcohol having a known concentration of 0.25 mg per mL .
Norethindrone acetate standard stock solution-Prepare a solution of USP Norethindrone Acetate RS in dehydrated alcohol having a known concentration of 0.15 mg per mL .
System suitability preparation—Transfer $800 \mu \mathrm{~L}$ of Estradiol standard stock solution, $600 \mu \mathrm{~L}$ of Norethindrone acetate standard stock solution, and $200 \mu \mathrm{~L}$ of Estrone standard stock solution to a suitable flask containing 10.0 mL of Diluent.

## Standard preparation-Prepare a solution of Estradiol

 standard stock solution and Norethindrone acetate standard stock solution in Diluent having an accurately known concentration of about $20 \mu \mathrm{~L}$ per ml and $10 \mu \mathrm{~L}$ per mL , respectively.Assay preparation—Add 12 Tablets into a measured amount of Diluent, to obtain a solution having an estradiol concentration of about $20 \mu \mathrm{~L}$ per mL and a norethindrone acetate concentration of about $10 \mu \mathrm{~L}$ per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a diode array detector and a $4.6-\times 150-\mathrm{mm}$ column that contains packing L1. The flow rate is about 1.0 mL per minute. Perform an investigational run to determine the retention times for estradiol and norethindrone acetate. Thus, the absorption of estradiol at 280 nm and norethindrone acetate at 254 nm can be included in a single run by altering the wavelength. Chromatograph the System suitability preparation, and record the peak areas as directed for Procedure: the resolution, $R$, between estradiol and estrone acetate is not less than 1.8. Chromatograph the Standard preparation, and record the peak area as directed for Procedure: the relative standard deviation for replicate injections is not more than $3 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the estradiol and norethindrone acetate peaks. Calculate the quantity, in mg, of estradiol $\left(\mathrm{C}_{18} \mathrm{H}_{24} \mathrm{O}_{2}\right)$ in each of the Tablets taken by the formula:

$$
(V C / 12)\left(r_{U} / r_{S}\right)
$$

in which $V$ is the volume, in mL , of Diluent taken to prepare the Assay preparation; $C$ is the concentration, in mg per mL , of USP Estradiol RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively. Calculate the quantity, in mg, of norethindrone acetate $\left(\mathrm{C}_{22} \mathrm{H}_{28} \mathrm{O}_{3}\right)$ in each of the Tablets taken by the formula:

$$
(V C / 12)\left(r_{U} / r_{s}\right),
$$

in which $V$ is the volume, in mL , of Diluent used in the $A s$ say preparation; $C$ is the concentration, in mg per mL , of USP Norethindrone Acetate RS in the Standard prepara-
tion; and $r_{U}$ and $r_{S}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP28)

## Briefing

Ethacrynic Acid Tablets, USP 27 page 755. It is proposed to revise the Dissolution test to make a correction in the preparation of the Medium.
(BPC: M. Marques) RTS-41591-1

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: $\quad 0.1 \mathrm{M}$ phosphate buffer, prepared by mixing 13.6 g of monobasic potassium phosphate and 96.2 mL of 0.1 N
-92.2 mL of $1 \mathrm{~N}_{\mathbf{\square} 2 \mathrm{~S}}$ (USP28)
sodium hydroxide with water to obtain 1000 mL of a solution having a pH of $8.0 \pm 0.05 ; 900 \mathrm{~mL}$.

Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-Determine the amount of $\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{Cl}_{2} \mathrm{O}_{4}$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 277 nm on filtered portions of the solution under test, suitably diluted with Medium, in comparison with a Standard solution having a known concentration of USP Ethacrynic Acid RS in the same medium.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{13} \mathrm{H}_{12} \mathrm{Cl}_{2} \mathrm{O}_{4}$ is dissolved in 45 minutes.

## BRIEFING

Famotidine for Oral Suspension. Because there is no existing USP monograph for this dosage form, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedure in the test for Related compounds and the Assay is based on analyses performed with the Inertsil ODS-3 brand of L1 column. The typical retention time for the famotidine peak is about 14 minutes.
(PA4: E. Gonikberg; AMB: D. Porter; NL: C. Barnstein; PSD: C. Okeke) RTS-41090-1

## Add the following:

## ■Famotidine for Oral Suspension

» Famotidine for Oral Suspension contains the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of famotidine $\left(\mathrm{C}_{8} \mathrm{H}_{15} \mathrm{~N}_{7} \mathrm{O}_{2} \mathrm{~S}_{3}\right)$ when constituted as directed. It contains one or more suitable buffers, colors, diluents, flavors, and preservatives.

Packaging and storage-Preserve in tight containers, protected from light. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ —USP Famotidine RS.
Identification-The retention time of the famotidine peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, obtained as directed in the Assay.

Microbial limits $\langle 61\rangle$-The total aerobic microbial count is not more than 100 cfu per $g$. The total combined molds and yeasts count is not more than 100 cfu per g . It meets the requirements of the tests for the absence of Salmonella species and Escherichia coli.
$\mathbf{p H}\langle 791\rangle$ : between 6.5 and 7.5 , in the suspension constituted as directed in the labeling.

Uniformity of dosage units $\langle 905\rangle$ : meets the requirements for Content Uniformity.

## Related compounds-

Buffer Solution, Solution A, Solution B, and Diluent-Prepare as directed in the Assay.
Standard solution-Use the Standard preparation, prepared as directed in the Assay.

System suitability stock solution-Weigh approximately 16 mg of Famotidine into a $50-\mathrm{mL}$ volumetric flask, dissolve in 1.0 mL of 1 N hydrochloric acid, heat at $80^{\circ}$ for 30 minutes, and cool to room temperature. Add 2.0 mL of 1 N sodium hydroxide, heat at $80^{\circ}$ for 30 minutes, and cool to room temperature. Add 1.0 mL of 1 N hydrochloric acid to neutralize, and dilute with Diluent to volume.

System suitability solution-Weigh approximately 16 mg of Famotidine into a $50-\mathrm{mL}$ volumetric flask, add 10 mL of Diluent, and sonicate to dissolve. Add 5 drops of hydrogen peroxide solution, heat at $80^{\circ}$ for 15 minutes, and cool to room temperature. Add 20 mL of System suitability stock solution, and dilute with Diluent to volume.

Test solution-Use the Assay preparation, prepared as directed in the Assay.

Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay, with the following addition. Chromatograph the System suitability solution and identify the famotidine peak and the peaks due to impurities listed in Table 1. Record the peak responses as directed for Procedure: the resolution, $R$, between the famotidine peak and the impurity D peak is greater than 1.5 .

## Table 1

| Name | Approximate Relative <br> Retention Time |
| :---: | :---: |
| Impurity A ${ }^{1}$ | 0.3 |
| Impurity B $^{2}$ | 0.5 |
| Impurity C $^{3}$ | 0.7 |
| Impurity D ${ }^{4}$ | 1.2 |

[^340]Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in percent, of the total of impurities C and D in the portion of Famotidine for Oral Suspension taken by the formula:

$$
625 C_{s}\left(r_{u} / r_{s}\right)
$$

in which $C_{S}$ is the concentration, in mg per mL , of USP Famotidine RS in the Standard solution; $r_{u}$ is the sum of the peak areas for impurities C and D obtained from the Test solution; and $r_{s}$ is the famotidine peak area obtained from the Standard solution: the total of impurities C and D is less than $2 \%$.

## Assay-

Buffer solution-Dissolve 13.6 g of sodium acetate trihydrate in 900 mL of water, adjust with glacial acetic acid to a pH of $6.0 \pm 0.1$, and dilute with water to 1 L .
Solution A-Prepare a mixture of Buffer solution and acetonitrile (93:7).

Solution B-Use acetonitrile.
Diluent-Dissolve 13.6 g of monobasic sodium phosphate in 900 mL of water, adjust with 1 M sodium hydroxide to a pH of $7.0 \pm 0.1$, and dilute with water to 1 L . Mix 930 mL of this solution with 70 mL of acetonitrile.

Standard preparation-Dissolve an accurately weighed quantity of USP Famotidine RS in Diluent to obtain a solution having a known concentration of about 0.16 mg per mL .

Assay preparation-Transfer to a $100-\mathrm{mL}$ volumetric flask an accurately measured portion of Famotidine for Oral Suspension, freshly mixed and free from air bubbles and constituted as directed in the labeling, equivalent to about 40 mg of famotidine, based on the labeled amount per mL
of the Suspension. Add 10 mL of methanol, sonicate for 5 minutes, add 70 mL of Diluent, sonicate for an additional 5 minutes, and dilute with Diluent to volume. Dilute 10.0 mL of this solution with Diluent to 25.0 mL , and filter.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $268-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The column temperature is maintained at $35^{\circ}$. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

| Time (minutes) | Solution A <br> (\%) | Solution B (\%) | Elution |
| :---: | :---: | :---: | :---: |
| 0-15 | 100 | 0 | isocratic |
| 15-42 | $100 \rightarrow 52$ | $0 \rightarrow 48$ | linear gradient |
| 42-43 | $52 \rightarrow 100$ | $48 \rightarrow 0$ | linear gradient |
| 43-45 | 100 | 0 | isocratic |

Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 2 ; the column efficiency is greater than 2000 theoretical plates; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of famotidine $\left(\mathrm{C}_{8} \mathrm{H}_{15} \mathrm{~N}_{7} \mathrm{O}_{2} \mathrm{~S}_{3}\right)$ in the portion of Famotidine for Oral Suspension taken by the formula:

$$
C D\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Famotidine RS in the Standard preparation; $D$ is the dilution factor, in mL, for famotidine in the Assay preparation;
and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{D S S}^{2 S}$ (USP28)

## Briefing

Famotidine Tablets, USP 27 page 776 and page 3057 of the First Supplement. Several changes are proposed in the test for Related compounds and the Assay. The term "related compound" in Table 1 is replaced with the term "impurity" to emphasize that these compounds are not available as USP Reference Standards. It is also proposed to round the relative retention times to one decimal place. In addition, there are some minor changes in the preparation of the System suitability solution.
(PA4: E. Gonikberg) RTS-41800-1

## Change to read:

■Related compounds-
Buffer solution, Mobile phase, Diluent, System suitability solution, Staded preparation, Assay preparation,

- ${ }^{\text {2S }}$ (USP28)
and Chromatographic system-Proceed as directed in the Assay. Standard solution-Use the Standard preparation

■as prepared in the Assay.m2s (USP28)
Test solution-Use the Assay preparation
■as prepared in the Assay:■2S (USP28)
Procedure-Separately inject a volume
■equal volumes $_{\text {п2S }}$ (USP28)
(about $50 \mu \mathrm{~L}$ ) of the
-Standard solution ${ }_{\text {2S (USP28) }}$
and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$
100(1 / F) C(D / L N)\left(r_{i} / r_{S}\right)
$$

in which $F$ is the relative response factor for each impurity peak (see Table 1 for values); $C$ is the concentration, in mg per mL , of USP Famotidine RS in the Standard solution; $L$ is the labeled amount, in mg , of famotidine in each Tablet; $N$ is the number of tablets taken to prepare the Test solution; $D$ is the dilution factor used to prepare the Test solution; $r_{i}$ is the peak area obtained for each individual impurity in the Test solution; and $r_{S}$ is the peak area for famotidine in the Standard solution. In addition to not exceeding the limits for each impurity in Table 1, not more than $1.5 \%$ of total impurities is found.

Table 1

| Approximate ${ }_{\text {2S }}$ (USP28) Relative Retention Time | Relative Response Factor (F) | Name | Limit (\%) |
| :---: | :---: | :---: | :---: |
| 0.38 | 1.0 | Fametidine related compeund $A$ | 1.0 |
| $\begin{gathered} 0_{0.4} \mathbf{n S S}_{0.6 S P 28)} \\ 0.65 \end{gathered}$ | 1.0 | -Impurity $\mathrm{A}_{\text {■2S (USP28) }}{ }^{1}$ <br> Famotidine related compound $B$ | 0.5 |
| $\begin{gathered} 0^{0.7} 7_{0.85} \text { (USP28) } \\ 0.85 \end{gathered}$ | 1.0 | -Impurity $\mathrm{B}_{\text {■2S (USP28) }}{ }^{2}$ <br> Famotidine related eompend $C$ | 0.5 |
|  | 1.3 | -Impurity C ${ }_{\text {■2S (USP28) }}{ }^{3}$ <br> Famotidine related eompound P | 0.5 |
| $\square^{1.2}{ }^{\text {п2S }}$ (USP28) |  | -Impurity $\mathrm{D}_{\mathbf{\square} 2 \mathrm{~S} \text { (USP28) }}{ }^{4}$ |  |

${ }^{1}$ 3-[2-(diaminomethyleneamino)-1,3-thiazol-4-ylmethylsulfinyl]- $N$-sulfamoyl-propanamidine
2 3-[2-(diaminomethyleneamino)-1,3-thiazol-4-ylmethylthio]-propanoic acid
${ }_{4}^{3}$ 3-[2-(diaminomethyleneamino)-1,3-thiazol-4-ylmethylthio]- $N$-sulfamoyl-propanamide
${ }^{4}$ 3-[2-(diaminomethyleneamino)-1,3-thiazol-4-ylmethylthio]-propanamide ${ }_{\text {1S }}$ (USP27)

## Change to read:

## Assay-

- Buffer solution-Dissolve 13.6 g of sodium acetate trihydrate in 750 mL of water. Add 1 mL of triethylamine, adjust with glacial acetic acid to a pH of 6.0 , and dilute with water to 1 L .

Mobile phase-Prepare a mixture of Buffer solution and acetonitrile (93:7), mix, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Dissolve 6.8 g of monobasic potassium phosphate in 750 mL of water, adjust with 1 M potassium hydroxide to a pH of 6.0 , and dilute with water to 1 L .

System suitability stock solution-Transfer 10 mg of famotidine to a $50-\mathrm{mL}$ volumetric flask, add 1 mL of 0.1 N hydrochloric acid, heat at $80^{\circ}$ for 30 minutes, and cool to room temperature. Add 2 mL of 0.1 N sodium hydroxide, heat at $80^{\circ}$ for 30 minutes, cool to room temperature, and neutralize by adding 1 mL of 0.1 N hydrochloric acid. Dilute with Diluent to volume. Transfer 10 mL of this solution to a separate $50-\mathrm{mL}$ volumetric flask containing 5 mg of famotidine dissolved in 8 mL of methanol. Dilute with Diluent to volume.
-Transfer 25 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, and dilute with Diluent to volume. [NOTE-This solu-
tion is stable for up to 1 month.] $]_{\text {2S }}$ (USP28)
System suitability solution-Transfer abt 1 mL
■approximately 1 to $1.5 \mathrm{~mL}_{\text {2S (USP28) }}$
of the System suitability stock solution to a suitable container, add 4
mL of Diltent and

## - ${ }^{\text {2S }}$ (USP28)

1 drop of hydrogen peroxide solution, and mix well. [NOTE-Prepare fresh daily.]

Standard preparation-Transfer about 10 mg of USP Famotidine RS, accurately weighed, into a $100-\mathrm{mL}$ volumetric flask, add 20 mL of methanol, and sonicate for 5 minutes. Dilute with Diluent to volume, and mix.

Assay preparation-Transfer not fewer than 10 Tablets to a 1-L volumetric flask. Add 200 mL of Diluent, and swirl to erode the Tablets. Add 200 mL of methanol, and stir by mechanical means
at 300 rpm for 1 hour. Dilute with Diluent to volume, mix, and filter. Quantitatively dilute a portion of the clear filtrate with Diluent to obtain a solution containing about 0.1 mg of famotidine per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $275-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The column temperature is maintained at $40^{\circ}$. The flow rate is about 1.4 mL per minute. Chromatograph the System suitability solution, and identify the famotidine peak and the peaks due to impurities degra dation products

- $\quad$ 2S (USP28)
listed in Table 1. Record the peak responses as directed for Procedure: the resolution, $R$, between the fametidine related eompound E
$\boldsymbol{m i m p u r i t y}_{\mathrm{C}}^{\mathbf{m} 2 \mathrm{~S} \text { (USP28) }}$
and famotidine peaks is not less than 1.3; the resolution, $R$, between the famotidine and famotidine related compeund D
-impurity $^{\mathrm{D}_{\text {■S }}}{ }_{\text {(USP28) }}$
peaks is not less than 1.3; and the capacity factor, $k^{\prime}$, for the famotidine peak is not less than 2.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is less than $2.0 \%$.

Procedure—Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg , of famotidine $\left(\mathrm{C}_{8} \mathrm{H}_{15} \mathrm{~N}_{7} \mathrm{O}_{2} \mathrm{~S}_{3}\right)$ in each Tablet taken by the formula:

$$
C(D / N)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Famotidine RS in the Standard preparation; $D$ is the dilution factor used to prepare the Assay preparation; $N$ is the number of Tablets taken to prepare the Assay preparation; and $r_{U}$ and $r_{S}$ are the peak areas obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP27)

Fexofenadine Hydrochloride Tablets. Because there is no existing USP monograph for this drug product, a new monograph is proposed. The liquid chromatographic system used for the Related compounds and Assay procedures was validated using a Zorbax SB-phenyl brand of L11 column. Typical retention times on this system are 5.5 minutes and 8.8 minutes for fexofenadine and fexofenadine related compound A, respectively. The Dissolution test was validated using a Spherisorb ODS brand of L1 column. Typical retention times are about 3.1 minutes for fexofenadine.
(PA1: K. Russo; BPC: M. Marques; PSD: C. Okeke; NL: C. Barnstein) RTS-40720-1; 40720-2

## Add the following:

## Fexofenadine Hydrochloride Tablets

## » Fexofenadine Hydrochloride Tablets contain not

 less than 95.0 percent and not more than 105.0 percent of the labeled amount of fexofenadine hydrochloride $\left(\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}\right)$.Packaging and storage-Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Fexofenadine Hydrochloride RS. USP Fexofenadine Related Compound A RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$-Weigh and finely powder a sufficient number of Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 60 mg of fexofenadine hydrochloride, to a capped tube. Add 10 mL of a mixture of acetonitrile and methanol (10:1), and shake or mix on a vortex mixer the sample for 1 to 2 minutes to disperse the sample. Allow the solution to stand for 10 minutes or centrifuge for 2 to 3 minutes. Pass the liquid into
a $50-\mathrm{mL}$ beaker using a $0.45-\mu \mathrm{m}$ polytetrafluorethlyene syringe filter. Evaporate the solvent until about 0.5 mL remains using a nitrogen stream with gentle heating (do not exceed $75^{\circ}$ ). Add 5 mL of water and 5 drops of dilute hydrochloric acid, and stir to induce precipitation. Chill in an ice bath for about 30 minutes. Filter the solution through a $10-$ to $15-\mu \mathrm{m}$ sintered-glass crucible. Dry the precipitate in an air oven for 1 hour at $105^{\circ}$. The IR absorption spectrum of a potassium bromide dispersion of the residue so obtained exhibits maxima only at the same wavelengths as that of a potassium bromide dispersion of a similar preparation using USP Fexofenadine Hydrochoride RS. To prepare the reference standard potassium bromide dispersion, transfer about 60 mg of USP Fexofenadine Hydrochloride RS to a capped test tube and proceed as directed beginning with "Add 10 mL of a mixture of acetonitrile and methanol (10:1)."
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Dissolution $\langle 711\rangle$ -
Medium: $\quad 0.001 \mathrm{~N}$ hydrochloric acid; 900 mL , deaerated.

Apparatus 2: 50 rpm .
Times: 10 and 30 minutes.
Procedure-Determine the percentages of the labeled amount of fexofenadine hydrochloride $\left(\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}\right)$ dissolved by using the following method.
Buffer solution-Dissolve 1.0 g of monobasic sodium phosphate, 0.5 g of sodium perchlorate, and 0.3 mL of concentrated phosphoric acid in 300 mL of water, and mix.
Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and Buffer solution (7:3). Make adjustments if necessary (see System suitability under Chromatography〈621〉).

Standard solution-[NOTE-A small amount of methanol, not exceeding $0.5 \%$ of the total volume, can be used to dissolve fexofenadine hydrochloride.] Dissolve an accurately weighed quantity of USP Fexofenadine Hydrochloride RS in Medium to obtain a solution having a known concentration similar to that expected for the solution under test.

Resolution solution-[NOTE-A small amount of acetic acid, not exceeding $5 \%$ of the total volume, can be used to dissolve fexofenadine hydrochloride related compound A.] Dissolve an accurately weighed quantity of USP Fexofenadine Related Compound A RS in water to obtain a solution having a known concentration of about 0.44 mg per mL . Transfer 1.0 mL of this solution into a vial, add 40 mL of the Standard solution, and mix.

Test preparation-Use portions of the solution under test filtered through a $0.45-\mu \mathrm{m}$ glass fiber filter.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ column containing packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the Resolution solution as directed for Procedure: the resolution, $R$, between fexofenadine and fexofenadine related compound A is not less than 2.0. Chromatograph the Standard solution as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$

Procedure-Separately inject equal volumes (approximately 2 to $3 \mu \mathrm{~g}$ column load of fexofenadine hydrochloride) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the fexofenadine peaks. Calculate the quantity, in mg , of fexofenadine hydrochloride $\left(\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}\right)$ dissolved in the Medium by the formula:

$$
C D\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the Standard solution; D is the dilution factor used in preparing the Test preparation; and $r_{U}$ and $r_{S}$ are the fexofenadine peak areas obtained from the Test preparation and the Standard solution, respectively.

Tolerances-Not less than $60 \%(Q)$ of the labeled amount of $\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}$ is dissolved in 10 minutes; and not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}$ is dissolved in 30 minutes.

Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

Water, Method $I\langle 921\rangle$-Grind and finely powder a sufficient number of Tablets, and transfer about 250 mg of the powder to a titration vessel containing titration medium heated to $50^{\circ}$ : not more than $8.5 \%$.

## Related compounds-

Diluent and Mobile phase-Prepare as directed in the Assay.

Sensitivity solution—Dilute 4.0 mL of Standard stock preparation, prepared as directed in the Assay, with Mobile phase to 100 mL . Dilute 6.0 mL of this solution with Mobile phase to 100 mL .

Related compound solution-Dissolve an accurately weighed quantity of USP Fexofenadine Related Compound A RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 0.05 mg per mL .

Standard stock solution-Use the Standard stock preparation, prepared as directed in the Assay.

Standard solution-Dilute accurate volumes of the Related compound solution and the Standard stock solution with Mobile phase to obtain a solution having known concentrations of about 0.015 and 0.0045 mg per mL of fexofenadine hydrochloride and fexofenadine related compound A, respectively.

Test stock solution-Use the Assay stock preparation. Test solution-Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed for Chromatographic system under Assay. Chromatograph the Sensitivity solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $6 \%$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.6 for fexofenadine related compound A , and 1.0 fexofenadine; the resolution, $R$, between fexofenadine and fexofenadine related compound A is not less than 7 ; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $1.4 \%$ and not more than $2.8 \%$ for fexofenadine and fexofenadine related compound A , respectively.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution, the Test stock solution, and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of fexofenadine related compound A in the portion of Tablets taken by the formula:

$$
100 C D\left(r_{i} / r_{s}\right) / N L
$$

in which $C$ is the concentration, in mg per mL , of fexofenadine related compound A in the Standard solution; $D$ is the dilution factor for the preparation of the Test stock solution in $\mathrm{mL} ; r_{i}$ and $r_{s}$ are the peak area responses of fexofenadine related compound A in the Test stock solution and Standard solution, respectively; $N$ is the number of Tablets used to prepare the Test stock solution; and $L$ is the label claim, in mg per Tablet, of fexofenadine hydrochloride. Calculate the percentage of the decarboxylated degradant [(+)-4-[1-hy-
droxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]isopropylbenzene; the relative retention time is 6.7] in the portion of Tablets taken by the formula:

$$
100 C D\left(r_{i} / r_{s}\right) / N L F
$$

in which $C$ is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the Standard solution; $D$ is the dilution factor for the preparation of the Test stock solution in mL ; $r_{i}$ is the peak area response of the decarboxylated degradant in the Test stock solution; $r_{s}$ is the peak area response of fexofenadine in the Standard solution; $N$ is the number of Tablets used to prepare the Test stock solution; $L$ is the label claim, in mg per Tablet, of fexofenadine hydrochloride; and $F$ is the relative response factor ( $F$ is 1.1) for the decarboxylated degradant ( $F$ is 1.0 for all other known and unknown impurities). Calculate the percentage of any other impurities in the portion of Tablets taken by the formula:

$$
100 r_{i} /\left(D r_{S}+r_{T}\right)
$$

in which $r_{i}$ is the individual peak area response for an individual unknown impurity in the Test stock solution; $D$ is the dilution factor, in mL , of the Test solution; $r_{s}$ is the peak area response for fexofenadine in the Test solution; and $r_{T}$ is the sum of the peak area responses of all unknown impurities in the Test stock solution: disregard any peak below $0.05 \%$; not more than $0.35 \%$ of fexofenadine related compound A is found; not more than $0.15 \%$ of the decarboxylated degradant is found; not more than $0.1 \%$ of any individual other impurity is found; not more than $0.15 \%$ total other impurities is found; and not more than $0.5 \%$ total impurities is found.

Assay-
Acid solution-Dilute 17 mL of glacial acetic acid with water to 1 L , and mix. Dilute 100 mL of this solution with water to 1 L .

Buffer solution-Dilute 15 mL of a solution containing acetonitrile and triethylamine $(1: 1)$ with Acid solution to 1 L. Adjust with phosphoric acid to a pH of 5.25 .
Diluent-Prepare a solution of acetonitrile and Acid solution (75:25).
Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (64:36). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).
Standard stock preparation-Dissolve an accurately weighed quantity of USP Fexofenadine Hydrochloride RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 0.25 mg per mL .

Standard preparation-Dilute an accurate volume of the Standard stock preparation with Mobile phase to obtain a solution having a known concentration of about 0.015 mg per mL.
Assay stock preparation-Transfer a sufficient number of whole Tablets (not fewer than 10) to a suitable volumetric flask, add Acid solution (equivalent to about $20 \%$ of the total flask volume), and shake by mechanical means at a high speed for about 30 minutes or until the Tablets are fully disintegrated and finely dispersed. Add acetonitrile (equivalent to about $80 \%$ of the total flask volume), and shake by mechanical means for 60 minutes. Dilute with Diluent to volume, and mix. Pass a portion of this solution through a polytetrafluorethylene filter having a $0.45-\mu \mathrm{m}$ or finer porosity, and use the filtrate. Dilute quantitatively, and step-
wise if necessary, with Diluent to obtain a solution containing about 1.2 mg of fexofenadine hydrochloride per mL.

Assay preparation-Dilute an aliquot of the Assay stock preparation quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution containing about 0.018 mg of fexofenadine hydrochloride per mL .
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L11. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $35^{\circ}$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $1.4 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the fexofenadine peaks. Calculate the quantity, in mg per Tablet, of fexofenadine hydrochloride $\left(\mathrm{C}_{32} \mathrm{H}_{39} \mathrm{NO}_{4} \cdot \mathrm{HCl}\right)$ in the portion of Tablets taken by the formula:

$$
C D\left(r_{U} / r_{S}\right) / N
$$

in which $C$ is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the Standard preparation; $D$ is the dilution factor used for the Assay preparation; $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively; and $N$ is the number of Tablets used in the Assay prepara-
tion.■2S (USP28)

Fosinopril Sodium; Fosinopril Sodium Tablets; Fosinopril Sodium and Hydrochlorothiazide Tablets. Because there are no existing USP monographs for this drug substance and dosage forms, new monographs, based on validated methods of analysis, are being proposed. The liquid chromatographic procedures in the test for Related compounds and in the Assay are based on analyses performed with the Resolve Silica (Waters) $5-\mu \mathrm{m}$ brand of L3 packing for Test 1 and the Assay, SAX (Whatman) $5-\mu \mathrm{m}$ brand of L12 packing for Test 2, and BDS Hypersil Phenyl (Keystone Scientific) $5-\mu \mathrm{m}$ brand of L11 packing for Test 3. Typical retention times for fosinopril sodium are about 6, 7, and 9 minutes for Tests 1,2 , and 3 , respectively.
(PA5: A. Wilk) RTS-40844-1

## Add the following:

## ■Fosinopril Sodium


$\mathrm{C}_{30} \mathrm{H}_{45} \mathrm{NNaO}_{7} \mathrm{P} \quad 585.64$
L-Proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)-propoxy](4-phenylbutyl)phosphinyl]acetyl]-, sodium salt, $\left[1\left[S^{*}\left(R^{*}\right)\right], 2 \alpha, 4 \beta\right]$ -
(4S)-4-Cyclohexyl-1-[(R)-[(S)-1-hydroxy-2-methylpro-poxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt [88889-14-9].
» Fosinopril Sodium contains not less than 97.5 percent and not more than 102.0 percent of $\mathrm{C}_{30} \mathrm{H}_{45} \mathrm{NNaO}_{7} \mathrm{P}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Fosinopril Sodium RS. USP Fosinopril Related Compound A RS. USP Fosinopril Related Compound B RS. USP Fosinopril Related Compound C RS. USP Fosinopril Related Compound D RS. USP Fosinopril Related Compound E RS. USP Fosinopril Related Compound F RS.

Identification-Infrared Absorption $\langle 197 \mathrm{M}\rangle$.
Water, Method II $\langle 921\rangle$ : not more than $0.2 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $0.002 \%$.

## Related compounds-

TEST 1—
Mobile phase, Resolution solution, and Chromatographic system-Proceed as directed in the Assay.

Test solution-Use the Assay preparation.
Procedure-Proceed as directed in the Assay, and measure the areas for each component in the chromatogram obtained, carrying out the chromatography to four times the retention time of the fosinopril sodium peak. Calculate the percentage of each individual related compound by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the response of any individual peak, other than the fosinopril sodium peak, and $r_{s}$ is the sum of the responses of all the peaks.

TEST 2-
Mobile phase-Prepare a degassed mixture of acetonitrile, water, and phosphoric acid (4000:15:2). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

## Test solution-Use the Assay preparation.

Resolution solution-Transfer about 1 mg of each of USP Fosinopril Related Compound C RS and USP Fosinopril Related Compound D RS to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Standard solution to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $214-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L12. The column temperature is maintained at $45^{\circ}$. The flow rate is about 0.9 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the fosinopril sodium and the fosinopril related compound C peaks is not less than 1.5.

Procedure-Inject about $20 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure the peak areas, carrying out the chromatography to two times the retention time of the fosinopril sodium peak. Calculate the percentages of fosinopril related compounds C and D only by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak of fosinopril related compound C or D , and $r_{s}$ is the sum of the responses of all the peaks.
TEST 3-
Mobile phase-Prepare a degassed mixture of acetonitrile and $0.2 \%$ phosphoric acid ( $560: 440$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Resolution solution-Transfer about 1 mg of each of USP Fosinopril Related Compound E RS and USP Fosinopril Related Compound F RS to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Mobile phase to volume, and mix.

Test solution-Transfer about 10 mg of Fosinopril Sodium, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Mobile phase to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $205-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L11. The column temperature is maintained at $45^{\circ}$. The flow rate is about 1 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the fosinopril related compound F and the fosinopril sodium peaks is not less than 1.5.

Procedure-Inject about $20 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure the peak areas, carrying out the chromatography to four times the retention time of the fosinopril sodium peak. Calculate the percentages of fosinopril related compounds E and F only by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the response of the peak of fosinopril related compound E or F , and $r_{s}$ is the sum of the responses of all the peaks. In addition to not exceeding the limits for impurities in Table 1, not more than $0.1 \%$ of any other individual impurity is found, and not more than $1.5 \%$ of total impurities is found.

## Table 1

| Relative | Fosinopril Re- |  | Limit |
| :---: | :---: | :---: | :---: |
| Retention Time | lated |  | $(\%)$ |
|  | Compound | Test |  |
| 2.0 | $\mathrm{~A}^{1}$ | 1 | 0.3 |
| 0.7 | $\mathrm{~B}^{2}$ | 1 | 1.0 |
| 1.2 | $\mathrm{C}^{3}$ | 2 | 0.3 |
| 1.3 | $\mathrm{D}^{4}$ | 2 | 0.3 |
| 0.8 | $\mathrm{E}^{5}$ | 3 | 0.3 |
| 0.9 | $\mathrm{~F}^{6}$ | 3 | 0.3 |

${ }^{1}$ (4S)-4-Cyclohexyl-1-[(4-phenylbutyl)phosphinyl]acetyl-L-proline
${ }^{2}$ (4R)-4-Cyclohexyl-1-[(R)-[(S)-1-hydroxy-2-methylpro-poxy](4-phenylbutyl)phosphinyl]acetyl-D-proline propionate (ester)
${ }^{3}$ Mixture of (4S)-4-Cyclohexyl-1-[(S)-[(S)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt and (4S)-4-Cyclohexyl-1[ $[(R)-[(R)$-1-hydroxy-2-methylpropoxy $]$ (4-phenylbutyl)pho-sphinyl]acetyl-L-proline propionate (ester), sodium salt
${ }^{4}$ (4R)-4-Cyclohexyl-1-[ $(R)-[(S)$-1-hydroxy-2-methylpro-poxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt
5 (4S)-4-Cyclohexyl-1-[(R)-[(S)-1-hydroxy-2-methylpro-poxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt
${ }^{6}$ (4S)-4-Cyclohexyl-1-[(R)-[(S)-1-hydroxy-ethoxy](4-phe-nylbutyl)phosphinyl]acetyl-L-proline propionate (ester)

Organic volatile impurities Method $I\langle 467\rangle$ : meets the requirements.

## Assay-

Mobile phase-Prepare a degassed mixture of acetonitrile, water, and phosphoric acid (2000:10:1). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Resolution solution-Transfer about 1 mg of each of USP Fosinopril Related Compound A RS and USP Fosinopril Related Compound B RS to a $100-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Mobile phase to volume, and mix.

Standard preparation-Dissolve an accurately weighed quantity of USP Fosinopril Sodium RS in Mobile phase to obtain a solution having a known concentration of about 0.10 mg per mL .

Assay preparation-Transfer about 25 mg of Fosinopril Sodium, accurately weighed, to a $250-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $214-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L3. The column temperature is maintained at $33^{\circ}$. The flow rate is about 1.2 mL per minute. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the fosinopril related compound B and the fosinopril sodium peaks is not less than 2.0 ; and the relative standard deviation of the fosinopril sodium peak response for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatogram, and measure the peak responses for the major peaks. Calculate the amount, in mg, of $\mathrm{C}_{30} \mathrm{H}_{45} \mathrm{NNaO}_{7} \mathrm{P}$ in the portion of Fosinopril Sodium taken by the formula:

$$
250 C_{S}\left(r_{U} / r_{s}\right)
$$

in which $C_{S}$ is the concentration, in mg per mL , of USP Fosinopril Sodium RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard prepapration, respectively. $\boldsymbol{m}_{2}$ (USP28)

Briefing

Fosinopril Sodium Tablets-See briefing under Fosinopril Sodium. The chromatographic procedure in the Dissolution test was developed with the Apex C18 brand of L1 packing.
(PA5: A. Wilk; BPC: M. Marques) RTS-40844-2

## Add the following:

## ■Fosinopril Sodium Tablets

» Fosinopril Sodium Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fosinopril sodium $\left(\mathrm{C}_{30} \mathrm{H}_{45} \mathrm{NNaO}_{7} \mathrm{P}\right)$.

Packaging and storage-Preserve in tight containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Fosinopril Sodium RS. USP Fosinopril Related Compound A RS. USP Fosinopril Related Compound G RS.

## Identification-

## A: Infrared Absorption $\langle 197 \mathrm{~F}\rangle$ -

Test specimen-Transfer a portion of the finely powdered Tablets equivalent to about 25 mg of fosinopril sodium to a $100-\mathrm{mL}$ beaker containing 40 mL of water. Heat at $25^{\circ}$ for 5 minutes with stirring, and filter through a medium-porosity fritted-disc funnel. Centrifuge the filtrate at 2500 rpm for 30 minutes. Adjust the filtrate to a pH of 3 with phosphoric acid to precipitate the fosinopril, and filter through a fritted-disc funnel. Dissolve the precipitate by passing chloroform through the filter, and evaporate the chloroform solution
to dryness under a current of air. Proceed as directed, using the oily residue so obtained and a similarly prepared residue from 25 mg of USP Fosinopril Sodium RS.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, as obtained in the Assay.

Dissolution $\langle 711\rangle$ -
Medium: water; 900 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and $0.2 \%$ phosphoric acid ( $64: 36$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Resolution solution-Prepare a solution in Mobile phase containing about 0.02 mg per mL of each of USP Fosinopril Sodium RS and USP Fosinopril Related Compound G RS.

Test solution-Use portions of the solution under test passed through a $1.2-\mu \mathrm{m}$ acrylic filter. [NOTE-Do not use glass filters.].

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column, maintained at $40^{\circ}$, that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 3 mL per minute. Chromatograph the Resolution solution and the Standard solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the fosinopril sodium peak and the fosinopril related compound G peak is not less than 1.7; and the relative standard deviation for replicate injections of the Standard solution is not more than 2.0\%.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of a filtered portion of the solution under test and a Standard solution having a known concentration of USP Fosino-
pril Sodium RS in the same medium, and record the chromatograms. Measure the responses for the major peaks, and calculate the amount of $\mathrm{C}_{30} \mathrm{H}_{45} \mathrm{NNaO}_{7} \mathrm{P}$ dissolved.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{30} \mathrm{H}_{45} \mathrm{NNaO}_{7} \mathrm{P}$ is dissolved in 30 minutes.

Uniformity of dosage units: meet the requirements.

## Limit of related compound A-

Mobile phase, Diluent, and Chromatographic systemProceed as directed in the Assay.

Standard solution-Dissolve an accurately weighed quantity of USP Fosinopril Related Compound A RS in methanol to obtain a solution having a known concentration of about 0.1 mg per mL . Dilute with Diluent to obtain a solution having a final known concentration of 0.0025 mg per mL .

Test solution-Use the Assay preparation.
Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatogram, and measure the peak responses for the major peaks. Calculate the percentage of fosinopril related compound A in the portion of Tablets taken by the formula:

$$
1000 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of the fosinopril related compound A in the Standard solution; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Test solution and the Standard solution, respectively. Not more than $4 \%$ is found.

## Assay-

Mobile phase-Prepare a degassed mixture of methanol and $0.2 \%$ phosphoric acid ( $78: 22$ ). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Diluent-Prepare a mixture of 0.2 M urea solution and acetonitrile ( $80: 20$ ).

Resolution solution-Prepare a solution in Diluent containing $30 \mu \mathrm{~g}$ of USP Fosinopril Related Compound A RS and $70 \mu \mathrm{~g}$ of USP Fosinopril Sodium RS per mL.

Standard preparation-Dissolve an accurately weighed quantity of USP Fosinopril Sodium RS to obtain a solution having a known concentration of about 0.1 mg per mL .
Assay preparation-Transfer not fewer than 10 Tablets to a $500-\mathrm{mL}$ volumetric flask, add 400 mL of Diluent, and stir for 40 minutes. Dilute with Diluent to volume, mix, and centrifuge. Quantitatively dilute an accurately measured volume ( $V_{S} \mathrm{~mL}$ ) of the clear supernatant with Diluent to obtain a solution ( $V_{A} \mathrm{~mL}$ ) containing about 0.1 mg of fosinopril sodium per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the Resolution solution and the Standard preparation and record the peak responses as directed for Procedure: the relative retention time is 0.4 for related compound A , and 1.0 for fosinopril sodium; the resolution, $R$, between the fosinopril sodium and fosinopril related compound A peaks is not less than 2.0 ; and the relative standard deviation for replicate injections of the Standard preparation is not more than 2.0\%.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Continue the chromatography up to 1.5 times the retention time of the fosinopril sodium peak. Calculate the quantity, in mg , of fosi-
nopril sodium $\left(\mathrm{C}_{30} \mathrm{H}_{45} \mathrm{NNaO}_{7} \mathrm{P}\right)$ in the portion of Tablets taken by the formula:

$$
50 C\left(V_{A} / V_{S}\right)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Fosinopril Sodium RS in the Standard preparation; $V_{A}$ is the volume, in mL , of the Assay preparation; $V_{S}$ is the volume, in mL , of supernatant taken for the Assay preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP28)

## BRIEFING

Fosinopril Sodium and Hydrochlorothiazide Tablets-See briefing under Fosinopril Sodium. The chromatographic procedure in the Dissolution test was developed with the Zorbax Stable Bond CN brand of L10 packing.
(PA5: A. Wilk; BPC: M. Marques) RTS-40844-3

## Add the following:

## ■Fosinopril Sodium and Hydrochlorothiazide Tablets

» Fosinopril Sodium and Hydrochlorothiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount
of fosinopril sodium $\left(\mathrm{C}_{30} \mathrm{H}_{45} \mathrm{NNaO}_{7} \mathrm{P}\right)$ and of hydrochlorothiazide $\left(\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{ClN}_{3} \mathrm{O}_{4} \mathrm{~S}_{2}\right)$.

Packaging and storage-Preserve in tight containers, and store at controlled room temperature.

USP Reference standards $\langle 11\rangle —$ USP Benzothiadiazine
Related Compound A RS. USP Fosinopril Sodium RS. USP Fosinopril Related Compound A RS. USP Fosinopril Related Compound H RS. USP Hydrochlorothiazide RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~F}\rangle-$
FOSINOPRIL SODIUM-Transfer a portion of the finely powdered Tablets, equivalent to about 25 mg of fosinopril sodium, to a $100-\mathrm{mL}$ beaker containing 40 mL of water, heat at $30^{\circ}$ for 5 minutes with stirring, and filter through a funnel having a medium-porosity fritted disk. Centrifuge the filtrate at 2500 rpm for 30 minutes. Adjust the filtrate with hydrochloric acid to a pH of 1 to precipitate the fosinopril, and filter through a fritted-disk funnel. Dissolve the precipitate by passing metyl iosobutyl ketone through the filter, and evaporate the filtrate to dryness under a stream of nitrogen. Proceed as directed, using the oily residue so obtained and a similarly prepared residue from 25 mg of USP Fosinopril Sodium RS.

HYDROCHLOROTHIAZIDE-Transfer a portion of the finely powdered Tablets, equivalent to about 37.5 mg of hydrochlorothiazide, to a $250-\mathrm{mL}$ beaker containing 120 mL of water, heat at $30^{\circ}$ for 5 minutes with stirring, and filter through a funnel having a medium-porosity fritted disk. Wash the precipitate with 60 mL of methylene chloride and glacial acetic acid ( $90: 10$ ) mixture, and discard the filtrate. Dissolve the precipitate by passing 10 mL of methyl isobutyl ketone through the filter, and evaporate the filtrate
to dryness under a stream of nitrogen. Proceed as directed, using the waxy residue so obtained and a similarly prepared residue from 37 mg of USP Hydrochlorothiazide RS.

B: The retention times of the fosinopril sodium and hydrochlorothiazide peaks in the chromatogram of the Assay preparation correspond to those of the Standard preparation, as obtained in the Assay for fosinopril sodium and Assay for hydrochlorothiazide, respectively.

Dissolution $\langle 711\rangle$ -
Medium: water, 900 mL .
Apparatus 2: 50 rpm .
Time: 30 minutes.
Mobile phase-Prepare a filtered and degassed mixture of 0.01 M monobasic potassium phosphate ( pH 3.0 ), methanol, and acetonitrile ( $45: 35: 20$ ). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Standard stock solutions-Separately dissolve about 20 mg of USP Fosinopril Sodium RS and USP Hydrochlorothiazide RS accurately weighed in 6 mL of methanol, and dilute with water to obtain solutions (Standard stock solution $A$ and $B$ ) having known concentrations of about 0.1 mg per mL of USP Fosinopril Sodium RS and USP Hydrochlorothiazide RS, respectively.
Standard solution-Mix 25 mL of Standard stock solution B and $x 25 \mathrm{~mL}$ of Standard stock solution $A$, and dilute with water to $200 \mathrm{~mL}, x$ being the ratio of the respective labeled amounts, in mg , of fosinopril sodium to that of hydrochlorothiazide per Tablet.
Resolution solution-Transfer 5 mg of USP Fosinopril Related Compound H RS into a $100-\mathrm{mL}$ volumetric flask, and dissolve in 5 mL of methanol. Add 2.0 mL of Standard
stock solution B, dilute with methanol to volume, and mix.
Test solution-Use portions of the solution under test passed through a $1.2-\mu \mathrm{m}$ acrylic filter. [NOTE-Do not use glass filters.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a variable wavelength detector set at 210 nm and 272 nm and a $4.6-\mathrm{mm} \times$ $25-\mathrm{cm}$ column, maintained at $40^{\circ}$ that contains $5-\mu \mathrm{m}$ packing L10. The flow rate is about 1.3 mL per minute. With the detector set at 215 nm , chromatograph the Resolution solution and the Standard solution, and record the peak responses as directed for Procedure: the resolution, $R$, between the fosinopril related compound H peak and hydrochlorothiazide peak is not less than 1.5 ; and the relative standard deviation for replicate injections of the Standard solution is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of a filtered portion of the solution under test and the Standard solution, and record the chromatograms with the detector set at 272 nm from 0 to 5 minutes and at 210 from 5 to 9 minutes, for hydrochlorothiazide and fosinopril sodium, respectively. Measure the responses for the major peaks, and calculate the amount of $\mathrm{C}_{30} \mathrm{H}_{45} \mathrm{NNaO}_{7} \mathrm{P}$ and of $\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{ClN}_{3} \mathrm{O}_{4} \mathrm{~S}_{2}$ dissolved.

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{30} \mathrm{H}_{45} \mathrm{NNaO}_{7} \mathrm{P}$ and not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{ClN}_{3} \mathrm{O}_{4} \mathrm{~S}_{2}$ are dissolved in 30 minutes.

Uniformity of dosage units: meet the requirements.

## Related compounds-

TEST 1—
Mobile phase, Diluent, and Chromatographic system-
Proceed as directed in the Assay for fosinopril sodium.

Standard solution-Dissolve an accurately weighed quantity of USP Fosinopril Related Compound A RS in methanol to obtain a solution having a known concentration of about 0.1 mg per mL . Dilute an aliquot ( 5 in 200) in Diluent to obtain a solution containing 0.0025 mg per mL .

Test solution-Use the Assay preparation, prepared as directed in the Assay for fosinopril sodium.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses for the major peaks. Disregard the peak for hydrochlorothiazide. Calculate the percentage of fosinopril related compound A in the portion of Tablets taken by the formula:

$$
20 C(D / L)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of fosinopril related compound A in the Standard solution; D is the volume, in mL , of the Test solution; $L$ is the labeled amount, in mg per Tablet, of fosinopril sodium; and $r_{U}$ and $r_{S}$ are the peak responses of fosinopril related compound A obtained from the Test solution and the Standard solution, respectively. Not more than $4 \%$ of fosinopril sodium related compound A is found. Calculate the percentage of any other impurity in the portion of Tablets taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for each impurity; and $r_{s}$ is the sum of the responses of all of the peaks: not more than $0.1 \%$ of any other individual impurity is found, and not more than $5.0 \%$ of total impurities is found.

TEST 2-
Mobile phase and Chromatographic system-Proceed as directed in the Assay for hydrochlorothiazide.

Standard solution-Dissolve an accurately weighed quantity of USP Benzothiadiazine Related Compound A RS in methanol to obtain a solution having a known concentration of about 0.2 mg per mL . Dilute an aliquot ( 2 in 100) in Mobile phase to obtain a solution containing 0.004 mg per mL.

Test solution-Use the Assay preparation, prepared as directed in the Assay for hydrochlorothiazide.
Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Disregard the peak for fosinopril. Calculate the percentage of benzothiadiazine related compound A in the portion of Tablets taken by the formula:

$$
20 C(D / L)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of benzothiadiazine related compound A in the Standard solution; D is the volume, in mL , of the Test solution; $L$ is the labeled amount, in mg per Tablet, of hydrochlorothiazide; and $r_{U}$ and $r_{s}$ are the peak responses of benzothiadiazine related compound A obtained from the Test solution and the Standard solution, respectively. Not more than $0.5 \%$ of benzothiadiazine related compound A is found.

## Assay for fosinopril sodium-

Mobile phase-Prepare a degassed mixture of methanol and $0.2 \%$ phosphoric acid $(75: 25)$. Make adjustments if necessary (see System Suitability under Chromatography (621〉).

Diluent: a mixture of 0.2 M urea and acetonitrile ( $80: 20$ ).

Resolution solution-Prepare a solution in Mobile phase having a known concentration of about 0.1 mg per mL of each of USP Fosinopril Related Compound A RS and USP Fosinopril Sodium RS.
Standard preparation-Dissolve an accurately weighed quantity of USP Fosinopril Sodium RS in Diluent to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation-Place 5 Tablets in each of two 500mL volumetric flasks, add 400 mL of Diluent to each flask, shake for 45 minutes, dilute with Diluent to volume, and mix. Centrifuge a portion of the solution at 2000 rpm for 20 minutes. Mix equal volumes of the supernatant, accurately measured, and dilute, if necessary, to give an expected fosinopril sodium concentration of about 0.1 mg per mL.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a variable wavelength detector set at 215 nm and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the Resolution solution and the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are 0.4 for related compound A and 1.0 for fosinopril sodium; the resolution, $R$, between the fosinopril sodium and fosinopril related compound A peaks is not less than 4.0; and the relative standard deviation for replicate injections of the Standard preparation is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and
measure the responses for the major peaks. Continue the chromatography up to 1.5 times the retention time of the fosinopril sodium peak. Calculate the quantity, in mg , of fosinopril sodium $\left(\mathrm{C}_{30} \mathrm{H}_{45} \mathrm{NNaO}_{7} \mathrm{P}\right)$ in the portion of each Tablet taken by the formula:

$$
100(C D)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Fosinopril Sodium RS in the Standard preparation; $D$ is the dilution factor of the Assay preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## Assay for hydrochlorothiazide-

Mobile phase—Prepare a degassed mixture of $0.2 \%$ phosphoric acid and methanol ( $85: 15$ ). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).
Resolution solution-Prepare a solution in Mobile phase having a known concentration of about $12.5 \mu \mathrm{~g}$ per mL of USP Hydrochlorothiazide RS and $10 \mu \mathrm{~g}$ per mL of USP Benzothiadiazine Related Compound A RS.
Standard preparation-Dissolve an accurately weighed quantity of USP Hydrochlorothiazide RS in Mobile phase to obtain a solution having a known concentration of about $12.5 \mu \mathrm{~g}$ per mL .

Assay preparation-Place 5 Tablets in each of two 500mL volumetric flasks, add 50 mL of water to each flask, and shake for 15 minutes to disintegrate the Tablets. Add about 350 mL of methanol, shake for 45 minutes, dilute with methanol to volume, and mix. Mix 5.0 mL of each supernatant and dilute with Mobile phase to 100 mL , and mix, to give an expected hydrochlorothiazide concentration of about $12.5 \mu \mathrm{~g}$ per mL . Centrifuge a portion of the solution at 2000 rpm for 20 minutes.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a variable wavelength detector set at 271 nm and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the Resolution solution and the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are 0.7 for benzothiadiazine related compound A and 1.0 for hydrochlorothiazide; the resolution, $R$, between the hydrochlorothiazide and benzathiadiazine related compound A peaks is not less than 2.0; and the relative standard deviation for replicate injections of the Standard preparation is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Continue the chromatography up to 1.5 times the retention time of the hydrochlorothiazide peak. Calculate the quantity, in mg, of hydrochlorothiazide $\left(\mathrm{C}_{7} \mathrm{H}_{8} \mathrm{ClN}_{3} \mathrm{O}_{4} \mathrm{~S}_{2}\right)$ in the portion of each Tablet taken by the formula:

$$
100(C D)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Hydrochlorothiazide RS in the Standard preparation; $D$ is the dilution factor of the Assay preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\quad$ 2S (USP28)

## BRIEFING

Lansoprazole, USP 27 page 1068. On the basis of comments received, it is proposed to establish limits for individual impurities under the test for Chromatographic purity, and to lower the limit of total impurities from $1.0 \%$ to $0.6 \%$. Because Lansoprazole has limited stability in the sample diluent, it is proposed to specify that both Standard solution and Test solution should be injected within 10 minutes of preparation. It is also proposed to make changes in the Packaging and storage section.
(PA4: E. Gonikberg; PSD: C. Okeke) RTS-41341-1

## Change to read:

Packaging and storage-Preserve in wellelosed,
-tight, $_{\text {m }}$ (USP28)
light-resistant containers.
-Store at room temperature and protect from excessive heat. ${ }^{\text {2S }}$ (USP28)

## Change to read:

## Chromatographic purity-

Solution A: water.
Solution B-Prepare a filtered and degassed mixture of acetonitrile, water, and triethylamine ( $160: 40: 1$ ). Adjust with phosphoric acid to a pH of 7.0 .

Diluent-Prepare a mixture of Solution A and Solution B $(9: 1)$.
Blank solution-Prepare a mixture of Diluent and methanol (9:1).

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Resolution solution-[NOTE-Prepare immediately before using.] Dissolve 5 mg each of USP Lansoprazole RS and USP Lansoprazole Related Compound A RS in 200 mL of methanol. Pipet 1 mL of this solution into a $10-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.

System suitability solution-Dissolve a suitable quantity of USP Lansoprazole Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.025 mg per mL . Pipet 1 mL of this solution into a $10-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.

Standard solution-
[ [NOTE-Inject within 10 minutes of preparation.] $]_{\text {2S (USP28) }}$ Dissolve an accurately weighed quantity of USP Lansoprazole RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about $25 \mu \mathrm{~g}$ per mL . Pipet 1 mL of this solution into a $10-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.
-The final concentration of the Standard solution is about
$2.5 \mu \mathrm{~g}$ per mL . ${ }^{\text {2S }}$ (USP28)
Test solution-[NOTE-Prepare-immediately before using.
-Inject within 10 minutes of preparation.] ${ }_{\text {nes }}$ (USP28)
Transfer about 125 mg of Lansoprazole, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with methanol to volume, and mix. Pipet 1 mL of this solution into a $10-\mathrm{mL}$ volumetric flask, and dilute with Diluent to volume.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $285-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 0.8 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0-40$ | $90 \rightarrow 20$ | $10 \rightarrow 80$ | linear gradient |
| $40-50$ | 20 | 80 | isocratic |
| $50-51$ | $20 \rightarrow 90$ | $80 \rightarrow 10$ | linear gradient |
| $51-60$ | 90 | 10 | isocratic |

Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the resolution, $R$, between lansoprazole and lansoprazole related compound A is not less than 6. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $3 \%$.

Procedure-Separately inject equal volumes (about $40 \mu \mathrm{~L}$ ) of the Blank solution, the Standard solution, and the Test solution into the chromatograph, record the chromatograms, and
-identify the lansoprazole peak and the peaks due to impurities listed in Table 1. ${ }^{2 S}$ (USP28)
Measure the areas for the major peaks, excluding the peaks obtained from the Blank solution. Calculate the percentage of each impurity in the portion of Lansoprazole taken by the formula:

$$
\begin{gathered}
50(C / H)\left(r_{i} / r_{s}\right), \\
\square 50(C F / W)\left(r_{i} / r_{S}\right), \square_{2 S}(U S P 28)
\end{gathered}
$$

in which

- $F$ is the relative response factor for each impurity peak (see

Table 1 for values); ${ }^{2 S}$ (USP28)
$C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Lansoprazole RS in the Standard solution; $W$ is the weight, in mg , of Lansoprazole taken for the Test solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{S}$ is the peak response for lansoprazole obtained from the Standard solution: more than 4.0\% of obl impurities is found.
-In addition to not exceeding the limits for impurities in Ta ble 1 , not more than $0.6 \%$ of total impurities is found.

Table 1

| Approximate Relative <br> Retention Time | Relative Response Factor (F) |  |  |
| :---: | :---: | :--- | :---: |
| 1.1 | 1.22 | Lansoprazole related compound A | Limit (\%) |
| 0.8 | 0.76 | Impurity B | 0.4 |
| 1.2 | 1.27 | Impurity C | 0.1 |
| - | 1.00 | Other individual impurity | 0.1 |

## BRIEFING

Loratadine, page 3065 of the First Supplement and page 891 of PF 30(3) [May-June 2004]. It is proposed to revise the Labeling statement to indicate that it is necessary to state with which Related compounds test the article complies only if a test other than Test 1 is used.

## Add the following:

-Labeling-If a test for Related compounds other than Test 1 is used, then the labeling states with which Related compounds test the article complies. $\mathbf{m}$ 2S (USP28)
(PA1: K. Russo; NL: C. Barnstein) RTS-41792-1

## Change to read:

USP Reference standards $\langle 11\rangle$ —USP Loratadine $R S$.

- USP Loratadine Related Compound A RS. USP Loratadine Related Compound B RS. $\mathbf{m}_{2 \text { S (USP28) }}$


## Change to read:

## Related compounds-

$\square_{\text {NOTE-O }}$ On the basis of the synthetic route, perform either
Test 1 or Test 2. Test 2 is recommended if 4,8-dichloro-6,11-dihydro- $5 H$-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one is a potential related compound.

## TEST 1——2S (USP28)

Mobile phase and Diluent-Prepare as directed in the Assay.
Standard stock solution-Prepare as directed for Standard preparation in the Assay.
Standard solution-Pipet 5.0 mL of Standard stock solution into a $100-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix. Dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about $0.8 \mu \mathrm{~g}$ per mL .

Test solution-Use the Assay preparation.
Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The column temperature is maintained between $25^{\circ}$ and $35^{\circ}$. The flow rate is about 1 mL per minute. Chromatograph the Test solution, and record the peak areas as directed for Procedure: the relative retention times are about 0.79 for 4-(8-chloro-11-fluoro-6,11-dihydro$5 H$-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl and 1.0 for loratadine. Chromatograph the Standard solution, and record the peak area of the main peak as directed for Procedure: the relative standard deviation for replicate injections is not more than $4.0 \%$.

Procedure-Separately inject equal volumes (about $50 \mu \mathrm{~L}$ ) of the Test solution and the Standard solution into the chromatograph, record the chromatograms, and measure all the peak areas in the Test solution and the area of the main peak in the Standard solution. Calculate the percentage of each impurity in the portion of Loratadine taken by the formula:

$$
10,000(C / F)\left(r_{i} / r_{S}\right) / W
$$

in which $C$ is the concentration, in mg per mL , of USP Loratadine RS in the Standard solution; $F$ is the relative response factor for each impurity, if known ( $F$ is 0.25 for 4-(8-chloro-11-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl); $r_{i}$ is the peak area response for each impurity in the Test solution; $r_{S}$ is the peak area response of loratadine in the Standard solution; and $W$ is the quantity, in mg , of Loratadine taken to prepare the Test solution: not more than $0.2 \%$ of 4-(8-chloro-11-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)-1-piperidinecarboxylate ethyl is found; not more than $0.1 \%$ of any other individual impurity is found; and not more than $0.3 \%$ of total impurities is found.
${ }^{\text {© }}$ TEST $2-$
Solution A-Dissolve 0.96 g of 1-pentanesulfonic acid sodium salt in 900 mL of water. Adjust with phosphoric acid solution (1 in 10) to a pH of $3.00 \pm 0.05$, dilute with water to 1 L , filter, and degas.

Solution B-Use acetonitrile.
Mobile phase-Use variable mixtures of Solution A and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard solution-Dissolve accurately weighed quantities of USP Loratadine RS, USP Loratadine Related Compound A RS, and USP Loratadine Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution containing about 0.1 mg of each compound per mL . Transfer 1.0 mL of this solution to a $10-\mathrm{mL}$ volumetric flask, add 2 mL of Solution $A$, dilute with methanol to volume, and mix to obtain a solution having a known concentration of about 0.01 mg of each per mL.

Test solution-Transfer about 100 mg of Loratadine, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, and dissolve in 2 mL of methanol. Add 2 mL of Solution A, then dilute with methanol to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column containing $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.2 mL per minute. The chromatograph is programmed as follows.

| Time <br> $(\mathrm{min})$ | Solution A <br> $(\%)$ | Solution B <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 75 | 25 | isocratic |
| $0-20$ | $75 \rightarrow 50$ | $25 \rightarrow 50$ | linear gradient |
| $20-30$ | $50 \rightarrow 40$ | $50 \rightarrow 60$ | linear gradient |
| $30-35$ | $40 \rightarrow 30$ | $60 \rightarrow 70$ | linear gradient |


| Time | Solution A | Solution B |  |
| :---: | :---: | :---: | :--- |
| $(\mathrm{min})$ | $(\%)$ | $(\%)$ | Elution |
| $35-45$ | 30 | 70 | isocratic |
| $45-50$ | $30 \rightarrow 75$ | $70 \rightarrow 25$ | step gradient |

Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times and response factors are as follows in the table below. The resolution, $R$, between loratadine related compound A and loratadine related compound $B$ is not less than 1.5 ; and the relative standard deviation of the loratadine peak response from replicate injections is not more than $10 \%$.

| Related Compound | Relative Retention Time with respect to Loratadine | Relative Response Factor $(F)$ with respect to Loratadine |
| :---: | :---: | :---: |
| Loratadine related compound A | 0.50 | 1.00 |
| Loratadine related compound B | 0.53 | 0.89 |
| 8-Chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta-[1,2-b]pyridin-11-one | 0.70 | 0.60 |
| 8-Chloro-6,11-dihydro-11-[ $N$-methyl-4-piperidinyl]11-hydroxy-5 H -benzo[5,6]cyclohepta[1,2-b]pyridine | 0.75 | 0.46 |
| 4,8-Dichloro-6,11-dihydro-5 H -benzo[5,6]cyclohepta- <br> [1,2-b]pyridin-11-one | 1.23 | 0.92 |
| 8-Chloro-6,11-dihydro-11-[ $N$-ethoxy carbonyl-4-piperidinyl]-11-hydroxy-5 H -benzo[5,6]cyclohepta-[1,2-b]pyridine | 1.60 | 0.42 |
| 4,8-Dichloro-6,11-dihydro-11-[ $N$-ethoxy carbonyl-4-piperidylidene]-5 H -benzo[5,6]cyclohepta-[1,2-b]pyridine | 1.83 | 1.08 |
| Loratadine | 1.00 | 1.00 |

Procedure-Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Loratadine taken by the formula:
in which $C_{s}$ is the concentration, in mg per mL , of USP Loratadine RS in the Standard solution; $C_{T}$ is the concentration, in mg per mL of the Test solution; $F$ is the relative response factor as indicated in the table ( $F=1.0$ for unknown impurities); $r_{i}$ is the peak area response for the individual impurity in the Test solution; and $r_{s}$ is the peak response for loratadine in the Standard solution: not more than $0.1 \%$ of loratadine related compound A is found; not more than
$0.1 \%$ of loratadine related compound $B$ is found; less than $0.1 \%$ for each individual unknown impurity is found; and not more than $0.3 \%$ of total impurities is found.■2S (USP28)

## BRIEFING

Loratadine Oral Solution, page 3271 of the Second Supplement and page 1258 of $P F 30(4)$ [July-Aug. 2004]. It is proposed to revise the preparation of the Resolution solution in the test for Related compounds by adding a dilution step. This dilution is needed so that the resolution requirement can be met.
(PA1: K. Russo) RTS-41792-2

## Change to read:

## Related compounds-

Mobile phase-Prepare a mixture of 15 mmol of sodium dodecyl sulfate in a mixture of water and acetonitrile ( $1: 1$ ). Adjust with phosphoric acid to a pH of $2.6 \pm 0.1$, filter, and degas. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Prepare a mixture of Mobile phase and water (2:1).
System suitability solution 1-Dissolve an accurately weighed quantity of USP Loratadine RS, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.002 mg per mL .

System suitability solution 2-Quantitatively transfer 5.0 mL of System suitability solution 1 into a suitable container, dilute with Diluent to 50 mL , and mix.

Resolution solution-Transfer an amount of Oral Solution, equivalent to 20 mg of loratadine, into a screw-cap glass container. Add 1 mL of $3 \%$ aqueous hydrogen peroxide, and mix. Cap, and heat at $65^{\circ}$ for 18 to 24 hours.

- Allow to cool to room temperature, then dilute 5 mL with

Diluent to 25 mL .■2S (USP28)
Test solution-Transfer an accurately measured volume of Oral Solution, equivalent to about 5 mg of loratadine, to a $25-\mathrm{mL}$ volumetric flask, dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L7. The flow rate is about 2 mL per minute. The column temperature is maintained between $30^{\circ}$ and $40^{\circ}$. Chromatograph the Resolution solution, and record the peak areas as directed for Procedure: the relative retention times are about 0.70 for ethyl 4-[8-chloro-5,6-dihydro-4-(hydroxymethyl)-11 H -benzo[5,6]cyclohepta[1,2-b]pyr-idin-11-ylidene]-1-piperidinecarboxylate, 0.84 for ethyl 4-[8-chlo-ro-5,6-dihydro-2-(hydroxymethyl)-11 H -benzo $[5,6]$ cyclohep-$\mathrm{ta}[1,2-b]$-pyridin-11-ylidene]-1-piperidinecarboxylate, and 1.0 for
loratadine; and the resolution, $R$, between loratadine and ethyl 4-[8-chloro-5,6-dihydro-2-(hydroxymethyl)-11H-benzo[5,6]cyclo-hepta[1,2-b]pyridin-11-ylidene]-1-piperidinecarboxylate is not less than 3.0. Chromatograph System suitability solution 1, and record the peak area response of the loratadine peak as directed for Procedure: the tailing factor is not less than 0.7 and not greater than 1.1. Chromatograph System suitability solution 2, and record the peak area response of the loratadine peak as directed for Procedure: the relative standard deviation for replicate injections of System suitability solution 2 is not more than $10 \%$.

Procedure-Inject about $50 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure all the peak area responses. Calculate the percentage of each individual related compound in the portion of Oral Solution taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the individual peak response of each related compound in the Test solution; and $r_{s}$ is sum of the responses of all the peaks, excluding excipient peaks: not more than $0.3 \%$ of ethyl 4-[8-chloro-5,6-dihydro-4-(hydroxymethyl)-11H-benzo[5,6]cy-clohepta[1,2-b]-pyridin-11-ylidene]-1-piperidinecarboxylate is found; not more than $0.3 \%$ of ethyl 4-[8-chloro-5,6-dihydro-2-(hy-droxymethyl)-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yli-dene]-1-piperidinecarboxylate is found; not more than $0.2 \%$ of any other individual impurity is found; and the sum of all impurities is not more than $0.5 \%$.

## BRIEFING

Mangafodipir Trisodium, USP 27 page 1131, page 3272 of the Second Supplement, and page 1921 of $P F 29(6)$ [Nov.-Dec. 2003]. On the basis of comments received, storage conditions in the Packaging and storage section are corrected.
(PA5: A.Wilk; PSD: C. Okeke) RTS-40966-1

## Change to read:

Packaging and storage-Preserve in well-closed containers.

- Store at $25^{\circ}$, exeursiens permitted between $15^{\circ}$ and $30^{\circ}$
$\boldsymbol{m}_{\text {in }}$ a cold place. $\mathbf{m}_{2 \text { S }}$ (USP28) $\mathbf{m}^{2 S}$ (USP27)


## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■2S (USP28)

## Add the following:

-Other requirements-Where the label states that Mangafodipir Trisodium is sterile, it meets the requirements under Sterility Tests $\langle 71\rangle \cdot \mathbf{m}^{2 S}$ (USP28)

## Briefing

Megestrol Acetate Oral Suspension, USP 27 page 1153. On the basis of comments received that some approved products could not meet the Tolerances in the current Dissolution test, it is proposed to replace this test with separate tests for each of the approved products. In the absence of any adverse comments, it is proposed to implement this revision via the Second Interim Revision Announcement pertaining to USP 28-NF 23, with an official date of April 1, 2005.
(BPC: M. Marques) RTS-41682-1; 41739-1

## Add the following:

${ }^{\bullet}$ Labeling-When more than one test for Dissolution is given, the labeling states the test used only if Test 1 is not used. ${ }^{2}$

## Change to read:

Dissolution $\langle 711\rangle-$
Mediun: $0.5 \%$ sodium laurylsulfate-in water; 900 mL . Apparatus 2: 50 rpm
Procedure [NOTE-Use-separate-syringe-for each vesse1.] Withdraw more than $10-\mathrm{mL}$ of the Oral Suspension using a 10 mL syringe with a long cannula. Remove air bubbles from the sy ringe. Adjust the volume to the 10 mL matk on the syringe, and remove the needle. Wipe the tip of the syringe, and aeeurately weigh (gross weight). Operate the apparatus, and rapidly dispense the Oralsuspensien to the side of the vessel at about half way from the bettem. Similarly dispense the-Oral Suspension-into other versels. Aceurately weigh each syringe after dispensing the sample (fare weight). Record sample weights. After completion of the dissolution, pass an aliquet through a filter having a 0.45 सm peresity, and dilute 2.0 mL of the filtrate to 50.0 mL with Dissolution Me dium to ebtain a selution having a concentration of abeut 18 Hg per mL . Determine the ameunt of $\mathrm{C}_{24} \mathrm{H}_{22} \Theta_{4}$-dissolved by employing WVabsorption at the wavelength of maximam absorbance at about 292 nm on fltered pertions of the selution under test, in compar isen with a Standard solution having a known-concentration of USP Megestrol Acetate-RS in the-same-Meditut.

Time: 20 minutes.
Foleranes: Not less than $75 \%$ (Q) of the labeled amount of $\mathrm{E}_{24} \mathrm{H}_{22} \Theta_{4}$-is dissolved in 20 minutes.
${ }^{\bullet}$ TEST $1-$
Medium: $\quad 0.5 \%$ sodium lauryl sulfate in water; 900 mL .
Apparatus 2: 25 rpm .
Time: 30 minutes.
Standard solution-Transfer about 45 mg , accurately weighed, of USP Megestrol Acetate RS to a $250-\mathrm{mL}$ volumetric flask, add about 12 mL of methanol, and put the flask in a warm water bath until the solid is dissolved. Dilute with Medium to volume. The final concentration is about $18 \mu \mathrm{~g}$ of megestrol acetate per mL .

Procedure-Transfer to the surface of the Medium in the dissolution vessel an accurately measured volume of Oral Suspension, freshly mixed and free from air bubbles, equivalent to about 160 mg of megestrol acetate. Determine the amount of $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{4}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 292 nm on filtered portions of the solution under test, in comparison with the Standard solution. Calculate the percentage of megestrol acetate $\left(\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{4}\right)$ released by the formula:

$$
\frac{A_{U} \times C_{S} \times 900 \times 100}{A_{S} \times V \times L C}
$$

in which $A_{U}$ and $A_{S}$ are the absorbances obtained from the Test solution and Standard solution, respectively; $C_{s}$ is the concentration, in mg per mL, of the Standard solution; $V$ is the sample volume, in mL , of Oral Suspension taken; 900 is the volume, in mL , of Medium; 100 is the conversion factor to percentage; and $L C$ is the label claim, in mg per mL .

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{4}$ is dissolved in 30 minutes.

TEST 2-If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium: $\quad 0.5 \%$ sodium lauryl sulfate in water; 900 mL .
Apparatus 2: 25 rpm .

Time: 30 minutes.
Standard solution-Transfer about 45 mg , accurately weighed, of USP Megestrol Acetate RS to a $250-\mathrm{mL}$ volumetric flask. Add about 5 mL of methanol, and mix. Dilute with Medium to volume. Transfer 10 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, and dilute with Medium to volume. The final concentration is about $18 \mu \mathrm{~g}$ per mL .

Test solution-[NOTE-Use a separate syringe for each vessel.] Withdraw more than 10 mL of the Oral Suspension using a $10-\mathrm{mL}$ syringe with a long cannula. Remove air bubbles from the syringe. Adjust the volume to the $10-\mathrm{mL}$ mark on the syringe, and remove the needle. Wipe the tip of the syringe, and accurately weigh (gross weight). Operate the apparatus, and rapidly dispense the Oral Suspension to the side of the vessel at about half way from the bottom. Similarly dispense the Oral Suspension into other vessels. Accurately weigh each syringe after dispensing the sample (tare weight). Record sample weights. After completion of the dissolution, pass an aliquot through a nylon filter having a $0.45-\mu \mathrm{m}$ porosity, and dilute 2.0 mL of the filtrate with Medium to 50.0 mL to obtain a solution having a theoretical concentration of about $18 \mu \mathrm{~g}$ per mL .

Procedure-Determine the amount of $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{4}$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 292 nm , using $0.5-\mathrm{cm}$ pathlength cuvettes, on the Test solution in comparison with the Standard solution. Calculate the percentage of megestrol acetate $\left(\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{4}\right)$ released by the formula:

$$
\frac{A_{U} \times C_{S} \times 900 \times d \times 100}{A_{S} \times W_{U} \times L C}
$$

in which $A_{U}$ and $A_{S}$ are the absorbances obtained from the Test solution and Standard solution, respectively; $C_{S}$ is the concentration, in mg per mL, of the Standard solution; $d$ is
the density, in mg per mL, of the Oral Suspension obtained by dividing the weight of Oral Suspension taken by 10 mL ; $W_{U}$ is the weight, in mg , of Oral Suspension taken; 900 is the volume, in mL, of Medium; 100 is the conversion factor to percentage; and $L C$ is the label claim, in mg per mL .

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{4}$ is dissolved in 30 minutes.

TEST 3-If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3 .

Medium: $\quad 0.5 \%$ sodium lauryl sulfate in degassed water; 900 mL . Use ultrapure sodium lauryl sulfate with an assay content of not less than $99.0 \%$.

Apparatus 2: 50 rpm .
Time: 30 minutes.
Determine the amount of $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{4}$ dissolved employing the following method.

Mobile phase-Proceed as directed in the Assay.
Standard solution-Transfer about 11.5 mg , accurately weighed, of USP Megestrol Acetate RS to a $25-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume.
Test solution-Proceed as directed for Test 2, introducing the sample into the vessel over a 10 - to 15 -second time period (about 1 mL per second).
Chromatographic system (see Chromatography $\langle 621\rangle$ )Proceed as directed in the Assay.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of megestrol acetate $\left(\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{4}\right)$ released by the formula:

$$
\frac{r_{U} \times C_{S} \times 900 \times d \times 100}{r_{S} \times W_{U} \times L C},
$$

in which $r_{U}$ and $r_{S}$ are the peak responses obtained from the Test solution and Standard solution, respectively; $C_{S}$ is the concentration, in mg per mL, of the Standard solution; $d$ is the density, in mg per mL , of the Oral Suspension obtained by dividing the weight of Oral Suspension taken by 10 mL ; $W_{U}$ is the weight, in mg , of Oral Suspension taken; 900 is the volume, in mL , of Medium; 100 is the conversion factor to percentage; and $L C$ is the label claim, in mg per mL .

Tolerances-Not less than $80 \%(Q)$ of the labeled amount of $\mathrm{C}_{24} \mathrm{H}_{32} \mathrm{O}_{4}$ is dissolved in 30 minutes. $\bullet 2$

## Briefing

Mepivacaine Hydrochloride Injection, USP 27 page 1164. It is proposed to revise the Chromatographic system in the Assay to clarify the solutions used to determine the system suitability parameters.
(PA1: K. Russo) RTS-41678-1

## Change to read:

## Assay-

pH 6.3 Phosphate buffer-Dissolve 3.40 g of monobasic potassium phosphate and 4.35 g of dibasic potassium phosphate in 1000 mL of water, and adjust, if necessary, with potassium hydroxide or phosphoric acid to a pH of 6.3.

Mobile phase-Prepare a filtered and degassed mixture of pH 6.3 Phosphate buffer and acetonitrile ( $65: 35$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability preparation-Dissolve suitable amounts of methylparaben and USP Mepivacaine Hydrochloride RS in an appropriate volume of Mobile phase to obtain a solution containing about 0.05 mg per mL and 1.0 mg per mL , respectively.

Standard preparation-Dissolve an accurately weighed quantity of USP Mepivacaine Hydrochloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 1.0 mg per mL.

Assay preparation-Transfer a volume of Injection, equivalent to about 100 mg of mepivacaine hydrochloride, to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The liquid chromatograph is equipped with a $263-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25.0-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1.* The flow rate is about 1.0 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the relative retention times are about 1.4 for methylparaben and 1.0 for mepivacaine; the resolution, $R$, between methylparaben and mepivacaine is not less than 2.0 ; the capacity factor, $k^{\prime}$, for the mepivacaine peak is not less than 1.0 ; and the tailing factor for the mepivacaine peak is not more than 2.0.
-Chromatograph the Standard preparation, and record the
peak responses as directed for Procedure: $\quad$ 2S (USP28)
the relative standard deviation for replicate injections is not more than $2.0 \%$.
Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the mepivacaine peaks. Calculate the quantity, in mg, of mepivacaine hydrochloride $\left(\mathrm{C}_{15} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{O} \cdot \mathrm{HCl}\right)$ in the volume of Injection taken by the formula:

$$
100 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Mepivacaine Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Morantel Tartrate. Because there is no existing USP monograph for this article, a new monograph is being proposed. The Related compounds test is an HPLC procedure utilizing a $4.6-\mathrm{mm} \times$ $25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ L1 packing and a $226-\mathrm{nm}$ detector. The Assay is a titrimetric method with the test material being dissolved in anhydrous acetic acid and titrated with 0.1 N perchloric acid. Interested parties are encouraged to submit comments.
(VET: I. DeVeau) RTS-41471-1

[^341]
## Add the following:

## ■Morantel Tartrate

## $\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{~N}_{2} \mathrm{~S} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6} \quad 370.42$

Pyrimidine, 1,4,5,6-tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl)ethenyl]-, $(E)-,\left[R-\left(R^{*}, R^{*}\right)\right]$-2,3-dihydroxybutanedioate ( $1: 1$ ).
(E)-1,4,5,6-Tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl)vinyl]pyrimidine tartrate (1:1). [26155-31-7].

Morantel [20574-50-9].
» Morantel Tartrate contains not less than 98.5 percent and not more than 101.5 percent of $\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{~N}_{2} \mathrm{~S} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$, calculated on the dried basis.

Packaging and storage-Preserve in well-closed, light-resistant containers. Store at $25^{\circ}$, excursions permitted between $15^{\circ}$ and $30^{\circ}$.

Labeling-Label it to indicate it is for veterinary use only.
USP Reference standards $\langle 11\rangle$ —USP Morantel Tartrate RS.

Clarity and color of solution-Dissolve and dilute 0.25 g to 25.0 mL in carbon dioxide-free water. Solution is clear and yellow to greenish yellow in color.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: It meets the requirements of the test for Tartrate $\langle 191\rangle$.

C: The retention time of the morantel peak in the chromatogram of the Test solution corresponds to that in the chromatogram of Standard solution 1, as obtained in the test for Related compounds.

Melting temperature $\langle 741\rangle$ : $167^{\circ}$ to $172^{\circ}$.
$\mathbf{p H}\langle 791\rangle$ : between 2.8 and 3.2.
Solution: Dissolve and dilute 0.25 g to 25.0 mL in carbon dioxide-free water.

Loss on drying $\langle 731\rangle$ —Dry it at $100^{\circ}$ to $105^{\circ}$ to constant weight: it loses not more than $1.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ —not more than 20 ppm .
Related compounds-[NOTE-Conduct this test without exposure to daylight, and with the minimum necessary exposure to artificial light.]

Mobile phase-Mix 3.5 mL of triethylamine and 850 mL of water. Adjust with phosphoric acid to a pH of 2.5. Add 50 mL of tetrahydrofuran and 100 mL of methanol, and mix.

Tartrate solution-Prepare a solution containing about 0.15 mg tartaric acid per mL in Mobile phase.

Standard solution 1-Dissolve an accurately weighed quantity of USP Morantel Tartrate RS in Mobile phase to obtain a solution having a known concentration of about $5.0 \mu \mathrm{~g}$ per mL .

Standard solution 2-Dilute 2.0 mL of Standard solution $l$ to 100.0 mL with Mobile phase.

System suitability solution-Expose 10 mL of Standard solution 1 to daylight for 15 minutes before injection.
Test solution-Dissolve an accurately weighed quantity of Morantel Tartrate in Mobile phase to obtain a solution having a concentration of about 0.5 mg per mL .
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $226-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$
packing L1. The flow rate is about 0.75 mL per minute. Chromatograph the Tartrate solution, Standard solution 1, and System suitability solution, and record the peak areas as directed for Procedure: using the System suitability solution, the resolution between morantel and its preceding peak ( $(Z)$-isomer) is not less than 2.
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Tartrate solution, Standard solution 1, Standard solution 2, and the Test solution into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Disregarding the tartrate peak and any peak in the chromatogram of the Test solution less than the area of the principal peak in the chromatogram of Standard solution 2, calculate the area percentage of each impurity, relative to morantel, in the portion of Morantel Tartrate taken by the formula:

$$
100\left(C_{S} / C_{U}\right)\left(r_{i} / r_{s}\right)
$$

in which $C_{S}$ and $C_{U}$ are the concentration of morantel tartrate, in mg per mL, of Standard solution 1 and Test solution, respectively; and $r_{i}$ and $r_{s}$ are the peak areas of each individual impurity and morantel obtained from the Test solution and Standard solution 1, respectively: not more than $0.5 \%$ of any individual impurity is found, and not more than $1 \%$ of total impurities is found.

## Assay-

Dissolve 0.280 g in 40 mL of anhydrous acetic acid. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically (see Titrimetry $\langle 541\rangle$ ). One mL of 0.1 N perchloric acid is equivalent to 37.04 mg of $\mathrm{C}_{12} \mathrm{H}_{16} \mathrm{~N}_{2} \mathrm{~S} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6} \cdot \mathbf{\bullet} 2 \mathrm{~S}$ (USP28)

Briefing

Nabumetone Tablets, USP 27 page 1268. It is proposed to clarify the instructions in the Procedure for the Dissolution test.
(BPC: M. Marques) RTS-41725-1

## Change to read:

Dissolution $\langle 711\rangle$ -
Medium: sodium lauryl sulfate solution (2 in 100); 900 mL . Apparatus 2: 50 rpm .
Time: 45 minutes.
Procedure-Determine the amount of $\mathrm{C}_{15} \mathrm{H}_{16} \mathrm{O}_{2}$ dissolved by employing UV absorption

- from the difference between UV absorbances $_{\mathbf{m}_{2 S} \text { (USP28) }}$ at the wavelengths of maximum and minimum absorbance at about 270 nm and 296 nm , respectively, on filtered portions of the solution under test, suitably diluted with Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Nabumetone RS in the same medium.

Tolerances-Not less than $75 \%(Q)$ of the labeled amount of $\mathrm{C}_{15} \mathrm{H}_{16} \mathrm{O}_{2}$ is dissolved in 45 minutes.

## Briefing

Naltrexone Hydrochloride, USP 27 page 1277. In the test for Limit of total solvents, it is proposed to (1) revise the concentration of isopropyl alcohol in the Internal standard stock solution; (2) provide the concentration, in mg per mL , for the alcohol and methanol used to prepare the Standard solution; and (3) revise the formula for calculating the limit of solvents to reflect these changes. In addition, minor editorial style changes have been made.
(PA2: D. Bempong) RTS-41665-1

## Change to read:

Limit of total solvents-
Internal standard stock solution-Prepare a solution of isopropylaleohel, which has been tested and found to be free of methanol and aleohol, having a concentration of about 0.12 mg per mL.
-Transfer 6.0 mL of isopropyl alcohol to a $500-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. [NOTE--The isopropyl alcohol must be free of alcohol impurities.] $]_{\text {■S (USP28) }}$

Internal standard solution-Transfer 5.0 mL of the Internal standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Standard solution - Transfer 2.0 mL of anhydrous methaneland 2.0 mL of aleohel to a 100 mL volumetric flask, dilate with water volume, and mix.
-Prepare a solution of methanol and alcohol $\left(\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}\right)$ in water to obtain a solution having a known concentration
of about 16 mg of each per mL . ${ }^{2 \mathrm{~S}}$ (USP28)
Transfer 3.0 mL of this solution and 5.0 mL of Internal standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.
Test solution-Transfer about 75 mg of Naltrexone Hydrochloride, accurately weighed, to a suitable container, add 5.0 mL of $I n$ ternal standard solution, and shake to dissolve.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-The gas chromatograph is equipped with a flame-ionization detector and a $4-\mathrm{mm} \times 1.8$-m glass column packed with 80 - to $100-\mathrm{mesh}$ support S3. The column temperature is maintained at $150^{\circ}$, and the injection port and detector temperatures are maintained at $170^{\circ}$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.24 for methanol, 0.53 for alcohol, and 1.0 for isopropyl alcohol.
Procedure-Separately inject equal volumes (about $5 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the gas chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentages of methanol and alcohol in the portion of Naltrexone Hydrochloride taken by the formula:

$$
(240 / H)\left(R_{t}+R_{s}\right)
$$

$$
\boldsymbol{\bullet} 100\left(C_{S} / C_{U}\right)\left(R_{U} / R_{S}\right), \mathbf{■}^{2 S}(U S P 28)
$$

in which $W$ is the weight, in mg, of Naltrexene Hydrechloride in the Test solution;

- $C_{S}$ is the concentration, in mg per mL , of methanol or alcohol $\left(\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}\right)$ in the Standard solution; $C_{U}$ is the concentration, in mg per mL, of Naltrexone Hydrochloride in the

Test solution; ${ }^{2 S}$ (USP28)
and $R_{U}$ and $R_{S}$ are the peak response ratios of methanol or alcohol to isopropyl alcohol obtained from the Test solution and the Standard solution, respectively. To the sum of the percentages of methanol and alcohol, add the percentage of water as determined in the test for Water: the sum of water and alcoholic solvents is not more than $5.0 \%$ for the anhydrous form, and not more than $11.0 \%$ for the dihydrate form.

## BRIEFING

Nystatin, Neomycin Sulfate, Thiostrepton, and Triamcinolone Acetonide Ointment, USP 27 page 1353. It is proposed to revise the Assay for nystatin to replace the microbially based procedure with an HPLC method. This method is based on analysis performed with a $3.9 \mathrm{~mm} \times 15.0 \mathrm{~cm}$ Waters Nova-Pak brand of column that contains $4-\mu \mathrm{m}$ packing L1. Interested parties are encouraged to validate the analytical methods using other chromatographic columns and to submit comments to the USP Expert Committee on Veterinary Drugs (Standards).
(VET: I. DeVeau) RTS-41603-1; 41603-2

## Change to read:

Assay for nystatin-Preceed as directed for nystatim under Anti bieties Mierobial Assays $\langle 81\rangle$, blending a suitable, veeurately weighed pertion of Ointment in a high-speed blender for 3 to 5 minutes with a suffieient, aceurately measured volume of dimeth yformamide to give a convenient concentration. Dilute an ac eurately measured volume of the solution so obtained quantitatively with dimethylformamide to obtain a stock solution eontaining abeut 400 -USP Nystatin Units per mL. Dilute an aceurately measured volume of this stock solution quantitatively with Buffer No. 6 to obtain a Test Dilution having a concentration of nystatin assumed to be equal to the median dese level of the-Standaret.

- NOTE-Protect solutions that contain nystatin from ambi- $^{\text {n }}$ ent light.

Ammonium acetate buffer-Dissolve $10.8 \pm 1.0 \mathrm{~g}$ of ammonium acetate in 2500 mL of water. Adjust with acetic acid to a pH of $6.50 \pm 0.05$.

Mobile phase-Mix 2500 mL of Ammonium acetate buffer, 1000 mL of acetonitrile, and 500 mL of methanol. Pass through a $0.45-\mu \mathrm{m}$ nylon filter.
BHT solution-Weigh about 1.0 g of butylated hydroxytoluene, and transfer to a $1000-\mathrm{mL}$ volumetric flask. Dilute with methanol to volume, and mix well.

Standard preparation-In duplicate, dissolve an accurately weighed quantity of USP Nystatin RS in BHT solution to obtain a solution having a known concentration of about 5400 USP Nystatin Units per mL. Store in low-actinic glassware.

System suitability solution-Weigh about 50 mg of USP Nystatin RS, and transfer to a $50-\mathrm{mL}$ low-actinic volumetric flask. Add 0.5 mL of 0.01 N sodium hydroxide, and allow to sit for 1 minute. Add 5 mL of Ammonium acetate buffer. Add about 25 mL of methanol, and sonicate to dissolve. Dilute with methanol to volume, and store in low-actinic glassware.

Assay preparation-Thoroughly mix the Ointment prior to sampling. In duplicate, accurately weigh about 1.0 g of Ointment having a known density into a low-actinic sample bottle. Add 20.0 mL of BHT solution, and insert a polytefcoated magnetic stir bar having dimensions of about 12.7 $\mathrm{mm} \times 7.9 \mathrm{~mm}$. Clamp the bottles onto a suitable mixer mill, ${ }^{1}$ and mix for a minimum of 5 minutes at about 30 Hz. Centrifuge at about $1350 \times g$ for 5 minutes, or until the supernatant is clear. Transfer the supernatant to low-actinic glassware.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $304-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $4-\mu \mathrm{m}$ packing L1. The column temperature is maintained at $40^{\circ}$, and the flow rate is about 2.0 mL per minute. [NOTE-Solutions containing nystatin should be stored at $8^{\circ}$ until they can be injected into the chromatograph.] Chromatograph the Standard preparation and the System suitability solution, and record the peak areas as directed for Procedure: using the System suitability solution, the relative retention times for the nystatin A1 and nystatin A2 peaks are about 1.0 and 1.4, respectively; the column efficiency, using the nystatin A1 peak, is not less than 1200 theoretical plates; the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $3.0 \%$. [NOTE-After the conclusion of the run, rinse the column

[^342]with a mixture of acetonitrile and water $(85: 15)$ until the baseline is stable, and store in this solution. At the beginning of the next run, rinse with Mobile phase until the baseline is stable.]

Procedure-Separately inject equal volumes (about 15 $\mu \mathrm{L}$ ) of the duplicate Standard preparation and Assay preparation into the chromatograph, record the chromatograms, and measure the peak areas for nystatin A1 and nystatin A2. Calculate the quantity, in USP Nystatin Units, of nystatin in the portion of Ointment taken by the formula:

$$
20\left(C_{S} / W_{U}\right)\left(r_{u} / r_{s}\right),
$$

in which $C_{s}$ is the concentration of USP Nystatin RS, in USP Nystatin Units per mL, of the Standard preparation; $W_{U}$ is the weight, in g, of Ointment taken to prepare the Assay preparation; and $r_{u}$ and $r_{s}$ are the average peak areas of the sum of nystatin A1 and nystatin A2 obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{D L S}^{2 S}$ (USP28)

## BRIEFING

Ondansetron; Ondansetron Orally Disintegrating Tablets. Because there is no existing USP monograph for this article, these new monographs are being proposed. The liquid chromatographic procedure in the Assay and in the tests for Limit of ondansetron related compound $D$ and Related compounds is based on analyses performed with a Sperisorb Cyano brand of $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}, 5.0$ $\mu \mathrm{m}$ L10 column. Typical retention times for ondansetron and ondansetron related compound A are about 8.2 minutes and $9.2 \mathrm{~min}-$ utes, respectively, in the Assay and the test for Related compounds. Typical retention times for ondansetron related compound C , ondansetron related compound D , and ondansetron are about $6.7 \mathrm{~min}-$ utes, 7.8 minutes and 20.0 minutes, respectively, in the test for Limit of ondansetron related compound D.
(PA3: S. Salado) RTS—41043-1; 41043-2; 41613-1; 41613-2

## Add the following:

## ■Ondansetron


$\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O} \quad 293.36$
4 H -Carbazol-4-one, 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1 $H$-imidazol-1-yl)methyl]- $( \pm)$.
( $\pm$ )-2,3-Dihydro-9-methyl-3-[(2-methylimidazol-1-yl)-methyl]carbazol-4(1H)-one [99614-02-5].
» Ondansetron contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in light-resistant containers.

USP Reference standards $\langle 11\rangle-U S P$ Ondansetron $R S$. USP Ondansetron Related Compound C RS. USP Ondansetron Related Compound D RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The retention time of the major peak for ondansetron in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay

Water, Method Ia $\langle 921\rangle$ : not more than $3.0 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.

Chloride $\langle 221\rangle$ — To 1-g of the substance under test, add 30 to 40 mL of water, and warm gently, if necessary, until no more dissolves. Mix well, and pass through a filter paper that gives a negative test for chloride. Add I mL of nitric acid and 1 mL of silver nitrate TS. Dilute with water to 50 mL . Mix well, and allow to stand for 5 minutes protected from direct sunlight: any turbidity formed is not greater than that produced in a similarly treated control solution containing 0.3 mL of 0.020 N hydrochloric acid ( $0.02 \%$ ).

## Limit of ondansetron related compound D-

Phosphate buffer-Dissolve about 2.72 g of potassium phosphate monobasic in 900 mL of water. Adjust with 1 N sodium hydroxide or 0.5 N sodium hydroxide to a pH of 5.4 , dilute to 1000 mL , and mix well.

Mobile phase-Prepare a filtered and degassed mixture of phosphate buffer and acetonitrile ( $80: 20$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Standard solution-Dissolve an amount of USP Ondansetron Related Compound D RS in Mobile phase, and dilute stepwise with Mobile phase, to obtain a solution having a known concentration of about $0.4 \mu \mathrm{~g}$ per mL .
Resolution solution-Prepare a solution of USP Ondansetron Related Compound D RS and USP Ondansetron Related Compound C RS in Mobile phase having a known concentration of about $0.6 \mu \mathrm{~g}$ per mL and $1.0 \mu \mathrm{~g}$ per mL , respectively.
Test solution-Transfer about 50 mg of Ondansetron, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $328-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L10. The column temperature is maintained at $30^{\circ}$. The flow rate is about 1.5 mL per minute. Chromatograph the Reso-
lution solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.8 for ondansetron related compound C and 1.0 for ondansetron related compound D ; the resolution, $R$, between ondansetron related compound C and ondansetron related compound D is not less than 1.5. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency is not less than 8000 theoretical plates; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of ondansetron related compound D in the ondansetron taken by the formula:

$$
10(C / W)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Ondansetron Related Compound D RS in the Standard solution; $W$ is the weight, in mg , of ondansetron taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses of ondansetron related compound $D$ obtained from the Test solution and the Standard solution, respectively: not more than $0.10 \%$ is found.

## Related compounds-

Phosphate buffer, Mobile phase, Resolution solution, Standard preparation, and Chromatographic system-Prepare as directed in the Assay.

Test solution-Use the Assay preparation prepared as directed in the Assay.

Procedure-Inject a volume (about $10 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Ondansetron taken by the formula:

$$
100\left(r_{i} / r_{s}\right),
$$

in which $r_{i}$ is the peak area for each impurity; and $r_{s}$ is the sum of the areas of all the peaks: not more than $0.1 \%$ of any individual impurity is found; and not more than $0.5 \%$ of total impurities is found, including ondansetron related compound D. [NOTE-Disregard the peak corresponding to ondansetron related compound D at a relative retention time of about 0.4.]

Organic volatile impurities $\langle 467\rangle$ : meets the requirements.

Assay-
Phosphate buffer-Dissolve about 2.72 g of potassium phosphate monobasic in 900 mL of water. Adjust with 1 N sodium hydroxide or 0.5 N sodium hydroxide, to a pH of 5.4 , dilute to 1000 mL , and mix.
Mobile phase-Prepare a filtered and degassed mixture of Phosphate buffer and acetonitrile (52:48). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Resolution solution-Prepare a solution of USP Ondansetron RS and USP Ondansetron Related Compound A RS in Mobile phase having a known concentration of about 0.09 mg per mL and 0.05 mg per mL , respectively.
Standard preparation-Dissolve an accurately weighed quantity of USP Ondansetron RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.090 mg per mL .

Assay preparation-Transfer about 45 mg of Ondansetron, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix. Pipet 5.0 mL of this solution into a $50-\mathrm{mL}$ volumetric flask.

Dilute with Mobile phase to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )— The liquid chromatograph is equipped with a $216-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} 25-\mathrm{cm}$ column that contains packing L10. The flow rate is about 1.5 mL per minute. The column temperature is maintained at $30^{\circ}$. Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.1 for ondansetron related compound A and 1.0 for ondansetron; the resolution, $R$, between ondansetron related compound $A$ and ondansetron is not less than 1.5. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the tailing factor is not more than 2.0 ; and the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the ondansetron peaks. Calculate the quantity, in mg, of $\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}$ in the portion of Ondansetron taken by the formula:

$$
500 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Ondansetron RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\quad$ 2S (USP28)

## BRIEFING

Ondansetron Orally Disintegrating Tablets-See briefing under Ondansetron.
(PA3: S. Salado) RTS-41043-2; 41613-2

## Add the following:

## ■Ondansetron Orally Disintegrating Tablets

## » Ondansetron Orally Disintegrating Tablets con-

 tain the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ondansetron $\left(\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}\right)$.Packaging and storage-Preserve in light-resistant containers. Store at controlled room temperature

USP Reference standards $\langle 11\rangle$ —USP Ondansetron $R S$. USP Ondansetron Related Compound A RS. USP Ondansetron Related Compound D RS.

Identification-The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Disintegration-[To come.]
Dissolution $\langle 711\rangle$ - [To come.]
Uniformity of dosage units $\langle 905\rangle$ : meet the requirements.

Water, $\langle 921\rangle$ : not more than $4.0 \%$.

## Related compounds-

Phosphate buffer-Prepare as directed in the Assay.
Mobile phase-Prepare a filtered and degassed mixture of Phosphate buffer and acetonitrile (8:2). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

Ondansetron related compound D solution-Dissolve an amount of USP Ondansetron Related Compound D RS in acetonitrile, and dilute stepwise with Mobile phase, to obtain a solution having a known concentration of about 0.04 mg per mL .

2-Methylimidazole solution-Dissolve an amount of 2methylimidazole in acetonitrile, dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.04 mg per mL .

Standard stock solution-Dissolve an accurately weighed quantity of USP Ondansetron RS in acetonitrile, dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about 0.04 mg per mL.

System suitability solution-Transfer 5.0 of each, Standard stock solution, 2-Methylimidazole solution, and Ondansetron related compound D solution, to a $100-\mathrm{mL}$ volumetric flask. Dilute with Mobile phase to volume, and mix.

Standard solution-Pipet 5.0 mL of the Standard Stock solution into a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.
System sensitivity solution-Pipet 10.0 mL of the Standard solution into a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Test solution-Transfer 10 Tablets to an appropriate volumetric flask so that the final concentration is about $400 \mu \mathrm{~g}$ of ondansetron per mL. Add Mobile phase to fill about $60 \%$
of the flask capacity. Shake by mechanical means for about 5 minutes, and dilute with Mobile phase to volume. Centrifuge a portion of this solution at 3000 rpm for 10 minutes. Use the supernatant.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $216-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are given in the Table 1; the resolution, $R$, between ondansetron and any adjacent peak is not less than 1.5 ; the column efficiency is not less than 8000 theoretical plates for ondansetron; and the tailing factor for the ondasetron peak is not more than 2.0. Chromatograph the System sensitivity solution, and record the peak responses as directed for Procedure: the signal-to-noise ratio for the ondansetron peak is not less than 15. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $5.0 \%$.
Procedure-Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution and the Standard solution into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$
100(C / F)(V / D)\left(r_{i} / r_{\mathrm{s}}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Ondansetron RS in the Standard solution; $F$ is the relative response factor for each impurity as described in Table 1; $V$ is the volume, in mL , of the volumetric flask used to prepare the Test solution; $D$ is the amount, in mg , of ondansetron in the sample based on the labeled amount and number of dis-
integrating tablet taken; $r_{i}$ is the peak area of any impurity in the Test solution; and $r_{s}$ is peak area of ondansetron in the Standard solution: it meets the requirements specified in Table 1. [NOTE-The run time is about 60 minutes.]

Table 1

|  | Relative <br> Retention <br> time | Relative <br> Response | Limit |
| :--- | :---: | :---: | :---: |
| Compound name | $(\%)$ |  |  |
| 2-Methylimidazol | 0.16 | 0.5 | 0.15 |
| Ondansetron Re- | 0.45 | 1.2 | 0.12 |
| $\quad$ lated Compound |  |  |  |
| $\quad$ D |  |  |  |
| Ondansetron | 1.0 | - | - |
| Individual Unknown | - | 1.0 | 0.1 |
| Impurity |  |  |  |
| Total impurities | - | - | 0.5 |

## Assay-

## Diluent: $\quad 0.01 \mathrm{~N}$ hydrochloric acid

Phosphate buffer-Dissolve about 2.72 g of monobasic potassium phosphate in 1000 mL of water. Adjust with 1 N sodium hydroxide or 0.5 N sodium hydroxide to a pH of 5.4.

Mobile phase-Prepare a filtered and degassed mixture of phosphate buffer and acetonitrile ( $52: 48$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Ondansetron related compound A solution-Dissolve an amount of USP Ondansetron Related Compound A RS in Diluent, and dilute stepwise with Diluent, to obtain a solution having a known concentration of about 0.14 mg per mL .

Assay preparation concentrated-Transfer 10 Tablets to an appropriate volumetric flask so that the final concentration is about $400 \mu \mathrm{~g}$ of ondansetron per mL . Add Diluent to fill about $60 \%$ of the flask capacity. Shake by mechanical means for about 5 minutes, and dilute with Diluent to volume. Filter a portion of this solution through a $0.45-\mu \mathrm{m}$ polypropylene membrane, discarding the first 5 mL .
System suitability solution-Transfer 8.0 mL of ondansetron related compound A solution and 8.0 mL of the Assay preparation concentrated to a $50-\mathrm{mL}$ volumetric flask. Dilute with Diluent to volume, and mix.
Standard preparation-Dissolve an accurately weighed quantity of USP Ondansetron RS in Diluent, and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about $40 \mu \mathrm{~g}$ per mL.

Assay preparation-Transfer 5.0 mL of the Assay preparation concentrated to a $50-\mathrm{mL}$ volumetric flask. Dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $216-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.1 for ondansetron related compound A , and 1.0 for ondansetron; the resolution, $R$, between ondansetron related compound A and ondansetron is not less than 1.5 ; and the tailing factor is not more than 2.0 for the ondansetron peak. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the ondansetron peaks. Calculate the quantity, in mg, of ondansetron $\left(\mathrm{C}_{18} \mathrm{H}_{19} \mathrm{~N}_{3} \mathrm{O}\right)$ in the portion of Tablets taken by the formula :

$$
(10 V) C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Ondansetron RS in the Standard preparation; $V$ is the volume used to prepare the Assay preparation concentrated; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{m S S}^{2 S}$ (USP28)

## Briefing

Oxycodone Hydrochloride, USP 27 page 1375. It is proposed to revise the test for Limit of alcohol to provide the concentration, in mg per mL , of alcohol in the Standard solution. It is also proposed to reflect this change in the formula for calculating the limit of alcohol in the Procedure.
(PA2: D. Bempong) RTS-41437-1

## Change to read:

Limit of alcohol $\left(\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}\right)$ -
Internal standard stock solution-Transfer 6.0 mL of isopropyl alcohol to a $500-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix. [NOTE-The isopropyl alcohol must be free of alcohol impurities.]

Internal standard solution-Transfer 5.0 mL of Internal standard stock solution to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Standard solution-Transfer 2 mL of aleohol to a 100 mL vol tmetric flask, dilute with water to volume, and mix.
-Prepare a solution of alcohol in water to obtain a solution having a known concentration of about 16 mg of alcohol
$\left(\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}\right)$ per mL . $\mathbf{m}^{2 S}$ (USP28)
Pipet 3.0 mL of this solution and 5.0 mL of the Internal standard stock solution into a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

Test solution-Transfer about 240 mg of Oxycodone Hydrochloride, accurately weighed, to a $15-\mathrm{mL}$ centrifuge tube, add 5.0 mL of Internal standard solution, and mix to dissolve.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The gas chromatograph is equipped with a flame-ionization detector and a $4-\mathrm{mm} \times 1.8-\mathrm{m}$ glass column that is packed with $80-$ to 100 -mesh support S3, helium being used as the carrier gas. Prior to use, condition the column overnight at $235^{\circ}$ with a slow flow of carrier gas. The column is maintained at $150^{\circ}$, and the injection port and detector temperatures are maintained at $170^{\circ}$. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the resolution, $R$, between isopropyl alcohol and alcohol is not less than 2; the tailing factor for alcohol is not more than 1.5; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $5 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}$ in the portion of Oxycodone Hydrochloride taken by the formula:

$$
(240 / 4)\left(R_{4}+R_{s}\right)
$$

$$
\mathbf{\square} 100\left(C_{S} / C_{U}\right)\left(R_{U} / R_{S}\right), \llbracket 2 S(U S P 28)
$$

in which Wis the weight, in mg, of Oxyeodene Hydrochloride in the Test solution;

- $C_{S}$ is the concentration, in mg per mL, of alcohol $\left(\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}\right)$ in the Standard solution; $C_{U}$ is the concentration, in mg per mL , of oxycodone hydrochloride in the Test solu-
tion; 2 L (USP28)
and $R_{U}$ and $R_{S}$ are the ratios of the alcohol peak to the isopropyl alcohol peak obtained from the Test solution and the Standard solution, respectively. [NOTE The density of alcohol, 800 mg per mL , has been aecounted for in the ealeulations.]
-n2S (USP28)
Not more than $1.0 \%(\mathrm{w} / \mathrm{w})$ of alcohol $\left(\mathrm{C}_{2} \mathrm{H}_{5} \mathrm{OH}\right)$ is found.

Briefing

Phenylephrine Bitartrate, page 923 of $P F$ 30(3) [May-June 2004]. On the basis of comments received, it is proposed to make extensive revisions in the test for Chromatographic purity and also to revise the concentration of the Test solution in the test for Specific rotation.
(PA2: D. Bempong) RTS-41799-1

## Add the following:

## ■Phenylephrine Bitartrate

$\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6} \quad 317.3$
$R$-2-(Methylamino)-1-(3-hydroxyphenyl)ethanol, hydrogen tartrate.
(-)-1-(3-Hydroxyphenyl)-2-methylaminoethanol, hydrogen tartrate.
(-)-3 Hydroxy- $\alpha$-[(methylamino)methyl] benzenemethanol, hydrogen tartrate.
$1-m$-Hydroxy- $\alpha-[($ methylamino $)$ methyl $]$ benzyl alcohol, hydrogen tartrate [17162-39-0].
» Phenylephrine Bitartrate contains not less than 99.0 percent and not more than 100.5 percent of $\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO}_{2} \cdot \mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$, calculated on the dried basis.

Packaging and storage-Preserve in tight, light-resistant containers. Store at controlled room temperature.

USP Reference standards $\langle 11\rangle$ —USP Norphenylephrine Hydrochloride RS. USP Phenylephrine Hydrochloride RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The alkaline filtrate from the test for Specific rotation responds positively to the test for Tartrate $\langle 191\rangle$.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $-53^{\circ}$ and $-57^{\circ}$ for the prepared sample.
Test solution-Prepare a sample solution of about 24240 mg per mL in water. Make the solution slightly alkaline by adding concentrated ammonium hydroxide dropwise. Rub the wall of the vessel with a glass rod so that the base precipitates out. Filter the base under suction, wash with a little water and acetone, and dry at $105^{\circ}$ for 2 hours. Prepare and measure a 50 mg per mL solution of base precipitate in 1 M hydrochloric acid.
$\mathbf{p H}\langle 791\rangle$ : between 3.0 and 4.0 in $10 \% \mathrm{w} / \mathrm{v}$ aqueous solution.

Loss on drying $\langle 731\rangle$-Dry at $105^{\circ}$ to a constant weight: it loses not more than $0.5 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.

## Chromatographic purity-

Buffer solution-Dissolve 3.25 g of 1-octanesulfonic acid sodium salt monohydrate in 1 L of water. Adjust slowly with 3 M phosphoric acid to a pH of 2.8 .

Solution A-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (9:1).

Solution B—Prepare a filtered and degassed mixture of acetonitrile and Buffer solution $(9: 1)$.

Diluent-Prepare a mixture of Solution $A$ and Solution B (8:2).
System suitability solution-Dissolve accurately weighed quantities of USP Phenylephrine Hydrochloride RS, ner phenylephrine hydrochloride, 1 benzylphenylepherine base, and benzylphenylepherine hydrochloride and USP

Norphenylephrine Hydrochloride RS in Diluent, and dilute
quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 0.06 me per mL , 0.09 mg per mL, 0.07 mg per mL , and 0.05 mg per mL 1.0 mg per mL and $0.9 \mu \mathrm{~g}$ per mL , respectively.

Blank solution-Prepare a solution containing 0.8 mg per mL L $(+)$-tartaric acid in Diluent.

Test solution-Transfer 78 mg of Phenylephrine Bitartrate, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4-\mathrm{mm} \times 5.5-\mathrm{cm}$ column that contains packing L1. The column temperature and injector temperature are maintained at $45 \pm 2^{\circ}$. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 93 | 7 | equilibration |
| $0-10$ | $93 \rightarrow 3070$ | $7 \rightarrow 7030$ | linear gradi- |
| $10-1810.1$ | $3070 \rightarrow 93$ | $70-30 \rightarrow 7$ | ent |
|  |  |  | ear gradient |
| $10.1-18$ | 93 | 7 | equilibration |

Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0 .9-for nerphenylephrine, about 1.0 for ( ) phenylephrine, about 1.2 for phenylephrone, about 2.9 for 1 benzylphenylepherine, and about 3.1 for benzylphenylepherine HCl , the resolution, $R$, between norphenylephrine and ( - )-phenylephrine is not less than 1.5 ; the tailing factor of $(-)$-phenylephrine is less than 1.8 ; and the relative standard deviation for replicate injections is not more than $6 \% 5 \%$.

Procedure-fnject $10 \mu \mathrm{~L}$ of Separately inject equal volumes (about $4 \mu \mathrm{~L}$ ) of the Blank solution and the Test solution into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Phenylephrine Bitartrate taken by the formula:

$$
100\left(r_{i} / r_{s}\right)
$$

in which $r_{i}$ is the peak response for each impurity, and $r_{s}$ is the sum of the responses of all the peaks: man Q.2\% of any individual impurity is found, and not more than 0.5\%) fotalimpurities is found-[NOTE-Examine the chromatogram of the Blank solution for peaks and disregard any corresponding peaks observed in the chromatogram of the Test solution.] The limits of impurities are specified in the accompanying table.

|  | Approximate <br> Relative Reten- <br> tion Time | Limit (\%) |
| :--- | :---: | :---: |
| Compound | 1.0 | - |
| Phenylephrine | 0.9 | 0.2 |
| Norphenylephrine | 1.2 | 0.1 |
| Phenylephrone | 2.9 | 0.2 |
| Benzylphenylephrine | 3.1 | 0.1 |
| Benzylphenyl- |  |  |
| $\quad$ ephrone |  | 0.2 |
| Individual unknown |  | 0.5 |
| $\quad$ impurity | - |  |
| Total impurity |  |  |

Assay—Transfer about 280 mg of Phenylephrine Bitartrate, accurately weighed, to a $100-\mathrm{mL}$ beaker, and dissolve by stirring in 60 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrical-
ly. Perform a blank determination (see Titrimetry $\langle 541\rangle$ ), and make the necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 31.73 mg of $\mathrm{C}_{9} \mathrm{H}_{13} \mathrm{NO}_{2}$.
$\mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{6}$. ${ }^{2 \mathrm{~S}}$ (USP28)

## Briefing

Phenytoin Sodium, USP 27 page 1480 and page 1967 of $P F$ 29(6) [Nov.-Dec. 2003]. Several changes are proposed to clarify and correct the System suitability parameters in the test for Related compounds and the Assay. A revision of the calculation formula for other impurities in the test for Related compounds is proposed to include the molecular weights.
(PA3: S. Salado) RTS-41190-1

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■1S (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle$ -

- USP Endotoxin RS. ${ }^{1 \mathrm{IS} \text { (USP28) }}$

USP Phenytoin RS. USP Phenytoin Related Compound A RS. USP Phenytoin Related Compound B RS.

## Change to read:

## Related compounds-

Mobile phase, Standard stock preparation, System suitability stock solution, and System suitability solution-Prepare as directed in the Assay.

Standard solution-Dissolve accurately weighed quantities of benzophenone, USP Phenytoin RS, USP Phenytoin Related Compound A RS, and USP Phenytoin Related Compound B RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having known concentrations of $0.5 \mu \mathrm{~g}$ per $\mathrm{mL}, 1 \mu \mathrm{~g}$ per $\mathrm{mL}, 9 \mu \mathrm{~g}$ per mL , and $9 \mu \mathrm{~g}$ per mL , respectively.

Test solution-Use the Assay stock preparation.
Chromatographic system - Proceed as directed in the Assay, except to enly use the Systen sutability solution to valuate the sys tem suitability requirements.

■inject the Standard solution instead of the Standard preparation: the relative standard deviation for replicate injec-
tions is not more than $5.0 \%$ for each compound. ${ }^{2 S}$ (USP28)
Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of phenytoin related compound A, phenytoin related compound B , and benzophenone in the portion of Phenytoin Sodium taken by the formula:

$$
100(C / D)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of the respective analyte in the Standard solution; $D$ is the concentration, in $\mu \mathrm{g}$ per mL , of Phenytoin Sodium in the Test solution; and $r_{i}$ and $r_{S}$ are the peak responses for phenytoin related compound A , phenytoin related compound B, or benzophenone obtained from the Test solution and the Standard solution, respectively: not more than $0.9 \%$ each of phenytoin related compound A and phenytoin related compound B is found, and not more than $0.1 \%$ of benzophenone is found. Calculate the percentage of every other impurity in the portion of Phenytoin Sodium taken by the formula:

$$
100(C D)\left(r_{i}+x_{s}\right)
$$

$$
\mathbf{■}_{100(274.25 / 252.27)(C / D)\left(r_{i} / r_{S}\right), \square_{2 S}(U S P 28)}
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Phenytoin RS in the Standard solution;
-274.25 and 252.27 are the molecular weights of phenytoin
sodium and phenytoin, respectively; $\boldsymbol{m}_{2 S}$ (USP28)
$r_{i}$ and $r_{S}$ are the peak responses of each impurity obtained from the Test solution and the Standard solution, respectively; and the other term is as defined above. Not more than $0.9 \%$ of total impurities is found, excluding benzophenone.

## Add the following:

-Other requirements-Where the label states that Phenytoin Sodium is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Phenytoin Sodium Injection. Where the label states that Phenytoin Sodium must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Phenytoin Sodium Injection.■1S (USP28)

## Change to read:

## Assay-

Mobile phase_Prepare a filtered and degassed mixture of 0.05 M monobasic ammonium phosphate buffer, adjusted to a pH of 2.5 with phosphoric acid, acetonitrile, and methanol ( $45: 35: 20$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard stock preparation-Transfer about 100 mg of USP Phenytoin RS, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in Mobile phase, and sonicate, if necessary, to dissolve.

System suitability stock solution-Transfer 5.0 mL of the Standard stock preparation to a $50-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume to obtain a solution having a known concentration of about $100 \mu \mathrm{~g}$ per g .

System suitability solution Prepare solution
-Transfer about 75.0 mg of benzoin to a $50-\mathrm{mL}$ volumetric
flask, dissolve ${ }_{\mathbf{n} 2 \mathrm{~S}}$ (USP28)
in 10 mL of methanol, 1.5 me of benzein per mL,
■ ■ $2 S ~(U S P 28) ~_{\text {a }}$
and dilute with a mixture of 0.05 M monobasic ammonium phosphate buffer, previously adjusted with phosphoric acid to a pH of 2.5 and acetonitrile ( $45: 35$ ), to volume. Transfer 1.0 mL of the solution so obtained to a $10-\mathrm{mL}$ volumetric flask, and dilute with the System suitability stock solution to volume.

Standard preparation-Transfer 5 mL of the Standard stock preparation to a $100-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume.

Assay stock preparation-Transfer about 100 mg of Phenytoin Sodium, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Assay preparation-Transfer 5.0 mL of the Assay stock preparation to a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system-The liquid chromatograph is equipped with a $220-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Standard preparation, and record the responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $0.6 \%$.
-1.0\%.■2S (USP28)
Chromatograph the System suitability solution, and record the peak responses as directed for Procedure:

- the relative retention times are 1.0 for phenytoin and about


## 1.3 for benzoin; ${ }^{2 S}$ (USP28)

the column efficiency is not less than 9960

## -9400 ${ }_{\text {nS }}$ (USP28) <br> theoretical plates

- for the phenytoin peak; ${ }_{22 S}$ (USP28)
the tailing factor is not more than 1.5; and the relative standarde viation for replieate injections determined from the benzophenone peaks is not more than $7.0 \%$.
-resolution, $R$, between phenytoin and benzoin is not less


## than 1.5.■2S (USP28)

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the peak responses for the major peaks. Calculate the quantity, in mg , of $\mathrm{C}_{15} \mathrm{H}_{11} \mathrm{~N}_{2} \mathrm{NaO}_{2}$ in the portion of Phenytoin Sodium taken by the formula:

$$
2000 C(274.25 / 252.27)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Phenytoin RS in the Standard preparation; 274.25 and 252.27 are the molecular weights of phenytoin sodium and phenytoin, respectively; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Briefing

Physostigmine Salicylate Injection, USP 27 page 1486. It is proposed to to revise the USP Reference standards section and the Assay to reflect the use of USP Benzyl Alcohol RS in the preparation of the Benzyl alcohol-benzaldehyde solution. In addition, minor editorial changes have been made.
(PA3: S. Salado) RTS-41361-1

## Change to read:

USP Reference standards $\langle 11\rangle$ -
-USP Benzyl Alcohol RS.п2S (USP28)
USP Endotoxin RS. USP Physostigmine Salicylate RS.

## Change to read:

## Assay-

0.05 M Ammonium acetate-Dissolve 3.85 g of ammonium acetate in 1 L of water, and adjust, if necessary, with glacial acetic acid or ammonium hydroxide to a pH of $6 \pm 0.1$.

Mobile phase-Prepare a filtered and degassed mixture of equal volumes of acetonitrile and 0.05 M Ammonium acetate. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Benzyl alcohol-benzaldehyde solution-Prepare a mixture of $100 \mu \mathrm{~L}$ of benzyl aleohel
-USP Benzyl Alcohol $\mathrm{RS}_{\text {■2S (USP28) }}$
and $1 \mu \mathrm{~L}$ of benzaldehyde in each 400 mL of acetonitrile.
Standard preparation-Dissolve an accurately weighed quantity of USP Physostigmine Salicylate RS in Benzyl alcohol-benzaldehyde solution, and dilute quantitatively, and stepwise if necessary, with Benzyl alcohol-benzaldehyde solution to obtain a solution having a known concentration of about $30 \mu \mathrm{~g}$ per mL .

Assay preparation-Transfer an accurately measured volume of Injection, equivalent to about 3 mg of physostigmine salicylate, to a $100-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 30-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2 mL per minute. Separately chromatograph $10-\mu \mathrm{L}$ portions of the Benzyl alcohol-benzaldehyde solution and the Standard preparation, and record the peak responses as directed for Procedure [NOTE-If the components of the Benzyl alcohol-benzaldehyde solution co-elute, the Standard preparation will exhibit only two peaks instead of three]: in a suitable system, benzyl alcohol and benzaldehyde elute before physostigmine, the resolution, $R$, between the physostigmine peak and the adjacent peak (benzyl alcohol or benzaldehyde or the combination of these) is not less than 2.0 , the column efficiency determined from the analyte peak is not less than 1200 theoretical plates, and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{15} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{2}$. $\mathrm{C}_{7} \mathrm{H}_{6} \mathrm{O}_{3}$ in each mL of the Injection taken by the formula:

$$
0.1(C / V)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Physostigmine Salicylate RS in the Standard preparation; $V$ is the volume, in mL , of Injection taken; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

## BRIEFING

Propoxycaine Hydrochloride, USP 27 page 1576 and page 1567 of PF 29(5) [Sept.-Oct. 2003]. Because of potential safety issues regarding picrates, it is proposed to delete Identification test C.
(PA1: K. Russo) RTS-41743-1

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■1S (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle$ -

- USP Endotoxin RS. $\quad$ 1S (USP28)

USP Propoxycaine Hydrochloride RS.

## Change to read:

Identification-
A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle-$
Solution: $10 \mu \mathrm{~g}$ per mL .
Medium: water.
Absorptivities at 303 nm , calculated on the dried basis, do not differ by more than $3.0 \%$.

C: Dissolve about 100 mg in 10 mL of water, heat almest to beiling, and add, with stirring, 1 mL of a saturated solution of trinitrophenel in 20 pereent aleohel. Coolslowly, colleet the precipi tate on a flter, wash with a few small pertions of water, and dry in a zacumm-desiecater over phespherus pentexide for 18 heurs: the pierate so-obtained melts between $130^{\circ}$ and $138^{\circ}$, with decompesition (see Melting $\langle 744\rangle$ ). [Caution Pierates maty explede.]

D:

A solution (1 in 100) responds to the tests for Chloride $\langle 191\rangle$.

## Add the following:

-Other requirements-Where the label states that Propoxycaine Hydrochloride is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection. Where the label states that Propoxycaine Hydrochloride must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injec-
tion.1S (USP28)

## BRIEFING

Ramipril, USP 27 page 1623 . On the basis of comments received, it is proposed to replace the titration method in the Assay with a stability-indicating HPLC procedure. The new procedure is based on analyses performed using a Kromasil 100 C-18 brand of column containing $3-\mu \mathrm{m}$ packing L1. The typical retention time for ramipril is about 13 minutes.
(PA5: A.Wilk) RTS-40611-1

## Change to read:

" Ramipril contains not less than 98.0 percent and not more than 101.0

- 102.0 $0_{\text {2s }}$ (USP28)
percent of $\mathrm{C}_{23} \mathrm{H}_{32} \mathrm{~N}_{2} \mathrm{O}_{5}$, calculated on the dried basis.


## Change to read:

Assay Dissolve abeut 300 mg of Ramipril, aceurately weighed, in 25 mL of methanel, add 25 mL of water, and titrate with 0.1 N sodium hydroxide VS, determining the endpeint petentiometrieat y. Perform a blank determination, and make any neeessary correetion (see Titrimetty $\langle 544\rangle$ ). Each mL of 0.1 N soditum hydroxide is equivalent to 41.65 mg of $\mathrm{C}_{22} \mathrm{H}_{22} \mathrm{~N}_{2} \mathrm{O}_{5}$.
-Sodium dodecyl sulfate solution-Prepare a $1 \%$ solution of sodium dodecyl sulfate. Adjust with phosphoric acid to a pH of $2.4 \pm 0.1$, filter, and degas.

Mobile phase_Prepare a mixture of Sodium dodecyl sulfate solution and acetonitrile (55:45). Adjust with phosphoric acid to a pH of $2.75 \pm 0.1$, filter, and degas. Make adjustments if necessary (see System Suitability under

## Chromatography $\langle 621\rangle$ ).

System suitability preparation-Dissolve accurately weighed quantities of USP Ramipril RS and USP Ramipril Related Compound A RS in Mobile phase to obtain a solution having known concentrations of about 0.2 mg per mL and 0.01 mg per mL , respectively.

Standard preparation-Dissolve an accurately weighed quantity of USP Ramipril RS in Mobile phase to obtain a solution having a known concentration of about 0.2 mg per mL .

Assay preparation-Transfer about 100 mg of Ramipril, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in about 10 mL of acetonitrile, dilute with Mobile phase to volume, and mix. Pipet about 10 mL of this stock solution to a $50-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $210-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.8 mL per minute. Chromatograph the System suitability preparation, and record the peak responses as directed for Procedure: the resolution, $R$, between ramipril and ramipril related compound A is not less than 2.0 ; the column efficiency determined from the ramipril peak is not less than 4000 theoretical plates; and the relative standard deviation for replicate injections determined from the ramipril peak is not more than $1.0 \%$.

Procedure—Separately inject equal volumes (about 10 $\mu \mathrm{L})$ of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in mg , of $\mathrm{C}_{23} \mathrm{H}_{32} \mathrm{~N}_{2} \mathrm{O}_{5}$ in the portion of Ramipril taken by the formula:

$$
500 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Ramipril RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP28)

## Briefing

Ranitidine Hydrochloride, USP 27 page 1624 and page 1569 of $P F$ 29(5) [Sept.-Oct. 2003]; Ranitidine Oral Solution, USP 27 page 1626. It is proposed to replace the thin-layer chromatographic procedure in the test for Chromatographic purity and the liquid chromatographic procedure in the Assay with a single liquid chromatographic method. This proposed new procedure is based on analyses performed with the Waters Xterra MS brand of L1 column. The typical retention time for ranitidine is about 6.5 minutes. The new method requires an additional reference standard, USP Ranitidine Resolution Mixture RS, which contains Ranitidine Hydrochloride and four related impurities.
(PA4: E. Gonikberg) RTS-40648-1

## Add the following:

-Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■1S (USP28)

## Change to read:

USP Reference standards $\langle 11\rangle-$
-USP Endotoxin RS. 1 IS (USP28)
USP Ranitidine Hydrochloride RS. USP Ranitidine Related Com pand A RS. USP Ranitidine Related Compand BRS. USP Rani tidine Related Compund C RS.

- USP Ranitidine Resolution Mixture RS.■2S (USP28)


## Change to read:

## Chromatographic purity-

Fest solution-Prepare a solution in methanol containing 22.3 ms per mL of Ranitidine- Hydrochloride.

Standard solutions. Bissolve an aceurately weighed quantity of USP Ranitidine Hydrochloride RS in methanol, and dilute with methanol to obtain Standurd solution 4 , having a known concen tration of about 0.22 mg per mL . Dilute portions of Standard sotution 4 quantitatively with methanel to obtain Standurd solutions $B, C$, and $D$, having concentrations of 110,66 , and $11 \mu \mathrm{~s}$ per mL , respectively.

Resolution solution- Dissolve an aceurately weighed quantity ef USP Ranitidine Related Compernd $A$ PS in methanel to obtain a solution having a known concentration of about 1.27 mg per mL . Identification preparation Dissolve an aceurately weighed quantity of USP Renitidine Related Compound B-RS in methanel to obtain a solution having a known eoneentration of about 1 mg permb.

Proedure Separately apply $10 \mu \mathrm{~L}$ each of the Test solution, each of the Standerd solutions, and the Identification solution to a thin layer chrematographic plate (see-Chrematography $\langle 624\rangle$ ) eoated with a 0.25 mm layer of chromatographic siliea gel mixture. Separately apply an additional $10 \mu \mathrm{~L}$ of the Test solutionto the same plate, and on top of this applieation, apply $10 \mu \mathrm{~L}$ of the Re solution solution. Allow the spots to dry, and develop the chromat egrams in a solvent system consisting of a mixture of ethyl ace ate, isopropyl aleohol, ammenitm hydroxide, and water ( $25: 15: 5: 1$ ) until the solvent front has moved not less than 15 cm from the or igin. Remove the plate from the developing chamber, mark the sol vent front, and allow to air dry. Expose the plate to iodine vapors in a clesed chamber until the ehrematogram is fully revealed. Exam ine the plate, and compare the intensities of any secondary spets ebserved in the chromatogram of the Test solution with those of the prineipal spets in the chrematograms of Standerd solutions $A$, $B, C$, and $D$, and the Identification solution: the system suitability requirements are met if there is complete resolution between the primary spots in the chromatogram of the combined Test solution and Resolution solution, and if a spot is observed in the chromatogram of Standurd solution D. Any spot observed in the chrematogram of the Test solution at the $R_{L}$ value correspending to that of the prineipal spet produced by the Identifieation solution, is not greater in size or intensity than the principal spet obtained from Stand solution $B$, correspending to not more than $0.5 \%$; and no other spet in the chrematogram of the Test solution exceeds the size or intensity of the principal spot obtained from Standetrd solution $C(0.3 \%)$. The sum of the intensities of all seondary spets ebtained frem the Test solution correspends to not mere than $1.0 \%$.
-Diluent, Mobile phase, Resolution solution, and Chromatographic system-Proceed as directed in the Assay.
Standard solution-Prepare as directed for Standard

Test solution-Prepare as directed for Assay preparation.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and identify the ranitidine peak and the peaks due to impurities and degradation products listed in the table below.

| Relative <br> Retention Time | Name |
| :---: | :--- |
| 0.14 | Ranitidine simple nitroacetamide |
| 0.21 | Ranitidine oxime |
| 0.45 | Ranitidine amino alcohol |
|  | hemifumarate |
| 0.57 | Ranitidine diamine hemifumarate ${ }^{1}$ |
| 0.64 | Ranitidine $S$-oxide ${ }^{2}$ |
| 0.72 | Ranitidine $N$-oxide |
| 0.84 | Ranitidine complex nitroacetamide |
| 1.36 | Ranitidine formaldehyde |
| 1.75 | Adduct ranitidine bis-compound ${ }^{3}$ |

[^343]Measure the responses for the major peaks, and calculate the percentage of each impurity in the portion of Ranitidine Hy drochloride taken by the formula:

$$
20,000 C / W\left(r_{i} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of ranitidine hydrochloride in the Standard solution; $W$ is the weight, in mg , of Ranitidine Hydrochloride taken to prepare the Test solution; $r_{i}$ is the peak response for each impurity obtained from the Test solution; and $r_{s}$ is the ranitidine peak response obtained from the Standard solution: not more than $0.3 \%$ of
ranitidine bis-compound is found, not more than $0.1 \%$ of any other single impurity is found, and not more than $0.5 \%$ of total impurities is found. ${ }^{2 S}$ (USP28)

## Add the following:

-Other requirements-Where the label states that Ranitidine Hydrochloride is sterile, it meets the requirements for Sterility and Bacterial endotoxins under Ranitidine Injection. Where the label states that Ranitidine Hydrochloride must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for Bacterial endotoxins under Ranitidine Injection.■1S (USP28)

## Change to read:

Assay-
Mebile phase Prepare afftered and degassed mixtare of meth anol and 0.1 M aqueous ammenium aeetate (85:15). Make adjust ments if neeessary (see-System Suitability under Chromatography $\langle 621\rangle$.

Standard preparation Dissolvean aceurately weighed quantity of USP Ranitidine-Hydrechloride-PS in Mebile phase to obtain a solution having a known concentration of about 0.112 mg (equiv alent to - 0.100 mg of ranitidine base) per mL .

System sutability solution Dissolve aeeurately weighed quant tities of USP Ranitidine Hydrechloride RS andUSP Ranitidine Retated Compeund C RS in Mebile phase to obtain a solution having known concentrations of about 0.112 mg per mL and 0.01 mg per mL , respectively.

Assay preparation Transfer about 112 mg of Ranitidine Hy drechloride, aceurately weighed, to a $100-\mathrm{mL}$ volumetric flask. Bissolve in and dilute with Mobile phase to volume, and mix. Transfer 1.0 mL of this solution to a 10 mL velumetric flask, dilute with Mebile phase to volume, and mix.

Chromatographic system (see-Chromatography $\langle 624\rangle$ ) The liquid chromategraph is equipped with a 322 mm detector and a-4.6 $\mathrm{mm} \times 20-30 \mathrm{~cm}$ colum that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the Systent suitabit ity solution, and record the peak respenses as directed for Proce dure: the resolution, $R$, between ranitidine hydrochloride and $N$ [2 [[[5-[(dimethylamine)methyl] 2 faramyl]methyl]sulfayl]ethyl] $A^{N}$ methyl 2 nitre-1,1 ethenediamine (ranitidine related compeund C) is net less than 1.5. Chremategraph the Standard preparation, andrecord the peak respenses as directed for Procedure: the tailing factor for the ranitidine hydrechloride peak is not more than 2.0 ; the column efficieney determined from the ranitidine hydrechleride peak is net less than 700 theoretieal plates; and the relative standard deviation for replieate-injections is net mere than 2\%

Procedure Separately inject equal volumes (about $10 \mu \mathrm{\mu L}$ ) of the-Standard preparation and the Asisaypreparation inte the ehremategraph, record the ehrematograms, and measure the areas for
the major peaks. Calculate the quantity, in mg, of $\mathrm{G}_{42} \mathrm{H}_{22} \mathrm{~N}_{4} \Theta_{3} \mathrm{~S} \cdot \mathrm{HCl}$ in the pertion of Ranitidine Hydrochleride tak en by the formmat:-

$$
1000 C\left(r_{t}+r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Ranitidine Hydrechloride-RS in the Standerd preparation; and $x_{t}$ and $\Psi_{s}$ are the peak respenses obtained frem the Assay preparation and the standard prepariation, respectively.

- Phosphate buffer—Place approximately 1900 mL of water in a $2.0-\mathrm{L}$ volumetric flask, accurately add 6.8 mL of phosphoric acid, and mix. Accurately add 8.6 mL of $50 \%$ sodium hydroxide solution, and dilute with water to volume. If necessary, adjust with $50 \%$ sodium hydroxide solution or phosphoric acid to a pH of 7.1, and filter.
Solution A-Prepare a mixture of Phosphate buffer and acetonitrile ( $98: 2$ ).

Solution B-Prepare a mixture of Phosphate buffer and acetonitrile (78:22).
Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Diluent-Use Solution A.
Standard preparation-Dissolve an accurately weighed quantity of USP Ranitidine Hydrochloride RS in Diluent to obtain a solution having a known concentration of about 0.125 mg of ranitidine hydrochloride per mL .

Resolution solution-Dissolve an accurately weighed quantity of USP Ranitidine Resolution Mixture RS in Diluent to obtain a solution having a known concentration of about 0.003 mg of each related impurity per mL and about 0.13 mg of ranitidine hydrochloride per mL . [NOTE--USP Ranitidine Resolution Mixture RS contains ranitidine hydrochloride and four related impurities: ranitidine N -oxide, ranitidine complex nitroacetamide, ranitidine diamine hemifumarate, and ranitidine amino alcohol hemifumarate.]

Assay preparation-Transfer about 25 mg of Ranitidine Hydrochloride, accurately weighed, to a $200-\mathrm{mL}$ volumetric flask. Dissolve in and dilute with Diluent to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $230-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ column containing $3.5-\mu \mathrm{m}$ packing L1 that is stable from pH 1 to 12 . The flow rate is about 1.5 mL per minute. The column temperature is maintained at $35^{\circ}$. The chromatograph is programmed as follows

| Time | Solution $A$ | Solution $B$ |  |
| :---: | :---: | :---: | :--- |
| (minutes) | $(\%)$ | $(\%)$ | Elution |
| $0-10$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| $10-15$ | 0 | 100 | isocratic |
| $15-16$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $16-20$ | 100 | 0 | re-equilibration |

Chromatograph the Resolution solution, identify the peaks using the table of impurities and degradation products (found above), and record the peak responses as directed for Procedure: the resolution, $R$, between the peaks for ranitidine $N$-oxide and ranitidine complex nitroacetamide is not less than 1.5. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.0 \%$.

Procedure—Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quan-
tity, in mg , of $\mathrm{C}_{13} \mathrm{H}_{22} \mathrm{~N}_{4} \mathrm{O}_{3} \mathrm{~S} \cdot \mathrm{HCl}$ in the portion of Ranitidine Hydrochloride taken by the formula:

$$
200 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Ranitidine Hydrochloride RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.п2S (USP28)

## BRIEFING

Ranitidine Oral Solution, USP 27 page 1626. Comments were received that the HPLC method published in $P F 28$ (2) on page 360 did not separate all known impurities and degradation products of Ranitidine Hydrochloride. This proposal is now being canceled. The proposed new liquid chromatographic procedure is based on analyses performed with Waters Xterra MS brand of L1 column. The typical retention time for ranitidine is about 12 minutes. [NOTE-The HPLC method is different from the one proposed for Ranitidine Hydrochloride because of the need to separate the sweetener (saccharine).] In addition, the revision in the test for Chromatographic purity necessitates the deletion of Identification test $A$. It is also proposed to delete the test for Antimicrobial effectiveness testing. This test is a formulation development and stabil-ity-indicating test, not a release test; deletion of this test is consistent with other USP monographs for oral solutions. See also the briefing under Ranitidine Hydrochloride.
(PA4: E. Gonikberg; AMB: D. Porter) RTS-40648-2; 40648-3

## Change to read:

USP Reference standards $\langle 11\rangle —$ USP Ranitidine Hydrochloride RS. USP Ranitidine Related Compent A RS. USP Ramitidine Retat Compond $C$ PS

- USP Ranitidine Resolution Mixture RS.■2S (USP28)


## Change to read:

## Identification-

A: The $R_{f}$ value of the principal spot observed in the chremet togramof the Test preparation obtained as directed in the Chroma tographic purity test correspends to that obtained from the Stander preparation.

B:
■-2S (USP28)
The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

## Delete the following:

Antimierobial effeetiveness testing $\langle 54\rangle \div$ meets the requirements.m2S (USP28)

## Change to read:

## Chromatographic purity-

Test preparation [NOTE-Apply a quantity of extractives from Oral Solution to the chromatographic plate so as to achieve anominal leading of 200 ug of ranitidine.] Transfer a weighed quantity of Oral Solution, equivalent to 10 mg of ranitidine, to a suitable syringe. Attach the tip of the syringe to the top of a cartridge $(11 \mathrm{~mm} \times 12 \mathrm{~mm})$ of velume 0.5 mL containing 0.4 g of an L 4 packing for high pressure liquid chrematography that has been previously prepared by passage of 10 mL of methanol followed by passage of 20 mL of 0.5 M ammenia solution. Add 2.0 mL of $\theta .5 \mathrm{M}$ ammenia solution to the syringe and foree the mixture slow ly through the cartridge. Repent with 2 further 3 - mL pertions of $\theta .5 \mathrm{M}$ ammonia solution. Discard all the liquid that has traversed the cartridge. Pass 5 mL of a mixture of 0.1 M hydrechloric acid and methanol ( $3: 1$ ) through the eartridge, and colleet the eluant in a clean round bettom, 25 mL flask. Repent this with another 5 mb pertion of the same eluting mixture and collect the eluant in the same flack. Evaporate the contents of the flask to dryness at a temperatre not exee ling $30^{\circ}$. Redissolve the residte in 1.0 mL of a mixture of methanol and water ( $50: 50$ ).

Standardpreparation-DissolveUSP Ranitidine Hydrochloride RS in a mixttre of methanol and water ( $50: 50$ ) to obtain a solution having a known concentration of $448 \mu \mathrm{~g}$ (equivalent to -400 $\mu \mathrm{g}$ of ranitidine) per mL. Dilute portions of this Standerd preparation quantitatively with the mixture of methanel and water ( $50: 50$ ) to obtain solutions having eoncentrations of 224 ug per mL (Diluted


 huted stand preparation E), respectively.

Resolation prepatation DissolveUSP Ranitidine-Related Gempound A RS, 5 [ [ ( 2 aminoethyl)thio]methyl] N,N dimethyl $Z$ furammethanamine, hemifumarate salt, in methanol to obtain a solution having a known coneentration of 1.27 mg per mL.

Proedure Apply separately $10 \mu \mathrm{~L}$ of the Standard prepara tion, the Diluted standed preparations ( $A, B, C, D$, and $E$ ) and $20 \mu \mathrm{~L}$ (superposition of $2 \times 10 \mu \mathrm{~L}$ ) of the Test preparation to a suitable thin layer chromatographic plate (see Chromatography $\langle 624\rangle$ )coat with a 0.25 mm layer of chromategraphic siliea gel mixture. In addition, apply separately a futher loading of 10 HL of the Test preparation to the same plate, and on top of this applieation, apply $10 \mu \mathrm{~L}$ of the Resolution preparation. Perform the chromagraphy as deseribed in Chromagraphic purity under Ranitidine Hydrochloride. Examine the plate and compare the in
tensities of any secondary spots observed in the chromatogram of the Test preparation with those of the principal spets in the chromatograms of the Standerd preparation and Diluted standard pre parations ( $A, B, C, D$, and $E$ ): the system suitability requirements are met when there is complete resolution between the primary spots of the Test preparation and the Resolution preparation and if aspet is observed in the chromatogram of Diluted stal prepatation $E$. The major secondary spet is not greater in size or inten sity than the prineipal spot produced by the Standard preparation $(2.0 \%)$, and no other secondary spot is greater in size-or intensity than the prineipal spot produced by Diluted standat prepatation A(1.0\%). The sum of the intensities of all secondary spets obtained frem the Test preparan correspends to not more than $5.0 \%$. fNOTE-Spots established as arising from other compenents in the formulation are to be ignored.]

- [NOTE-All solutions should be transferred into polypropylene HPLC vials for analysis.]

Mobile phase, Resolution solution, and Chromatographic
system-Proceed as directed in the Assay.
Standard solution-Prepare as directed for the Standard preparation in the Assay.

Test solution-Prepare as directed for the Assay preparation.

Procedure-Separately inject equal volumes (about 15 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and identify the ranitidine peak and the peaks due to impurities and degradation products listed in the table below.

| Relative <br> Retention Time |  |
| :---: | :--- |
| 0.11 | Ranitidine simple nitroacetamide |
| 0.17 | Ranitidine oxime |
| 0.55 | Ranitidine $N$-oxide |
| 0.60 | Ranitidine amino alcohol hemifumarate |
| 0.67 | Ranitidine diamine hemifumarate ${ }^{1}$ |
| 0.77 | Ranitidine $S$-oxide ${ }^{2}$ |
| 0.80 | Ranitidine complex nitroacetamide |
| 1.13 | Ranitidine formaldehyde |

Measure the responses for the major peaks, and calculate the percentage of each impurity in the portion of Oral Solution taken by the formula:

$$
50,000 C / W\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of ranitidine in the Standard solution; $W$ is the weight, in mg , of ranitidine in the Test solution, based on the label claim; $r_{i}$ is the peak response for each impurity, obtained from the Test solution; and $r_{s}$ is the ranitidine peak response obtained from the Standard solution. Disregard any peak corresponding to the excipients present in the formulation. [NOTE-Relative retention times for sodium saccharin, propylparaben, and butylparaben are approximately $0.43,1.52$, and 1.59 , respectively.] Not more than $1.0 \%$ of any single impurity is found; and not more than $3.0 \%$ of total impurities is found. ${ }^{2 S}$ (USP28)

## Change to read:

Assay- [NOTE-Where peak respenses are indieated, use peak ar eas.]

Mebile phase, Standard prepatation, System stitability soltion, and Chrontatographic system Prepare as direetedin the Assay under Ranitidine Hydrochloride, the ehromatographic columa being fltted with a suitable pre coltmm alse containing packing L1.

Assay preparation Dilute an aceurately measured quantity of Oral Solution, quantitatively, and stepwise-if neeessary, with Me bile phase to-obtain a-selation having acencentration of 0.1 mg of ranitidine per mE .

Proedure Separately injeet an equal quantity (abeut $10 \mu \mathrm{H}$ ) of the-Standard preparation and the 4 sisat preparation into the ehrematograph, record the chromatograms, and measure the respenses for the major peaks. Calculate the quantity, in me, of $\mathrm{G}_{42} \mathrm{H}_{22} \mathrm{~N}_{4} \mathrm{O}_{3} \mathrm{~S}$ in the pertion of Oral Solution taken by the formula:-
$(314.40 / 350.86)(I / D)(C)\left(F_{t}+r_{s}\right)$,
in whieh 314.40 ant 350.86 are the meleeular weights of ranitidine and ranitidine hydrochloride respectively, $L$ is the labeled quantity of ranitidine in the-Oral Solation taken, $D$-is the-eoneentration, in my per mL, of ranitidine in the Assat preparation, on the basis of the labeled quantity and the extent of dilution, $C$ is the eoneentra tion, in mg per mL, of USP Renitidine-Hydrechleride-RS in the Standard preparation, and $r_{y}$ and $r_{s}$ are the peak respenses obfained from the Assay preparation and the Standard preparation, respectively.

- [NOTE-All solutions should be transferred into polypropylene HPLC vials for analysis.]

Carbonate buffer-Dissolve 16 g of anhydrous sodium carbonate in water to make 1 L , adjust with hydrochloric acid to a pH of 7.1, and filter.

Solution A-Prepare a mixture of water and Carbonate buffer ( $60: 40$ ). Adjust if necessary to a pH of $7.1 \pm 0.2$.
Solution B-Prepare a mixture of acetonitrile and Carbonate buffer ( $60: 40$ ). For each 1000 mL of Solution B, add 3.0 mL of hydrochloric acid, and mix thoroughly.

Mobile phase-Use variable mixtures of Solution $A$ and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Ranitidine Hydrochloride RS in water to obtain a solution having a known concentration of about 0.13 mg of ranitidine hydrochloride per mL . Calculate the concentration, $C$, in mg of ranitidine per mL , the molecular weights of ranitidine and ranitidine hydrochloride being 314.40 and 350.86 , respectively.

Resolution solution-Dissolve an accurately weighed quantity of USP Ranitidine Resolution Mixture RS in Diluent to obtain a solution having a known concentration of about 0.003 mg of each related impurity per mL and about 0.13 mg of ranitidine hydrochloride per mL . [NOTE-USP Ranitidine Resolution Mixture RS contains ranitidine hydrochloride and four related impurities: ranitidine $N$-oxide, ranitidine complex nitroacetamide, ranitidine diamine hemifumarate, and ranitidine amino alcohol hemifumarate.]
Assay preparation-Using "to contain" pipet, transfer the accurately measured volume of Oral Solution, equivalent to about 60 mg of ranitidine, based on the label claim, to a $500-\mathrm{mL}$ volumetric flask. Rinse the pipet with small portions of water, adding the rinsings to the flask, dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $230-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 10-\mathrm{cm}$ column containing $3.5-\mu \mathrm{m}$ packing L1 that is stable from pH 1 to 12 . The flow rate is about 1.0 mL per minute. The column temperature is maintained at $40^{\circ}$. The chromatograph is programmed as follows.

| Time | Solution A | Solution B |  |
| :---: | :---: | :---: | :--- |
| (minutes) | $(\%)$ | $(\%)$ | Elution |
| $0-12$ | $100 \rightarrow 70$ | $0 \rightarrow 30$ | linear gradient |
| $12-17$ | $70 \rightarrow 0$ | $30 \rightarrow 100$ | linear gradient |
| $17-21$ | 0 | 100 | isocratic |
| $21-21.1$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $21.1-25$ | 100 | 0 | re-equilibration |

Chromatograph the Resolution solution, identify the peaks using the table of impurities and degradation products (found above), and record the peak responses as directed for Procedure: the resolution, $R$, between the peaks for ranitidine diamine hemifumarate and ranitidine complex nitroacetamide is not less than 1.5 , and the resolution between the peaks for ranitidine $N$-oxide and ranitidine amino alcohol hemifumarate is not less than 1.5. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.5 \%$.

Procedure-Separately inject equal volumes (about 15 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ranitidine $\left(\mathrm{C}_{13} \mathrm{H}_{22} \mathrm{~N}_{4} \mathrm{O}_{3} \mathrm{~S}\right)$ in each mL of Oral Solution taken by the formula:
in which $C$ is the concentration, in mg per mL , of ranitidine in the Standard preparation; $V$ is the volume of Oral Solution taken to prepare the Assay preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP28)

## Briefing

Ropivacaine Hydrochloride. Because there is no existing USP monograph for this drug substance, a new monograph is being proposed. The reverse phase HPLC method used in the tests for Limit of ropivacaine related compound $A$ and Related compounds was validated using a Nova-pak C18 brand of L1 column. Ropivacaine related compound A (2,6-dimethylaniline) and ropivacaine elute at approximately 2.4 minutes and 5.4 minutes, respectively. The test for Enantiomeric purity is evaluated using a validated capillary electrophoresis procedure with UV detection. Ropivacaine ( $S$ enantiomer) and ropivacaine related compound B ( $R$ enantiomer) are separated using a fused silica column (Hewlett-Packard) and a run buffer containing 2,6-di- $O$-methyl- $\beta$-cyclodextrins; the migration times are approximately 24 and 25 minutes for the $R$ and $S$ enantiomers, respectively.
(PA1: K. Russo; AMB: D. Porter; PSD: C. Okeke; NL: C. Barnstein) RTS-40282-1; 40282-2; 40282-3; 40282-4; 41020-1; 41020-2

## Add the following:

## ■Ropivacaine Hydrochloride


$\mathrm{C}_{17} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O} \cdot \mathrm{HCl} \cdot \mathrm{H}_{2} \mathrm{O} \quad 328.89$

$$
500(C / V)\left(r_{U} / r_{S}\right)
$$

(S)-(-)-1-Propyl-2', $6^{\prime}$-pipecoloxylidine hydrochloride monohydrate [132112-35-7].
» Ropivacaine Hydrochloride contains not less than 98.5 percent and not more than 101.0 percent of $\mathrm{C}_{17} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O} \cdot \mathrm{HCl}$, calculated on the anhydrous basis.

Packaging and storage-Preserve in well-closed containers. Store at room temperature.

Labeling-Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

USP Reference standards $\langle 11\rangle$ —USP Bupivacaine Hydrochloride RS. USP Endotoxin RS. USP Ropivacaine Hydrochloride RS. USP Ropivacaine Related Compound A RS. USP Ropivacaine Related Compound B RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: A solution (1 in 100) responds to the test for Chloride $\langle 191\rangle$.

Bacterial endotoxins $\langle 85\rangle$-The level of bacterial endotoxins is such that the requirements under the relevant dosage form monograph(s) in which Ropivacaine Hydrochloride is used can be met. Where the label states that Ropivacaine Hydrochloride must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins is such that the requirements under the relevant dosage form monograph(s) in which Ropivacaine Hydrochloride is used can be met.

Color-Transfer an accurately weighed aliquot of Ropivacaine Hydrochloride, about 480 to 500 mg , into a $25-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with water to
volume. Pass the solution through a $5-\mu \mathrm{m}$ polyvinylidene filter (PVDF). Immediately measure the absorbance at 405 nm and at 436 nm , using a suitable spectrophotometer and a path length of 5 cm , and using water as the reference: the absorbance at 405 nm is not more than 0.030 , and the absorbance at 436 nm is not more than 0.025 .

## Clarity-

Hydrazine sulfate solution-Dissolve 1.0 g of hydrazine sulfate in water and dilute with water to 100 mL . Allow to stand 4 to 6 hours.

Hexamethylenetetramine solution-Transfer 2.5 g of hexamethylenetetramine to a $100-\mathrm{mL}$ glass-stoppered flask and dissolve in 25 mL of water. Do not dilute to volume.

Stock opalescence standard suspension-To the flask containing the Hexamethylenetetramine solution, add 25.0 mL of Hydrazine sulfate solution, mix, and allow to stand for 24 hours. This suspension is stable for up to 2 months when stored in a glass container free from surface defects. The suspension must not adhere to the flask and must be well mixed before use.

Opalescence standard suspension-Dilute 15.0 mL of the Stock opalescence standard suspension with water to 1000 mL . This suspension should be freshly prepared and may be stored for not more than 24 hours.

Reference suspension 1-Combine 5.0 mL of the Opalescence standard suspension and 95.0 mL of water. Shake before use.

Reference suspension 2-Combine 10.0 mL of the Opalescence standard suspension and 90.0 mL of water. Shake before use.

Test solution-Transfer about 480 to 500 mg of Ropivacaine Hydrochloride, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, and dilute with water to volume.

Procedure-Use identical tubes of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm . The depth of the layer is 40 mm . Compare the solutions in diffused daylight 5 minutes after the preparation of Reference suspension 1 and Reference suspension 2, viewing vertically against a black background. The diffusion of light must be such that Reference suspension 1 can readily be distinguished from water, and Reference suspension 2 can readily be distinguished from Reference suspension 1. The Test solution is considered clear if its clarity is the same as that of water or if its opalescence is not more pronounced than that of Reference suspension 1.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ :
Solvent: Dissolve about 200 g of sodium hydroxide in water, and dilute with water to 1 L . Combine 20 mL of this solution and 300 mL of water in a 1-L volumetric flask. Dilute with alcohol to volume.

Test solution: 10 mg per mL , in Solvent.
Procedure: Obtain readings at 365 nm : between $-210^{\circ}$ and $-255^{\circ}$.
$\mathbf{p H}\langle 791\rangle$ : between 4.5 and 6.0, in a solution (1 in 100).
Water, Method Ia $\langle 921\rangle$ : between $5.0 \%$ and $6.0 \%$. Perform the determination on 0.0900 to 0.1100 g of sample.

## Heavy metals-

pH 3.5 Acetate Buffer and Standard Lead Solution-Prepare as directed under Heavy Metals $\langle 231\rangle$.

Dilute lead standard solution-Dilute 10.0 mL of the Standard Lead Solution with water to 100 mL . Each mL of Dilute lead standard solution contains the equivalent of $1 \mu \mathrm{~g}$ of lead.
0.25 M Sodium sulfide solution-Dissolve about 6.0 g of sodium sulfide in 40 g of glycerol, then dilute with water to 100 mL . Filter using a cotton pad and store in a glass container protected from light.

Test Preparation-Prepare as directed under Heavy Metals, Method II $\langle 231\rangle$, using 3.97 to 4.00 g of ropivacaine hydrochloride.

Standard solution-Combine 10.0 mL of the Dilute lead standard solution with 2 mL of the Test Preparation and 2 mL of pH 3.5 Acetate Buffer, and mix.
Test solution-Combine 12 mL of the Test Preparation with 2 mL of pH 3.5 Acetate Buffer and mix.
Blank-Combine 10 mL of water, 2 mL of pH 3.5 Acetate Buffer, and 2 mL of the Test Preparation.

Procedure-Transfer the Blank to a color-comparison tube. Transfer the Standard solution and the Test solution to individual color-comparison tubes each containing 1 drop of 0.25 M Sodium sulfide solution. After 1 minute, compare the colors, viewing downward over a white surface: the Standard solution shows a slight brown color compared to the Blank; and the Test solution is not darker than the Standard solution ( $0.001 \%$ ).

## Limit of ropivacaine related compound A-

Buffer solution, Mobile phase, System suitability solution, and Chromatographic system-Prepare as directed for Related compounds.

Standard solution-Dissolve an accurately weighed quantity of USP Ropivacaine Related Compound A RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having a known concentration of about $0.13 \mu \mathrm{~g}$ per mL .

Test solution-Transfer about 100 mg of Ropivacaine Hydrochloride, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks: the signal-to-noise ratio of
the principal peak in the Standard solution is at least 10; and the response for any peak corresponding to ropivacaine related compound A (2,6-dimethylaniline) in the chromatogram obtained from the Test solution is not greater than the response of the major peak in the chromatogram obtained from the Standard solution ( $10 \mu \mathrm{~g}$ per g ).

## Related compounds-

Buffer solution-Combine 1.3 mL of sodium phosphate monobasic solution ( 138 g per L ) and 32.5 mL of disodium hydrogen phosphate dihydrate solution ( 89 g per L), and dilute with water to 1 L . The pH of this solution is 8.0 . Make adjustments if necessary.

Mobile phase-Prepare a degassed mixture of Buffer solution and acetonitrile (50:50). Make adjustments if necessary (see System suitability under Chromatography $\langle 621\rangle$ ).
System suitability solution-Dissolve accurately weighed quantities of USP Ropivacaine Hydrochloride RS and USP Bupivacaine Hydrochloride RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about $10 \mu \mathrm{~g}$ per mL of each compound.
Test solution-Transfer about 27.5 mg of Ropivacaine Hydrochloride, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Dilute test solution-Dilute 1.0 mL of the Test solution with Mobile phase to 100 mL . Dilute 1.0 mL of this solution with Mobile phase to 10 mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $240-\mathrm{nm}$ detector and a $3.9-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $4-\mu \mathrm{m}$ packing L1. The flow rate is about 1 mL per minute. Check the stability of the baseline by injecting Mobile phase. Run the chromatogram for at least 15 minutes. Chromatograph the System suitability solution and the Dilute test solution,
and record the peak responses as directed for Procedure: the relative retention times are 1.6 for bupivacaine and 1.0 for ropivacaine; the resolution, $R$, between ropivacaine and bupivacaine is not less than 6 (from the System suitability solution); and the signal-to-noise ratio of ropivacaine is at least 10 (from the Dilute test solution).

Procedure-Inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the System suitability solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Ropivacaine Hydrochloride taken by the formula:

$$
100\left(r_{U} / r_{s}\right)
$$

in which $r_{U}$ is the peak response for each impurity obtained from the Test solution; and $r_{s}$ is the sum of all peak responses obtained from the Test solution: not more than $0.2 \%$ of bupivacaine is found, less than $0.1 \%$ for any other individual impurity is found, and not more than $0.5 \%$ of total impurities is found.

## Enantiomeric purity-

Background electrolyte solution-Transfer 9.31 to 10.29 g of phosphoric acid to a 1-L volumetric flask, and dilute with water to volume. The pH is between 2.9 and 3.1. If necessary, adjust the pH with triethanolamine.

Run buffer-Prepare a solution containing approximately 13.3 mg of heptakis-(2,6-di- $O$-methyl)- $\beta$-cyclodextrin per mL of Background electrolyte solution. [NOTE-This solution is freshly prepared and passed through a $0.45-\mu \mathrm{m}$ filter.]
System suitability solution-Dissolve accurately weighed quantities of USP Ropivacaine Hydrochloride RS and USP Ropivacaine Related Compound B RS in water, and dilute
quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about $15 \mu \mathrm{~g}$ per mL of each compound.

Test solution-Transfer about 50 mg of Ropivacaine Hydrochloride, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask, and dissolve in and dilute with water.

Dilute test solution-Dilute 1.0 mL of the Test solution with water to 200 mL .

Capillary rinsing procedure-Use separate run buffer vials for capillary rinse and sample analysis. Rinse the capillary with water for 1 minute, with 0.1 N sodium hydroxide for 10 minutes, and with water for 3 minutes. If a new or dry capillary is being used, increase the sodium hydroxide rinse time to 30 minutes. Rinse the capillary between injections as follows: water for 1 minute, 0.1 N sodium hydroxide for 4 minutes, and water for 1 minute, then run buffer for 4 minutes. Rinse times are based on a rinse pressure of 1 bar.
System setup (see Capillary Electrophoresis $\langle 727\rangle$ )-The system is equipped with a $206-\mathrm{nm}$ detector and a $50-\mu \mathrm{m} \times$ $72-\mathrm{cm}$ fused silica column. The temperature is maintained at $30^{\circ}$. A voltage of $375 \mathrm{~V} / \mathrm{cm}$ is applied. The initial ramping is $500 \mathrm{~V} / \mathrm{s}$, positive polarity, and a resulting current of 40 to 45 $\mu \mathrm{A}$. Inject the Dilute test solution: the signal-to-noise ratio is at least 10. Inject the System suitability solution, and record the peak responses as directed for Procedure: the relative migration times are about 0.96 for ropivacaine related compound B ( $R$ enantiomer) and 1.0 for ropivacaine ( $S$ enantiomer); the resolution, $R$, between ropivacaine related compound B and ropivacaine is not less than 3.7. The analysis run time is about 30 minutes. If needed, increase the resolution by increasing the concentration of heptakis-(2,6-di- $O$-methyl)- $\beta$-cyclodextrin or by lowering the system temperature.

Procedure-Separately inject equal volumes of the Run buffer and of water to ensure there are no interfering peaks ( 50 mbar for 5.0 seconds followed by injection of Run buffer at 50 mbar for 1.0 second). Inject the Test solution into the electrophoresis system, record the electropherograms, and measure the peak responses for ropivacaine and ropivacaine related compound B . Calculate the percentage of ropivacaine related compound $B$ in the portion of Ropivacaine Hydrochloride taken by the formula:

$$
100\left(r_{R} / M_{R}\right) /\left(r_{s} / M_{s}\right),
$$

where $r_{R}$ is the peak response of ropivacaine related compound B obtained from the Test solution; $r_{s}$ is the peak response of ropivacaine obtained from the Test solution; and $M_{R}$ and $M_{S}$ are the migration times, in minutes, of ropivacaine related compound B and ropivacaine, respectively: not more than $0.5 \%$ ropivacaine related compound B is found.

System shutdown-After the analysis, rinse the capillary for 10 minutes with 0.1 N sodium hydroxide, then for 10 minutes with water. Dry the capillary before storage.

Other requirements-Where the label states that Ropivacaine Hydrochloride is sterile, it meets the requirements for Sterility Tests $\langle 71\rangle$ and Labeling under Injections $\langle 1\rangle$.

Assay-Dissolve an accurately weighed quantity of Ropivacaine Hydrochloride, approximately 1000 mg , in 10 mL of water and 40 mL of alcohol. Add 1.0 mL of 1 N hydrochloric acid, and titrate with 1 N sodium hydroxide VS. Two equivalence points are obtained; the difference in titrant volume corresponds to the amount of ropivacaine hydrochloride. Each mL of 1 N sodium hydroxide is equivalent to 310.9 mg of anhydrous ropivacaine hydrochloride $\left(\mathrm{C}_{17} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O} \cdot \mathrm{HCl}\right) \cdot{ }^{\mathbf{n} 2 \mathrm{~S}}$ (USPP28)

Sargramostim, USP 27 page 1674. It is proposed to make minor changes in the Definition to better describe the product.
(BNT: L. Callahan) RTS-41798-1

## Change to read:

» Sargramostim is a highly purified glycosylated protein consisting of 127 amine acids. It has the property to generate gramulocyte, macrophage, and mixed granulocyte macrephage colonies from hematepoietic progenitor cells found in bene marrow. It is produced by recombinant DNA synthesis in yeast culture, and
-Sargramostin is a single chain, glycosylated polypeptide of 127 amino acid residues expressed from Saccharomyces cerevisiae. The glycoprotein primarily consists of three molecular species having relative molecular weights of approximately $19,500,16,800$, and 15,500 due to different levels of glycosylation. Sargramostim has the property to generate granulocyte, macrophage, and mixed granulocyte macrophage colonies from hematopoietic progenitor cells found in bone marrow.
$\mathrm{It}_{\mathbf{n} 2 \mathrm{~S}(\text { USPP8) }}$
possesses the primary sequence of the natural form of granulocyte-macrophage colony-stimulating factor with a substitution in the amino acid residue at position 23 ( $\mathrm{Leu}_{23}$ in place of $\mathrm{Arg}_{23}$ ). It has a biological potency of not less than 73.0 percent and not more than 146.0 percent of the potency stated on the label, the potency being 5.6 million USP Sargramostim Units per mg of protein. The presence of host cell DNA and host cell protein impurities in Sargramostim is process-specific; the limits of these impurities are determined by validated methods.

BRIEFING

Sotalol Hydrochloride, USP 27 page 1716 and page 3084 of the First Supplement. It is proposed to correct the formulas in the test for Related compounds to express the value of the results in percent.
(PA5: A. Wilk) RTS-41775-1

## Change to read:

## Related compounds-

Mobile phase-Proceed as directed in the Assay.
Standard solution-Dissolve accurately weighed quantities of USP Sotalol Hydrochloride RS, USP Sotalol Related Compound A RS, USP Sotalol Related Compound B RS, and USP Sotalol Related Compound C RS in Mobile phase, and dilute quantitatively, and stepwise if necessary, with Mobile phase to obtain a solution having known concentrations of about $6 \mu \mathrm{~g}$ of each per mL .

Test solution-Transfer about 200 mg of Sotalol Hydrochloride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Mobile phase to volume, and mix.

Chromatographic system-Prepare as directed in the Assay. Chromatograph the Standard solution, and record the peak heights as directed for Procedure: the relative retention times are about 0.65 for sotalol hydrochloride related compound B, 1.0 for sotalol hydrochloride, 1.2 for sotalol hydrochloride related compound A , and 1.4 for sotalol hydrochloride related compound C ; the resolution, $R$, between sotalol hydrochloride related compound A and sotalol hydrochloride is not less than 2.0; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about $25 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the heights for the major peaks. Calculate the percentage of each sotalol hydrochloride related compound in the portion of Sotalol Hydrochloride taken by the formula:

$$
\theta .1(C / H)\left(r_{i}, H_{s}\right),
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of the appropriate USP Related Compound Reference Standard in the Standard solution; $W$ is the weight, in mg , of Sotalol Hydrochloride taken to prepare the Test solution; and $r_{i}$ and $r_{S}$ are the peak heights for the corresponding related compound obtained from the Test solu-
tion and the Standard solution, respectively. Calculate the percentage of other impurities in the portion of Sotalol Hydrochloride taken by the formula:

$$
\begin{gathered}
\theta .1(C / H)\left(r_{\ldots} \not r_{s}\right), \\
\mathbf{\bullet}_{10(C / W)\left(r_{s i} / r_{s}\right), \boldsymbol{m}_{2 S}(U S P 28)}
\end{gathered}
$$

in which $C$ is the concentration, in mg

## 

per mL, of USP Sotalol Hydrochloride RS in the Standard solution; $W$ is the weight, in mg , of Sotalol Hydrochloride taken to prepare the Test solution; $r_{s i}$ is the sum of the peak heights for all impurities, other than the related compounds, obtained from the Test solution; and $r_{S}$ is the peak height of sotalol obtained from the Standard solution. Not more than $0.3 \%$ each of sotalol hydrochloride related compound A and sotalol hydrochloride related compound B is found; not more than $0.4 \%$ of sotalol hydrochloride related compound C is found; not more than $0.3 \%$ of other impurities is found; and not more than $0.5 \%$ of total impurities is found.

## Briefing

Sufentanil Citrate Injection, USP 27 page 1731. It is proposed to add a note to the Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ test under Identification to clarify that in cases where sample dilution with Mobile phase is not required, Water for Injection is used as the medium for preparing the Standard solution.

$$
\text { (PA2: D. Bempong) } \quad \text { RTS-41675-1 }
$$

## Change to read:

## Identification-

A: Ultraviolet Absorption $\langle 197 \mathrm{U}\rangle$ -
Solution: $50 \mu \mathrm{~g}$ per mL.
Medium: Use Mobile phase prepared as directed in the Assay.

- [NOTE-For samples that do not require dilution to achieve $50 \mu \mathrm{~g}$ per mL , use Water for Injection as the medium for the Standard solution. $]_{\text {nes (USP28) }}$

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

## Briefing

Sumatriptan Nasal Spray, page 119 of $P F$ 29(1) [Jan.-Feb. 2003]. Several modifications are made to this proposed monograph to identify the compounds quantified, and to clarify the procedures used.
(PA3: S. Salado) RTS-39992-1

## Add the following:

## ■Sumatriptan Nasal Spray

» Sumatriptan Nasal Spray is an aqueous, buffered solution of Sumatriptan. It is supplied in a form suitable for nasal administration. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of sumatriptan $\left(\mathrm{C}_{14} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S}\right)$.

Packaging and storage-Preserve in tight, light-resistant containers, and store between $2^{\circ}$ and $30^{\circ}$.

USP Reference standards $\langle 11\rangle$ — USP Sumatriptan Succinate RS. USP Sumatriptan Succinate Related Compound A RS. USP Sumatriptan Succinate Related Compound B C RS.

USP Sumatriptan Succinate Related Impurities RS.
Identification, Infrared Absorption $\langle 197 \mathrm{M}\rangle$ -
Test specimen-To the contents of 1 vial of Nasal Spray add 1 mL of a saturated sodium chloride solution. Add 1 mL of a saturated solution of sodium carbonate, and shake vigorously for about 30 seconds. To the solution so obtained, add 2 mL of isopropyl alcohol, shake vigorously for about 30 seconds, and allow to stand until the phases separate. Transfer the organic phase to a suitable glass vial. Repeat the extraction with a second $2-\mathrm{mL}$ portion of isopropyl al-
cohol, and transfer the organic phase to the same vial. Evaporate the solution under a stream of nitrogen. Dry the residue in an oven at $100^{\circ}$ for 30 minutes, allow to cool to room temperature in a desiccator, and prepare a mull by the addition of 1 to 2 drops of mineral oil.

Microbial limits $\langle 61\rangle$-It meets the requirements of the tests for absene of Staphyloce atreus, Pseudomantas aeruginesta, and Bite Tolerant Organisms. The total aerobie mierobial 100 per mber The total aerobic microbial count does not exceed 100 cfu per mL , and it meets the requirements of the tests for absence of Staphylococcus aureus and Pseudomonas aeruginosa in 1 mL .
$\mathbf{p H}\langle 791\rangle$ : between 5.0 and 6.0.
Deliverable volume-Test 10 vials separately. Weigh each vial before and after actuation, and calculate the individual volume delivered, in $\mu \mathrm{L}$, by the formula:

$$
\left(W_{1}-W_{2}\right) / D,
$$

in which $W_{1}$ and $W_{2}$ are the weights, in mg , of the individual vials before and after actuation, respectively; and $D$ is the density of the nasal solution. Calculate the mean volume delivered. The volume of each spray delivered is between 80 and $120 \mu \mathrm{~L}$, and the mean volume is between 90 and 110 $\mu \mathrm{L}$.

Limit of sumatriptan related compound A-
10M Ammanium acetate solution, Mobile phase, and
Chromatographie system- Proeed as directed in the test
for Limit of related eompruthd 4 under Sumathiptant.
10 M Ammonium acetate solution-Dissolve 77.1 g of ammonium acetate in 100 mL of water.

Mobile phase-Prepare a filtered and degassed mixture of methanol and 10 M Ammonium acetate solution (9:1). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Diluent-Proceed as described in the Assay.
Standard solution-Dissolve an accurately weighed quantity of USP Sumatriptan Succinate Related Compound A RS in Mobile phase, Diluent and dilute quantitatively, and stepwise if necessary, with Mobile phase Diluent to obtain a solution having a known concentration of about 0.007 mg per mL (equivalent to about 0.005 mg per mL of $\mathrm{C}_{14} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{2}$ ).
Test solution-Dissolve an appropriate volume of Nasal Spray in Diluent to obtain a solution having a concentration of about 1.0 mg of sumatriptan per mL .
Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $282-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 20-\mathrm{cm}$ column that contains packing L3. The flow rate is about 2.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $5 \%$.

Procedure-Proeed direeted in the test for Limit of retatemplan A minder Sumatriply inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of sumatriptan succinate related compound A in the portion of Nasal Spray taken by the formula:

$$
100(495.7 / 613.8)\left(C_{S} / C_{U}\right)\left(r_{U} / r_{s}\right)
$$

in which the terms are as defined therein. 495.7 and 613.8 are the molecular weights of sumatriptan related compound A and sumatriptan succinate related compound A, respectively; $C_{S}$ is the concentration, in mg per mL , of USP Sumatriptan Succinate Related Compound A RS in the Standard solution; $C_{U}$ is the concentration, in mg per mL , of sumatrip$\tan$ in the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses
for sumatriptan related compound A from the Test solution and the Standard solution, respectively: Not more than $1.5 \%$ is found.

## Chromatographic purity Related compounds-

Pilluent, Buffer solution, Mobile phase, Standerd prepa pation, System sulitability solution, and Chromatographie fystem- Prepare as directed in the Assay under Sumatimiptan.

Diluent-Proceed as directed in the Assay.
Buffer solution-Dissolve about 1.7 mL of dibutylamine, about 0.6 mL of phosphoric acid, and about 3.9 g of monobasic sodium phosphate dihydrate in water. Adjust with a solution of $50 \%(\mathrm{w} / \mathrm{v})$ sodium hydroxide to a pH of about 7.5 , dilute with water to 1000 mL , and mix.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile ( $3: 1$ ). Make adjustments if necessary (see System Suitability under Chromatography〈621〉).

System suitability solution-Dissolve accurately weighed quantities of USP Sumatriptan Succinate RS and USP Sumatriptan Succinate Related Compound C RS in Diluent to obtain a solution having known concentrations of about 1.4 mg per mL and 0.001 mg per mL , respectively.

Identification solution-Prepare a solution of USP Sumatriptan Succinate Related Impurities RS in Diluent having a concentration of about 3 mg per mL .
System suitability solution Dissolve aceurately weighed quantities of USP Sumatriptan Surecinate RS and USP St matriptan Stwecinate Related Compound B RS in Diltuent to obtain a solution having known coneentrations of about

## 4.4 mg per mL and 0.001 mg per mL , respectively.

Test solution-Dissolve an appropriate volume of Nasal Spray in Diluent to obtain a solution having a concentration of about 1.0 mg of sumatriptan per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $282-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 20-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for sumatriptan succinate related compound C and 1.0 for sumatriptan; and the resolution, $R$, between sumatriptan succinate related compound C and sumatriptan is not less than 1.5 . Chromatograph the Identification solution, and record the peak responses as directed for Procedure: identify the peaks according to Table 1.

Table 1

| Compound Name | Relative <br> Retention |
| :--- | :---: |
|  | Time |
| [3-[2-(Dimethylamino- $N$-oxide)ethyl]-1 $H$ - <br> indol-5-yl]- $N$-methylmethanesulfonamide | about 0.3 |
| [3-[2-(Methylamino)ethyl]-1 $H$-indol-5-yl]- | about 0.6 |
| $\quad N$-methylmethanesulfonamide |  |
| Sumatriptan succinate related compound C about 0.9 <br> Sumatriptan 1.0 <br> [3-[2-(Aminoethyl)-1H-indol-5-yl]- about 0.4 <br> $N$-methylmethanesulfonamide  |  |

Procedure-Proe as direct for Chron purityRelated empounds under Sumatriptam. Inject a volume (about $10 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatogram, and measure all of the
peak responses. Calculate the percentage of each impurity in the portion of Nasal Spray taken by the formula:

$$
100 F_{i}\left(r_{i} / r_{s}\right)
$$

in which $F$ is the relative response factor, which is equal to 2.89 for any impurity with a 1 -[3-[2-dimethylamino)ethyl]-3-hydroxy-2-oxo-2,3-dihydro-1 H -indol-5-yl]- N -methylmethanesulfonamide that has a relative retention time of $0.46,4.55$ for any impurity with 3a-hydroxy-1,1-dimethyl-5-\{[methylamino)sulfonyl]methyl $\}-1,2,3,3 \mathrm{a}, 8,8 \mathrm{a}$, hexahydropyrrolo $[2,3-b]$ indol-1-ium that has a relative retention time of 0.64 , and 1.0 for all other impurities; ther terms are dine therein. $r_{i}$ is the peak response for each impurity; and $r_{s}$ is the sum of the responses of all the peaks: not more than $1.5 \%$ of any impurity is found, and the total of all impurities, including the amount found in the test for Limit of sumatriptan related compound $A$, is not more than 4.0\%.

## Assay-

## Diluent, Buffer solution, Mebile phase, Systen suitability

solution, Standerd preparation, and Chromatographic syis tem- Proceed as directed in the Assay under Sumatriptan.

Diluent-Dissolve 3.9 g of monobasic sodium phosphate dihydrate in water. Adjust with a solution of $50 \%(\mathrm{w} / \mathrm{v})$ sodium hydroxide to a pH of about 6.5 , and dilute with water to 1000 mL . Mix 750 mL of this solution with 250 mL of acetonitrile.

Buffer solution-Dissolve about 1.7 mL of dibutylamine, about 0.6 mL of phosphoric acid, and about 3.9 g of monobasic sodium phosphate dihydrate in water. Adjust with a solution of $50 \%(\mathrm{w} / \mathrm{v})$ sodium hydroxide to a pH of about 6.5 , dilute with water to 1000 mL , and mix.

Mobile phase-Prepare a filtered and degassed mixture of Buffer solution and acetonitrile (3:1). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

System suitability solution-Dissolve accurately weighed quantities of USP Sumatriptan Succinate RS and USP Sumatriptan Succinate Related Compound C RS in Diluent to obtain a solution having known concentrations of about 0.14 mg per mL and 0.07 mg per mL , respectively.

Standard preparation-Dissolve an accurately weighed quantity of USP Sumatriptan Succinate RS, and dissolve in Diluent to obtain a solution having a known concentration of about 0.14 mg per mL .

Assay preparation-Dissolve an appropriate volume of Nasal Spray in Diluent to obtain a solution having a known concentration of about 1.00 .1 mg of sumatriptan per mL .

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $282-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 20-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for sumatriptan succinate related compound C and 1.0 for sumatriptan; and the resolution, $R$, between sumatriptan succinate related compound C and sumatriptan is not less than 1.5. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.5 \%$.

## Procedure -Proee directed in the Assa minder Stt

 Separately inject equal volumes (about $10 \mu \mathrm{~L}$ ) of the Standard preparation and Assay preparation intothe chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the amount of suma$\operatorname{triptan}\left(\mathrm{C}_{14} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S}\right)$, in mg, in the portion of Nasal Spray taken by the formula:

$$
(295.4 / 413.5) C_{S} D\left(r_{U} / r_{S}\right)
$$

in which $C_{S}$ is the concentration, in mg per mL , of sumatriptan succinate in the Standard preparation; $D$ is the dilution factor used in preparing the Assay preparation; and the other terms are as defined therein. ${ }^{2 S}$ (USP28)

## BRIEFING

Thioguanine, USP 27 page 1831. It is proposed to revise the Assay by replacing the current UV method with an HPLC method. This method has greater specificity and accuracy, and it also detects the guanine impurity; therefore, a test for Limit of guanine is being introduced. Finally, it is proposed that the specification ranges of the Assay and the test for Nitrogen content be increased to account for the guanine impurity. In the proposed procedures for the Assay and the test for Limit of guanine, the liquid chromatograph is equipped with a $248-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 5-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1.
(PA6: L. Evans) RTS-40236-1; 41766-1

## Change to read:

» Thioguanine is anhydrous or contains one-half molecule of water of hydration. It contains not less than 97.0
-96.0 $\mathbf{m}_{\text {2S (USP28) }}$
percent and not more than 100.5 percent of $\mathrm{C}_{5} \mathrm{H}_{5} \mathrm{~N}_{5} \mathrm{~S}$, calculated on the dried basis.

## Change to read:

Nitrogen content-Determine the nitrogen content as directed under Nitrogen Determination, Method II $\langle 461\rangle$, using about 100 mg , accurately weighed. Each mL of 0.1 N sulfuric acid is equivalent to 1.401 mg of N . Not less than $40.6 \%$
$\mathbf{- 4 0 . 2}^{40} \mathbf{m}_{\text {2S }}$ (USP28)
and not more than $43.1 \%$, calculated on the dried basis, is found.

## Add the following:

## - Limit of guanine-

Mobile phase-Proceed as directed in the Assay.
Standard solution-Dissolve an accurately weighed quantity of guanine in 0.01 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.04 mg per mL . Pipet 1.0 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, and dilute with Mobile phase to volume to obtain a solution having a known concentration of $0.4 \mu \mathrm{~g}$ per mL .

Test solution-Transfer about 40 mg of Thioguanine, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with 0.01 N sodium hydroxide to volume, and mix. Transfer 10.0 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, dilute with Mobile phase to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a 248 -nm detector and a $4.6-\mathrm{mm} \times 5-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.60 for guanine and 1.0 for thioguanine; the resolution, $R$, between guanine and thioguanine is not less than 3.0 ; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than $5.0 \%$ for the guanine peak.

Procedure-Separately inject equal volumes (about 10
$\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the
responses for the major peaks. Calculate the percentage of guanine in the portion of Thioguanine taken by the formula:

$$
100(C / W)\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of guanine in the Standard solution; $W$ is the weight, in mg , of Thioguanine taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak responses of guanine obtained from the Test solution and the Standard solution, respectively: not more than $2.5 \%$ is found. ${ }^{2 S}$ (USP28)

## Change to read:

Assay-Transfer about 100 mg of Thiogtanine, previously dried and aceurately weighed, to a 100 mL velumetric flack, dissolve in a mixtre of 15 mL of water and 1.5 mL of 1 N sodium hydroxide, dilute with water to velume, and mix. Transfer 10.0 mL of this solution to second 100 mL velumetric flask, add- dilute hydrochlerie acid ( 1 in 100) to volume, and mix. Finally, transfer 5.0 mL of the last solution to a third $100-\mathrm{mL}$ volumetric flask, then add dilute hydrechloric acid ( 1 in 100) to volume, and mix. Concomitantly determine the absorbances of this solution and a solution of USP Thiogranime RS, in the same meditm, having a knownconcentration of about 5 ug per mL, in 1 cm cells at the wavelength of max imum absorbance at about 348 nm , with a suitable spectrophotometer, using dilute hydrochloric acid ( 1 in 100) as the blank. Calculate the quantity, in mg, of $\mathrm{C}_{5} \mathrm{H}_{5} \mathrm{~N}_{5} \mathrm{~S}$ in the pertion of Thiog

$$
20 C\left(A_{t}+A_{s}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL, of USP Thiogurnine PS in the Standard solution; and $A_{t}$ and $A_{s}$ are the absorbances of the solution from Thioguanine and the Standard-solution, respee tively.

- Phosphoric acid solution-Carefully add 1 mL of phosphoric acid to 99 mL of water, and mix.
Mobile phase-Prepare a filtered and degassed solution of 0.05 M monobasic sodium phosphate. Adjust with phosphoric acid to a pH of 3.0. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Thioguanine RS in 0.01 N sodium hydroxide, and dilute quantitatively, and stepwise if necessary, to
obtain a solution having a known concentration of about 0.4 mg per mL . Pipet 10.0 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, and dilute with Phosphoric acid solution to volume to obtain a solution having a known concentration of 0.04 mg per mL .
Assay preparation-Transfer about 40 mg of Thioguanine, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with 0.01 N sodium hydroxide to volume, and mix. Transfer 10.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, dilute with Phosphoric acid solution to volume, and mix.
Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $248-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 5-\mathrm{cm}$ column that contains packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative retention times are about 0.60 for guanine and 1.0 for thioguanine, and the relative standard deviation for replicate injections is not more than 2.0\%.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{5} \mathrm{H}_{5} \mathrm{~N}_{5} \mathrm{~S}$ in the portion of Thioguanine taken by the formula:

$$
1000 C\left(r_{U} / r_{S}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Thioguanine RS in the Standard preparation; and $r_{U}$ and $r_{S}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively. $\mathbf{2 S}$ (USP28)

Tolcapone, page 939 of PF 30(3) [May-June, 2004]. Several changes are proposed to indicate the actual experimental conditions used in the tests for Absorptivity and Related compounds.
(PA3: S. Salado) RTS-41735-1

## Add the following:

## -Tolcapone


$\mathrm{C}_{14} \mathrm{H}_{11} \mathrm{NO}_{5} \quad 273.24$
Methanone, (3,4-dihydroxy-5-nitrophenyl)(4-methylphenyl).
3,4-Dihydroxy-4'-methyl-5-nitrobenzophenone [134308-13-7].

## Change to read:

» Tolcapone contains not less than 98.5 percent and not more than 101.5 percent of $\mathrm{C}_{14} \mathrm{H}_{11} \mathrm{NO}_{5}$, calculated on the dried anhydrous $^{\mathbf{2 s}}$ (USP28) ${ }^{\text {and }}$ solvent-free basis.

Packaging and storage-Preserve in tight, light-resistant containers between $20^{\circ}$ and $25^{\circ}$.

USP Reference standards $\langle 11\rangle —$ USP Tolcapone RS. USP Tolcapone Related Compound A RS. USP Tolcapone Related Compound B RS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

## Change to read:

## Absorptivity-

-Diluent-Dilute 100 mL of 1 N hydrochloric acid with dehydrated alcohol to 1000 mL . ${ }^{\text {2S }}$ (USP28)

Test preparation-Prepare a solution of Tolcapone having a concentration of 0.01 mg per mL in 0.1 Naleoholic hydroehloric - Diluent. $\boldsymbol{m}^{2 S}$ (USP28)
Procedure-Proceed as directed under Spectrophotometry and Light-Scattering $\langle 851\rangle$, and measure the absorbance: the maximum is between 265.2 and 269.3 , and the absorptivity is between 752.9-799.3-75.29 and 79.93. ${ }^{2 S}$ (USP28)

Water, Method $I\langle 921\rangle$ : not more than $0.1 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.1 \%$.
Heavy metals, Method II $\langle 231\rangle$ : $0.002 \%$.

## Limit of residual solvents-

Alcohol stock solution-Transfer $6.3 \mu \mathrm{~L}$ of dehydrated alcohol, using a microsyringe, to a $50-\mathrm{mL}$ volumetric flask containing dimethylformamide, and mix.
Methylene chloride stock solution-Transfer $3.8 \mu \mathrm{~L}$ of methylene chloride, using a microsyringe, to a $50-\mathrm{mL}$ volumetric flask containing dimethylformamide, and mix.
Standard solution-Transfer 10.0 mL of Alcohol stock solution and 1.0 mL of Methylene chloride stock solution to a $50-\mathrm{mL}$ volumetric flask. Dilute with dimethylformamide to volume, and mix.

Test solution-Transfer about 200 mg of Tolcapone, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, add 7 mL of dimethylformamide, and sonicate to dissolve. Dilute with dimethylformamide to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The gas chromatograph is equipped with a flame-ionization detector, a $0.53-\mathrm{mm} \times 30-\mathrm{m}$ fused-silica column coated with $3.0-\mu \mathrm{m}$ G43 stationary phase, and a $0.53-\mathrm{mm} \times 5-\mathrm{m}$ fused silica column coated with $3.0-\mu \mathrm{m}$ G3 stationary phase. The carrier gas is helium, flowing at a rate of 5 mL per minute. The column temperature is maintained at $35^{\circ}$. The injection port and detector temperatures are maintained at $120^{\circ}$ and $260^{\circ}$, respectively. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention time is about 0.7 for alcohol and 1.0 for methylene chloride; and the relative standard deviation for replicate injections is not more than $10.0 \%$.
Procedure-Separately inject equal volumes (about $1 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentages ( $\mathrm{w} / \mathrm{w}$ ) of alcohol and methylene chloride in the portion of Tolcapone taken by the formula:

$$
(1000 D)(C / W)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{L}$ per mL , of each solvent in the Standard solution; $D$ is the density, in mg per $\mu \mathrm{L}$, of each solvent at $20^{\circ}$; $W$ is the weight, in mg , of Tolcapone taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak areas of the appropriate analyte obtained from the Test solution and the Standard solution, respectively: not more than $0.25 \%$ of alcohol is found; and not more than $0.01 \%$ of methylene chloride is found. [NOTE-Condition the column at $220^{\circ}$ for 15 minutes after each injection.]

## Change to read:

## Related compounds-

TEST 1-
Adsorbent: $\quad 0.25-\mathrm{mm}$ layer of chromatographic $5-\mu \mathrm{m}$ - $\mathbf{n} 2 S$ (USP28) , silica gel mixture with a suitable fluorescing substance (see Chromatography $\langle 621\rangle$ ).

Standard solution 1-Dissolve an accurately weighed portion of USP Tolcapone RS in chloroform, and dilute quantitatively, and stepwise if necessary, with chloroform to obtain a solution having a known concentration of 0.4 mg per mL .

Standard solution 2-Transfer 2.0 mL of Standard solution 1 to a $10-\mathrm{mL}$ volumetric flask, dilute with chloroform to volume, and mix.

Standard solution 3-Transfer 1.0 mL of Standard solution 1 to a $10-\mathrm{mL}$ volumetric flask, dilute with chloroform to volume, and mix.

Standard solution 4-Transfer 5.0 mL of Standard solution 3 to a $100-\mathrm{mL} \cdot 10-\mathrm{mL}^{\mathbf{\Omega}}{ }^{2 S}$ (USP28) , volumetric flask, dilute with chloroform to volume, and mix.

Test solution-Transfer about 200 mg of Tolcapone, accurately weighed, to a $5-\mathrm{mL}$ volumetric flask, dissolve in and dilute with chloroform to volume, and mix. [NOTE-Prepare this solution last and chromatograph immediately.]

Application volume: $10 \mu \mathrm{~L}$.
Developing solvent system: a mixture of chloroform, -anhydrous ${ }^{2 S}$ (USP28) formic acid, and ethyl acetate ( $83: 15: 2$ ).

Procedure-Apply the Test solution and each of the Standard solutions as directed for Thin-Layer Chromatography under Chromatography $\langle 621\rangle$ at about 4 cm from the lower edge of the plate. $\mathbf{M S}^{2 S}$ (USP28) Dry the plate in a current of
cold air, and view it under short-wavelength UV light. The $R_{F}$ values of analytes are as follows.

| Compound | $R_{F}$ |
| :--- | :---: |
| Tolcapone related compound A | about 0.2 |
| Tolcapone | about 0.5 |
| Tolcapone related compound B | about 0.7 |

Compare any spot at $R_{F}$ of 0.0 in the chromatogram obtained from the Test solution with the principal spot of Standard solution 2, Standard solution 3, and Standard solution 4, and obtain the approximate amount: not more than $0.1 \%$ of any impurity at $R_{F}$ of 0.0 is found. [NOTE-The $R_{F}$ of tolcapone related compound A and tolcapone related compound B are given just for reference. They are quantified in Test 2.]

TEST 2-
Diluent, System suitability solution, Mobile phase, and Chromatographic system-Proceed as directed in the Assay.

Standard solution-Use the Standard preparation, prepared as directed in the Assay.

Test solution-Use the Assay preparation.
Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of each impurity in the portion of Tolcapone taken by the formula:

$$
(50,000 F)(C / W)\left(r_{i} / r_{s}\right),
$$

in which $C$ is the concentration, in mg per mL , of USP Tolcapone RS in the Standard solution; $F$ is the relative response factor of the impurity according to the table below; $W$ is the weight, in mg , of Tolcapone, calculated on the sol-vent- and water-free basis, used to prepare the Test solution;
$r_{i}$ is the peak area for any impurity in the Test solution; and $r_{s}$ is the peak area for tolcapone in the Standard solution: the impurities meet the requirements given in the table below.

|  | Relative <br> Retention <br> Time | Relative <br> Response <br> Factor | Limit (\%) |
| :---: | :---: | :---: | :---: |
| Compound Name | about 0.6 | 1.14 | 0.1 |
| Tolcapone related <br> compound A | 1.0 | - | - |
| Tolcapone |  |  |  |
| Tolcapone related <br> compound B | 1.36 | 0.98 | 0.2 |
| Unknown impuri- <br> ties | - | 1.0 | 0.1 indi- <br> vidual, 0.2 <br> total un- <br> known |
| Total impurities | - | - | 0.5 |

## Assay-

Diluent-Prepare a mixture of methanol and acetonitrile (24:15).

System suitability solution-Dissolve an accurately weighed quantity of USP Tolcapone Related Compound A RS, USP Tolcapone RS, and USP Tolcapone Related Compound B RS in Diluent; and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about $5 \mu \mathrm{~g}$ per $\mathrm{mL}, 5 \mu \mathrm{~g}$ per mL , and $10 \mu \mathrm{~g}$ per mL , respectively. Transfer 2.0 mL of this solution to a $100-\mathrm{mL}$ volumetric flask, add about 63 mL of Diluent, dilute with water to volume, and mix.
Mobile phase-Prepare a filtered and degassed mixture of methanol, 0.05 M monobasic potassium phosphate having a pH of $2.0 \pm 0.1$, and acetonitrile ( $8: 7: 5$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard preparation-Dissolve an accurately weighed quantity of USP Tolcapone RS in Diluent; and dilute quantitatively, and stepwise if necessary, with Diluent to obtain a solution having a known concentration of about 1.0 mg per mL . Transfer 5.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, add about 27.5 mL of Diluent, dilute with water to volume, and mix.

Assay preparation-Transfer about 50 mg of Tolcapone, accurately weighed, to a $50-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent to volume, and mix. Transfer 5.0 mL of this solution to a $50-\mathrm{mL}$ volumetric flask, add about 27.5 mL of Diluent, dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—
The liquid chromatograph is equipped with a $230-\mathrm{nm}$ detector and a $4.0-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.6 for tolcapone related compound $\mathrm{A}, 1.0$ for tolcapone, and about 1.4 for tolcapone related compound B ; and the resolution, $R$, between tolcapone related compound B and tolcapone is not less than 4.0. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $1.0 \%$.

Procedure-Separately inject equal volumes (about 20
$\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the areas for the major tolcapone peaks. Calculate the quantity, in mg, of $\mathrm{C}_{14} \mathrm{H}_{11} \mathrm{NO}_{5}$ in the portion of Tolcapone taken by the formula:

$$
500 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Tolcapone RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■1S (USP28)

## Briefing

Triclosan, USP 27 page 1888. It is proposed to replace the reagents (4-chlorophenol; 2-4-dichlorophenol; 1,3,7-trichlorodiben-zo-p-dioxin; 2,8-dichlorodibenzo-p-dioxin; 2,8-dichlorodibenzofuran; 2,4,8-trichlorodibenzofuran) with the corresponding USP Reference Standards in the test for Limit of monochlorophenols and 2,4-dichlorophenol and in the test for Limit of 1,3,7-tri-chlorodibenzo-p-dioxin, 2,8-dichlorodibenzo-p-dioxin, 2,8dichlorodibenzofuran, and 2,4,8-trichlorodibenzofuran.
(PA7b: B. Davani) RTS-41691-1

## Change to read:

USP Reference standards $\langle 11\rangle-$
-USP 2,4-Dichlorophenol RS. USP Parachlorophenol
RS. n2S $_{\text {(USP28) }}$
USP Triclosan RS.

- USP Triclosan Related Compounds Mixture A RS.■2S (USP28)


## Change to read:

## Limit of monochlorophenols and 2,4-dichlorophenol-

Phosphate buffer-Transfer about 1.38 g of anhydrous monobasic sodium phosphate and about 1.42 g of dibasic sodium phosphate to a 1-L volumetric flask, dissolve in and dilute with water to volume, and mix.

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile and Phosphate buffer ( $1: 1$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Quantitatively dissolve accurately weighed quantities of 4 chlorophenel and 2,4-diehlorephenel
-USP Parachlorophenol RS and USP 2,4-Dichlorophenol
$\mathrm{RS}_{\mathbf{1} 2 \mathrm{~S} \text { (USP28) }}$
in acetonitrile, dilute with an equal volume of water, and mix. Transfer a portion of this solution to a suitable container, and dilute quantitatively, and stepwise if necessary, with a mixture of acetonitrile and water $(1: 1)$ to obtain a solution having known concentrations of about $0.5 \mu \mathrm{~g}$ of 4 -chlorophenel
$\square_{\text {parachlorophenol }}^{{ }_{\text {2S }}}$ (USP28)
and $0.1 \mu \mathrm{~g}$ of 2,4-dichlorophenol per mL .
Test solution-Transfer about 250 mg of Triclosan, accurately weighed, to a $25-\mathrm{mL}$ low-actinic volumetric flask, dissolve in 20 mL of acetonitrile, dilute with water to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a coulometric electrochemical detector with electrode 1 set at 0.45 V and electrode 2 set at 0.75 V , both having a positive (oxidative) polarity and a $4.6-\mathrm{mm}$ $\times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative standard deviation for replicate injections is not more than $9.0 \%$ for 2,4 -dichlorophenol.

Procedure-Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. The peak responses for 4 chlorophenel
■parachlorophenolı2S (USP28)
and 2,4-dichlorophenol in the chromatogram of the Test solution are not greater than the corresponding peaks in the chromatogram of the Standard solution.

## Change to read:

Limit of 1,3,7-trichlorodibenzo-p-dioxin, 2,8-dichlorodibenzo-p-dioxin, 2,8-dichlorodibenzofuran, and 2,4,8-trichlorodiben-zofuran-

Mobile phase-Prepare a filtered and degassed mixture of acetonitrile, water, and glacial acetic acid (70:30:0.1). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard solution-Transfer aceurately weighed quantities of 2,8 diehlerodibenzofuran, and $2,4,8$ triehlorodibenzofuran to a volumetric flask, add accurately measured volumes of $1,3,7 \mathrm{tri}$ ehlorodibenzo $p$ dioxin and 2,8 dichlorodibenzo $p$ dioxin, and dissolve in methanol. Dilute quantitatively, and stepwise if neeessary, with methanel to obtain a solution having concentrations of about $0.5,1.0,0.5$, and $1.0 \mu \mathrm{k}$ per mL, respectively.

■■2S (USP28)
Test solution-Transfer about 2.0 g of Triclosan, accurately weighed, to a screw-capped centrifuge tube, add 5 mL of 2 N potassium hydroxide, and shake for 10 minutes to dissolve. Add 3 mL of $n$-hexane, shake for 10 minutes, and allow the phases to separate. Transfer the organic layer to a suitable container, add another 3 mL of $n$-hexane to the aqueous layer, shake for 10 minutes, and allow the phases to separate. Transfer the organic layer to the previous extract, discard the aqueous layer, add 3 mL of 2 N potassium hydroxide to the combined organic layers, shake for 10 min utes, and allow the phases to separate. Discard the aqueous layer, add another 3 mL of 2 N potassium hydroxide to the combined organic layers, shake for 10 minutes, and allow the phases to separate. Transfer the organic layer to a suitable container, and evaporate with the aid of a stream of nitrogen to dryness. Dissolve the residue in 1.0 mL of methanol, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a 220 -nm detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the Stand
-USP Triclosan Related Compounds Mixture A

## RS, ■2S (USP28) $^{\text {( }}$

and record the peak responses as directed for Procedure: the relative retention times are about 0.59 for 2,8-dichlorodibenzofuran, 0.71 for 2,8 -dichlorodibenzo- $p$-dioxin, 0.88 for $2,4,8$-trichlorodi-
benzofuran, and 1.0 for 1,3,7-trichlorodibenzo- $p$-dioxin; and the relative standard deviation for replicate injections is not more than $15.0 \%$, determined from the 2,8-dichlorodibenzo-p-dioxin peak.

Procedure-Inject a volume (about $20 \mu \mathrm{~L}$ ) of the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. The peak response for 2,8 diehlorodibenzofuran, 2,8 diehlorodibenzo p-doxin, $2,4,8$ triehlorodibenzoftran, and $1,3,7$ triehlorodibenzo $p$ dioxin obtained frem the Test solt tion are not greater than the corresponding peaks obtained from the Standed solution
-Calculate the concentration of each analyte in the portion of Triclosan taken by the formula:

$$
(C / W)\left(r_{i} / r_{s}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of the respective analyte in the USP Triclosan Related Compounds Mixture A RS; $W$ is the weight, in g , of Triclosan taken; and $r_{i}$ and $r_{S}$ are the peak responses for the respective analyte obtained from the Test solution and the USP Triclosan Related Compounds Mixture A RS, respectively: not more than 0.25 ppm of 2,8-dichlorodibenzofuran is found; not more than 0.5 ppm of 2,4,8-trichlorodibenzofuran is found; not more than 0.25 ppm of $1,3,7$-trichlorodibenzo- $p$-dioxin is found; and not more than 0.5 ppm of 2,8-dichlorodibenzo- $p$-dioxin is found.■2S (USP28)

BRIEFING

Vancomycin Hydrochloride, USP 27 page 1930. It is proposed to add a new test and acceptance criteria to monitor the amount of monodechlorovancomycin present in Vancomycin Hydrochloride. The liquid chromatographic procedures in the test for Limit of monodechlorovancomycin are based on analyses performed with the RP18 XTerra ${ }^{\text {tm }}$ brand of L1 column. In the test for Chromatographic purity, it is proposed to clarify the peak integration in the Procedure section. In addition, editorial style changes have made in the test for Chromatographic purity.
(PA7b: B. Davani) RTS-41790-1

## Change to read:

USP Reference standards $\langle 11\rangle —$ USP Vancomycin Hydrochloride $R S$.

- USP Vancomycin B with Monodechlorovancomycin $R S$.

■2S (USP28)

## Change to read:

## Chromatographic purity-

Triethylamine buffer-Mix 4 mL of triethylamine and 2000 mL of water, and adjust with phosphoric acid to a pH of 3.2.

Solution A-Prepare a mixture of Triethylamine buffer, acetonitrile, and tetrahydrofuran (92:7:1), and degas briefly.

Solution B-Prepare a suitable mixture of Triethylamine buffer, acetonitrile, and tetrahydrofuran $(70: 29: 1)$, and degas briefly.

Mobile phase-Use variable mixtures of Solution A and Solution $B$ as directed for Chromatographic system. Make adjustments if necessary (see Chromatography $\langle 621\rangle$ ), changing the acetonitrile proportion in Solution A to obtain a retention time of 7.5 to 10.5 minutes for the main vancomycin peak.

Resolution solution-Prepare a solution of USP Vancomycin Hydrochloride RS in water containing 0.5 mg per mL , heat at $65^{\circ}$ for 48 hours, and allow to cool.

Test preparation A-Prepare a solution of Vancomycin Hydrochloride in Solution $A$ containing 10 mg per mL .

Test preparation B-Transfer 2.0 mL of Test preparation $A$ to a $50-\mathrm{mL}$ volumetric flask, dilute with Solution $A$ to volume, and mix. Chromatographic system (see Chromatography $\langle 621\rangle$ )—The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The flow rate is about 2 mL per minute. The chromatograph is programmed as follows.

| Time <br> (minutes) | Solution $A$ <br> $(\%)$ | Solution $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| $0-12$ | 100 | 0 | isocratic |
| $12-20$ | $100 \rightarrow 0$ | $0 \rightarrow 100$ | linear gradient |
| $20-22$ | 0 | 100 | isocratic |
| $22-23$ | $0 \rightarrow 100$ | $100 \rightarrow 0$ | linear gradient |
| $23-30$ | 100 | 0 | isocratic |

Chromatograph the Resolution solution, and record the peak responses as directed for Procedure: the elution order is resolution compound 1 , vancomycin B , and resolution compound 2 . The resolution, $R$, between resolution compound 1 and vancomycin B is not less than 3.0; and the column efficiency, calculated from the vancomycin B peak, is not less than 1500 theoretical plates. Resolution compound 2 is eluted at between 3 and 6 minutes after the start of the period when the percentage of Solution $B$ is increasing from $0 \%$ to $100 \%$.

Procedure-[NOTE-Where baseline separation is not achieved, peak areas are defined by vertical lines extended from the valleys between peaks to the baseline.
-The main component peak may include a fronting shoulder, which is attributed to monodechlorovancomycin. This shoulder should not be integrated separately.] $]_{\text {n2S }}$ (USP28) Separately inject equal volumes (about $20 \mu \mathrm{~L}$ ) of Test preparation $A$ and Test preparation $B$ into the chromatograph, record the chromatograms, and measure the area responses for all of the peaks. [NOTE-Correct any peak observed in the chromatograms obtained from Test preparation $A$ and Test preparation $B$ by subtracting the
area response of any peak observed in the chromatogram of Solution $A$ at the corresponding elution time.] Calculate the percentage of vancomycin $B$ in the specimen tested by the formula:

$$
2500 r_{B} /\left(25 r_{B}+r_{A}\right)
$$

in which $r_{B}$ is the corrected area response of the main peak obtained in the chromatogram of Test preparation $B$; and $r_{A}$ is the sum of the corrected area responses of all the peaks, other than the main peak, in the chromatogram obtained from Test preparation A: not less than $80.0 \%$ of vancomycin B is found. Calculate the percentage of each other peak taken by the formula:

$$
100 r_{A i} /\left(25 r_{B}+r_{A}\right),
$$

in which $r_{A i}$ is the corrected area response of any individual peak, other than the main peak, obtained in the chromatogram of Test preparation A: not more than $9.0 \%$ of any peak other than the main peak is found.

## Add the following:

-Limit of monodechlorovancomycin-[NOTE-The System suitability solution, Working standard solution, and Test solution are to be refrigerated immediately after preparation and during analysis, using a refrigerated autosampler. The solutions are stable at refrigerated conditions for 4 days.]

Mobile phase-Prepare a filtered and degassed mixture in a 1-L volumetric flask that is initially half filled with water. Dissolve 2.2 g of 1-heptanesulfonic acid sodium salt, add 125 mL of acetonitrile and 10 mL of acetic acid, and dilute with water to volume, making adjustments if necessary (see System Suitability under Chromatography (621〉).
Rinse solution-Prepare a solution containing approximately $10 \%(\mathrm{v} / \mathrm{v})$ acetonitrile in water, to be used as the rinse solution for the needle and column.

System suitability solution-Dissolve an accurately weighed quantity of USP Vancomycin B with Monodechlorovancomycin RS that contains approximately 50 mg of vancomycin B in water in a $50-\mathrm{mL}$ volumetric flask to obtain a solution having a known concentration of about 1 mg of vancomycin B per mL.
Working standard solution-Transfer 5.0 mL of the System suitability solution to a $100-\mathrm{mL}$ volumetric flask, and dilute with water to volume. The final concentration is approximately 0.05 mg of vancomycin $B$ per mL .

Test solution-Transfer about 100 mg of Vancomycin Hydrochloride, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.

## Blank: water

Chromatographic system (see Chromatography $\langle 621\rangle$ )-
The liquid chromatograph is equipped with a $280-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains packing L1 and is maintained at a constant temperature of about $60^{\circ}$. The flow rate is about 1.5 mL per minute. The autosampler cooler temperature is maintained at $5^{\circ}$. The Blank and Working standard solution run time is 90 minutes, and the System suitability solution and Test solution run time is 120 minutes. [NOTE-This test is sensitive to temperature changes. To preheat the Mobile phase, Working standard solution, and Test solution, a length of tubing of at least 3 feet should be placed preceding the column within the column heater.] Chromatograph the Blank and the System suitability solution. There should be no peaks in the Blank chromatogram that interfere with the vancomycin B and monodechlorovancomycin peaks. The retention time of the vancomycin B peak is between 32 and 42 minutes. The monodechlorovancomycin elutes at a retention time ratio of approximately 1.1 compared to 1.0 for the main component, vancomycin B. The retention time of the monodechlorovancomycin peak in the Test solution chromatogram must be within $\pm 3.0 \%$ of the mean retention time of the monodechlorovancomycin peaks in the chromatogram of the Working standard solution. The resolution, $R$, between vancomycin B and monodechlorovancomycin is not less than 1.9 , using the chromatogram from the System suitability solution; and the relative standard deviation for replicate injections of the Working standard solution is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 50 $\mu \mathrm{L}$ ) of the Blank, System suitability solution, Working standard solution and Test solution into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the percentage of monodechlorovancomycin in the portion of Vancomycin Hydrochloride taken by the formula:

$$
0.1\left(W_{S} / W_{U}\right)\left(r_{U} / r_{S}\right) P
$$

in which $W_{s}$ is the weight, in mg, of the USP Vancomycin B with Monodechlorovancomycin RS in the Working standard solution; $W_{U}$ is the weight, in mg , of Vancomycin Hydrochloride taken to prepare the Test solution; $r_{U}$ is the peak area response of the monodechlorovancomycin peak in the Test solution; $r_{s}$ is the average peak area response of the vancomycin B peaks in the Working standard solution; and $P$ is the vancomycin B purity of the USP Vancomycin B with Monochlorovancomycin RS: not more than 4.7\% of monodechlorovancomycin is found. $\quad$ 2S (USP28)

## BRIEFING

Vecuronium Bromide, page 193 of $P F$ 30(1) [Jan.-Feb. 2004]. It is proposed to make minor changes to the Diluent in the Assay to minimize the degradation of Vecuronium Bromide. A Note is proposed to be added when preparing the Mobile phase in the test for Related compounds and when preparing Solution B in the Assay to prevent the loss of volatile components. An equilibration time is proposed in the test for Related compounds, and the chemical and IUPAC names for Vecuronium Bromide are added under the Procedure. In addition, editorial style changes have been made.
(PA3: R. Ravichandran) RTS-41189-1

## Add the following:

## ■ Vecuronium Bromide

$\mathrm{C}_{34} \mathrm{H}_{57} \mathrm{BrN}_{2} \mathrm{O}_{4} \quad 637.75637 .73$
Piperidinium, 1-[(2 $\beta, 3 \alpha, 5 \alpha, 16 \beta, 17 \beta)$-3,17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide. 1-(3 $3,17 \beta$-Dihydroxy- $2 \beta$-piperidino- $5 \alpha$-androstan-16 $\beta, 5 \alpha$ -yl)-1-methylpiperidinium bromide, diacetate [50700-72-6].
» Vecuronium Bromide contains not less than 98.0 percent and not more than 102.0 percent of $\mathrm{C}_{34} \mathrm{H}_{57} \mathrm{BrN}_{2} \mathrm{O}_{4}$, calculated on the dried basis.

Packaging and storage-Preserve in tight containers, and store at room temperature.

USP Reference standards $\langle 11\rangle$ —USP Endotoxin RS. USP Pancuronium Bromide RS. USP Vecuronium Bromide RS. USP Vecuronium Bromide Related Compound A RS. USP Vecuronium Bromide Related Compound B RS. USP Vecuronium Bromide Related Compound C RS. USP Vecuronium Bromide Related Compound $\triangle$ F RS. USP Veenmium Bro mide Related Compound ERS.

## Identification-

A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

Specific rotation $\langle 781 \mathrm{~S}\rangle$ : between $-16^{\circ}$ and $-20^{\circ}$, at $20^{\circ}$.
Test solution: 10 mg per mL , in dehydrated alcohol.
Bacterial endotoxins $\langle 85\rangle$ : not more than 10 USP Endotoxin Units per mg of vecuronium bromide.

Loss on drying $\langle 731\rangle$-Dry it at $80^{\circ}$ for 2 hemrs to constant weight: it loses not more than 2.0\% of its weight. Dry it at $105^{\circ}$ for two hours: it loses not more than $2.0 \% 2.5 \%$ of its weight.

## Related compounds-

Solution A, Solution B, Mobile phase, and Diluent Proeeed directed in the Assay.

System suitability solution Dissolve aceurately weighed quantities of USP Vecuronium Bromide RS and USP Vecuronium Bromide Related Compound $A$ RS in Diluen ob tain a solution having known concentrations of about 0.5 mg per mL and 0.4 mg per mL , respectively.

Fest solution Dissolve an aceurately weighed quantity of Veeuronium Bromide in Piltent obtain a solution having a concentration of about 4 my per mL.
Chromatographic system Prepare as directed in the As say. Chromatograph the System suitability solution, and re eord the peak respenses as directed for Proecture: the relative retention times are about 0.85 for vecuronitm bremide related compound $\Lambda$ and 1.0 for vecuronimm bromide; the resolution, $R$, between vectronitm bromide and veetrenium bremide related compend $\Lambda$ is not less than 5.0 ; the eolumn efficiency is not less than 5000 theoretieal plater; the tailing factors for vecuronimm bromide and vecuronium bromide related compeund $\Lambda$ are not more than 2.0 ; and the relative standard deviation for replieate injections is not more than 2.0\%

Procedure Inject a volume (about $20 \mu \mathrm{~L})$ of the Test so tution into the chromatograph, record the chromatogram, and measure the peak respenses. Caleulate the pereentage of any impurity in the pertion of Vecurenium Bromide taken by the formula:

$$
100(+,+7),
$$

in which + is the peak respense for each individual impurity, and $x$ is the sum of the respenses of all the peaks: not more than 2\% of total impurities is found.

## TEST 1-

Pragenderff's reagent Mix 850 mg of bismuth subnitrate with 40 mL of water and 10 mL of glacial acetic acid (Solution A). Dissolve 8 g of potassitum-iodide in 20 mL of water (Solution B). Mix Solution A and Solution B. Dilute 1.0 mL of the selution so obtained with 10 mL of $50 \%$ (v/ $V$ ) glacial acetic acid solution.
$5 \%-H y d r o g e n$ peroxide solution- Dilute about 16.6 mL of $30 \%$ hydrogen peroxide with water to 100 mL .

Sodiantiodide solution Dissolve 1.5 g of soditm-iodide in 50 mL of acetone.

Diltent Prepare a mixture of acetonitrile and chloroform ( $9: 1$ )

Adsorbent: 0.1 mm layer of ehrematographic $5-\mu \mathrm{m}$ - sit ien gel mixture (see-Chromatography $\langle 624\rangle$ ).

Fest solution Transfer about 50 mg of Vecuronium Bro mide, aceurately weighed, to a 5 - mL volumetric flask. Dis solve in and diltute with Diltent to volume, and mix.

Standard solution 1 Dissolve an aceurately weighed pertion of USP Vecuronium Bromide RS in Diluent, and dilete quantitatively, and-stepwise if neeessary, with Dilthent to-obtain a solution having a known concentration of 10 Hg per mL.

Standard solution 2 Dissolve aceurately weighed per tiens of USP Vecurenium Bromide Related Compeund D A RS, USP Vectrenitm Bremide-Related Compeund B RS, USP Vecuronium Bromide Related Compound E D RS, and USP Pancurenium Bromide RS in Diluent, and dilute quantitatively, and stepwise if neeessary, with Diluent to obtain a selution having known concentrations of about $20 \mu \mathrm{~g}$ per $\mathrm{mL}, 20 \mu \mathrm{~g}$ per $\mathrm{mL}, 20 \mu \mathrm{~g}$ per mL , and 10 нg per mL , respectively.

Application voltme: 10 mL .
Developing solvent system: a mixtare of Soditm iodide
solution, acetone, and methyl ethyl ketone $(5: 5: 1)$.
Procedtre-Proceed as directed for Thin-Layer Chromt tography under Chromatography $\langle 624\rangle$. Dry the plate for 2 minttes in a current of cold air, and spray it with $5 \%$ Hydrogen peroxide solution. Dry it in a current of air and then spray with Dragendorff's reagent. Repeat the procedure begimning with "spray it with $50 \%$ Hydregen peroxide solth tion'': the spet corresponding to the principal spot ebtained from Standard solution 1 is visible; the $R_{t}$ values Of analytes are as follows:

| Analyte | $R_{\text {F }}$ |
| :---: | :---: |
| pancurenitm bremide | about 0.25 |
| +ecurenitum bromide | about 0.50 |
| *ecurenitum bremide re |  |
| eompound D-A | about 0.70 |
| vecurenimm bromide re |  |
| eompound B | about 0.69 |
| vecurenitm bromide re |  |
| eompound ED | about 0.85 |
| Any spot in the chromatogram obtained from the Test solt |  |
| tim, except for the principal-spet, is not more intense than |  |
| the correspending spot in the chromatogram obtained from |  |
| Standerd solution 2: not more than 0.2\% each of vecure- |  |
| fitm bromide related compound D A, veeurenitum bromide |  |

related compeund $B$, and vecuronitum bromide relatedeompeund E $D$-is found; and not more than $0.1 \%$ of paneure nitum bremide is found. Any unknown spet obtained in the chromategram of the Test solution is not mere intense than the prineipal spet in the chromatogram obtained frem the Standard soltion 1: net more than 0.1\% of any individ wal unknown impurity is found.

## TEST 2

Pragenderff's reagent, Diluent, Test solution, and $5 \%$ Hy dregen perexide solution-Proceed as directed in Test 1.

Sodiun iodide solution 1 Dissolve 1.5 g of sodium io dide in 95 mL of isopropyl aleohol.

Sodith iodide solution 2 Proceed as directed for Soditan iodide solution in Test 1.

Adsorbent: 0.1 mm layer of chromatographic 5 - mm sit iea gel mixatre (see-Chromatography $\langle 624\rangle$ ).

Standerd solution Dissolve an aceurately weighed pertion of USP Vecuronium Bromide Related Compound C RS in Diltent to obtain a solution having a known concentration of 20 mg per mL .

Application voltate: $10 \mu \mathrm{~L}$.
Developing solvent systen 1: a mixture of Sodium io dide solttion 1 and water (95:5).

Peveloping solvent systen 2: a mixture of Soditan io dite solution 2, acetone, and methyl ethyl ketone (5:5:1).

Procedure Apply the Test solution on the right corner of
the plate at 1.5 cm frem each side. Introduce the plate inte the unsaturated developing ehamber containing Developing solvent system 1. Cover, and maintain the-system until the solvent front has moved to a point about 10 em above the initial applieation. Dry the plate in acurrent of cold air until the isepropyl aleohol odor disappears. Retate the plate- $90^{\circ}$, eensidering the side of the previous depesition of the Test solution as base. Apply the Standard solution at 1.5 cm from the base and at not less than 1.5 cm frem the line to which
the solvent front has moved previously. Introduce the plate inte the saturated developing chamber containing Developthg solvent system 2. Cover, and maintain the system until the solvent ascends to a peint about 8 cm above the initiat spets. Dry the plate for 2 mintes in actrrent of cold air, and spray it with $5 \%$ Hydrogen perexide solution. Dry it in a eurrent of cold air, and then spray with Dragendorff's reagent. Repent the procedure, starting from" spray it with 5\% Hydrogen peroxide solttion": the spot correspending to the prineipal-spet obtained from the-Standard solution is visible. Any spet in the chromatogram obtained from the Test solution is not more intense than the respective spet in the chromatogram obtained from the Standard solution: not more than $0.2 \%$ of vecuronium bromide related compound $C$ is found; and not more than $1.0 \%$ of total impurities is found, the results of Test 1 and Test 2 being added.

Cation suppressor regeneration solution: $\quad 0.02 \mathrm{M}$ tetrabutylammonium hydroxide.

Mobile phase—Mix 1500 mL of filtered water, 250 mL of filtered methanol, 45 mL of filtered tetrahydrofuran, and 1 mL of hydrochloric acid in a $2000-\mathrm{mL}$ volumetric flask. Leave at room temperature for few minutes, and dilute with water to volume. Mix, flter, and degas. [NOTE-Avoid evaporation of tetrahydrofuran during degassing.]

Standard solution-Dissolve an accurately weighed quantity of USP Vecuronium Bromide RS, USP Pancuronium Bromide RS, USP Vecuronium Bromide Related Compound A RS, USP Vecuronium Bromide Related Compound B RS, USP Vecuronium Bromide Related Compound C RS, and USP Vecuronium Bromide Related Compound F RS in 0.0025 N hydrochloric acid, and dilute quantitatively and stepwise if necessary, to obtain a solution having a known concentration of about $5 \mu \mathrm{~F} 0.005 \mathrm{mg}$ of each compound per mL .

Test solution-Transfer about 25 mg of Vecuronium Bromide, accurately weighed, to a $25-\mathrm{mL}$ volumetric flask. dis solve Add 0.5 mL of acetonitrile, dilute with 0.0025 N hydrochloric acid to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid-ion chromatograph is equipped with a conductivity detector, a $4-\mathrm{mm}$ cation suppressor and a $4.6-\mathrm{mm} \times 25-$ cm column that contains packing L1. The flow rate is about 1.5 mL per minute. The flow rate for the cation suppressor is about 2 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are given in Table 1; the ratio of the height of the vecuronium bromide related compound A F peak to the height of the valley between the vecuronium bromide related compound A F peak and the pancuronium bromide peak is not less than 2.0 ; and the relative standard deviation for replicate injections is not more than $10.0 \%$ for each compound. [NOTE-The system may need equilibration for 4 hours.]

Procedure-Separately inject equal volumes (about 25 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each vecuronium bromide related compound in the portion of Vecuronium Bromide taken by the formula:

## $2.5(\mathrm{ClH})\left(\mathrm{F}_{4}+\mathrm{F}_{s}\right)$,

$$
2500(C / W)\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in $\# \mathrm{mg}$ per mL , of the relevant USP Reference Standard in the Standard solution; $W$ is the weight, in mg , of Vecuronium Bromide taken to prepare the Test solution; and $r_{U}$ and $r_{S}$ are the peak areas for the correspondent vecuronium bromide related compound obtained from the Test solution and Standard solu-
tion, respectively: the limits of impurities are specified in Table 1. [NOTE-Use the peak area of vecuronium bromide in the Standard solution as $r_{s}$ to calculate any unknown impurity.]

Table 1

| Compound | Relative |  |
| :---: | :---: | :---: |
|  | Retention Time | Limit \% |
| Pancuronium bromide | about 0.5 | 0.5 |
| Vecuronium bromide related compound $\mathrm{F}^{1}$ | about 0.6 | 0.5 |
| Vecuronium bromide related compound $\mathrm{C}^{2}$ | about 0.86 | 0.5 |
| Vecuronium bromide | 1.0 | - |
| Vecuronium bromide related compound $\mathrm{A}^{3}$ | about 2.0 | 0.3 |
| Vecuronium bromide related compound $\mathrm{B}^{4}$ | about 2.6 | 0.5 |
| Unknown | - | 0.1 |
| Total | - | 1.0 |

${ }^{1} 3$-deacetyl vecuronium bromide, (Piperidinium, 1[(2 $2,3 \alpha, 5 \alpha, 16 \beta, 17 \beta)$-17-acetyloxy-3-hydroxy-2-(1-piperi-dinyl)androstan-16-yl]-1-methyl bromide)
${ }^{2}$ 3,17- Bis deacetyl vecuronium bromide; (Piperidinium, 1$[(2 \beta, 3 \alpha, 5 \alpha, 16 \beta, 17 \beta)$-3,17-dihydroxy-2-(1-piperidinyl)an-drostan-16-yl]-1-methyl bromide)
${ }^{3}$ Dipiperidino diol diacetate; ( $3 \alpha, 17 \beta$-diacetyl-oxy- $2 \beta, 16 \beta$ -bispiperidinyl- $5 \alpha$-androstan)
${ }^{4}$ 17-deacetyl vecuronium bromide; (Piperidinium, 1[(2 $\beta, 3 \alpha, 5 \alpha, 16 \beta, 17 \beta)$-3-acetyloxy-17-hydroxy-2-(1-piperi-dinyl)androstan-16-yl]-1-methyl bromide)

## Assay-

Solution A-Transfer 8.0 g of sodium perchlorate to a $1000-\mathrm{mL}$ volumetric flask, dissolve in 6.0 mL of water, dilute with acetonitrile to volume, mix, filter, and degas.

Solution B-Prepare a mixture of methanel and 25\% ammonium hydroxide antaning 0.03 M ammenium chloride (992:8) Transfer 3.2 g of ammonium chloride to a $2000-\mathrm{mL}$
volumetric flask, dissolve in 16 mL of ammonium hydroxide, dilute with methanol to volume, mix, filter, and degas. [NOTE-Avoid excessive degassing to prevent the loss of ammonium hydroxide.].

Mobile phase-Prepare a mitered mixe of Solution $A$ and Solution $B(3: 2)$. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).
Diluent-Pipet $10.0-1.0 \mathrm{~mL}$ of 1 M N hydrochloric acid into a $1000-\mathrm{mL}$ volumetric flask, dilute with acetonitrile to volume, and mix.
Standard preparation-Dissolve an accurately weighed quantity of USP Vecuronium Bromide RS in Diluent to obtain a solution having a known concentration of about 0.5 mg per mL .

Assay preparation - Dissolve an aceuraty weighed
quantity of Vectronitm Bromide in Diluent to obtain a so
lution having a concentration of about 0.5 mg per mL .
Transfer about 50 mg of Vecuronium Bromide, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with Diluent, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L3. The flow rate is about 0.5 mL per minute. The column temperature is maintained at $40^{\circ}$. Chromatograph the Standard preparation, and record the peak responses as directed for Procedure: the column efficiency is not less than 5000 theoretical plates; and the relative standard deviation for replicate injections is not more than $2.0 \%$.

Procedure-Separately inject equal volumes (about 20 $\mu \mathrm{L}$ ) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and
measure the responses for the major peaks. Calculate the quantity, in mg, of $\mathrm{C}_{34} \mathrm{H}_{57} \mathrm{BrN}_{2} \mathrm{O}_{4}$ in the portion of Vecuronium Bromide taken by the formula:

$$
\epsilon\left(x_{t}+x_{s}\right)
$$

$$
100 C\left(r_{U} / r_{s}\right)
$$

in which $C$ is the concentration, in mg per mL , of USP Vecuronium Bromide RS in the Standard preparation; and $r_{U}$ and $r_{s}$ are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.■2S (USP28)

## BRIEFING

Excipients, USP and NF Excipients, Listed by Category, NF 22 page 2809, page 3355 of the Second Supplement, and page 1659 of $P F 30(5)$ [Sept.-Oct. 2004]. It is proposed to add an introductory paragraph to the section Excipients, USP and NF Excipients, Listed by Category and to add a number of excipients to some of the following categories: Buffering Agent, Coating Agent, Emulsifying and/or Solubilizing Agent, Flavors and Perfumes, Ointment Base, Plasticizer, Solvent, Suspending and/or Viscosity-increasing Agent, Tablet Binder, Tablet Disintegrant, Tablet and/or Capsule Lubricant, Vehicle, and Wetting and/or Solubilizing Agent. It is also proposed to delete Ferric Oxide, Black from the Color section; to change Charcoal to Charcoal, Activated in the Sorbent section; and to replace Lactose with Lactose, Anhydrous and Lactose Monohydrate in the Tablet and/or Capsule Diluent section.
(EMC) RTS-41670-1

## Add the following:

-In the following reference table, the grouping of excipients by functional category is intended to summarize the most typically identified purpose that these excipients serve in drug product formulations. The list of substances included in each category is not comprehensive. The statement of
category is intended neither to limit in any way the choice or use of the substance nor to indicate that it has no other
utility.■2S (NF23)

## Change to read:

Acidifying Agent
Acetic Acid
Acetic Acid, Glacial
Eitric Acid
${ }^{4}$ Citric Acid, Anhydrous $\mathbf{A N F 2 3}$
${ }^{\mathbf{\Delta}}$ Citric Acid Monohydrate ${ }_{\mathbf{A} N F 23}$
Fumaric Acid
Hydrochloric Acid
Hydrochloric Acid, Diluted
Malic Acid
Nitric Acid
Phosphoric Acid
Phosphoric Acid, Diluted
Propionic Acid
Sulfuric Acid
Tartaric Acid

## Change to read:

Antifoaming Agent
Dimethicone

- Myristic Acid ${ }_{\text {■2S (NF23) }}$
${ }_{\square}$ Palmitic Acid ${ }_{\text {■1S (NF23) }}$
Simethicone


## Change to read:

Antimicrobial Preservative
Benzalkonium Chloride
Benzalkonium Chloride Solution
Benzethonium Chloride
Benzoic Acid
Benzyl Alcohol
Butylparaben
${ }^{\boldsymbol{\Delta}}$ Cetrimonium Bromide $\mathbf{\Delta N F 2 2}$
Cetylpyridinium Chloride
Chlorobutanol
Chlorocresol
Cresol
Ethylparaben
Methylparaben
Methylparaben Sodium
Phenol
${ }^{\Delta}$ 2-Phenoxyethanol $\mathbf{A N F 2 3}$
Phenylethyl Alcohol
Phenylmercuric Acetate
Phenylmercuric Nitrate
Potassium Benzoate
Potassium Sorbate
Propylparaben
Propylparaben Sodium
Sodium Benzoate

Sodium Dehydroacetate
Sodium Propionate
Sorbic Acid
Thimerosal
Thymol

## Change to read:

## Antioxidant <br> Ascorbic Acid <br> Ascorbyl Palmitate <br> Butylated Hydroxyanisole <br> Butylated Hydroxytoluene <br> Hypophosphorous Acid <br> Monothioglycerol <br> Potassium Metabisulfite <br> Propyl Gallate <br> Sodium Formaldehyde Sulfoxylate <br> Sodium Metabisulfite <br> ${ }^{\mathbf{4}}$ Sodium Sulfite $_{\mathbf{A} N F 23}$ <br> Sodium Thiosulfate <br> Sulfur Dioxide <br> Tocopherol <br> Tocopherols Excipient

## Change to read:

Buffering Agent
Acetic Acid
${ }^{\Delta}$ Adipic Acid ${ }_{\mathbf{\Delta N F 2 3}}$
Ammonium Carbonate
Ammonium Phosphate
Boric Acid
Gitric Acid
${ }^{\Delta}$ Citric Acid, Anhydrous $\mathbf{\Delta N F 2 3}$
${ }^{\Delta}$ Citric Acid Monohydrate $\mathbf{\Delta N F 2 3}$
Lactic Acid
Phosphoric Acid
Potassium Citrate
Potassium Metaphosphate

- Potassium Phosphate, Dibasic $\boldsymbol{m}_{\text {2S }}$ (NF23)

Potassium Phosphate, Monobasic
Sodium Acetate
Sodium Citrate
Sodium Lactate Solution
Sodium Phosphate, Dibasic
Sodium Phosphate, Monobasic
${ }^{\boldsymbol{\Delta}}$ Succinic Acid $\mathbf{A N F 2 3}$

Change to read:
Coating Agent
-Ammonio Methacrylate Copolymer ${ }_{\text {1S (NF23) }}$
-Ammonio Methacrylate Copolymer Dispersion $_{\text {(2S }}$ (NF22)
Carboxymethylcellulose, Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)

Cellulose Acetate

## Gellulose Acetate Butyrate

${ }^{\mathbf{4}}$ Cellaburate $\mathbf{\Delta N F 2 3}$
Cellulose Acetate Phthalate (see Cellacefate)
■ Copovidone $_{\boldsymbol{\square} 1 \mathrm{~S}(\mathrm{NF} 23)}$
${ }^{\text {■ Corn Syrup Solids }}{ }_{\text {■ (NF23) }}$
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose ${ }^{\mathbf{\Delta}}$ (see Hypromellose) $\mathbf{A N F 2 2}$
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
${ }^{\boldsymbol{4}}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) $\mathbf{\Delta N F 2 2 ~}^{\text {a }}$

- Hypromellose Acetate Succinate ${ }_{\text {1s }}$ (NF23)

Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)

- Maltodextrin $_{\text {■ } 2 \text { S (NF23) }}$

Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate
Shellac
$\square_{\text {-Starch, Pregelatinized Modified }}^{\text {■1S (NF23) }}$
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

## Change to read:

## Color

Caramel
Ferric Oxide, red, yellow, black,

$$
■_{12 S}(N F 23)
$$

or blends

## Change to read:

Emollient
Alkyl (C12-15) Benzoate
${ }^{\text {■Hydrogenated Soybean Oil}}{ }_{\text {1S (NF22) }}$
-Polydecene $\mathbf{■ 1 S ~ ( N F 2 3 ) ~}$

## Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Cholesterol
Diethanolamine (Adjunct)
${ }^{\bullet}$ Diethylene Glycol Stearates ${ }_{\text {1S }}$ (NF22)

Ethylene Glycol Stearates $_{\text {■ }}^{1 S}$ (NF22)
${ }^{\Delta}$ Glyceryl Distearate $\mathbf{\Delta N F 2 2 ~}$
${ }_{\Delta}^{\Delta}$ Glyceryl Monolinoleate ${ }_{\text {A }}{ }^{\text {UF22 }}$
${ }^{\Delta}$ Glyceryl Monooleate ${ }_{\text {AFF22 }}$
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 40 Stearate

- Polyoxyl Lauryl Ether ${ }_{1 S}$ (NF22)
- Polyoxyl Stearyl Ether ${ }_{1 S}$ (NF22)

Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
-Sodium Cetostearyl Sulfate $_{\text {■ }}^{\text {(NF22) }}$
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
-Sorbitan $^{\text {Sesquioleate }}{ }_{\text {■2S (NF23) }}$
-Sorbitan Trioleate $_{\text {■2S (NF23) }}$
Stearic Acid
Trolamine
Wax, Emulsifying

## Change to read:

## Flavors and Perfumes


Anethole
Benzaldehyde
Ethyl Vanillin
$\boldsymbol{\bullet E t h y l}$ Acetate $_{\boldsymbol{m}_{2 S}(N F 23)}$
$\mathbf{- M a l t o l}_{\text {■1S (NF23) }}$
Menthol
Methyl Salicylate
Monosodium Glutamate
Peppermint
Peppermint Oil
Peppermint Spirit
Rose Oil
Rose Water, Stronger
Thymol
Vanillin

## Change to read:

## Humectant

${ }^{-}$Corn Syrup Solids ${ }_{\text {■ }}$ (NF23)
Glycerin
Hexylene Glycol
Propylene Glycol
Sorbitol
${ }^{\bullet}$ Sorbitol, Anhydrized Liquid ${ }_{\text {■S (NF23) }}$

- Tagatose $_{\text {п. } 2 \mathrm{~S}}$ (NF23)


## Change to read:

## Ointment Base

Eaprylocaproyl-Maeregolglyeerides
-Caprylocaproyl Polyoxylglycerides $_{\text {■ }_{1 S}(\text { NF23 }}$
Diethylene Glycol Monoethyl Ether
-Lauroyl Macrogolglycerides $_{\text {■1S (NF23) }}$
Lineoyl Maeregelglyeerides
■Lineoyl Polyoxylglycerides $_{\mathbf{■ 1 S}^{\text {(NF23) }}}$
Lanolin
Ointment, Hydrophilic
Ointment, White
Oleoyl Macrogolglyeerides
-Oleoyl Polyoxylglycerides ${ }_{\text {(SS (NF23) }}$
Ointment, Yellow
Polyethylene Glycol Ointment

- Monomethyl Ether $_{\text {■2S (NF23) }}$

Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White

- Polydecene ${ }_{\text {1s (NF23) }}$

Rose Water Ointment
Squalane
Stearoyl Macregelegyecrides
-Stearoyl Polyoxylglycerides $_{\mathbf{m}_{1 S}(N F 23)}$
Vegetable Oil, Hydrogenated, Type II

## Change to read:

## Plasticizer

Acetyltributyl Citrate
Acetyltriethyl Citrate
Castor Oil
Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin
Polyethylene Glycol
-Polyethylene Glycol Monomethyl Ether ${ }_{\text {2s (NF23) }}$
Propylene Glycol

- Sorbitol, Anhydrized Liquid ${ }_{\text {■1S (NF23) }}$

Triacetin
Tributyl Citrate
Triethyl Citrate

## Change to read:

## Polymer Membrane

-Ammonio Methacrylate Copolymer ${ }_{\text {1S (NF23) }}$
-Ammonio Methacrylate Copolymer Dispersion $_{\mathbf{\square 2 S}}$ (NF22)
Cellulose Acetate
Gellulese Acetate Butyrate
${ }^{\boldsymbol{\Delta}}$ Cellaburate $\mathbf{\Delta N F 2 3}$

## Change to read:

## Sequestering Agent

Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)
${ }^{\mathbf{4}}$ Sodium Tartrate $\mathbf{\Delta N F 2 3}$

## Change to read:

## Solvent

Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol
Eapryloeaproyl Macrogelglyeerides
-Caprylocaproyl Polyoxylglycerides ${ }_{\text {■1S (NF23) }}$
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
■Lauroyl Macrogolglycerides $_{\mathbf{■}_{1 S} \text { (NF23) }}$
Lineoyl Macrogolglyeerides
-Lineoyl Polyoxylglycerides $_{\text {■1S (NF23) }}$
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Oleoyl Macrogelglyeerides
■Oleoyl Polyoxylglycerides $_{\mathbf{■}_{1 S}(\text { NF23 }}$
Peanut Oil

- Polydecene $\mathbf{1 1 S ~ ( N F 2 3 ) ~}^{\text {(2ly }}$

Polyethylene Glycol

Propylene Glycol
Sesame Oil
Stearoyl Macrogelghyerides
-Stearoyl Polyoxylglycerides $\mathbf{■ 1 S}_{1 \text { (NF23) }}$

Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

## Change to read:

Sorbent
Cellulose, Powdered
Charcoal,

- Activated ${ }_{\text {■2S }}{ }_{(N F 23)}$

Siliceous Earth, Purified

## Change to read:

Suspending and/or Viscosity-increasing Agent Acacia
Agar
-Alamic Acid ${ }_{\text {■ } 2 \text { S (NF23) }}$
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
${ }^{\text {- Carbomer Homopolymer }}{ }_{\text {1S (NF23) }}$
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium
${ }^{\text {■ Corn Syrup Solids }}{ }_{\text {■ }}$ (NF23)
Dextrin
Gelatin
Gellan Gum $_{\text {(1S (NF22) }}$
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose ${ }^{\mathbf{4}}$ (see Hypromellose) $\boldsymbol{\Delta N F 2 2}$
${ }^{\boldsymbol{4}}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) $\mathbf{\Delta N F 2 2}^{\text {N }}$
Magnesium Aluminum Silicate

- Maltodextrin $_{\text {■ } 2 S}$ (NF23)

Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate

- Starch, Corn ${ }_{\text {■ }}$ (NF23)
-Starch, $^{\text {Potato }}{ }_{\text {1S (NF23) }}$
${ }^{\boldsymbol{\Delta}}$ Starch, Tapioca $\mathbf{A N F 2 2}$
■Starch, Wheat.1S (NF23)
Tragacanth
Xanthan Gum

Change to read:
Sweetening Agent
${ }^{\boldsymbol{\Delta}}$ Acesulfame Potassium $\mathbf{\Delta N F 2 3}$
Aspartame
${ }^{\Delta}$ Aspartame Acesulfame $\mathbf{A N F 2 2}$
${ }^{\text {- Corn Syrup Solids }}{ }_{\text {■1S (NF23) }}$
Dextrates
Dextrose
Dextrose Excipient
Fructose
${ }^{\mathbf{\Delta}}$ Galactose $\mathbf{\Delta N F 2 3}$
${ }^{-}$Maltose $\mathbf{m}^{\text {2S }}$ (NF22)
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

- Tagatose $_{\text {■ } 2 \text { (USP28) }}$

Change to read:
Tablet Binder
Acacia
Alginic Acid
-Ammonio Methacrylate Copolymer ${ }_{\text {1S (NF23) }}$
-Ammonio Methacrylate Copolymer Dispersion $\mathbf{D S S}_{\text {(NF22) }}$
${ }^{\Delta}$ Carbomer Homopolymer ${ }_{\mathbf{A} N F 23}$
Carboxymethylcellulose, Sodium
Cellulose, Microcrystalline
${ }^{-}$Copovidone ${ }_{\text {■S (NF23) }}$

- Corn Syrup Solids ${ }_{\text {■ }}$ (NF23)

Dextrin
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
-Low-Substituted Hydroxypropyl Cellulose $_{\text {2S }}$ (NF23) $^{\text {( }}$
Hydroxypropyl Methylcellulose $^{\mathbf{4}}$ (see Hypromellose) ${ }_{\mathbf{\Delta N F 2 2}}$
${ }^{\wedge}$ Hypromellose (formerly Hydroxypropyl Methylcellulose) $\mathbf{\Delta N F 2 2 ~}^{\text {a }}$

- Hypromellose Acetate Succinate ${ }_{\text {1S (NF23) }}$
- Maltodextrin $\mathbf{■ S ~}^{\text {S }}$ (NF23)
- Maltose ${ }_{\text {2S }}$ (NF22)

Methylcellulose
Polyethylene Oxide
Povidone
${ }^{\boldsymbol{\Delta}}$ Starch, Corn $\boldsymbol{\Delta N F 2 3}$
${ }^{\mathbf{4}}$ Starch, Potato ${ }_{\mathbf{\Delta} N F 23}$
Starch, Pregelatinized
-Starch, Pregelatinized Modified ${ }_{\text {IS (NF23) }}$
${ }^{\Delta}$ Starch, Tapioca ${ }_{\mathbf{A N F 2 2}}$
${ }^{\boldsymbol{\Delta}}$ Starch, Wheat ${ }_{\Delta N F 23}$
Syrup

## Change to read:

Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered
${ }^{\text {- Corn Syrup Solids }}{ }_{\text {■1S (NF23) }}$
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose
-Lactose, Anhydrous $_{\mathbf{■}^{2 S} \text { (NF23) }}$
-Lactose Monohydrate $_{\text {■2S (NF23) }}$

- Maltodextrin $_{\text {■2S }}{ }^{\text {(NF23) }}$
${ }^{-}$Maltose $\mathbf{m}_{\text {2S }}{ }^{\text {(NF23) }}$
Mannitol
Sorbitol
Stareh
${ }^{\mathbf{\Delta}}$ Starch, Corn $_{\mathbf{\Delta N F 2 3}}$
${ }^{\Delta}$ Starch, Potato $\mathbf{A N F 2 3}$
Starch, Pregelatinized

${ }^{\boldsymbol{\Delta}}$ Starch, Tapioca ${ }_{\mathbf{A F F 2 2}}$
${ }_{\text {© }}$ Starch, Wheat $\boldsymbol{A N F 2 3}$
Sucrose
Sugar, Compressible
Sugar, Confectioner's

| Change to read: |
| :---: |
| Tablet Disintegrant |
| Alginic Acid |
| Cellulose, Microcrystalline |
| Croscarmellose Sodium |
| Crospovidone |
| -Low-Substituted Hydroxypropyl Cellulose $_{\text {■ } 2 \text { S (NF23) }}$ <br> - Maltose $_{\text {. } 2 \mathrm{~S}}$ (NF22) |
| Polacrilin Potassium |
| Sodium Starch Glycolate |
| Starel |
| ${ }^{\mathbf{\Delta}}$ Starch, Corn ${ }_{\mathbf{\Delta N F} 23}$ |
| ${ }^{\mathbf{4}}$ Starch, Potato ${ }_{\mathbf{a} N F 23}$ |
| Starch, Pregelatinized |
| -Starch, Pregelatinized Modified ${ }_{\text {1S (NF23) }}$ <br> ${ }^{\boldsymbol{\Delta}}$ Starch, Tapioca ${ }_{\mathbf{\Delta F 2 2}}$ |
|  |  |
|  |
| Change to read: |
| Tablet and/or Capsule Lubricant Calcium Stearate Glyceryl Behenate Magnesium Stearate Mineral Oil, Light Polyethylene Glycol |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |
|  |
|  |
|  |
|  |
|  |
| - Polysorbate $40{ }_{\text {■ } 2 \text { S (NF23) }}$ |
| - Polysorbate 60■2S (NF23) |
| - Polysorbate $80{ }_{\text {■ } 2 \text { S (NF23) }}$ |
| -Sodium Lauryl Sulfate ${ }_{\text {■ } 2 S}$ (NF23) |
| Sodium Stearyl Fumarate |
| -Sorbitan Monolaurate ${ }_{\text {■ } 2 \text { S (NF23) }}$ |
| -Sorbitan Monooleate ${ }_{\text {■ }}{ }^{\text {S }}$ (NF23) |
| -Sorbitan Monopalmitate ${ }_{\text {■2S }}{ }^{\text {(NF23) }}$ |
| -Sorbitan Monostearate ${ }_{\text {п2S }}$ (NF23) |
| - Sorbitan Sesquioleate ${ }_{\text {■2S }}{ }^{\text {(NF23) }}$ |
| -Sorbitan Trioleate ${ }_{\text {■ } 2 \text { S (NF23) }}$ |

## Change to read:

Tablet Disintegrant
Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone
-Low-Substituted Hydroxypropyl Cellulose $\boldsymbol{■}^{\text {2S (NF23) }}$
${ }^{-}$Maltose ${ }_{\text {2S (NF22) }}$
Sodium Starch Glycolate
Stareh
${ }^{\mathbf{\Delta}}$ Starch, $\operatorname{Corn}_{\mathbf{\Delta N F 2 3}}$
${ }^{\Delta}$ Starch, Potato $\mathbf{A N F 2 3}^{\text {N }}$
Starch, Pregelatinized
■Starch, Pregelatinized Modified $_{\text {■S (NF23) }}$
${ }^{\boldsymbol{4}}$ Starch, Tapioca ${ }_{\mathbf{\Lambda F F 2 2}}$
${ }^{\Delta}$ Starch, Wheat ${ }_{\Delta N F 23}$

## Change to read:

Tablet and/or Capsule Lubricant
Calcium Stearate
Glyceryl Behenate
Magnesium Stearate
Mineral Oil, Light

- Polyoxyl 10 Oleyl Ether ${ }_{\text {. }}{ }^{\text {S }}$ (NF23)
-Polyoxyl 20 Cetostearyl Ether ${ }_{\text {■2S }}{ }^{\text {(NF23) }}$
-Polyoxyl 35 Castor Oil ${ }_{\text {2S (NF23) }}$
-Polyoxyl 40 Hydrogenated Castor Oil $\mathbf{m}_{\text {2S (NF23) }}$
-Polysorbate 20■2S (NF23)
- Polysorbate $40_{\text {■2S (NF23) }}$
-Polysorbate 60【2S (NF23)
-Polysorbate $8 \mathbf{m}_{\text {■ } 2 \text { S (NF23) }}$
■Sodium Lauryl Sulfate $_{\text {■2S (NF23) }}$
Sodium Stearyl Fumarate
-Sorbitan Monolaurate $\boldsymbol{■}_{\text {2S (NF23) }}$
-Sorbitan Monooleate ${ }_{\text {■2S (NF23) }}$
-Sorbitan Monopalmitate $\boldsymbol{m}_{\text {2S (NF23) }}$
■Sorbitan Monostearate ${ }_{\text {■2S (NF23) }}$
- Sorbitan Sesquioleate ${ }_{\text {■2S (NF23) }}$
-Sorbitan Trioleate $_{\boldsymbol{■}}{ }^{\text {S }}{ }^{\text {(NF23) }}$


## Stearic Acid

Stearic Acid, Purified
Talc
Vegetable Oil, Hydrogenated, Type I
Zinc Stearate

## Change to read:

## Tonicity Agent

${ }^{\text {■ Corn Syrup Solids }}{ }_{\text {■ }}$ (NF23)
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

## Change to read:

## Vehicle

FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound
${ }^{-}$Corn Syrup Solids ${ }_{\text {■ }}{ }^{\text {S (NF23) }}$

- Dextrose $\boldsymbol{m}_{\text {2S }}$ (NF23)

Peppermint Water
Sorbitol Solution
Syrup
OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
-Polydecene ${ }_{\text {■ }}^{1 S}$ (NF23)
Safflower Oil
Sesame Oil
Soybean Oil
Squalane
SOLID CARRIER Sugar Spheres
STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

## Change to read:

Wetting and/or Solubilizing Agent
Benzalkonium Chloride
Benzethonium Chloride
Cetylpyridinium Chloride

Docusate Sodium
Nonoxynol 9
Octoxynol 9
Poloxamer
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 40 Stearate
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Sodium Lauryl Sulfate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
-Sorbitan $^{\text {Sesquioleate }}{ }_{\text {■2S (NF23) }}$
■Sorbitan Trioleate $_{\text {■2S (NF23) }}$
Tyloxapol

## DIETARY SUPPLEMENTS MONOGRAPHS

## BRIEFING

Chondroitin Sulfate Sodium, USP 27 page 1980, page 3093 of the First Supplement, and page 197 of PF 30(1) [Jan.-Feb. 2004]. It is proposed to modify the language of the Labeling section. See also briefing under Chondroitin Sulfate Sodium Tablets.
(DSB: G. Giancaspro) RTS-41084-3

## Change to read:

Labeling-Label it to indieate the species of the source from whieh the aticle was derived.
-Label it to state the source(s) from which the article was derived, whether bovine, porcine, avian, or a mixture of any of them. $\boldsymbol{m}_{2 S}$ (USP28)

## Delete the following:

## ${ }^{\Delta}$ Test for absence of elostriditht-species-

Fest Preparation-Provide separate-10 s specimens for each of the tests alled for below. Dissolve Chendroitin-Sulfate Sodimm in pH 7.2Phosphate buffer. [NOTE-On the basis of results for Pre patratyry Testing, modify the Test Preparation as appropriate.]

Preparatyry Testing Ineubate Clostriditm spargenes (ATCC No. 11437) for 18 to 24 hours, and then dilute with $p H 7.2$ Phor phate Buffer. Ineeulate the Test Preparation, to obtain a finalcen eentration of less than 100 -fur per mL . Controls containing the inoculum but without the material under test are prepared at the same time. Proceed as directed under Procedure, making sure to evaluate the growth after each time a medimm is added.

Resulto Proeed as direeted for Preparatyy Testing under Mi erobial Limit Tests Dietay Supplements $\langle 2024\rangle$ -

## REINFORCED-MEDHM-FOR-CLOSTPIDIA

| Beef Extract | 10.0-8 |
| :---: | :---: |
| Peptone | 10.089 |
| Yeast Extract | 3.0-9 |
| Soluble-Stareh | 1.0-9 |
| Glueose-Menehy drate- | 5.08 |
| Eysteine-Hydrochloride- | 0.5-9 |
| Sodium-Chloride | 5.0 - |
| Soditm Acetate | 3.0 g |
| Agar | $0.5-8$ |
| Whater | 1000 mL |

Pissolve agar in water by heating to beiling, while stiming con tinmously. Adjust the pH if neeessary, and sterilize.
pH after sterilization: $6.8 \pm 0.2$.

## GOLUMBIA AGAR

| Pancreatic Digest of Casein | $10.0{ }^{-8}$ |
| :---: | :---: |
| Meat Peptic digest | 5.08 |
| Heart Pancreatic digest | 3.08 |
| Yeast Extract | 5.0 g |
| Gorn-Stareh | 1.085 |
| Sodium-Chloride | 5.08 |
| Agat | $15.0{ }^{\text {¢ }}$ |
| Water | 00 mL |

Pissolve agar in water by heating to beiling with entinteus stir ring. If neeessary, adjust the pH . Sterilize, and allow to eool to-45 $5-50^{\circ}$. Add gentamicin sulfate, equivalent about 20 mg of gen tamiein base, and pour into Petri dishes.
pH after sterilization: $7.3 \pm 0.2$.
Procedure Take equal pertions of the Test Preparation, heat one to $80^{\circ}$ for 10 minntes, and cool rapidly. Transfer 10 mL of each pertion to separate containers, each containing each 100 mL of Reinforeed Mediun for Clostridith, and ineubate under an aerobie conditions at $35^{\circ}$ to $37^{\circ}$ for 48 hours. After incubation subeulture each specimen-on-Columbich Medinn to which gentamicin has been added, and incubate under anaerobic conditions at $35^{\circ}$ to $37^{\circ}$ for 48 hours. Examine the plates, and interpret as follows: if no growth of Gram positive rods is detected, the test specimen meets the requirement for the absence of Clostridium species.

If growth oeeurs, subeulture each distinet colony on Columbiat Agar Medium, and separately ineubate in aerobie and in anaerebie eonditions at $35^{\circ}$ to $37^{\circ}$ for 48 hours. The oceurrence of only ant aerobic growth of Gram positive bacilli, giving a negative catalase reaction, indientes the presence of Clastridium sparegenes species. To perform the catalase test, transfer diseretecolonies to glass slides, and apply a drop of dilute hydrogen peroxide-solution:
the reaction is negative if no gas bubbles evolve. If the test speci men exhibits nene of these characteristics, it meets the requirement for the absence of Clostridinm-species. $\triangle$ USP28

## Change to read:

Electrophoretic purity (see Electrophoresis $\langle 726\rangle$ )+M
${ }^{\mathbf{\Delta}} 0.1 M_{\Delta U S P 28}$
Barium acetate buffer, pH 5.0-Dissolve about 225.43 - E
$\Delta_{25.24}^{\mathrm{g}_{\mathbf{\Delta S P} 28}}$
of barium acetate in water, and dilute with water to 900 mL . Adjust with acetic acid to a pH of 5.0 , dilute with water to 1 L , and mix. Q. 4 M Bainm barimm acetate in water, and dilute with water to 900 mL . Adjust with acetic acid to pH H of 5.0 , dilute with water to 1 liter, and mix.
${ }_{\text {StuSP28 }}$ -
Staining reagent: $0.08 \%$ aztre $A$ solution.
${ }^{\Delta} 0.1 \%$ toluidine blue in acetic acid; dissolve 1 g of toluidine
blue in 1000 mL of 0.1 M acetic acid. $\Delta$ USP28
Standard solution 1-Prepare a solution of USP Chondroitin Sulfate Sodium RS in water having a known concentration of about 3 mg per mL.
${ }^{\mathbf{\Delta}} 30 \mathrm{mg}$ per $\mathrm{mL} . \mathbf{\Delta U S P 2 8}$
Standard solution 2-Dilute 1 mL of Standard solution 1 with water to 100 mL ,
© 50 mL , $\triangle$ USP28
and mix.
Stadad solution 3- Prepare a solution eontaining 1.0 gof phenol red TS in 100 mL water.
${ }^{\Delta}$ AUSP28
Test solution-Transfer 150 mg of Chondroitin Sulfate Sodium, accurately weighed, to a 50 mL
${ }^{\Delta} 5.0-\mathrm{mL}_{\mathbf{4}}{ }^{\text {USP28 }}$
volumetric flask, dissolve in and dilute with water to volume, and mix.

Procedure-Adhere a cellephane-shee the of a cooling plate of the electrophoretic equipment by means of some water dreps. Remove any air bubbles. Soak a eut $6 \times 12 \mathrm{~cm}$ cellulose nitrate gel having a $0.45 \mathrm{\mu m}$ porosity in 0.4 M Barium acelat buf fer, pH 5.0 for 5 minutes, and remove any excess solution between the filter paper and the cellulose strip. Apply $10 \mu \mathrm{\mu}$ each of Stan dated solution 1, Standard solution 2, Standard solution 3, and the Fest solution as bands to the gel near the athode. [NOTE-Back the eellophane sheet with a plastic shee for protection to prevent the gel from breaking; otherwise use a supported nitrocellulose membrane, and place it on top-of the eellophane-sheet.] Attach the strip to the support bridge of an electrophoresis chamber con taining 1 M Batiun etate buffer, pHI. 5.0 in each side of the eham ber. Ensure that each end of the strip is in contact with $1 M$ Bariumt teete buffer, pH 5.0. Conneet the electrodes, clese the cover, start the water circulation for gel cooling until the temperature of the plate is about $10^{\circ}$, and apply a 20 mA current at about 330 V for 1 hour. Switeh off the eutrient, disconneet the electrodes, remove the plastic sheet, and immerse the gel in the Staining reagent for 10 minutes. Wash with water to remove any unbound Staining re agent, and compare the bands: the electropherogramobtained from the Test solution exhibits a major band that is similar in pesition to the band obtained from Standard solution 1. The band obtained from Standurd solution - 3 remains red ( $\mathrm{p} H$ buffering eapacity), and the band correspending to Standed solution 2 is clearly visible
at a mobility similar to the band obtained from Standard solution 1. Any secendary band in the electropherogram of the Test solution is not more intense than the band obtained from Standerd solution -2. Net mere than $1 \%$ of any individual impurity is found.
${ }^{\Delta}$ Fill the chambers of an electrophoresis apparatus suitable for separations on cellulose acetate membranes ${ }^{1}$ (a small submarine gel chamber or one dedicated to membrane media) with 0.1 M Barium acetate buffer, pH 5.0. Soak a cellulose acetate membrane about 5 to $6 \mathrm{~cm} \times 12$ to 14 cm in 0.1 M Barium acetate buffer, pH 5.0 for 10 minutes, or until evenly wetted, then blot dry between two sheets of absorbent paper. Using an applicator ${ }^{2}$ suitable for electrophoresis, apply equal volumes (about $0.5 \mu \mathrm{~L}$ ) of the Test solution, Standard solution 1, and Standard solution 2 to the brighter side of the membrane, held in position in an appropriate applicator stand or on a separating bridge in the chamber. Ensure that both ends of the membrane are dipped at least 0.5 to 1.0 cm deep into the buffer chambers. Apply a constant 60 V (about 6 mA at the start) for 2 hours. [NOTE-Perform the application of solutions and voltage within 5 minutes, because further drying of the blotted paper reduces sensitivity.] Place the membrane in a plastic staining tray, and with the application side down, float or gently immerse in Staining reagent for 5 minutes. Then stir the solution gently for 1 minute. Remove the membrane, and destain in $5 \%$ acetic acid until the background clears. Compare the bands. The electropherogram obtained from the Test solution exhibits a major band that is identical in position to the band obtained from Standard solution 1. The band obtained from Standard solution 2 is clearly visible at a mobility similar to the band obtained from Standard solution 1. Any secondary band in the electropherogram of the Test solution is not

[^344]more intense than the band obtained from Standard solution 2. Not more than $2 \%$ of any individual impurity is found. Document the results by taking a picture within 15 minutes of completion of destaining. $\triangle$ USP28

## Change to read:

## Limit of protein-

${ }^{\wedge}$ Alkaline cupric tartaric reagent-Dissolve 200 mg of sodium tartrate dihydrate in 10 mL of water, and mark as Solution A. Dissolve 100 mg of cupric sulfate in 10 mL of water, and mark as $S o$ lution $B$. Dissolve 2.0 g of anhydrous sodium carbonate in 0.1 M sodium hydroxide, dilute with 0.1 M sodium hydroxide to 100 mL , and mark as Solution C. Mix well 1 mL of Solution $A$ and 1 mL of Solution B, and to the mixture slowly add 100 mL of Solution $C$ with stirring. Use within 24 hours, and discard afterwards. $\Delta$ USP27

Standard solution-Transfer an accurately measured volume of 7 percent bovine serum albumin certified standard to a suitable container, and dilute quantitatively and stepwise with water to obtain a solution having a known concentration of about $35 \mu \mathrm{~g}$ per mL .

Test solution-Transfer an accurately weighed amount of Chondroitin Sulfate Sodium, equivalent to 60 mg of the dried substance, to a $100-\mathrm{mL}$ volumetric flask, dissolve in and dilute with water to volume, and mix.

Procedure—Add 2.0 mL of freshly prepared ${ }^{\mathbf{\Delta}}$ Alkaline cupric tartaric reagent ${ }_{\Delta S P 27}$ to test tubes containing 2.0 mL of water, 2.0 mL of the Test solution, or 2.0 mL of the Standard solution, and mix. After about 10 minutes, add 1.0 mL of Folin-Ciocalteu phenol TS,
${ }^{\boldsymbol{\Delta}}$ diluted with water (1:5) and $\boldsymbol{\Delta U S P 2 8}$ prepared immediately before use, to each test tube, and mix
©immediately and vigorously. $\quad$ USP28
After 30 minutes, measure the absorbance of each solution at 750 nm against the blank. The absorbance of the Test solution is not greater than the absorbance of the Standard solution: not more than $6.0 \%$ of proteins is found, calculated on the dried basis.

## Change to read:

## Content of ${ }^{\boldsymbol{\Delta}}$ chondroitin sulfate sodium-_USP27

Cetylpyridinium chloride solution - Prepare a solution of cetylpyridinium chloride in water having a concentration of about 1 mg per mL.
${ }^{\Delta}$ Degas before use.
Diluent-Weigh about 297 mg of monobasic potassium phosphate, 492 mg of dibasic potassium phosphate, and 250 mg of polysorbate 80 , and transfer into a $1-\mathrm{L}$ beaker. Dissolve in 1000 mL of water, and adjust with potassium hydroxide or phosphoric acid to a pH of $7.0 \pm 0.2$. USSP28.
Standard solutions - Transfer about 30 mg of USP Chondroitin Sulfate Sodium RS, aceurately weighed, to a $25-\mathrm{mL}$ volumetric flask. Dissolve in 6 mL of water, add 1 mL of pH 7.2 phesphate buffer solution (see Buffer Solutions under Solutions in the section Reagents, Indicatoris, and Solutions),
${ }^{\text {A Prepare a solution having a known concentration of USP }}$
Chondroitin Sulfate Sodium RS in water, $\mathbf{\Delta S S P 2 8}$
and dilute with water, quantitatively and stepwise if necessary, to obtain three Standard solutions having known concentrations of about 1.2 mg per mL, 0.8 mg per mL, and 0.4 mg per mL, respec tively.
${ }^{\boldsymbol{\Delta}} 1.5 \mathrm{mg}$ per $\mathrm{mL}, 1.0 \mathrm{mg}$ per mL , and 0.5 mg per mL , respectively. $\mathbf{U S S P 2 8}$

Test solution-Transfer about 100 mg of dried Chondroitin Sulfate Sodium, accurately weighed, to a $100-\mathrm{mL}$ volumetric flask, dissolve in 30 mL of water, 5 mL of $\mathrm{p} H .7 .2$ pherfer selution (see Buffer Solutions under Solutions in the seetion Retgents, Indicator's, and Solutions),
${ }^{\Delta}$ AUSP28
dilute with water to volume, and mix.
Procedure-Transfer 5.0 mL of each Standard solution and the Test solution to four separate titration vessels, and add about 30 mL of water. Stir until a steady reading is obtained using a photerode to determine the endpeint turbidimetrically, either at $420 \mathrm{~nm}, 550$ nm , or 660 mm . Set the instrument to zere if absorbance is being menitered or not less than 70\% if transmittance is used. Titrate with Cetylpyridinium chloride solution. Frem a linear regression equation caleulated using the volumes of Cetylpyridinium chloride selution consumed, and the mass, in mor, of USP Chendroitin-Sut fate-Sodium- RS ,

ムand add about 25 mL of Diluent. Use a phototrode to determine the endpoint turbidimetrically, at $420 \mathrm{~nm}, 550 \mathrm{~nm}$, or 660 nm . Stir until a steady reading is obtained. Set the instrument to zero in absorbance mode. Titrate with Cetylpyridinium chloride solution. From a linear regression equation derived from the volumes of Cetylpyridinium chloride solution consumed, and the masses, in mg, of USP Chondroitin Sulfate Sodium RS in the aliquots of the respective

## Standard solutions, $\mathbf{A}$ USP28

determine the mass of ${ }_{\triangle U S P 27}$ chondroitin sulfate sodium in the aliquot of the Test solution taken. Calculate the percentage of ${ }^{\boldsymbol{\Delta}}{ }^{\text {USP27 }}$ chondroitin sulfate sodium in the portion ${ }^{\boldsymbol{\Delta}}{ }_{\text {USSP27 }}$ taken by the formula:

$$
2000(M / W),
$$

in which $M$ is the mass of ${ }^{\boldsymbol{\Delta}}$ Chondroitin Sulfate Sodium $\mathbf{\Delta U S P 2 7 ~}$
${ }^{4}$ found ${ }_{\triangle U S P 28}$
in the aliquot of the Test solution; and $W$ is the weight, in mg , of Chondroitin Sulfate Sodium taken to prepare the Test solution.

## Briefing

Chondroitin Sulfate Sodium Tablets, USP 27 page 1982, page 3093 of the First Supplement, and page 200 of PF 30(1) [Jan.-Feb. 2004]. The current label requires declaration of the species used to prepare the chondroitin sulfate sodium. The monograph allows preparation from bovine, avian, and porcine cartilages. A request to remove species declaration, based on the lack of validated tests to determine the origin, was received at USP. After consideration of the request, the committee decided to retain the declaration of the sources in the labeling section of the monograph with minor clarifying language. The current official monograph for Chondroitin Sulfate Sodium Tablets directs that the label state the content of chondroitin sulfate sodium on the dried basis, but also allows the label to state the content on the hydrous basis. Because prominence could be given to either the dried weight or the hydrous weight, leading to consumer confusion, it is proposed to modify the labeling statement by requiring declaration of the dried content on the front panel of the labels.
(DSB: G. Giancaspro) RTS-41084-1

## Change to read:

Labeling-Label it to indicate the species of the source from which the chondroitin used to prepare the Tablets was derived. PThe label states the content of chondroitin sulfate sodium on the dried basis; the correspending content of chondroitin-sulfate sodium on the hydrous basis may atso be-stated. .nys (fopen)
-Label it to state the source(s) of chondroitin sulfate sodium, whether bovine, porcine, avian, or a mixture of any of them. The label states on the front panel the content of chondroitin sulfate sodium on the dried basis. $\quad$ 2S (USP28)

## Change to read:

Identification-
+M
${ }^{\mathbf{\Delta}} 0.1 M_{\Delta U S P 28}$
Barium acetate buffer, pH 5.0; 9.4M Bater, pH 5.0;

4 4 USP28
Staining reagent; and Procedure-Proceed as directed in Electrophoretic purity under Chondroitin Sulfate Sodium.

Standard solution-Use the Standard solution of middle concentration in the test for Content of chondroitin sulfate sodium.

Test solution-Prepare as directed in the test for Content of chondroitin sulfate sodium. The principal spot obtained from the Test solution has the same migration as the principal spot obtained from the Standard solution.

## Change to read:

Disintegration and dissolution $\langle 2040\rangle$ : meet the requirements for Dissolution.

Medium: water; 900 mL .
Apparatus 2: 75 rpm .
Time: 60 minutes.
Cetylpyridinium chloride solution, stand solution,
${ }^{\Delta}$ Standard solutions, $\mathbf{\Delta U S P 2 8}$
and Test solution-Prepare as directed in the test for Content of chondroitin sulfate sodium
©under Chondroitin Sulfate Sodium. $\Delta$ USP28
Procedure-Proceed as directed in the test for Content of chondroitin sulfate sodium, adjusting the volume of the aliquot
${ }^{\Delta}$ and the concentrations of the Standard solutions, $\triangle$ USP28
if necessary. Calculate the quantity, in mg , of chondroitin sulfate sodium dissolved in the pertion-of Tablets taken
© $\Delta$ USP28
by the formula:

## $900 C$,

in which $C$ is the concentration, in mg per mL , of chondroitin sulfate sodium in the solution under test.

Tolerances-Not less than $75 \%$ of the labeled amount of chondroitin sulfate sodium is dissolved in 60 minutes.

## Change to read:

## Content of chondroitin sulfate sodium-

Cetylpyridinium chloride solution-Prepare a solution of cetylpyridinium chloride in water having a concentration of about 1 mg per mL .
${ }^{\text {© }}$ Diluent—Weigh about 297 mg of monobasic potassium phosphate, 492 mg of dibasic potassium phosphate, and 250 mg of polysorbate 80 , and transfer into a 1-L beaker. Dissolve in approximately 900 mL of water, and adjust with potassium hydroxide or phosphoric acid to a pH of $7.0 \pm 0.2$.
Dilute with water to 1 L , and mix thoroughly. $\mathbf{\Delta U S P 2 8}$ Standard solutions-Prepare as directed in the test for Content of $\boldsymbol{\Delta}_{\text {chondroitin sulfate sodium }}^{\mathbf{\Delta U S P 2 7}}$ under Chondroitin Sulfate Sodium.

Test solution-Weigh and finely powder not fewer than $20 \mathrm{Tab}-$ lets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of chondroitin sulfate sodium, to a $100-\mathrm{mL}$ volumetric flask, add 30 mL of water and 5 mL of pH 7.2 phes phate buffer solution (see Buffer Solutions under Solutions in the section Reagents, Indicators, and Solutions),
${ }^{\Delta} 60 \mathrm{~mL}$ of water, $\mathbf{\Delta}$ USP28
and shake to suspend the powder in solution. Sonicate in a $65^{\circ}$ water bath for 20 minutes. Remove from the bath, stir with a magnetie stirrer
$\Delta^{\text {or shake }}{ }_{\mathbf{\Delta} U S P 28}$
for 5 minutes, dilute with water to volume, and centrifuge
${ }^{\Delta}$ or pass through a suitable filter. $\Delta U S P 28$

Procedure-Separately transfer 5.0 mL of each Standard solution and the Test solution to separate titration vessels, and add about 30 mL of water
$\Delta_{25} \mathrm{~mL}$ of Diluent $_{\mathbf{\Delta U S P 2 8}}$
to each. Stir until a steady reading is obtained, using a phototrode to determine the endpoint turbidimetrically, at 420,550 , or 660 nm . Set the instrument to zero if
$\mathbf{\Delta i n}_{\mathbf{\Delta U S P 2 8}}$
absorbance is being menitored or to not less than 70\% if transmit
tance is used.
$\Delta_{\text {mode. }}$ USP28
From a linear regression equation calculated using the volumes of Cetylpyridinium chloride solution consumed and the mass, in mg , of USP Chondroitin Sulfate Sodium RS, determine the mass of chondroitin sulfate sodium in the aliquot of the Test solution taken. Calculate the amount, in mg , of chondroitin sulfate sodium in the portion of Tablets taken by the formula:

## 20M,

in which $M$ is the mass of Chondroitin Sulfate Sodium in the aliquot of the Test solution.

## BRIEFING

Glucosamine and Chondroitin Sulfate Sodium Tablets, USP 27 page 2012, page 3093 of the First Supplement, and page 201 of PF 30(1) [Jan.-Feb. 2004]-See briefing under Chondroitin Sulfate Sodium Tablets.
(DSB: G. Giancaspro) RTS-41084-2

## Change to read:

Labeling-The label indicates the types of glucosamine salts contained in the article and the species source from which chondroitin was derived. ${ }^{\text {P/ The label states the content of chendreitin sulfate }}$ sodirm on the dried basis; the correspending content of chondro-itim-sulfate sodium on the hydrous basis may also be

-Label it to state the source(s) of chondroitin sulfate sodium, whether bovine, porcine, avian, or a mixture of any of them. The label states on the front panel the content of chondroitin sulfate sodium on the dried basis. $\boldsymbol{m}^{2 S}$ (USP28)

## Change to read:

Disintegration and dissolution $\langle 2040\rangle$ : meet the requirements for Dissolution.

Medium: water; 900 mL .
Apparatus 2: 75 rpm .
Time: 60 minutes.
Determine the amount of $\mathrm{C}_{6} \mathrm{H}_{13} \mathrm{NO}_{5}$ dissolved by employing the following method.

Diluent, 0.2 M Borate buffer, Derivatizing reagent, Mobile phase, and Chromatographic system-Proceed as directed in the test for Content of glucosamine.

Standard solution-Prepare as directed in the test for Content of glucosamine. Dilute with a suitable quantity of water, if necessary. Test solution-Use the solution under test.
Procedure-Proceed as directed in the test for Content of glucosamine. Calculate the quantity, in mg , of $\mathrm{C}_{6} \mathrm{H}_{13} \mathrm{NO}_{5}$ dissolved by the formula:

$$
(179.17 / 215.63)(900 C)\left(r_{U} / r_{S}\right)
$$

in which the terms are as defined therein.
Tolerances-Not less than 75\% of the labeled amount of $\mathrm{C}_{6} \mathrm{H}_{13} \mathrm{NO}_{5}$ is dissolved in 60 minutes.

Determine the amount of chondroitin sulfate $\boldsymbol{\Delta}_{\text {Sodium }}^{\Delta U S P 27}{ }^{\text {dis- }}$ solved by employing the following method.

Cetylpyridinium chloride solution, Stan Test soltion
${ }^{\boldsymbol{\Delta}}$ Diluent, Standard solutions, and Test solution $\quad$ USP28
-Prepare as directed in the test for Content of chondroitin sulfate sodium
©under Chondroitin Sulfate Sodium Tablets. $\triangle$ USP28
Procedure-Proceed as directed in the test for Content of chondroitin sulfate sodium
©under Chondroitin Sulfate Sodium Tablets, $\mathbf{\Delta S P 2 8}$ adjusting the volume of the sample
${ }^{\Delta}$ or the concentrations of the standards, $\triangle$ USP28
if necessary. Calculate the quantity, in mg , of chondroitin sulfate sodium dissolved by the formula:

$$
900 C
$$

in which $C$ is the concentration, in mg per mL , of chondroitin sulfate sodium in the solution under test.

Tolerances-Not less than $75 \%$ of the labeled amount of chondroitin sulfate sodium is dissolved in 60 minutes.

## Change to read:

Content of chondroitin sulfate sodium-
Cetylpyridinium chloride solution, Standard solution,
${ }^{\mathbf{\Delta}}$ Diluent, Standard solutions, $\mathbf{\Delta U S P 2 8}$
Test solution, and Procedure-Proceed as directed in the test for Content of chondroitin sulfate sodium under Chondroitin Sulfate
${ }^{\mathbf{4}}$ Sodium ${ }_{\mathbf{\Delta U S P} 27}$ Tablets.

BRIEFING

Lycopene, page 574 of PF 30(2) [Mar.-Apr. 2004]. The Expert Committee has received new data on the isomer ratio of this article. Therefore, it is proposed to change the limits for other related compounds calculated as lycopene in the test for Content of all-E-lycopene, 5Z-lycopene, and related compounds under Procedure.
(DSB: G. Giancaspro) $\quad$ RTS-41813-1

## Add the following:

## ■ Lycopene

$\mathrm{C}_{40} \mathrm{H}_{56} \quad 536.88 \quad[502-65-8]$.
» Lycopene is a mixture of geometrical isomers of lycopene. It contains not less than 96.0 percent and not more than 101.0 percent of lycopene $\left(\mathrm{C}_{40} \mathrm{H}_{56}\right)$, calculated on the dried basis.

Packaging and storage-Preserve in tight, light-resistant containers, under inert gas, and store in a cool place.

USP Reference standards $\langle 11\rangle$ —USP Lycopene RS.
Labeling-Label it to indicate whether the article is obtained from natural sources or is prepared synthetically. If obtained from natural sources, label it to indicate the natural source, including its Latin binomial.

## Identification-

A: Ultraviolet-Visible Absorption $\langle 197 \mathrm{U}\rangle-$
Spectral range: 300 to 700 nm .
Solution-Prepare as directed below for the Test solution in the test for Content of lycopene.

Ratio: $A_{476} / A_{508}$, between 1.10 and 1.14 .

B: The retention time of the major peak in the chromatogram of the Test solution corresponds to that in the chromatogram of the Standard solution, as obtained in the test for Content of all-E-lycopene, 5Z-lycopene, and related compounds.

Loss on drying $\langle 731\rangle$-Dry it in vacuum over phosphorus pentoxide at $40^{\circ}$ for 4 hours: it loses not more than $0.2 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.2 \%$.
Heavy metals, Method II $\langle 231\rangle$ : not more than $10 \mu \mathrm{~g}$ per g.

Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

## Content of all-E-lycopene, $5 Z$-lycopene, and related compounds- <br> Mobile phase-Prepare a filtered and degassed mixture of

 tert-butyl methyl ether, methanol, and tetrahydrofuran (784: $665: 74$ ). Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).Standard solution-Dissolve a suitable quantity of USP Lycopene RS in Mobile phase to obtain a solution containing about 2 mg per 100 mL .

Test solution-Transfer about 15 mg of Lycopene to a 25 mL volumetric flask, and dissolve in tetrahydrofuran containing 50 mg of butylated hydroxytoluene per L. Dilute with the same solvent to volume. Pipet 2 mL into a $50-$ mL volumetric flask, and add 8 mL tetrahydrofuran. Dilute with tert-butyl methyl ether to volume. Use this solution for injection.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $472-\mathrm{nm}$ detector, a $4.6-\mathrm{mm} \times 25-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing

L61, and a second column connected in series containing 3$\mu \mathrm{m}$ packing L61. The flow rate is about 1.0 mL per minute. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the relative retention times are about 1.07 for 5Z-lycopene, and 1.0 for all- $E-l y-$ copene; the resolution, $R$, between all- $E$-lycopene and $5 Z-$ lycopene is not less than 1.0; the tailing factor is not less than 0.8 and not more than 2.0 ; and the relative standard deviation for replicate injections for the all- $E$-lycopene is not more than $2.0 \%$. [NOTE-New columns may require up to 30 injections before the system suitability requirements are met.]

Procedure-Inject about $10 \mu \mathrm{~L}$ of the Test solution into the chromatograph, record the chromatogram, and measure the peak area responses. Calculate the percentage of related compounds in the portion of Lycopene taken by the formula:

$$
T\left(r_{s} / r_{T}\right)
$$

in which $T$ is the percentage of total lycopene isomers obtained in the test for Content of lycopene; $r_{s}$ is the sum of the responses of all peaks except the peak for all- $E$-lycopene and the peak for $5 Z$-lycopene; and $r_{T}$ is the total detected area. Not more than $7.0 \% 9.0 \%$ of other related compounds calculated as lycopene are found. Calculate the percentage of the $5 Z$-lycopene isomer in the portion of Lycopene taken by the formula:

$$
T\left(r_{s z} / r_{T}\right),
$$

in which $r_{s z}$ is the peak response for the 5Z-lycopene isomer, and the other terms are as described above. Not more than
$23.0 \%$ of the $5 Z$-lycopene isomer is found. Calculate the percentage of all- $E$-lycopene taken by the formula:

$$
T\left(r_{E} / r_{T}\right)
$$

in which $r_{E}$ is the peak response of the all- $E$-lycopene isomer, and the other terms are as described above. Not less than $70.0 \%$ of all- $E$-lycopene is found.

## Content of lycopene-

Test stock solution-Transfer about 25 mg of Lycopene to a $100-\mathrm{mL}$ volumetric flask, add about 25 mg of butylated hydroxytoluene and about 60 mL of methylene chloride, and sonicate to dissolve. Dilute with methylene chloride to volume.

Test solution-Transfer 2.0 mL of the Test stock solution to a $200-\mathrm{mL}$ volumetric flask, and dilute with cyclohexane to volume.

Procedure-Determine the absorbance of the Test solution at the wavelength of maximum absorbance at about 476 nm , using cyclohexane as the blank. Calculate the percentage of $\mathrm{C}_{40} \mathrm{H}_{56}$ in the portion of Lycopene taken by the formula:

$$
1000 \mathrm{~A} / 331 \mathrm{~W},
$$

in which $A$ is the absorbance of the Test solution; $W$ is the weight, in g , of Lycopene taken to prepare the Test stock solution; and 331 is the absorptivity of the pure lycopene in cyclohexane. $\quad$ 2S (USP28)

## Briefing

Lycopene Preparation, page 576 of PF 30(2) [Mar.-Apr. 2004]. The Expert Committee has received new data on the isomer ratio of this article. Therefore, it is proposed to change the limits for other related compounds calculated as lycopene and for the 5Z-lycopene isomer in the tests for Content of all-E-lycopene, 5Z-lycopene, and related compounds under Procedure. In addition, it is proposed to delete the test Residue on ignition and relax the limit for Water because the natures of different suitable carriers influence the results of these tests.
(DSB: G. Giancaspro) RTS-41813-2; 41198-2

## Add the following:

## ■Lycopene Preparation

» Lycopene Preparation is a combination of Lycopene with one or more inert substances and suitable antioxidants. It may be in a solid or oily liquid form. It contains not less than 95.0 percent and not more than 120 percent of the labeled amount of lycopene $\left(\mathrm{C}_{40} \mathrm{H}_{56}\right)$, calculated on the anhydrous basis.

Packaging and storage-Preserve in tight, light-resistant containers under inert gas. Store the oil preparations in a cool place and the solid preparations at controlled room temperature.

Labeling-Label it to state the name and content of added antioxidants and inert substances. Label it to indicate whether the article is prepared with lycopene from natural sources or with synthetic lycopene. If prepared with lycopene from natural sources, label it to indicate the natural source, including its Latin binomial.

USP Reference standards-USP Lycopene RS.
Identification, Ultraviolet-Visible Absorption $\langle 197 \mathrm{U}\rangle$ FOR OILY PREPARATIONS-

Spectral range: 300 to 700 nm .
Solution-Prepare as directed below for the Test solution in Content of lycopene (test for oily preparations).
Ratio: $A_{476} / A_{508}$ between 1.10 and 1.14 in cyclohexane. FOR SOLID PREPARATIONS-

Spectral range: 300 to 700 nm .
Solution-Prepare as directed below for the Test solution in Content of lycopene (test for solid preparations).

Ratio: $A_{472} / A_{504}$ between 1.09 and 1.13 in isopropyl alcohol.

Water, Method I $\langle 921\rangle$ : not more than $1.0 \% .8 .0 \%$.
Residue on ignition- $\langle 281$ ):- not more than $1.0 \%$.
Organic volatile impurities, Method IV $\langle 467\rangle$ : meets the requirements.

Solvent-Use dimethylformamide.
Content of all-E-lycopene, 5Z-lycopene, and related compounds-
Mobile phase, Standard solution, and Chromatographic system-Proceed as directed for Content of all-E-lycopene, 5Z-lycopene, and related compounds under Lycopene.

Test solution for oil preparations-Transfer a quantity of oil preparation, equivalent to about 15 mg of lycopene, to a $25-\mathrm{mL}$ volumetric flask, and dissolve in tetrahydrofuran containing 50 mg of butylated hydroxytoluene per L. Dilute with the same solvent to volume. Pipet 2 mL into a $50-\mathrm{mL}$ volumetric flask, and add 8 mL of tetrahydrofuran. Dilute with tert-butyl methyl ether to volume. Use this solution for injection.

Test solution for solid preparations-Transfer a quantity of solid preparation, equivalent to 5 mg of lycopene, into a $250-\mathrm{mL}$ volumetric flask, and add about 60 units of bacterial alkaline protease preparation or another suitable enzyme
and about 25 mg of butylated hydroxytoluene. Add 2.5 mL of water, place in an ultrasonic bath at $50^{\circ}$ for 10 minutes, and shake occasionally until the material is finely divided with no lumps. Add 5 mL of tetrahydrofuran and 40 mL of dehydrated alcohol, and place again for about 1 minute in the ultrasonic bath. Cool to room temperature, and dilute with tert-butyl methyl ether to volume. Shake vigorously. Allow the precipitate to settle, and filter the supernatant.

Procedure-Proceed as directed for Content of all-E-lycopene, 5Z-lycopene, and related compounds under Lycopene. Calculate the percentage of related compounds in the portion of Lycopene Preparation taken by the formula:

$$
r_{s} / r_{T}
$$

in which $r_{s}$ is the sum of the responses of all peaks except the peak for all-E-lycopene and the peak for 5Z-lycopene, and $r_{T}$ is the total detected area in the chromatogram: not more than $7.0 \% 14.0 \%$ of other related compounds calculated as lycopene is found. Calculate the percentage of 5Z-lycopene isomer in the portion of Lycopene Preparation taken by the formula:

$$
r_{5 z} / r_{T}
$$

in which $r_{5 z}$ is the peak response for the 5Z-lycopene isomer, and the other terms are as described above: not more than $23.0 \% 30.0 \% 23.0 \%$ of the $5 Z-$ lycopene isomer is found. Calculate the percentage of all- $E$-lycopene in the portion of Lycopene Preparation taken by the formula:

$$
r_{E} / r_{T}
$$

in which $r_{E}$ is the peak response of the all- $E$-lycopene isomer, and the other terms are as described above: not less than $70.0 \% 65.0 \%$ of all- $E$-lycopene is found.

## Content of lycopene-

## TEST FOR OILY PREPARATIONS-

Test stock solution-Transfer an accurately weighed quantity of Lycopene Preparation containing about 25 mg of lycopene to a $100-\mathrm{mL}$ volumetric flask, and add about 25 mg of butylated hydroxytoluene and about 60 mL of methylene chloride. Sonicate to dissolve, and dilute with methylene chloride to volume.

Test solution-Transfer 2.0 mL of the Test stock solution to a $200-\mathrm{mL}$ volumetric flask, and dilute with cyclohexane to volume.

Procedure-Determine the absorbance of the Test solution at the wavelength of maximum absorbance at about 476 nm , using cyclohexane as the blank. Calculate the percentage of lycopene in the portion of Lycopene Preparation taken by the formula:

$$
1000 \mathrm{~A} / 331 \mathrm{~W},
$$

in which $A$ is the absorbance of the Test solution; $W$ is the weight, in g , of the portion of Lycopene Preparation taken to prepare the Test stock solution; and 331 is the absorptivity of the pure lycopene in cyclohexane.

## TEST FOR SOLID PREPARATIONS-

Test stock solution-Transfer an accurately weighed quantity of Lycopene Preparation containing about 5 mg of lycopene into a $200-\mathrm{mL}$ volumetric flask. Add about 60 units of bacterial alkaline protease preparation or another suitable enzyme and about 25 mg of butylated hydroxytoluene. Add 2.5 mL of diluted ammonium hydroxide ( 2 in 100). Incubate in a water bath (about $40^{\circ}$ ) until the matrix has dissolved (about 1 to 2 minutes), while rotating the flask to avoid having material stick to the glass surface. Add 5 mL of tetrahydrofuran, and shake until no colored precipitate remains. Add another portion of 2 mL of tetrahydrofuran. Add 40 mL of dehydrated alcohol, and shake until the mixture is
homogeneous. Add 100 mL of diethyl ether, and shake vigorously. Dilute with diethyl ether to volume, shake vigorously, and allow to stand until the solid has settled.

Test solution-Transfer 2.0 mL of the supernatant from the Test stock solution to a $25-\mathrm{mL}$ volumetric flask, and dilute with isopropyl alcohol to volume.
Procedure-Determine the absorbance of the Test solution at the wavelength of maximum absorbance at about 472 nm , using isopropyl alcohol as the blank. Calculate the percentage of lycopene in the portion of Lycopene Preparation taken by the formula:

$$
250 \mathrm{~A} / 320 \mathrm{~W},
$$

in which $A$ is the absorbance of the Test solution; $W$ is the weight, in g , of the portion of Lycopene Preparation taken to prepare the Test stock solution; and 320 is the absorptivity of the pure lycopene in isopropyl alcohol.■2S (USP28)

Briefing

Psyllium Husk, USP 27 page 1602. The tests for Heavy extraneous matter and Light extraneous matter are being proposed for revision to eliminate the use of the solvent carbon tetrachloride, a highly toxic solvent that is banned from many laboratories. Silicates (sand) account for much of the Heavy extraneous matter that is also detected by the test for Acid-insoluble ash, another test in this monograph. Based on that fact, the deletion of the test for Heavy extraneous matter is proposed. In the test for Light extraneous matter, the use of the solvent mixture of carbon tetrachloride and dichloroethylene is replaced by the use of the less hazardous solvent trichloroethylene, which has a similar specific gravity of 1.45. In addition, it is proposed to revise the limit for Light extraneous matter to represent the quality of the commercially available material. Changes in the Definition reflect the standard names in Herbs of Commerce 2nd Ed.
(DSB: G. Giancaspro) RTS-41674-1

## Change to read:

» Psyllium Husk is the cleaned, dried seed coat (epidermis) separated by winnowing and thrashing from the seeds of Plantago ovata Ferskal

## -Forssk., ${ }^{\text {2S }}$ (USP28)

known in commerce as Blond Psyllium or Indian Psyllium or Ispaghula, or from Plantago psyllium Limé or from Plantago indie Limé (Plantago arenaria Waldstein et Kitaibel)
-Plantago arenaria Waldst. \& Kit. (Plantago psyllium L.) ${ }^{25}$ (uSP28)
known in commerce as Spanish or French Psyllium (Fam. Plantaginaceae), in whole or in powdered form.

## Change to read:

Light extraneous matter-[NOTE-Perform this test in a wellventilated hood.] Pransfer 15.0 g to 250 mL separator. Addabout 90 mL of a liquid mixture of carbon tetrachloride and ethylene diehleride (about 2:1), having a specific gravity of 1.45 . Shake for 30 seconds, and allow to settle for 30 seconds. Repent the shaking and settling twice more. Drain all the material and liguid exeept the flanting layer. Add 25 mL of the liquid mixture, stirearefully, allow to settle, and drain as before. Repeat the washing of the floating layer twiee more, but use only 10 mL of the liquid mixture each time. Transfer the washed floating layer to a tared beaker, heat on a steam bath until the odor of the liquid no longer persists, dry at $40^{\circ}$ for 3 hours, allow to cool in a desicentor, and weigh: the limit is $15 \%$
-Transfer 99 to 101 g of Psyllium Husk, weighed to 0.1 g accuracy, to a $1000-\mathrm{mL}$ tall-form beaker. Add about 800 mL of trichloroethylene, previously adjusted to a temperature of $24^{\circ}$ to $26^{\circ}$, and maintain this temperature throughout the test. Stir the husk for about 5 seconds, and allow it to settle while protecting the surface from drafts in the hood.

Remove the floating material with a spoon made of 50-mesh screen, and transfer the material to a piece of filter paper in a dish. Stir the husk mixture again, allow it to settle, remove the floating material again, and combine it with the material on the paper. Repeat this procedure until no more material appears on the surface. Dry the removed material with the paper in a hood and then in an oven at $40^{\circ}$ for 3 hours. Cool to room temperature. Weigh the filter paper with the mate-
rial. Brush the material off the paper, weigh the paper, and then calculate the percent of light extraneous matter: no more than $5 \%$ is found. ${ }^{2 S}$ (USP28)

## Delete the following:

퓰 Heayy extraneous matter [NOTE Perform this test in a-wellventilated heod. Transfer 10.0 g to a 250 mL separater. Add abeut 80 mL of carben tetrachloride, and-shake for 1 minate. Allow te stand for 5 minutes. Drain inte atared 1000 mL beaker the nommt eilagineus material that sinks to the bettom, taking care not to drain any of the floating material. Heat in a hot air oven, at atemperature net exceeding $90^{\circ}$, until the odor of the liquid no longer persists, allow to cool in a desiceator, and weigh: the limit is $1.1 \%$ - 2 (USP28)

## MONOGRAPHS (NF)

BRIEFING

Acetyltributyl Citrate, $N F 22$ page 2816; Acetyltriethyl Citrate, NF 22 page 2817; Tributyl Citrate, NF 22 page 2948; Triethyl Citrate, NF 22 page 2949. In response to comments received regarding the unavailability of the temperature programmable injector required for the Assay, it is proposed to replace the temperature programmable injector in the Assay with a split injection system.
(EMC: D. Bempong) RTS-41597-4

## Change to read:

## Assay-

System suitability solution-Prepare a solution in toluene containing about 30 mg each of USP Acetyltributyl Citrate RS and USP Tributyl Citrate RS per mL.

Assay preparation-Transfer about 300 mg of Acetyltributyl Citrate, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with toluene to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The gas chromatograph is equipped with an eolumn, temperattreprogrammable injector,

- ${ }^{\text {2S }}$ (NF23)
a flame-ionization detector maintained at about $275^{\circ}$,
-a split injection system with a split ratio of about $30: 1$, (п2S (NF23)
and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ column bonded with a $0.5-\mu \mathrm{m}$ layer of phase G42. The column temperature is programmed to be maintained at about $80^{\circ}$ for 0.5 minute, then to increase to about $220^{\circ}$ at a rate of $20^{\circ}$ per minute, and to hold at about $220^{\circ}$ for $10 \mathrm{~min}-$ utes. The injection port temperature is programme be

■ ${ }^{\text {²S }}$ (NF23)
maintained at about $85^{\circ}$. for 0.5 minute, then increase to about $225^{\circ}$ at a rate of $20^{\circ}$ per minute, and to hold at about $225^{\circ}$ for 10 mintutes.

- $\quad$ 2S (NF23)

Helium is used as the carrier gas at a flow rate of about 2.3 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for tributyl citrate and 1.0 for acetyltributyl citrate; the resolution, $R$, between tributyl citrate and acetyltributyl citrate is not less than 1.5; and the relative standard deviation for replicate injections is not more than $2.0 \%$ determined from both the tributyl citrate and acetyltributyl citrate peaks, based on area percent calculation.

Procedure-Inject $1 \mu \mathrm{~L}$ of the Assay preparation into the chromatograph, record the chromatogram, and measure all of the peak areas, excluding the solvent peak. Calculate the percentage of $\mathrm{C}_{20} \mathrm{H}_{34} \mathrm{O}_{8}$ in the portion of Acetyltributyl Citrate taken by the formula:

$$
100(A / B)
$$

in which $A$ is the acetyltributyl citrate peak area response; and $B$ is the sum of the area responses of all the peaks.

BRIEFING

Acetyltriethyl Citrate, NF 22 page 2817—See briefing under Acetyltributyl Citrate.
(EMC: D. Bempong) RTS-41597-3

## Change to read:

## Assay-

System suitability solution-Prepare a solution in toluene containing about 30 mg each of USP Acetyltriethyl Citrate RS and USP Triethyl Citrate RS per mL.

Assay preparation-Transfer about 300 mg of Acetyltriethyl Citrate, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with toluene to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The gas chromatograph is equipped with en columm, programmable injector,
$\square_{\text {■2S (NF23) }}$
a flame-ionization detector maintained at about $275^{\circ}$,
■a split injection system with a split ratio of about $30: 1$, п2S (NF23)
and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ column bonded with a $0.5-\mu \mathrm{m}$ layer of phase G42. The column temperature is programmed to be maintained at about $80^{\circ}$ for 0.5 minute, then to increase to about $220^{\circ}$ at a rate of $20^{\circ}$ per minute, and to hold at about $220^{\circ}$ for $10 \mathrm{~min}-$ utes. The injection port temperature is programme be

- n $_{\text {2S }}$ (NF23)
maintained at about $85^{\circ}$. for 0.5 mintte, then in increase to about $225^{\circ}$ at a rate of $20^{\circ}$ per mintte, and to hold at about $225^{\circ}$ for 10 minters.
- $\quad$ 2S (NF23)

Helium is used as the carrier gas at a flow rate of about 2.3 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for triethyl citrate and 1.0 for acetyltriethyl citrate; the resolution, $R$, between triethyl citrate and acetyltriethyl citrate is not less than 1.5; and the relative standard deviation for replicate injections is not more than $2.0 \%$ determined from both the triethyl citrate and acetyltriethyl citrate peaks, based on area percent calculation.
Procedure-Inject $1 \mu \mathrm{~L}$ of the Assay preparation into the chromatograph, record the chromatogram, and measure all of the peak areas, excluding the solvent peak. Calculate the percentage of $\mathrm{C}_{14} \mathrm{H}_{22} \mathrm{O}_{8}$ in the portion of Acetyltriethyl Citrate taken by the formula:

$$
100(A / B)
$$

in which $A$ is the acetyltriethyl citrate peak area response; and $B$ is the sum of the area responses of all the peaks.

Briefing

Hypromellose Acetate Succinate, page 976 of PF 30(3) [MayJune 2004]. It is proposed to revise the Definition to indicate that the content of methoxy, hydroxypropoxy, acetyl, and succinoyl groups are determined on the dried basis. It is also proposed to revise the Identification test to include germanium crystal ATR tip as an alternative to diamond crystals, and also remove a requirement to prepare duplicate samples in the test for Limit of free acetic and succinic acids.
(EMC: D. Bempong) RTS-41804-1

## Add the following:

## -Hypromellose Acetate Succinate

Hydroxypropyl methylcellulose acetate succinate.
Cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate.

Cellulose, 2-hydroxypropyl methyl ether, acetate succinate [71138-97-1].
» Hypromellose Acetate Succinate is a mixture of acetic acid and monosuccinic acid esters of hydroxypropyl methylcellulose. When dried at $105^{\circ}$ for 1 hour, it It contains not less than 12.0 percent and not more than 28.0 percent of methoxy groups $\left(-\mathrm{OCH}_{3}\right)$, not less than 4.0 percent and not more than 23.0 percent of hydroxypropoxy groups ( $-\mathrm{OCH}_{2} \mathrm{CHOHCH}_{3}$ ), not less than 2.0 percent and not more than 16.0 percent of acetyl groups $\left(-\mathrm{COCH}_{3}\right)$, and not less than 4.0 percent and not more than 28.0 percent of succinoyl groups ( $-\mathrm{COC}_{2} \mathrm{H}_{4} \mathrm{COOH}$ ), calculated on the dried basis.

Packaging and storage-Preserve in tight containers. Store at room temperature. Avoid excessive heat and freez ing. Protect from moisture. No storage requirements specified.

Labeling-Label it to indicate its nominal viscosity type.
USP Reference standards $\langle 11\rangle$ —USP Hypromellose Acetate Succinate RS.

Identification,-Infrated Absorption-(197K),on undried specimen. Infrared Absorption $\langle 197 \mathrm{~A}\rangle$ —Do not dry specimens. Use a Fourier transform infrared spectrometer fitted with a suitable accessory for single bounce attenuated total reflectance (see Spectrophotometry and Light-Scattering $\langle 851\rangle$ ) with a diamond or germanium crystal. Acquire a background single-beam spectrum with a clean diamond or germanium crystal sampling plate in place. Place the sample on the diamond or germanium crystal sampling sur-
face with a microspatula or equivalent. For best results, the sample should cover the crystal surface under the pressure point tip. Using the pressure device, apply pressure to the sample, making sure the sample remains centered under the pressure tip. Acquire a single-beam spectrum of the sample, and make the necessary corrections for the background. Release the pressure device, and clear it from the sample area. Wipe the sample off the crystal and pressure device tip, and rinse both with acetone. The IR spectrum so obtained exhibits maxima only at the same wavelengths as a similarly obtained spectrum of USP Hypromellose Acetate Succinate RS.

Viscosity $\langle 911\rangle$ -
Sodium hydroxide solution-Immediately before use, dissolve 4.3 g of sodium hydroxide in carbon dioxide-free water to make 1000 mL .

Procedure-To 2.00 g of Hypromellose Acetate Succinate, previously dried, add Sodium hydroxide solution to make 100.0 g , insert a stopper into the vessel, and dissolve by constant shaking for 30 minutes. Adjust the temperature of the solution to $20 \pm 0.1^{\circ}$, and determine the viscosity in a suitable viscosimeter, as directed for Procedure for Cellulose Derivatives under Viscosity $\langle 911\rangle$. Its viscosity is not less than $80 \%$ and not more than $120 \%$ of that stated on the label.

Loss on drying $\langle 731\rangle$ —Dry it at $105^{\circ}$ for 1 hour: it loses not more than $5.0 \%$ of its weight.

Residue on ignition $\langle 281\rangle$ : not more than $0.20 \%$, determined at $600 \pm 50^{\circ}$.

Heavy metals, Method II $\langle 231\rangle$ : $0.001 \%$.
Limit of free strecinic acid-Transfer about 1.5 g of Hypromellose Acetate Suceinate, previously dried at $105^{\circ}$ for 4 hour and acemately weighed, to a separator, dissolve in

50 mL of a mixture of dehydrated aleohel and diehloremethane $(3: 2, v / v)$, add 75 mL of water with shaking, and then add 50 mL of hexane and 1 g of sodium chloride.

Shake well, and separate the lower water layer. Extract the ergenic layer with 50 mL of water, and combine the washing and the water layer. Add 3-drops of phenolphthaleinTS, and titrate with 0.1 N soditm hydroxide VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N soditm hydroxide-is equivalent 10 5.904 mg of $\mathrm{C}_{4} \mathrm{H}_{6} \mathrm{O}_{4}$ : not mere than $1.0 \%$ is found.

## Limit of free acetic and succinic acids-

Phosphoric acid solution-Transfer 1.0 mL of 1.25 M phosphoric acid into a $50-\mathrm{mL}$ volumetric flask, and dilute with water to volume.
0.02 M Phosphate buffer-Dissolve 5.44 g of monobasic potassium phosphate in 2 L of water.

Diluent-Adjust 0.02 M Phosphate buffer with 1 N sodium hydroxide to a pH of 7.5 .

Acetic acid stock solution-Add approximately 20 mL of water to a stoppered, $100-\mathrm{mL}$ volumetric flask, place the flask on a balance, and tare. Transfer 2.0 mL of the glacial acetic acid to the flask, and record the weight of the acid added. Fill the flask with water to volume. Transfer 6.0 mL of this solution into a $100-\mathrm{mL}$ volumetric flask, and dilute with water to volume.

Succinic acid stock solution-Accurately weigh about 130 mg of succinic acid into a $100-\mathrm{mL}$ volumetric flask. Add about 50 mL of water, and swirl the contents until the succinic acid is fully dissolved. Fill the flask with water to volume.

Mobile phase-Adjust the 0.02 M Phosphate buffer to a pH of 2.8 by the dropwise addition of 6 M phosphoric acid. Filter through a $0.22-\mu \mathrm{m}$ nylon filter.

Standard solution-Transfer 4.0 mL of the Acetic acid stock solution into a $25-\mathrm{mL}$ volumetric flask. To the same flask, transfer 4.0 mL of the Succinic acid stock solution, dilute with Mobile phase to volume, and mix. Prepare this solution in duplicate.

Test solution-Accurately weigh about 102 mg of Hypromellose Acetate Succinate into a glass vial. Transfer 4.0 mL of Diluent to the vial, and stir the content for 2 hours. Then, transfer 4.0 mL of the Phosphoric acid solution to the same vial to bring the pH of the Test solution to 3 or less. Invert the vial several times to ensure complete mixing, centrifuge, and use the clear supernatant as the Test solution. Prepare this solution in duplieate.

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $215-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The column temperature is maintained between $20^{\circ}$ and $30^{\circ}$. The flow rate is about 1 mL per minute, and the run time is about 15 minutes. Chromatograph the first preparation of the Standard solution, and record the peak responses as directed for Procedure: the column efficiency, determined from the succinic acid peak, is not less than 8000 theoretical plates; the tailing factor of this peak is between 0.9 and 1.5; and the relative standard deviation for six replicate injections is not more than $2.0 \%$ for each peak. Chromatograph the second preparation of the Standard solution: the difference in peak areas between the two standard solutions for both acetic and succinic acid peaks does not exceed $2 \%$. [NOTE-After each run sequence, the column should be flushed first by $50 \%$ water and $50 \%$ acetonitrile for 60 minutes and then by $100 \%$ methanol for 60 minutes. The column should be stored in $100 \%$ methanol.]

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the
peak areas corresponding to acetic and succinic acids. Calculate the percentage of free acetic acid, $A_{\text {free }}$, in the portion of Hypromellose Acetate Succinate taken by the formula:

$$
0.0768\left(W_{A} / W\right)\left(r_{U A} / r_{S A}\right)
$$

in which $W_{A}$ is the weight of glacial acetic acid, in mg, used to prepare the Acetic acid stock solution; $W$ is the weight of Hypromellose Acetate Succinate, in mg, used to prepare the Test solution; and $r_{U A}$ and $r_{S A}$ are the peak responses for acetic acid obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of free succinic acid, $S_{\text {free }}$ in the Hypromellose Acetate Succinate taken by the formula:

$$
1.28\left(W_{s} / W\right)\left(r_{U S} / r_{s s}\right)
$$

in which $W_{S}$ is the weight of succinic acid, in mg, used to prepare the Succinic acid stock solution; $r_{U S}$ and $r_{s S}$ are the peak responses for succinic acid obtained from the Test solution and the Standard solution, respectively; and $W$ is as defined above: the sum of free acetic acid and free succinic acid found does not exceed $1.0 \%$.

## Content of acetyl and succinoyl groups-

Phosphoric acid solution, Acetic acid stock solution, Succinic acid stock solution, Mobile phase, Standard solution, and Chromatographic system-Proceed as directed in the test for Limit of free acetic and succinic acids.

Test solution-Accurately weigh about 12.4 mg of Hypromellose Acetate Succinate into a glass vial. Transfer 4.0 mL of 1.0 N sodium hydroxide to the vial, and stir the solution for 4 hours. Then, add 4.0 mL of 1.25 M phosphoric acid to the same vial to bring the pH of the solution to 3 or less.

Invert the test sample solution vial several times to ensure complete mixing, and filter through a $0.22-\mu \mathrm{m}$ filter. Use the clear filtrate as the Test solution.

Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas corresponding to acetic and succinic acids. Calculate the percentage of acetic acid, $A$, in the portion of Hypromellose Acetate Succinate taken by the formula:

$$
0.0768\left(W_{A} / W_{U}\right)\left(r_{U A} / r_{S A}\right)
$$

in which $W_{A}$ is the weight of acetic acid, in mg , used to prepare the Acetic acid stock solution; $W_{U}$ is the weight of Hypromellose Acetate Succinate, in mg , used to prepare the Test solution; and $r_{U A}$ and $r_{S A}$ are the peak responses for acetic acid obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of acetyl groups $\left(-\mathrm{COCH}_{3}\right)$ in the portion of Hydroxypropyl Methylcellulose Acetate Succinate taken by the formula:

$$
0.717\left(A-A_{\text {free }}\right)
$$

in which $A_{\text {free }}$ is the percentage of free acetic acid, as determined in the test for Limit of free acetic and succinic acids; and $A$ is as defined above. Calculate the percentage of succinic acid, $S$, in the portion of Hypromellose Acetate Succinate taken by the formula:

$$
1.28\left(W_{S} / W_{U}\right)\left(r_{U S} / r_{S S}\right)
$$

in which $W_{S}$ is the weight of succinic acid, in mg , used to prepare the Succinic acid stock solution; $W_{U}$ is as defined above; and $r_{U S}$ and $r_{S S}$ are the peak responses for succinic acid obtained from the Test solution and the Standard solution,
respectively. Calculate the percentage of succinoyl groups $\left(-\mathrm{COC}_{2} \mathrm{H}_{4} \mathrm{COOH}\right)$ in the portion of Hydroxypropyl Methylcellulose Acetate Succinate taken by the formula:

$$
0.856\left(S-S_{\text {free }}\right)
$$

in which $S$ is as defined above; and $S_{\text {free }}$ is the percentage of free succinic acid, as determined in the test for Limit of free acetic and succinic acids.

Content of methoxy and hydroxypropoxy groups-
[Gaution Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps in the preparation of the Test solution and the Standard solution in aproperly functioning heөd. Specific safety practicestobefollowed are to be iden tified to the analyist performing this test.]

Hydriodic acid Use a reagent having a specifle gravity of at least 1.69 , equivalent to $55 \% \mathrm{HH}$

Imtermal stamdard solution Transfer about 2.5 giof tolut ene, aceurately weighed, to a $100-\mathrm{mL}$ voltametric flask con taining 10 mE of $\theta$-xylene, diltete with $\theta-x y l e n e$ to volume, and mix.

Standardsolution Inte a suitable serum vial weigh about 135 mg of adipie acid and 4.0 mL of Hydriodic acid, pipet 4 mL of Internal standard solntion inte the vial, andelose the vial-securely with a suitable septum stepper. Weigh ac eurately the vial and contents, add 30 世L-0f isopropyliodide łhrough the-septam with a-syringe, weigh again, and caleut late the weight of isopropyliodide added, by difference. Similarly, add 90 HE of methyliodide weigh again, and cat eutate the weight of methyl iodide added, by difference. Shake, and allow the layers to-separate.

Fest solution Transfer about 0.065 g of Hypromellese Acetate Suceinate, previeusly dried at $105^{\circ}$ for 1 hour and acetrately weighed, to a $5-\mathrm{mL}$ thiek walled reaction viat
equipped with a presstre-tight septum-ype-clestre, add an amount of adipic acid equal to the weight of the test specimen, and pipet 2 mL of Internal standard solution into the vial. Coutiously pipet 2 mL of Hydriodic acid into the mix ture, immediately eap the vial tightly, and weigh aceurately. Mix the contents of the vial continuousty while heating at $150^{\circ}$ for 60 mimutes. Allow the vial to cool for about 45 minutes, and weigh again. If the weight less is greater that 10-mg, diseard the mixture, and prepare anether Test preparation.

Chromatographic system The gas ehromategraph is equipped with a thermal conductivity detector and a-4 mm $* 1.8$ m glass columm packed with 20\% liquid phase- 628 on 100 to 120 mesh stuppert SIC that is not silanized. Helium is used as the carrier gas, and the temperature of the eolumn is maintained at $130^{\circ}$. Chrematograph the Standard solution, and record the peak respenses as directed for Pro eedure: the relative retention times of methyliodide, iseprepyliodide, toluene, ande-xylene are approximately $1.0,2.2$, 3.6, and 8.0, respectively; and theresolation, $R$, between the foltene and isopropyliodide peaks is net less than 2.0 .

Calibration Inject about 2 HL of the upper layer of the Standard selation inte the-gas chromatograph, and recert the ehromategrams. Caleulate the relative respense facter, $F_{4,}$ of equal weights of toluene and methyliodide taken by the formala:

$$
Q_{H}+R_{\text {sif }}
$$

in which $Q_{4}$ is the quantity ratio of methyliodide to toluene in the Standard solution, and $R_{\text {suf }}$ is the peak area ratio- of methyl iodide to toluene obtained from the Standard solutien. Similarly, caleulate the relative respense facter, $F_{q}$, of
equal weights of toltene and isopropyl iodide taken by the formula:-

$$
Q+R_{s}
$$

in which $Q_{2}$ is the quantity ratio of isepropyl iodide to tolu ene in the Standard solution, and $R_{\text {si }}$ is the peak area ratiof of isopropyl iodide to toltene obtained from the Standard sotution.

Procedtre Inject about $2 \mu \mathrm{~L}$ of the upper layer of the Fest solution inte the gas chromatograph, and record the ehromagrams. Caleulate the percentage of methoxy groups ( $\mathrm{OCH}_{3}$ ) in the pertion of Hypromellose Acetate Strecinate taken by the formula:-

$$
2(31 / 142) F_{\neq} R_{41}\left(H_{f}+W_{t}\right)
$$

in which $31 / 142$ is the ratio of the formma weights of the methoxy group and methyliodide; $F_{\text {a }}$ is-defined under Cat ibration; $R_{\text {mu }}$ is the ratio of the area of the methyl iodide peak to that of the tolmene peak obtained from the Test sothtion, $W_{f}$ is the weight, in g , of toltene used to prepare the Internal standard solution; and $\mathrm{H}_{4}$-is the weight, in g, of Hypromellose Acetate Stuecinate taken to prepare the Test solution. Similarly, caleulate the pereentage of hydroxyprepexy greups ( $\mathrm{OCH}_{2} \mathrm{CHOHCH}_{3}$ ) in the pertion of Hypremellose Acetate-Suceinate taken by the formula:-
in which $75 / 170$ is the ratio of the formala weights of the hydroxypropexy group and isopropyliodide; $F_{f}$ is defined tader Calibration; $R_{w}$ is the ratio of the area of the iseprepyl iodide peak to that of the toluene peak obtained from the Fest solution; $W_{7}$ is the weight, in g, of toltene used to prepare the Internal standerd solution; and $H_{+}$is the weight, in g, of Hypromellose Acetate Stucinate taken to prepare the Test solution.

Content of suceinoyl groups Transfer about 1g of Hypremellose Acetate-Suceinate, previously dried at 105º for 1 hour and aceurately weighed, to a conieal flask, dissolve in 50 mL of a mixture of alcohol, acetone, and water $(2: 2: 1, v / v)$, add 2 dreps of phenelphthalein TS, and titrate with 0.1 N soditm hydroxide VS. Perform a blank determination, and make any necessary corrections. Caleulate the percentage of surcineyl greups by the formula:-

$$
(1.0108 V / H) \quad 1.71205
$$

in which $V$ is the volume, in mL , of 0.1 N soditm hydroxide eonsumed after correction for the blank; $W$ is the weight, in g, of Hypromellose Acetate Succinate taken; and $S$ is the pereentage of free-strecinic acid found as directed in the test for Limit of free suceinic acid.

## Content of acetylgroups

Apparatus Use the apparatus illustrated in Figure 1.

$$
z(75 / 170) F R_{\Delta}\left(H_{t}+H_{t}\right)
$$



Figure 1: Apparatus for Determination of Content of Ace Groups

## Internal stad solution Transfer 1.0 mL of propionie

acid inte a $250-\mathrm{mL}$ volumetric flack, and dilute with Diltent to volume-

Piltent Use diluted phosphoric acid (1 in 5000).
Standard solution- Transfer about 100 mg of glacial acetic acid, aecurately weighed, into a $100-\mathrm{mL}$ volumetrie flask, and dilute with Diluent to volume. Transfer 15 mL Of this-selution to anether $100-\mathrm{mL}$ veltumetric flack, add 5.0 mL of the Internal standtard solution, and dilute-with

Biltent to voltame.

Test solution Transfer about 150 mg of Hypromellese Acetate-Stuecinate, previously dried at $105^{\circ}$ for 1 hour and aceurately weighed, to decompesition flask D , add 5 mL - of soditm hydroxide TS, dissolve by shaking, and decompose in a water bath at $60^{\circ}$ for 2 hours. After cooling, add 5 mL of diluted phesphoric acid ( 1 in 6 ), and immediately eonstruet the apparatus as shown in Figure 1. Dip the decomposition flask and steam generator B in the oil bath at $155^{\circ}$, while passing nitrogen from nitrogen induction fube H at a rate of 1 to 2 bubbles per seeond, continue the distillation at
the same temperature, andeollect the distillate in measuring eylinder $G$. Take 60 mL of the distillate, wash the inside of enndenser $F$ with 10 mL of water, combine the washing with the distillate in a 100 mL volumetric flask, add 5.0 mL of the Internal standard solution, and dilute with water to vol the.

Chromatographic system The gas chromatograph is equipped with a flame ionization detector and a-3-mm $-*$ Z-m glass coltmm packed with 60 - $0-80$ mesh support S2. The carrier gas is helitum, and the temperature of the coltamm is maintained at $180^{\circ}$. Adjust the flow rate so that the inter nal standard peak elutes in about 5 minutes. Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the elution order is acetic acid, followed by the internal standard peak. The resolution, $R$, between these peaks is not less than 2.0; and the relative standard deviation for replicate injections is not more that $2.0 \%$ for each of the peaks.

Procedure Separately inject equal volumes (about $2 \mu \mathrm{~L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and meastre the respenses for the major peaks. Caleulate the ratio, $R_{t}$, of the area of the acetic acid peak to the area of the internat stan dard peak in the chrematogram obtained frem the Test sotttion, and similarly ealeulate the ratio, $R_{s}$, in the ehromatogram obtained frem the Standard solution. Cateu tate the percentage of ace groups ( $\mathrm{COCH}_{3}$ ) in the pertion of Hypromellose Acetate Suecinate taken by the formula:

$$
\left(R_{L}+R_{s}\right)\left(H_{s}+H\right) \times 0.15 \times 71.68
$$

in which $W_{s}$ is the weight, in mg , of glacial acetic acid used to prepare the Standard solution; Wis the weight, in mo, of the pertion of Hypromellose Acetate-Suecinate taken; and the other terms are as defined therein.

Content of methoxy and 2-hydroxypropoxy groups-[Caution-Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps in the preparation of the Test solution and the Standard solution in a properly functioning hood. Specific safety practices to be followed are to be identified to the analyst performing this test.]

Hydriodic acid—Use a reagent having a specific gravity of at least 1.69 , equivalent to $55 \%$ hydrogen iodide.

Solution $A$-Prepare a mixture of water and methanol (90:10).

Solution B-Prepare a mixture of methanol and water (85: 15).

Mobile phase-Use variable mixtures of Solution A and Solution B as directed for Chromatographic system. Make adjustments if necessary (see System Suitability under Chromatography $\langle 621\rangle$ ).

Standard stock solution-Transfer 2 mL of $o$-xylene into a stoppered, $10-\mathrm{mL}$ volumetric flask, place the flask on a balance, and tare. Add about $200 \mu \mathrm{~L}$ of methyl iodide, insert the stopper into the flask, and accurately weigh: the weight of methyl iodide is about 350 mg . Tare the flask again, add about $34 \mu \mathrm{~L}$ of isopropyl iodide, and accurately weigh the flask: the recorded weight of isopropyl iodide is about 50 mg. Dilute with $o$-xylene to volume, and mix.

Standard solution-Transfer about 85 mg of adipic acid into an $8-\mathrm{mL}$ vial (or other suitable container), add 2 mL of Hydriodic acid, and add 2.0 mL of the Standard stock solution. Shake and allow the phases to separate. Carefully transfer approximately 1.5 mL of the $o$-xylene (top) layer to a small vial, making sure that the bottom aqueous layer is not disturbed. Transfer 1.0 mL of this solution into a 10 mL volumetric flask, and dilute with methanol to volume. [NOTE-This solution is stable for 8 hours at $5^{\circ}$.]

Test solution-Accurately weigh about 65 mg of Hypromellose Acetate Succinate into a $5-\mathrm{mL}$ reaction vial, add 2.0 mL of $o$-xylene and about 100 mg of adipic acid. Add 2.0 mL of Hydriodic acid, and close the vial tightly with a cap. [Caution-Use a cap that has a top safety relief valve, such as a Minniert valve, to prevent accidental explosion of the vial under high pressure when heated.] Weigh the vial before heating, and place the vial into a heating block at $150^{\circ}$. Shake the vial after 5 minutes and after 30 minutes of heating. Remove the vial from the heating block after 1 hour of heating, and cool. Weigh the vial. If the weight loss is greater than 10 mg , discard the mixture, and prepare another reaction solution. Carefully transfer approximately 1.5 mL of the top $o$-xylene layer into a small glass vial, making sure that the bottom aqueous layer is not disturbed. Transfer 1.0 mL of this solution into a $10-\mathrm{mL}$ volumetric flask, and dilute with methanol to volume. [NOTE-This solution is stable for 8 hours at $5^{\circ}$.]

Chromatographic system (see Chromatography $\langle 621\rangle$ )The liquid chromatograph is equipped with a $254-\mathrm{nm}$ detector and a $4.6-\mathrm{mm} \times 15-\mathrm{cm}$ column that contains $5-\mu \mathrm{m}$ packing L1. The column temperature is maintained at $30^{\circ}$. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

| Time | Solution A <br> (minutes) | Solution B $B$ <br> $(\%)$ | Elution |
| :---: | :---: | :---: | :--- |
| 0 | 70 | 30 | equilibration |
| $0-8$ | $70 \rightarrow 40$ | $30 \rightarrow 60$ | linear gradient |
| $8-10$ | $40 \rightarrow 15$ | $60 \rightarrow 85$ | linear gradient |
| $10-17$ | 15 | 85 | isocratic |

[NOTE-These gradient elution times are established on an HPLC system with a dwell volume of approximately 2.0
mL . The injection time can be adjusted relative to the start of a run to accommodate the change in dwell volume from one HPLC system to another to achieve the separation described.] Chromatograph the Standard solution, and record the peak responses as directed for Procedure: the column efficiency, determined from the methyl iodide peak, is not less than 10,000 theoretical plates; the tailing factor of this peak is between 0.9 and 1.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$ for each peak.
Procedure-Separately inject equal volumes (about 10 $\mu \mathrm{L}$ ) of the Standard solution and the Test solution into the chromatograph, record the chromatograms, and measure the peak areas corresponding to methyl iodide and isopropyl iodide. Calculate the percentage of methoxy groups $\left(-\mathrm{OCH}_{3}\right)$ in the portion of Hypromellose Acetate Succinate taken by the formula:

$$
4.38\left(W_{M} / W\right)\left(r_{U M} / r_{S M}\right)
$$

in which $W_{M}$ is the weight of methyl iodide, in mg, used to prepare the Standard stock solution; $W$ is the weight of Hypromellose Acetate Succinate, in mg, used to prepare the Test solution; and $r_{U M}$ and $r_{S M}$ are the peak responses for methyl iodide obtained from the Test solution and the Standard solution, respectively. Calculate the percentage of 2-hydroxypropoxy groups $\left(-\mathrm{OCH}_{2} \mathrm{CHOHCH}_{3}\right)$ in the portion of Hypromellose Acetate Succinate taken by the formula:

$$
8.84\left(W_{I} / W\right)\left(r_{U I} / r_{S I}\right)
$$

in which $W_{I}$ is the weight of isopropyl iodide, in mg, used to prepare the Standard stock solution; $r_{U I}$ and $r_{S I}$ are the peak responses for isopropyl iodide obtained from the

Test solution and the Standard solution,respectively; and $W$ is as defined above. $\quad$ 2S (NF23)

## BRIEFING

> Monoglyceride Citrate. Because there is no existing NF monograph for this excipient, a new monograph is being proposed. This new monograph is based on the Monoglyceride Citrate monograph in the Food Chemical Codex, 5th Edition, page 294 and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) monograph published in FAO Food and Nutrition Paper, No. 52 (1992).
(EMC: D. Bempong; PSD: C. Okeke; NL: L. Paul) RTS-41365-1

## Add the following:

## -Monoglyceride Citrate

Citric acid ester of glyceryl monooleate [36291-32-4].
» Monoglyceride Citrate is a mixture of glyceryl monooleate and its citric acid monoester, manufactured by the reaction of glyceryl monooleate with citric acid under controlled conditions. It contains not less than 14.0 percent and not more than 17.0 percent total citric acid, calculated on the anhydrous basis.

Packaging and storage-Preserve in well-closed containers. No storage requirements specified.

USP Reference standards $\langle 11\rangle$ —USP Citric Acid RS.

## Identification-

A: Reflux 1 g of sample with 15 mL of 0.5 N potassium hydroxide solution in dehydrated alcohol for 1 hour. Add 15 mL of water, acidify with diluted hydrochloric acid (about 6 mL ). Oil drops or a white to yellowish-white solid is produced that is soluble in 5 mL of hexane. Remove the hexane layer, extract again with 5 mL of hexane and again remove the hexane layer. Keep the resulting aqueous layer for Identification tests $B$ and $C$.

B: Evaporate 1 mL of the aqueous layer resulting from Identification test $A$ in a porcelain dish. The residue meets the requirements of the test for Citrate $\langle 191\rangle$.
C: Transfer 5 mL of the aqueous layer resulting from Identification test $A$ into a test tube. Add excess calcium hydroxide as a powder, place in boiling water for 5 minutes, shaking several times, cool, and filter. Transfer one drop of the filtrate into a test tube and add about 50 mg of potassium hydrogen sulfate. On top of the test tube, place a filter paper moistened with a reagent for acrolein consisting of a mixture of a $5 \%$ nitroprusside solution in water and a $20 \%$ piperidine solution in water $(1: 1)$. Heat the test tube. If the filter paper turns blue, the presence of glycerin is indicated. The color changes to light red after addition of sodium hydroxide TS.

Acid value $\langle 401\rangle$ : between 70 and 100 .
Saponification value $\langle 401\rangle$ : between 260 and 265.
Water, Method $I\langle 921\rangle$ : not more than $0.2 \%$.
Residue on ignition $\langle 281\rangle$ : not more than $0.3 \%$, about 1 g , accurately weighed, being used.

Heavy metals, Method II $\langle 231\rangle$ : $0.001 \%$.

## Content of citric acid-

Standard preparation-Dissolve an accurately weighed quantity of USP Citric Acid RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about $230 \mu \mathrm{~g}$ per mL .

Test preparation-Transfer about 150 mg of Monoglyceride Citrate, accurately weighed, into a saponification flask, add 50 mL of $4 \%$ potassium hydroxide solution in dehydrated alcohol, and reflux for 1 hour. Acidify the reaction mixture with hydrochloric acid to a pH of 2.8 to 3.2 , transfer into a $400-\mathrm{mL}$ beaker, and evaporate to dryness on a steam bath. Quantitatively transfer the contents of the beaker into a separator, using no more than 50 mL of water, and extract with three $50-\mathrm{mL}$ portions of petroleum ether, discarding the extracts. Transfer the water layer to a $100-\mathrm{mL}$ volumetric flask, dilute with water to volume, and mix.
Procedure—Pipet 2.0 mL each of the Standard preparation and of the Test preparation into separate $40-\mathrm{mL}$ graduated centrifuge tubes. Add 2 mL of a 1 in 2 sulfuric acid solution and 11 mL of water to each tube. Boil for 3 min utes, cool, and add 5 mL of bromine TS to each tube. Dilute to 20 mL , allow to stand for 10 minutes, and centrifuge. Transfer 4.0 mL of each solution into separate $19-\times 110-$ mm test tubes, add 1 mL of water, 0.5 mL of a 1 in 2 sulfuric acid solution, and 0.3 mL of 1 M potassium bromide, and shake. Add 0.3 mL of 1.5 N potassium permanganate, shake, and allow to stand for 2 minutes. Add 1 mL of a saturated solution of ferrous sulfate, shake, allow to stand for 2 minutes, and then dilute to 10 mL with water. Add 10.0 mL of $n$-hexane (previously washed with sulfuric acid, followed by a water wash, and then dried over anhydrous sodium sulfate), shake vigorously for 2 minutes, and centrifuge at low speed for 1 minute. Transfer 5.0 mL of the hexane extract into a $20-\times 145-\mathrm{mm}$ tube containing 10.0 mL of $4 \%$ sodi-
um sulfide solution, and briefly shake vigorously (three oscillations only). Centrifuge the mixture at low speed for 1 minute. Immediately determine the absorbance of each aqueous layer in a $1-\mathrm{cm}$ cell at 450 nm with a suitable spectrophotometer, using a reagent blank in the reference cell. Calculate the quantity, in mg, of citric acid in the Monoglyceride Citrate taken by the formula:

$$
0.1 C\left(A_{U} / A_{S}\right)
$$

in which $C$ is the concentration, in $\mu \mathrm{g}$ per mL , of USP Citric Acid RS in the Standard preparation; and $A_{U}$ and $A_{S}$ are the absorbances obtained from the Test preparation and the Standard preparation, respectively.■2S (NF23)

## Briefing

Polyisobutylene, page 3175 of the First Supplement and page 1564 of the Fifth Interim Revision Announcement in PF 30(5) [Sept.-Oct. 2004]. On the basis of comments received indicating difficulties when performing the test for Molecular weight for me-dium- and high-molecular weight grades of Polyisobutylene, it is proposed to replace this test with a test for Viscosity that is based on the manufacturer's procedure and specifications. It is also proposed to revise the Definition and Labeling sections to include the use of stabilizers.
(EMC: E. Gonikberg) RTS-41791-1

## Change to read:

» Polyisobutylene is a synthetic polymer produced by the low-temperature polymerization of isobutylene in liquid ethylene, methylene chloride, or hexane, using an aluminum-chloride or boron-trifluoride catalyst.
-It may contain a suitable stabilizer..n2S (NF23)

## Change to read:

Labeling-Label it to indicate the neminal molecular weight and the solvent used in the polymerization process.
-range for intrinsic viscosity or the range for Staudinger Index, and the name and quantity of any added stabilizer. [nOTE-The Staudinger Index is equal to 100 times the intrinsic viscosity.] $]_{\text {2S (NF23) }}$

## Delete the following:

## -Moleeular weight-

Solven-Use diisobutylene.
Fest solution 1 Dissolve 1g of Polyisobutylene, acemrately weighed, in 95 mL of Solvent, filter into a 100 mL volumetric flack, dilute with Solvent to volume, and mix. Transfer 50.0 mL of the solution so obtained into a tared dish, evaperate on a steam bath for about 1 hour, and then complete the vaporation to dryness by heating in the waymoren at $70^{\circ}$ to constant weight. Caleulate the coneentration of Test solution-1.

Fest solution 2 Transfer 2.0 mL of Test soldtion 1 to a -50 mL volumetric flask, and dilute with Solvent to volume. Calculate the eoncentration of Test solution-2.

Fest solution 3- Transfer 5.0 mL of Test soldtion 1 to a -50 mL velumetric flask, and dilute with Solvent to volume. Caleulate the erneentration of Test solution-3.

Fest solution - Transfer 10.0 mL of Test solution 1 to 0.50 mL volumetric flask, and dilute with Solvent to volume. Caleulate the ementration of Test solution-4.

Procedure Using a Cannon Fenske, or equivalent viseometer, having dimensions such that the flow time is not less than 200 sec ends, measure the flow of the Solvent and of each of the four Test solutions at $20^{\circ}$. Caleulate the specific viseesity, $\mathrm{m}_{\boldsymbol{p}}$, of Test solut tion - by the formma:

$$
\left(t \pi_{4}\right)-1
$$

in which $t_{4}$ is the flow time, in seconds, of the Solvent; and $t$ is the flow time, in seconds, of Test solution 1. Caleulate the redured vis eosity of Test solution 1 by the formula:

$$
\#_{\ldots} d C
$$

in which $\mathrm{n}_{\boldsymbol{s}}$ is the speeifie viseosity, caleulated above; and $C$ is the eencentration, in s per $100-\mathrm{mL}$, of Test solution 1. Caleulate the speeific viseosity and the redueed viseosity of Test solutions 2, 3, and 4 in the same manner as Test solution 1.

Plot the redured viseosity of each solution against coneentration, and extrapolate to zero-concentration to obtain the intrinsic viseosity, [n]. Finally, caleulate the molecular weight of Polyisobutylene by the formula:-

$$
([\eta] / K)^{+\ldots,},
$$

in which $K$ is $3.60 \times 10^{-4}$ and is 0.64 .! 2 S (NF23)

## Add the following:

-Viscosity $\langle 911\rangle$ —
Solvent-Use isooctane.
Test solution-Prepare a solution of Polyisobutylene in the Solvent having a known concentration as indicated in Table 1. [NOTES--The solution must be homogeneous before testing. For the Polyisobutylene having a Staudinger Index
of 100 and higher, add the Solvent to the weighed material, and allow it to stand in an oven at $80^{\circ}$ for 12 to 24 hours. A heated mechanical shaker may be used to shorten the dissolution time; it is recommended to use a gentle shaker to avoid shearing the polymers. Take adequate precautions to prevent evaporation of the solvent.]

Table 1

| Staudinger Index ${ }^{1}$ | Concentration, $\mathrm{g} \mathrm{per} \mathrm{cm}^{3}$ |
| :---: | :---: |
| $25-60$ | 0.01 |
| $60-100$ | 0.005 |
| $100-350$ | 0.002 |
| $350-700$ | 0.001 |

${ }^{1}$ The Staudinger Index is equal to 100 times the intrinsic viscosity.

Procedure-Using a suitable Ubbelohde capillary viscosimeter having dimensions such that the flow time is not less than 200 seconds, immersed into a controlled temperature bath, measure the flow of the Solvent and of the Test solution at $20^{\circ}$. Repeat the procedure three times, and calculate the average. [NOTE-Before each measurement, let the solutions be temperature equilibrated for 10 minutes.]

Calculate the reduced viscosity $J$ by the formula:

$$
\left(t / t_{0}-1\right) / C,
$$

in which $t_{0}$ is the average flow time, in seconds, of the Solvent; $t$ is the average flow time, in seconds, of the Test solution; and $C$ is the concentration, in g per $\mathrm{cm}^{3}$, of the Test solution.

Calculate the Staudinger Index, $J_{0}$, by the formula:

$$
J /\left[1+0.31\left(t / t_{0}-1\right)\right],
$$

in which the terms are defined above: it is within the limits specified on the label. 2S $^{\text {S (NF23) }}$

Tributyl Citrate, NF page 2948—See briefing under Acetyltributyl Citrate.
(EMC: D. Bempong) RTS-41597-2

## Change to read:

## Assay-

System suitability solution-Prepare a solution in toluene containing about 30 mg each of USP Tributyl Citrate RS and USP Acetyltributyl Citrate RS per mL.

Assay preparation-Transfer about 300 mg of Tributyl Citrate, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with toluene to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The gas chromatograph is equipped with an on colmm, temperatreprogrammable injector,

- m2S (NF23)
a flame-ionization detector maintained at about $275^{\circ}$,
-a split injection system with a split ratio of about


## $30: 1$, ■ $^{\mathrm{S}}$ (NF23)

and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ column bonded with a $0.5-\mu \mathrm{m}$ layer of phase G42. The column temperature is programmed to be maintained at about $80^{\circ}$ for 0.5 minute, then to increase to about $220^{\circ}$ at a rate of $20^{\circ}$ per minute, and to hold at about $220^{\circ}$ for $10 \mathrm{~min}-$ utes. The injection port temperature is programmed be

maintained at about $85^{\circ}$. for 0.5 minute, then to increase to about
$225^{\circ}$ at a rate of $20^{\circ}$ per minute, and to hold at about $225^{\circ}$ for 10 minuter.

- $\quad$ 2S (NF23)

Helium is used as the carrier gas at a flow rate of about 2.3 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for tributyl citrate and 1.0 for acetyltributyl citrate; the resolution, $R$, between tributyl citrate and acetyltributyl citrate is not less than 1.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$ determined from both the tributyl citrate and acetyltributyl citrate peaks, based on area percent calculation.

Procedure-Inject $1 \mu \mathrm{~L}$ of the Assay preparation into the chromatograph, record the chromatogram, and measure all of the peak areas, excluding the solvent peak. Calculate the percentage of $\mathrm{C}_{18} \mathrm{H}_{32} \mathrm{O}_{7}$ in the portion of Tributyl Citrate taken by the formula:

$$
100(A / B)
$$

in which $A$ is the tributyl citrate peak area response; and $B$ is the sum of the area responses of all the peaks.

Triethyl Citrate, NF page 2949—See briefing under Acetyltributyl Citrate.
(EMC: D. Bempong) RTS-41597-1

## Change to read:

## Assay-

System suitability solution-Prepare a solution in toluene containing about 30 mg each of USP Triethyl Citrate RS and USP Acetyltriethyl Citrate RS per mL.

Assay preparation-Transfer about 300 mg of Triethyl Citrate, accurately weighed, to a $10-\mathrm{mL}$ volumetric flask, dissolve in and dilute with toluene to volume, and mix.

Chromatographic system (see Chromatography $\langle 621\rangle$ )—The gas chromatograph is equipped with an on colmm, temperatreprogrammable injector,

- m2S (NF23)
a flame-ionization detector maintained at about $275^{\circ}$,
-a split injection system with a split ratio of about
$30: 1$, ${ }^{2 S}$ (NF23)
and a $0.32-\mathrm{mm} \times 30-\mathrm{m}$ column bonded with a $0.5-\mu \mathrm{m}$ layer of phase G42. The column temperature is programmed to be maintained at about $80^{\circ}$ for 0.5 minute, then to increase to about $220^{\circ}$ at a rate of $20^{\circ}$ per minute, and to hold at about $220^{\circ}$ for $10 \mathrm{~min}-$ utes. The injection port temperature is pregrammed be
- m2S (NF23)
maintained at about $85^{\circ}$. for 0.5 minute, then to inerease to about $225^{\circ}$ at a rate of $20^{\circ}$ per mintute, and to hold at about $225^{\circ}$ for 10 minutes.

Helium is used as the carrier gas at a flow rate of about 2.3 mL per minute. Chromatograph the System suitability solution, and record the peak responses as directed for Procedure: the relative retention times are about 0.9 for triethyl citrate and 1.0 for acetyltriethyl citrate; the resolution, $R$, between triethyl citrate and acetyltriethyl citrate is not less than 1.5 ; and the relative standard deviation for replicate injections is not more than $2.0 \%$ determined from both the triethyl citrate and acetyltriethyl citrate peaks, based on area percent calculation.

Procedure-Inject $1 \mu \mathrm{~L}$ of the Assay preparation into the chromatograph, record the chromatogram, and measure all of the peak areas, excluding the solvent peak. Calculate the percentage of $\mathrm{C}_{12} \mathrm{H}_{20} \mathrm{O}_{7}$ in the portion of Triethyl Citrate taken by the formula:

$$
100(A / B)
$$

in which $A$ is the triethyl citrate peak area response; and $B$ is the sum of the area responses of all the peaks.

## GENERAL CHAPTERS

## General Tests and Assays

## General Requirements for Tests and Assays

## BRIEFING

〈11〉 USP Reference Standards, USP 27 page 2111, page 3310 of the Second Supplement, the Third Interim Revision Announcement on page 785 of PF 30(3) [May-June 2004], the Fourth Interim Revision Announcement on page 1150 of PF 30(4) [July-Aug. 2004], the Fifth Interim Revision Announcement on page 1559 of PF 30(5) [Sept.-Oct. 2004], page 793 of PF 26(3) [May-June 2000], page 1101 of $P F$ 26(4) [July-Aug. 2000], page 1832 of $P F$ 27(1) [Jan.-Feb. 2001], page 3071 of $P F 27(5)$ [Sept.-Oct. 2001], page 433 of $P F$ 28(2) [Mar.-Apr. 2002], page 839 of $P F$ 28(3) [May-June 2002], page 1224 of $P F$ 28(4) [July-Aug. 2002], page 1468 of $P F$ 28(5) [Sept.-Oct. 2002], page 1913 of PF 28(6) [Nov.-Dec. 2002], page 710 of PF 29(3) [May-June 2003], page 1137 of $P F$ 29(4) [July-Aug. 2003], page 1601 of PF 29(5) [Sept.-Oct. 2003], page 2022 of PF 29(6) [Nov.-Dec. 2003], page 211 of $P F$ 30(1) [Jan.-Feb. 2004], page 613 of $P F$ 30(2) [Mar.-Apr. 2004], page 998 of $P F 30(3)$ [May-June 2004], page 1338 of $P F$ 30(4) [July-Aug. 2004], and page 1674 of PF 30(5) [Sept.-Oct. 2004].
(HDQ) RTS-40282-6; 40282-7; 40282-8; 40648-1; 408441; 40844-2; 40844-3; 41691-1; 41471-3; 41187-1; 41613-4

## Add the following:

-USP 2,4-Dichlorophenol RS-[To come.] ${ }_{\text {2S }}$ (USP28)

## Add the following:

■USP Fosinopril Sodium RS—[To come.] $]_{\text {2S (USP28) }}$

## Add the following:

- USP Fosinopril Related Compound A RS—[To
come.] $]_{\text {2S (USP28) }}$


## Add the following:

-USP Fosinopril Related Compound B RS—[To come.] $]_{\text {2S (USP28) }}$

## Add the following:

-USP Fosinopril Related Compound C RS—[To come.] $]_{\text {2S (USP28) }}$

## Add the following:

-USP Fosinopril Related Compound D RS—[To come.] $]^{2 S}$ (USP28)

## Add the following:

- USP Fosinopril Related Compound E RS—[To come.] ${ }_{\text {WS }}$ (USP28)


## Add the following:

-USP Fosinopril Related Compound F RS—[To come.] $]_{\text {2S (USP28) }}$

## Add the following:

-USP Fosinopril Related Compound G RS—[To come.] $]_{\text {2S (USP28) }}$

## Add the following:

- USP Fosinopril Related Compound H RS—[To come.] $]_{\text {2S (USP28) }}$


## Add the following:

- USP Morantel Tartrate RS—[To come.] $]_{\text {2S (USP28) }}$

Add the following:
-USP Near-Infrared Calibrator RS—[To come.] $]_{\text {2S }}$ (USP28)

## Add the following:

-USP Parachlorophenol RS—[To come.] $]_{\text {2S (USP28) }}$

## Add the following:

-USP Ranitidine Resolution Mixture RS— It is a mixture of ranitidine hydrochloride and four related impurities: ra-nitidine- $N$-oxide, ranitidine complex nitroacetamide, ranitidine diamine hemifumarate, and ranitidine amino alcohol hemifumarate.

Ranitidine- $N$-oxide: $N, N$-dimethyl[5-[[[2-[[1-(methyla-mino)-2-nitroethenyl]amino]ethyl]sulphanyl]methyl]furan-2-yl]methanamine $N$-oxide.

Ranitidine complex nitroacetamide: $N-[2-[[[5-[(d i m e t h y l-$ amino)methyl]furan-2-yl]methyl]sulphanyl]ethyl]-2-nitroacetamide.
Ranitidine diamine hemifumarate (related compound $A$ ):
[5-[[(2-aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine, hemifumarate salt].
Ranitidine amino alcohol hemifumarate: [5-[(dimethyl-amino)methyl]furan-2-yl]methanol—[To come.] $]_{\text {2S (USP28) }}$

## Add the following:

- USP Ropivacaine Hydrochloride RS— [To come.] $]_{\text {■ } 2 \text { (USP28) }}$


## Add the following:

-USP Ropivacaine Related Compound A RS [2,6-dimethylaniline hydrochloride] $\left(\mathrm{C}_{8} \mathrm{H}_{12} \mathrm{ClN} \triangleleft 157.64 \triangleleft\right.$ CAS-21436-98-6)-[To come.] $]_{\text {2S (USP28) }}$

## Add the following:

-USP Ropivacaine Related Compound B RS [ $(R)$-ropivacaine hydrochloride monohydrate; $(R)-(-)$-1-propylpiperi-dene-2-carboxylic acid (2,6-dimethylphenyl)-amide hydrochloride monohydrate] $\left(\mathrm{C}_{17} \mathrm{H}_{26} \mathrm{~N}_{2} \mathrm{O} \diamond 328.89\right)$ [To come.] $]_{\text {2S (USP28) }}$

## Add the following:

-USP Triclosan Related Compounds Mixture A RS-
[To come.] ${ }_{\text {■S }}$ (USP28)

## Add the following:

-USP Vancomycin B with Monodechlorovancomycin RS—[To come.] $]_{\text {2S (USP28) }}$

## Add the following:

-USP Vecuronium Bromide Related Compound A RS
† $3 \alpha, 17 \beta$ dihydroxy $2 \beta, 16 \beta$ dipiperidinyl $5 \alpha$-andrestane,
3,17-d $[3 \alpha, 17 \beta$-diacetyl-oxy- $2 \beta, 16 \beta$-bispiperidi-
nyl-5 $\alpha$-androstan] $\left(\mathrm{C}_{33} \mathrm{H}_{54} \mathrm{~N}_{2} \mathrm{O}_{4} \diamond 542.79\right)$-[To
come.] $]_{\text {2S (USP28) }}$

## Add the following:

-USP Vecuronium Bromide Related Compound B RS
†3, $17 \beta$ dihydroxy $2 \beta, 16 \beta$-dipiperidinyl- $5 \alpha$ andrestane, $3-$ acetate, monomethobromide] [piperidinium, 1-[(2 $\beta, 3 \alpha,-$ $5 \alpha, 16 \beta, 17 \beta$ )-3-acetyloxy-17-hydroxy-2-(1-piperidinyl)an-drostan-16-yl]-1-methyl bromide] $\left(\mathrm{C}_{32} \mathrm{H}_{55} \mathrm{BrN}_{2} \mathrm{O}_{3} \diamond\right.$ 595.69)-[To come.] ${ }_{\text {■S }}$ (USP28)

## Add the following:

-USP Vecuronium Bromide Related Compound C RS § $3 \alpha, 17 \beta$ dihydroxy $2 \beta, 16 \beta$ dipiperidinyl $5 \alpha$ androstane, momethermide [piperidinium, $1-[(2 \beta, 3 \alpha, 5 \alpha,-$ $16 \beta, 17 \beta$ )-3,17-dihydroxy-2-(1-piperidinyl)androstan-16-yl]-1-methyl bromide] $\left(\mathrm{C}_{30} \mathrm{H}_{53} \mathrm{BrN}_{2} \mathrm{O}_{2} \diamond 553.66\right)$ - [ To come.] ${ }_{\text {WS }}$ (USP28)

## Add the following:

-USP Vecuronium Bromide Related Compound F RS Name to $\{3 x, 17 \beta$-dihydroxy $2 \beta, 16 \beta$-dipiperidinyl $5 x$ andrestane, 17 acetate, menemethebromide+ [piperidinium, 1-[(2 $\beta, 3 \alpha, 5 \alpha, 16 \beta, 17 \beta)$-17-acetyloxy-3-hydroxy-2-(1-piperidinyl)androstan-16-yl]-1-methyl bromide] $\left(\mathrm{C}_{26} \mathrm{H}_{4+} \mathrm{NO}_{3} \diamond 415.64\right)\left(\mathrm{C}_{32} \mathrm{H}_{55} \mathrm{BrN}_{2} \mathrm{O}_{3} \diamond 595.69\right)$-[To come.] ${ }_{\text {2S (USP28) }}$

# Physical Tests and Determinations 

## BriEfing

〈621〉Chromatography, USP 27 page 2272, page 3325 of the Second Supplement, and page 1687 of $P F 30(5)$ [Sept.-Oct. 2004]. The Expert Committee on Pharmaceutical Analysis 2 has proposed additional revisions to the Interpretation of Chromatograms and Glossary of Symbols sections.
(PA2: H. Pappa) RTS-40760-1

## Change to read:

## INTRODUCTION

This chapter defines the terms and procedures used in chromatography and provides general information. Specific requirements for chromatographic tests and assays of

- procedures for $_{\text {■2S (USP28) }}$
drug substances and dosage forms, including adsorbent and developing solvents, are given in the individual monographs.

Chromatography is defined as a procedure by which solutes are separated by a dynamic differential migration process in a system consisting of two or more phases, one of which moves continuously in a given direction and in which the individual substances exhibit different mobilities by reason of differences in adsorption, partition, solubility, vapor pressure, molecular size, or ionic charge density. The individual substances thus ebtined
$■_{\text {separated }}^{\text {nis }}{ }_{\text {(USP28) }}$
can be identified or determined by analytical methods.
-procedures.m2S (USP28)
The general chromatographic technique requires that a solute undergo distribution between two phases, one of them fixed (stationary phase), the other moving (mobile phase). It is the mobile phase that transfers the solute through the medium until it eventually emerges separated from other solutes that are eluted earlier or later. Generally, the solute is transported through the separation medium by means of a flowing stream of a liquid or a gaseous solvent known as the "eluant." The stationary phase may act through adsorption, as in the case of adsorbents such as activated alumina ; silien gel, and ion exehange resins,
$\square_{\text {and silica gel, }}^{\boldsymbol{\square}}{ }_{2 S}$ (USP28)
or it may act by dissolving the solute, thus partitioning the latter between the stationary and mobile phases. In the latter process, a liquid coating held on an inert support serves as the stationary phase.
-In the latter process, a liquid coated onto an inert support, or chemically bonded onto silica gel, or directly onto the
wall of a fused silica capillary, serves as the stationary
phase.n2S (USP28)
Partitioning is the predominant mechanism of separation in gasliquid chromatography, paper chromatography, and forms of column chromatography
$■^{-a n d}$ thin-layer chromatography $\boldsymbol{m}_{2 S}$ (USP28)
designated as liquid-liquid ehremagraphy.

In practice, separations frequently result from a combination of adsorption and partitioning effects.
-Other separation principles include ion exchange, ion-pair formation, size exclusion, hydrophobic interaction, and chiral recognition. $\mathbf{m}_{2 S}$ (USP28)

The types of chromatography useful in qualitative and quantitative analysis that are employed in the $U S P$ tests and assays

■procedures $_{\mathbf{■ 2 S}}$ (USP28)
are column, gas, paper, thin-layer,
-(including high-performance thin-layer chromatogra-
phy), $\mathbf{m}_{2 S}$ (USP28)
and pressurized liquid chromatography (commonly called highpressure or high-performance liquid chromatography). Paper and thin-layer chromatography are ordinarily more useful for purposes of identification, because of their convenience and simplicity. Column chromatography offers a wider choice of stationary phases and is useful for the separation of individual compounds, in quantity, from mixtures. Beth gas chromatography and pressurized liquid chrematography require more elaberate apparatus and usually provide high resolution methods that will identify and quantitate very small ameunts of material.
-Modern high-performance thin-layer chromatography, gas chromatography, and pressurized liquid chromatography require more elaborate apparatus but usually provide high resolution and identify and quantitate very small amounts of material.п2S (USP28)

Use of Reference Substances in Identity Tests-In paper and thin-layer chromatography, the ratio of the distance (this distance being measured to the point of maximum intensity of the spot

traveled on the medium by a given compound to the distance traveled by the front of the mobile phase, from the point of application of the test substance, is designated as the $R_{F}$ value of the compound. The ratio between the distances traveled by a given compound and a reference substance is the $R_{R}$ value. $R_{F}$ values vary with the experimental conditions, and thus identification is best accomplished where an authentic specimen of the compound in question is used as a reference substance on the same chromatogram.

For this purpose, chromatograms are prepared by applying on the thin-layer adsorbent or on the paper in a straight line, parallel to the edge of the chromatographic plate or paper, solutions of the substance to be identified, the authentic specimen, and a mixture of nearly equal amounts of the substance to be identified and the authentic specimen. Each sample application contains approximately the same quantity by weight of material to be chromatographed. If
the substance to be identified and the authentic specimen are identical, all chromatograms agree in color and $R_{F}$ value and the mixed chromatogram yields a single spot; i.e., $R_{R}$ is 1.0 .

## Change to read:

## THIN-LAYER CHROMATOGRAPHY

In thin-layer chromatography, the adsorbent is a relatively thin, uniform layer of dry, finely powdered material applied to a glass, plastic, or metal sheet or plate, glass plates being most commonly employed. The coated plate can be considered an "open chromatographic column" and the separations achieved may be based upon adsorption, partition, or a combination of both effects, depending on the particular type of suppert,
$\square_{\text {stationary phase, }}$ [2S (USP28)
its preparation, and its use with different solvents. Thin-layer chromatography on ion-exchange films
-layers $_{\text {■2S (USP28) }}$
can be used for the fractionation of polar compounds. Presumptive identification can be effected by observation of spots

- or zones $_{\mathbf{1 2 S}}$ (USP28)
of identical $R_{F}$ value and about equal magnitude obtained, respectively, with an unknown and a reference sample chromatographed on the same plate. A visual comparison of the size of the spets
$\boldsymbol{-}_{\text {or intensity of the spots or zones }}^{\mathbf{m}_{2 S} \text { (USP28) }}$
may serve for semiquantitative estimation. Quantitative measurements are possible by means of densitometry, flurresence, and flurese senee quenching;
-(absorbance or fluorescence measurements), $\quad$ 2S (USP28)
or the spots may be carefully removed from the plate, followed by elution with a suitable solvent and spectrophotometric measurement. For two-dimensional thin-layer chromatography, the chromatographed plate is turned at a right angle and again chromatographed, usually in another chamber equilibrated with a different solvent system.

Apparatus-Acceptable apparatus and materials for thin-layer chromatography consist of the following.

Flat glass plates of convenient size, typieally $20 \mathrm{~cm} \times 20 \mathrm{~cm} .^{+}$
An aligning trayor a flat surface upon which to align and rest the plates during the applieation of the adserbent.

A starage rack to hold the prepared plates during drying and trampertation. The rack holding the plates should be kept in a desicenter or be capable of being sealed in order to protect the plates from the environment after removal from the drying oven.

The adsorbent consists of finely divided adsorbent materials, nomally 5 to $-40 \mu \mathrm{~m}$ in diameter, suitable for chromatography. It ean be applied direetly to the glass plate or ean be bended to the plate by means of plaster of paris (hydrated caleimm-sulfate) [at a ratio of $5 \%$ to $15 \%]$ or with stareh paste or other binders. The for mer will not yield as hard a surface as will the stareh, but it is net affected by strongly oxidizing spray reagents. The adsorbent may eontain fluereseing material to aid in the visualization of spets that absorb ultraviolet light.

A spreater, which, when moved over the glass plate, will apply a uniferm layer of adsorbent of desired thickness over the entire strface of the plate.

A developing chamber that can accommodate one or more plates and can be properly elosed and sealed as described under Ascend ing Chromatography. The chamber is fitted with a plate support rack that supports the plates, back to back, with the lid of the chamber in place.

A template (generally made of plastic) to aid in placing the test spets at deffinite intervals, to mark distanees as needed, and to aid im tabeling the plates.

A graduated micropipet capable of delivering $10 \mu \mathrm{~L}$ volumes. Total volumes of test and standard solutions are specified in the individual menegraph.

Areagent spratyer that willemit a finespray and will not itself be attacked by the reagent.

An ultraviolet light sottree suitable for observations with short $(254 \mathrm{~nm})$ and long $(360 \mathrm{~nm})$ UV wavelengths.

- A TLC or HPTLC plate. The chromatography is generally carried out using precoated plates or sheets (on glass, aluminum, or polyester support) of suitable size. It may be necessary to clean the plates prior to separation. This can be done by migration of, or immersion in, an appropriate solvent. The plates may also be impregnated by procedures such as development, immersion, or spraying. At the time of use, the plates may be activated, if necessary, by heating in an oven at $120^{\circ}$ for 20 minutes. The stationary phase of TLC plates has an average particle size of $10-15 \mu \mathrm{~m}$, and that of HPTLC plates an average particle size of $5 \mu \mathrm{~m}$. Commercial plates with a preadsorbant zone can be used if they are specified in a monograph. Sample applied to the preabsorbant region develops into sharp, narrow bands at the pre-absorbant-sorbent interface. Alternatively, flat glass plates of convenient size, typically $20 \mathrm{~cm} \times 20 \mathrm{~cm}$ can be coated as described under Preparation of Chromatographic Plates.

A suitable manual, semiautomatic, or automatic application device can be used to ensure proper positioning of the plate and proper transfer of the sample, with respect to volume and position, onto the plate. Alternatively, a template can be used to guide in manually placing the test spots at definite intervals, to mark distances as needed, and to aid in labeling the plates. For the proper application of the solutions, micropipets, microsyringes, or calibrated disposable capillaries are recommended.

[^345]For ascending development, a chromatographic chamber made of inert, transparent material and having the following specifications is used: a flat bottom or twin trough, a tightly fitted lid, and a size suitable for the plates. For horizontal development, the chamber is provided with a reservoir for the mobile phase, and it also contains a device for directing the mobile phase to the stationary phase.

Devices for transfer of reagents onto the plate by spraying, immersion, or exposure to vapor and devices to facilitate any necessary heating for visualization of the separated spots or zones.
A UV light source suitable for observations under short ( 254 nm ) and long ( 365 nm ) wavelength UV light.

A suitable device for documentation of the visualized chromatographic result.

Procedure-Apply the prescribed volume of the test solution and the standard solution in sufficiently small portions to obtain circular spots of 2 to 5 mm in diameter ( 1 to 2 mm on HPTLC plates) or bands of 10 to 20 mm by 1 to 2 mm ( 5 to 10 mm by 0.5 to 1 mm on HPTLC plates) at an appropriate distance from the lower edge-during chromatography the application position must be 3 mm (HPTLC) to 5 mm (TLC) above the level of the developing solvent - and from the sides of the plate. Apply the solutions on a line parallel to the lower edge of the plate with an interval of at least 10 mm ( 5 mm on HPTLC plates) between the centers of spots or 4 mm ( 2 mm on HPTLC plates) between the edges of bands, and allow to dry.

Ascending Development-Line at least one wall of the chromatographic chamber with filter paper. Pour into the chromatographic chamber a quantity of the mobile phase sufficient for the size of the chamber to give, after impregnation of the filter paper, a level of depth appropriate to the dimension of the plate used. For saturation of the chromato-
graphic chamber, close the lid, and allow the system to equilibrate. Unless otherwise indicated, the chromatographic separation is performed in a saturated chamber.

Place the plate in the chamber, ensuring that the plate is as vertical as possible and that the spots or bands are above the surface of the mobile phase, and close the chamber. The stationary phase faces the inside of the chamber. Remove the plate when the mobile phase has moved over the prescribed distance. Dry the plate, and visualize the chromatograms as prescribed. For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

Horizontal Development-Introduce a sufficient quantity of the developing solvent into the reservoir of the chamber using a syringe or pipet. Place the plate horizontally in the chamber, connect the mobile phase direction device according to the manufacturer's instructions, and close the chamber. If prescribed, develop the plate starting simultaneously at both ends. Remove the plate when the mobile phase has moved over the distance prescribed in the monograph. Dry the plate, and visualize the chromatograms as prescribed.

For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

Detection-Observe the dry plate first under short-wavelength UV light ( 254 nm ) and then under long-wavelength UV light ( 365 nm ) or as stated in the monograph. If further directed, spray, immerse, or expose the plate to vapors of the specified reagent, heat the plate when required, observe, and compare the test chromatogram with the standard chromatogram. Document the plate after each observation. Measure and record the distance of each spot or zone from the point
of origin, and indicate for each spot or zone the wavelength under which it was observed. Determine the $R_{F}$ values for the principal spots or zones (see Glossary of Symbols).

Quantitative Measurement-Using appropriate instrumentation, substances separated by TLC and responding to ultraviolet-visible (UV-Vis) irradiation prior to or after derivatization can be determined directly on the plate. While moving the plate or the measuring device, the plate is examined by measuring the reflectance of the incident light. Similarly, fluorescence may be measured using an appropriate optical system. Substances containing radionuclides can be quantified in three ways: (1) directly by moving the plate alongside a suitable counter or vice versa; (2) by cutting the plates into strips and measuring the radioactivity on each individual strip using a suitable counter; or (3) by scraping off the stationary phase, dissolving it in a suitable scintillation cocktail, and measuring the radioactivity using a liquid scintillation counter (see Radioactivity $\langle 821\rangle$ ).

The apparatus for direct quantitative measurement on the plate is a densitometer that is composed of a mechanical device to move the plate or the measuring device along the x axis and the $y$-axis, a recorder, a suitable integrator or a computer; and, for substances responding to UV-Vis irradiation, a photometer with a source of light, an optical device capable of generating monochromatic light, and a photo cell of adequate sensitivity, all of which are used for the measurement of reflectance. In the case where fluorescence is measured, a suitable filter is also required to prevent the light used for excitation from reaching the photo cell while permitting the emitted light or specific portions thereof to pass. The linearity range of the counting device must be verified.

For quantitative tests, it is necessary to apply to the plate not fewer than three standard solutions of the substance to be examined, the concentrations of which span the expected
value in the test solution (e.g., $80 \%, 100 \%$, and $120 \%$ ). Derivatize with the prescribed reagent, if necessary, and record the reflectance or fluorescence in the chromatograms obtained. Use the measured results for the calculation of the amount of substance in the test solution.

## Preparation of Chromatographic Plates-

## Apparatus-

Flat glass plates of convenient size, typically $20 \mathrm{~cm} \times 20$ cm .

An aligning tray or a flat surface upon which to align and rest the plates during the application of the adsorbent.

A storage rack to hold the prepared plates during drying and transportation. The rack holding the plates should be kept in a desiccator or be capable of being sealed in order to protect the plates from the environment after removal from the drying oven.

The adsorbent consists of finely divided adsorbent materials, normally 5 to $40 \mu \mathrm{~m}$ in diameter, suitable for chromatography. It can be applied directly to the glass plate or can be bonded to the plate by means of plaster of Paris (calcium sulfate hemihydrate [at a ratio of $5 \%$ to $15 \%$ ]) or with starch paste or other binders. The plaster of Paris will not yield as hard a surface as will the starch, but it is not affected by strongly oxidizing spray reagents. The adsorbent may contain fluorescing material to aid in the visualization of spots that absorb UV light.

A spreader, which, when moved over the glass plate, will apply a uniform layer of adsorbent of desired thickness over the entire surface of the plate. $\quad$ 2S (USP28)

Procedure-[note-In this procedure, use purified water that is obtained by distillation.] Clean the

- glass ${ }_{\text {2S }}$ (USP28)
plates scrupulously, as by immersion in chromie acideleansing mixture,
-using an appropriate cleaning solution (see Cleaning Glass Apparatus $\langle 1051\rangle$ ), $\boldsymbol{m}_{2 S}$ (USP28)
rinsing them with copious quantities of water until the water runs off the plates without leaving any visible water or oily spots, then dry. It is important that the plates be completely free from lint and dust when the adsorbent is applied.

Arrange the plate or plates on the aligning tray, place a $5-\times 20-$ cm plate adjacent to the front edge of the first square plate and another $5-\times 20-\mathrm{cm}$ plate adjacent to the rear edge of the last square, and secure all of the plates so that they will not slip during the application of the adsorbent. Position the spreader on the end plate opposite the raised end of the aligning tray. Mix 1 part of adsorbent with 2 parts of water (or in the ratio suggested by the supplier) by shaking vigorously for 30 seconds in a glass-stoppered conical flask, and transfer the slurry to the spreader. Usually 30 g of adsorbent and 60 mL of water are sufficient for five $20-\times 20-\mathrm{cm}$ plates. Complete the application of adsorbents using plaster of Paris binder within 2 minutes of the addition of the water, because thereafter the mixture begins to harden. Draw the spreader smoothly over the plates toward the raised end of the aligning tray, and remove the spreader when it is on the end plate next to the raised end of the aligning tray. (Wash away all traces of adsorbent from the spreader immediately after use.) Allow the plates to remain undisturbed for 5 minutes, then transfer the square plates, layer side up, to the storage rack, and dry at $105^{\circ}$ for 30 minutes. Preferably place the rack at an angle in the drying oven to prevent the condensation of moisture on the back sides of plates in the rack. When the plates are dry, allow them to cool to room temperature, and inspect the uniformity of the distribution and the texture of the adsorbent layer; transmitted light will show uniformity of distribution, and reflected light will show uniformity of texture. Store the satisfactory plates over silica gel in a suitable chamber.

Place fwe filter paper wieks, 18 cm in height and ws wide as the length of the developing chamber, into the chamber, add about 100 mL of the solvent (sufficient to have depth of 5 to 10 mm at the bettom of the chamber), seal the cover to the top of the chamber, and allow the system to equilibrate; it is essential that the wieks become completely wet. Altematively, the chamber may be com pletely lined with fllter paper. In either ease, assure that the filter paper dips into the solvent at the bettem of the chamber. Where Faper saturation of the chamber by these methods is undesirable, it is so indiented in the individual monograph.

Apply the test solution and the standard solution, as directed in the individual menegraph, at peints about 1.5 cm apart and about 2 em from the lower edge of the plate the lower edge is the first part over which the spreader moved in the applieation of the adsorbent layer), and allow to dry. Avoid physieal distubanee of the adsor bent during the spoting procedure (by the pipetor other applientor) or when handling the plates. The template will aid in determining the spot points and the 10 to 15 cm distance through which the solvent front should pass.

Place a mark $10 t 015 \mathrm{~cm}$ above the spet peint. Arrange the plate en the supporting rack (test spots toward the bottom), and intre duce the rack into the developing chamber. Allow the solvent in the chamber to reach the lower edge of the adsorbent, but do not allow the spot points to be immersed. Put the cover in place, and maintain the system until the solvent aseends to a peint 10.015 cm above the initial spots, this ustally requires about 15 minutes to 4 hour. Remove the plate frem the developing chamber, mark the solvent front, air dry the plates, and observe first mender short wavelength UV light ( 254 nm ) and then under long wavelength UV light $(360 \mathrm{~nm})$. Measure and record the distance of each spot from the point of origin, and indieate for each spe the wavelength under which it was observed. Determine the $R_{f}$ values for the principal spots (see Glossafy of Symbols). If further directed, spray the spots with the reagent specified, observe, and compare the test chromat egram with the standard ehrematogram.

## Contintrows Development Thin-Layyr Chromatography

In contrast to conventional thin layer chromatography, which is earried out in a closed tank, the continuous development or contintous flow technique allows the upper end of the plate to project through a slot in the cover of the developing chamber. When the developing solvent reaches the slot, continuous ovaporation-oceurs, producing a steady flow of solvent over the plate. In conventional thin layer chromatography, spot migration ceases when the solvent reaches the top of the plate, after which the spots simply enlarge by diffusion. In the continteus flow process, spet migratien contintes as long as the plate remains in the tank and the developing solvent is not exhatusted.

Development may be continued for several hours after the set vent reaches the top of the plate, to provide adequate migration of the spots. Usually spots of a standard solution, a test solution, and a mixture of equal amounts of test and standard solutions, are initially applied at a standard distanee from the base of the plate. Identity of the standard and test substances is confimed by their migrating equal distanees from the origin and by the observation that the two substanees applied as mixture-show no tendency to separate.

A major advantage of continuous development thin layer chromatography stems from the greater solvent selectivity for solvents of low solvent strength. Solvent strength refers to the property of a developing solvent that eauses solutes to migrate, and it is strongly influeneed by the polarity of the solvent. Inereasing the solvent strength by adding a more polar solvent eauses the $R_{r}$ value to in erease. Solvent selectivity refers to the ability of a solvent system to produce different $R_{L}$ values for closely related substances. In eonventional thin layer chromatography, a solvent system giving an $R_{f}$ value in the range of 0.3 to 0.7 , but with adequate selectivity to permit separation of the substanees being examined is usually selected. It is muth easier to find solvent systems producing adequate migration than to find those affording adequate selectivity.

Solvent systems of lower strength generally exhibit higher selec tivity, but are difficult to employ in conventional thin layer chromatography because they result in very little migration before the solvent reaches the top-of the plate. Migration may be increased, however, by repented drying and redevelopment of the plate or, more conveniently, by providing means for evaporation of solvent at the top of the plate, which results in continurus development. Two techniques are used: contintuous development and short bed eontintrous development thin layer chromatography.

An $R_{\text {L }}$ value cannet be measured in continurus development thin layer chrematography. Substances may be compared either by their migration distance over a fixed period of time or by comparisen with the migration of a standard substance applied to the plate.

## GONTINUOUS PEVEELOPMENT

Apparatus Acceptable apparatus and materials foricentinteus development thin layer chromatography are the same as those de seribedunder conventional Thin Lafyer Chrematography, exeeptas follows.

A developing chamber is used that consists of a rectangular tank, approximately $23 \mathrm{~cm} \times 23 \mathrm{~cm} \times 9 \mathrm{~cm}$, equipped with a glass solvent trough and a platform about 3.75 cm high to elevate the solvent trough above the base of the tank. The chamber is fitted with a cover having a $21 \times 6 \mathrm{em}$ slot in the front edge.

Procedure- Apply the standard solution, the test solution, and a mixture of equal amounts of the standard solution and the test solution to a line about 2 cm from the base of the plate. Place the plate in the elevated empty solvent trough with the adsorbent en the underside of the leaning plate. The adsorbent rests against a piece of heavy (about 1 mm thiek) ${ }^{2}$ filter paper measuring $20 \mathrm{~cm}-x$

[^346]3 cm , folded lengthwise and placed over the front edge of the tank. Place the developing solvent in the trough; set the cover in place, and seal all openings except where the adsorbent contacts the paper wiek. The plate extends about 1 cm beyend the top of the tank. After the solvent reaches the top of the plate, allow development to continue for an appropriat time. Then remove and dry the plate, and detect the spets by suitable means.

## SHORT BED-CONTINUOUS DEVELOPMENT

A major advantage of the short bed technique derives from the fact that solvent velecity is inversely related to bed length. Since spet migration depends upen the total amount of solvent passing over the plate, the short bed permits useful migration to be ob fained in a reasonable time with solvent having very low solvent strength. Lower diffusion in solvents of low solvent strength produres smaller and more dense spots, which enhances both detect ability and diseernment of small differences in migration distance.

Apparatus Aceeptable apparatus and materials for short bed eontinuous development thin layer chromatography are the same as those described under conventional Thin Layer Chromatograt phy, except as follows.

A shallow developing ehamber ${ }^{3}$ approximately $22 \mathrm{~cm}-9-\mathrm{cm}$ $* 3 \mathrm{~cm}$, equipped with a cover plate and tight fittimg polytef wings that enable the chamber to be sealed against the plate, is used. The-
inside bettom of the chamber contains ridges that suppert the plate and allow it to be inserted at different angles, thereby varying the length of the plate contained within the tank.

Procedure-Apply the standard-solution, the test solution, and a mixtre of equal parts of the standard solution and the test solth tion to a line about 2 cm from the base of the plate. Place the plate in the developing chamber (adsorbent side up), and add the develeping solvent to the chamber. No paper wick is employed. After the solvent reaches the top of the plate, allow development to continue for an appropriate time. Then remove and dry the plate, and detect the spets by sutitable means.
${ }^{\text {■ }}$ 2S (USP28)

## Change to read:

## INTERPRETATION OF CHROMATOGRAMS

Figure 1 represents a typical chromatographic separation of two substances, 1 and 2, where $t_{1}$ and $t_{2}$ are the respective retention times; and $h, h / 2$, and $W_{h 2}$ are the height, the half-height, and the width at half-height, respectively, for peak $1 . W_{1}$ and $W_{2}$ are the respective widths of peaks 1 and 2 at the baseline. Air peaks are a feature of gas chromatograms and correspond to the solvent front in liquid chromatography.


[^347]

Fig. 1. Chromatographic separation of two substances

Chromatographic retention times are characteristic of the compounds they represent but are not unique. Coincidence of retention times of a test and a reference substance can be used as a feature in construction of an identity profile but is insufficient on its own to establish identity. Absolute retention times of a given compound vary from one chromatogram to the next. Comparisens are nermat
 eulated by the equation:-

where $t_{z}$ and $t_{4}$-are the retention times, measured from the point of injection, of the test and reference substances, respectively, deter mined under identical experimental conditions on the same col umn, and $t_{4}$.is the retention time of a nomretained substanee, such as methame in the ease of gas chrematography.

In this and the following expressions, the corresponding retention volumes or linear separations on the chromatogram, both of which are direetly propertienal to retention time, may be substitut
 may be estimated frem the retention times measured from the peint

-Due to the fact that most procedures do not need to identify an unretained peak, comparisons are normally made in terms of relative retention times $R_{r}$ :

$$
R_{r}=\frac{t_{2}}{t_{1}}
$$

where $t_{2}$ and $t_{l}$ are the retention times, measured from the point of injection, of the test and the reference substances, respectively, determined under indentical experimental conditions on the same column.
Other procedures may identify the peak position using the relative retention $r$ :

$$
r=\frac{t_{2}-t_{M}}{t_{1}-t_{M}}
$$

where $t_{M}$ is the retention time of a non-retained marker,
which needs to be defined in the procedure. $\quad$ 2S (USP28)
The number of theoretical plates, $N$, is a measure of column efficiency. For Gaussian peaks, it is calculated by the equation:


$$
N=16\left(\frac{t}{W}\right)^{2}, \square_{2 S(U S P 28)}
$$

where $t$ is the retention time of the substance and $W$ is the width of the peak at its base, obtained by extrapolating the relatively straight sides of the peak to the baseline. $\Pi_{\text {m }}$ is the peak width at half height, obtained directly by electronic integrators.

■-2S (USP28)
The value of $N$ depends upon the substance being chromatographed as well as the operating conditions such as mobile phase or carrier gas flow rates and temperature, the quality of the packing, the uniformity of the packing within the column and, for capillary columns, the thickness of the stationary phase film, and the internal diameter and length of the column.

The separation of two components in a mixture, the resolution, $R$, is determined by the equation:

$$
R=\frac{2\left(t_{2}-t_{1}\right)}{W_{2}+W_{1}}
$$

in which $t_{2}$ and $t_{1}$ are the retention times of the two components, and $W_{2}$ and $W_{1}$ are the corresponding widths at the bases of the peaks obtained by extrapolating the relatively straight sides of the peaks to the baseline.

Where electronic integrators are used, it may be convenient to determine the resolution, $R$, by the equation:

$$
R=\frac{2\left(t_{2}-t_{1}\right)}{1.70\left(W_{1, h / 2}+\mathrm{W}_{2, h / 2}\right)}
$$

and to determine the number of theoretical plates, $N$, by the equation:

$$
N=5.54\left(t / W_{h / 2}\right)^{2}
$$

$\square_{\text {where }} W_{h / 2}$ is the peak width at half-height, obtained direct-

## ly by electronic integrators. $\quad$ 2S (USP28)

However, in the event of dispute, only equations based on peak width at baseline are to be used.

Peak areas and peak heights are usually proportional to the quantity of compound eluting. These are commonly measured by electronic integrators but may be determined by more classical approaches. Peak areas are generally used but may be less accurate if peak interference occurs. For manual measurements, the chart should be run faster than usual, or a comparator should be used to measure the width at half-height and the width at the base of the peak, to minimize error in these measurements. For accurate quantitative work, the components to be measured should be separated from any interfering components. Peak tailing and fronting and the measurement of peaks on solvent tails are to be avoided.

Chromatographic purity tests for drug raw materials are sometimes based on the determination of peaks due to impurities, expressed as a percentage of the area due to the drug peak. It is preferable, however, to compare impurity peaks with those in the chromatogram of a standard at a similar concentration. The standard may be the drug itself at a level corresponding to, for example, $0.5 \%$ impurity, or in the case of toxic or signal impurities, a standard of the impurity itself.

## Change to read:

## SYSTEM SUITABILITY

System suitability tests are an integral part of gas and liquid chromatographic methods. They are used to verify that the

- detection sensitivity, ${ }^{\text {2S }}$ (USP28)
resolution, and reproducibility of the chromatographic system are adequate for the analysis to be done. The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such.
-The detection sensitivity is a measure used to ensure the suitability of a given chromatographic procedure for the complete detection of the impurities in the Chromatographic purity or Related compounds tests by injecting a volume of a quantitation limit solution equal to that of the Test solution. Unless otherwise specified in the individual monograph, the quantitation limit solution may be prepared by dissolving the drug substance Reference Standard in the same solvent as that used for the Test solution at a $0.05 \%$ concentration level relative to the amount of drug substance in the Test solution for drug substances, and a $0.1 \%$ level relative to the amount of drug substance in the Test solution for drug products. The signal-to-noise ratio for the drug substance peak obtained with the quantitation limit solution should be not less than 10.m2S (USP28)

The resolution, $R$, [NOTE-All terms and symbols are defined in the Glossary of Symbols] is a function of the column efficiency, $N$, and is specified to ensure that closely eluting compounds are resolved from each other, to establish the general resolving power of the system, and to ensure that internal standards are resolved from the drug. Column efficiency may be specified also as a system suitability requirement, especially if there is only one peak of interest in the chromatogram; however, it is a less reliable means to ensure resolution than direct measurement. Column efficiency is a measure of peak sharpness, which is important for the detection of trace components.

Replicate injections of a Standard preparation used in the assay or other standard solution are compared to ascertain whether requirements for precision are met. Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation, $S_{R}$, if the requirement is $2.0 \%$ or less; data from six replicate injections are used if the relative standard deviation requirement is more than $2.0 \%$.

The tailing factor, $T$, a measure of peak symmetry, is unity for perfectly symmetrical peaks and its value increases as tailing becomes more pronounced (see Fig. 2). In some cases, values less than unity may be observed. As peak asymmetry increases, integration, and hence precision, becomes less reliable.


Fig. 2. Asymmetrical chromatographic peak
These tests are performed by collecting data from replicate injections of standard or other solutions as specified in the individual monograph. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions (see Procedures under Tests and Assays in the General Notices). Adjustments of operating eonditions to meet system suit ability requirements may be neeessary.
-If adjustments of operating conditions to meet system suitability requirements are necessary, each of the following is the maximum speciffation variation that can be considered, unless otherwise directed in the monograph. Adjustments are permitted only when Referenee Standards suitable standards (including Reference Standards) are available for all amalytes compounds used in the suitability test and are used to show that the adjustments have improved the quality of the chromatography in meeting system suitability requirements. Adjustments to chromatographic systems performed in order to comply with system suitability requirements are not to be made to compensate for column failure or to circumvent replacing a deteriorated column. The changes described below may require additional validation data unless the user can verify the suitability of the method under the new conditions. This verification consists of assessing the analytical performance characteristics that can be affected by the change (e.g., specificity, linearity, precision, accuracy) to ensure the adequacy of the method. Multiple adjustments that may have a cumulative effect in the performance of the system are to be avoided.
pH of Mobile Phase (HPLC)-The pH of the aqueous buffer used in the preparation of the mobile phase can be adjusted to within $\theta .2 \pm 0.2$ units of the value or range specified.

Concentration of Salts in Buffer (HPLC)—The concentration of the salts used in the preparation of the aqueous buffer used in the mobile phase can be adjusted to within $\pm 10 \%$, provided the permitted pH variation (see above) is met.

Ratio of Components in Mobile Phase (HPLC) The amount of the miner The following adjustment limits apply to minor components of the mobile phase (specified at $50 \%$ or less). The amount(s) of these component(s) can be adjusted by $\pm 30 \%$ relative. or $\pm 2 \%$ abselute (i.e., in relation to the total mobile phase), whichever is latger. However, the change in any component cannot exceed $\pm 10 \%$ absolute (i.e., in relation to the total mobile phase), nor can the final concentration of any component be reduced to zero. Adjustment can be made to one minor component in a ternary mixture. Examples of adjustments for binary and ternary mixtures are given below.

## Binary Mixtures-

SPECIFIED RATIO OF 50 : 50 - Thirty percent of 50 is $15 \%$ absolute, but this exceeds the maximum permitted change of $\pm 10 \%$ absolute in either component. Therefore, the mobile phase ratio may be adjusted only within the range of $40: 60$ to $60: 40$.

SPECIFIED-RATЮ-OF-95:5_Thirty percent of 5-is $1.5 \%$ abse tate. Hetwever, beeause adjustmentsupto $+2 \%$ absolute are allowed, the ratio may be adjusted within the range of 93.7 $5-97: 3$

SPECIFIED RATIO OF 2 : 98 - Thirty percent of 2 is $0.6 \%$ absolute. In this case an absolute adjustment of $\pm 2 \%$ is net at lowed because it would reduce the amount of the first eempenent to zere. Therefore the maximum allowed adjustment is within the range of $1.4: 98.6$ to $2.6: 97.4$.

## Ternary Mixtures-

SPECIFIED RATIO OF $60: 35: 5$-For the second component, $30 \%$ of 35 is $10.5 \%$ absolute, which exceeds the maximum permitted change of $\pm 10 \%$ absolute in any component. Therefore the second component may be adjusted only within the range of $25 \%$ to $45 \%$ absolute. For the third component, $30 \%$ of 5 is $1.5 \%$ absolute. Since $\pm 2 \%$ absolete is permit ted and provides more flexibility, the third compenent may be adjusted within the range of $3 \%$ to $7 \%$ absolute. In all cases, a sufficient quantity of the first component is used to give a total of $100 \%$. Therefore, mixture ranges of $50: 45: 5$ to $70: 25: 5$ or $58: 35: 7$ to- $62: 35: 3$ $58.5: 35: 6.5$ to $61.5: 35: 3.5$ would meet the requirement.

## Detector Wavelength of UV-Visible Detector

 (HPLC)—Deviations from the wavelengths specified in the method are not permitted. The procedure specified by the detector manufacturer, or another validated procedure, is to be used to verify that error in the detector wavelength is, at most, $\pm 3 \mathrm{~nm}$.Column Length (GC, HPLC): can be adjusted by as much as $70 \% \pm 70 \%$.

Column Inner Diameter (GC, HPLC): can be adjusted by as much as $\pm 25 \% 50 \% . \pm 25 \%$ for HPLC and $\pm 50 \%$ for GC .

Film Thickness (Capillary GC): can be adjusted by as much as $-50 \%$ to $100 \%$.

Particle Size (HPLC): can be reduced by as much as $50 \%$.

Particle Size (GC): going from a larger to a smaller or a smaller to a larger (if it is the same "Range Ratio", which is the diameter of the largest particle divided by the diameter of the smallest particle) particle size GC mesh support is acceptable, provided the chromatography meets the requirements of the system suitability.

Flow Rate (GC, HPLC): can be adjusted by as much as $\pm 50 \%$.

Injection Volume (GC, HPLC): can be reduced as far as is consistent with accepted precision and detection limits. It may be increased to as much as twice the volume specifled, provided there are ne adverse-ffects-on factors sueh as baseline, peak shapes, resolution, linearity, and retention times.

Column Temperature (HPLC): can be adjusted by as much as $\pm 20^{\circ} . \pm 10^{\circ}$. Column thermostating is recommended to improve control and reproducibility of retention time.

Golumn Oven Temperature (GC): can be adjusted by as much as $\pm 2 \%$, in terms of abselute temperature. $\pm 10 \%$.

Oven Temperature Program (GC)—Adjustment of temperatures is permitted as stated above. For the times specified for the temperature to be maintained or for the temperature to be changed from one value to another, an adjustment of up to $\pm 20 \%$ is permitted.

## Gradient Elution (HPLC) The configuration of the

equipment employed may signifieantly alter the resolution, retention time, and relative retentions described in the meth od. Should this ocetr, it may be due to exeess-dwell time, which is the volume between the peint at which the weet
thants meet and the top-of the columm. 2 2S (USP28)
Unless otherwise directed in the monograph, system suitability parameters are determined from the analyte peak.

To ascertain the effectiveness of the final operating system, it should be subjected to suitability testing. Replicate injections of the standard preparation required to demonstrate adequate system precision may be made before the injection of samples or may be interspersed among sample injections. System suitability must be demonstrated throughout the run by injection of an appropriate control preparation at appropriate intervals.

The control preparation can be a standard preparation or a solution containing a known amount of analyte and any additional materials useful in the control of the analytical system, such as excipients or impurities. Whenever there is a significant change in equipment or in a critical reagent, suitability testing should be performed before the injection of samples. No sample analysis is acceptable unless the requirements of system suitability have been met. Sample analyses obtained while the system fails
$\mathbf{■}_{\text {system suitability }} \mathbf{m}_{2 \text { S }}$ (USP28)
requirements are unacceptable.

## Change to read:

## GLOSSARY OF SYMBOLS

To promote uniformity of interpretation, the following symbols and definitions are employed where applicable in presenting formulas in the individual monographs.
-Where a different symbol or definition is used in an individual monograph, the monograph text takes precedence
(see General Notices). ${ }^{\text {n2S }}$ (USP28)
[NOTE-Where the terms $W$ and $t$ both appear in the same equation they must be expressed in the same units.]

$$
\begin{aligned}
& * \\
& \text { relative retention, } \\
& e_{k}, e_{,}, e_{4} \\
& \text { eoneentrations of Reference-Standard, inter } \\
& \text { mal standard, and analyte in a particular solut } \\
& \text { tion. } \\
& \epsilon_{4} \quad \text { enneentration ratio of analyte and internal } \\
& \text { standard in test solution or Assay preparation, } \\
& \epsilon_{s} \quad \text { encentration ratio of Reference Standard and } \\
& \text { internal- standard in Standard solution, } \\
& \boldsymbol{f}^{\text {■2S }} \text { (USP28) } \\
& \text { distance from the peak maximum to the lead- } \\
& \text { ing edge of the peak, the distance being mea- } \\
& \text { sured at a point } 5 \% \text { of the peak height from } \\
& \text { the baseline. } \\
& k^{\prime} \text { capacity factor, } \\
& k^{\prime}=\frac{\text { amount of substance in stationary phase }}{\text { amount of substance in mobile phase }} \\
& k^{\prime}=\frac{\text { time spent by substance in stationary phase }}{\text { timespent by substance in mobile phase }}=\frac{t}{t_{n}}-1 . \\
& \boldsymbol{m}^{\prime}=\frac{\text { time spent by substance in stationary phase }}{\text { time spent by substance in mobile phase }}=\frac{t}{t_{M}}-1 . \square_{2 \mathrm{~S}(\text { USP28 })}
\end{aligned}
$$

$N$
$Q_{4}$

Es
$\mathbf{■}_{N}=16\left(\frac{t}{W}\right)^{2}$ or $N=5.54\left(\frac{t}{W_{h / 2}}\right)^{2} . \mathbf{■ V S ( U S P 2 8 )}$

Standard, internal-standard, and analyte in apartieular solution.
quantity ratio of analyte and internal standard in test solution or Assay preparation,

quantity ratio of Referenee Standard and internal standard in Standard solution,

relative retention,


$$
r=\frac{t_{2}-t_{M}}{t_{1}-t_{M}}
$$

$r_{i}$
$\mp_{t} r_{I S} \quad$ peak response of the internal standard
obtained from a chromatogram. $\quad$ 2S (USP28) peak response of the Reference Standard obtained from a chromatogram.
peak response of the analyte obtained from a chromatogram.
resolution between two chromatographic peaks,

$$
R=\frac{2\left(t_{2}-t_{1}\right)}{W_{1}+W_{2}}
$$

$$
\text { or } R=\frac{2\left(t_{2}-t_{1}\right)}{1.70\left(W_{1, h / 2}+W_{2, h / 2}\right)} \square_{2 \mathrm{~S}(U S P 28)}
$$

$R_{F} \quad$ chromatographic retardation factor equal to the ratio of the distance from the origin to the center of a zone divided by the distance from the origin to the solvent front.
$R_{p}$ relative retention
$R_{r}=\frac{\text { distance traveled by test substance }}{\text { distance traveled by standard }}$.
$\boldsymbol{m}_{\boldsymbol{R}_{R}}$ 2S (USP28)
${ }^{-} R_{r-\boldsymbol{\square}}$ 2S (USP28)
${ }^{\bullet} R_{\text {rel }}$
$R_{S}$
relative retention time


$$
R_{r}=\frac{t_{2}}{t_{1}}
$$

relative retardation

$$
R_{\text {rel }}=\frac{\text { distance traveled by test substance }}{\text { distance traveled by standard }} \mathbf{m}_{2 s(\text { USP28) }}
$$

peak response ratio for a Standard preparation containing Reference Standard and internal standard,


$$
R_{S}=\frac{r_{s}}{r_{I S}} ■ 2 \mathrm{~S}(U S P 28)
$$

$R_{U}$
$S_{R}(\%)$
$T$
$t$
$t_{a}$
W
$W_{h / 2}$
$W_{0.05}$
peak response ratio for Assay preparation containing the analyte and internal standard,


$$
R_{U}=\frac{r_{U}}{r_{I S}} \quad \text { ■2S(USP28) }
$$

relative standard deviation in percentage,

$$
S_{R}(\%)=\frac{100}{\bar{X}}\left[\frac{\sum_{i=1}^{N}\left(X_{i}-\bar{X}\right)^{2}}{N-1}\right]^{1 / 2},
$$

where $X_{i}$ is an individual measurement in a set of $N$ measurements and $X$ is the arithmetic mean of the set. tailing factor,

$$
T=\frac{W_{0.05}}{2 f}
$$

retention time measured from time of injection to time of elution of peak maximum. retention time of nonretarded component, air with thermal conductivity detection. width of peak measured by extrapolating the relatively straight sides to the baseline. width of peak at half height. width of peak at $5 \%$ height.

## Change to read:

## CHROMATOGRAPHIC REAGENTS

The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer. [NOTE-Particle sizes given in this listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category of packings or phases listed below, there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

## Packings

L1-Octadecyl silane chemically bonded to porous silica or ceramic micro-particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L2-Octadecyl silane chemically bonded to silica gel of a controlled surface porosity that has been bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L3-Porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.
L4-Silica gel of controlled surface porosity bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L5-Alumina of controlled surface porosity bonded to a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L6-Strong cation-exchange packing-sulfonated fluorocarbon polymer coated on a solid spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.

L7-Octylsilane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L8-An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support,

- 3 to $\mathbf{m}_{1 S}$ (USP28)
$10 \mu \mathrm{~m}$ in diameter.
L9- $10-\mu \mathrm{m}$ irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating.

L10-Nitrile groups chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L11—Phenyl groups chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L12-A strong anion-exchange packing made by chemically bonding a quaternary amine to a solid silica spherical core, 30 to $50 \mu \mathrm{~m}$ in diameter.
L13-Trimethylsilane chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L14-Silica gel $10 \mu \mathrm{~m}$ in diameter
■1 (USP28)
having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating,
-5 to $10 \mu \mathrm{~m}$ in diameter. $\quad$ 1S (USP28)
L15-Hexylsilane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L16-Dimethylsilane chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L17-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form, 7 to $11 \mu \mathrm{~m}$ in diameter.

L18-Amino and cyano groups chemically bonded to porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L19-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the calcium form, about $9 \mu \mathrm{~m}$ in diameter.

L20-Dihydroxypropane groups chemically bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L21-A rigid, spherical styrene-divinylbenzene copolymer, 5 to $10 \mu \mathrm{~m}$ in diameter.
L22-A cation-exchange resin made of porous polystyrene gel with sulfonic acid groups, about $10 \mu \mathrm{~m}$ in size.

L23-An anion-exchange resin made of porous polymethacrylate or polyacrylate gel with quaternary ammonium groups, about $10 \mu \mathrm{~m}$ in size.

L24-A semi-rigid hydrophilic gel consisting of vinyl polymers with numerous hydroxyl groups on the matrix surface, 32 to $63 \mu \mathrm{~m}$ in diameter. ${ }^{5}$

L25-Packing having the capacity to separate compounds with a molecular weight range from 100-5000 (as determined by polyethylene oxide), applied to neutral, anionic, and cationic water-soluble polymers. A polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contained some residual carboxyl functional groups) was found suitable.

L26-Butyl silane chemically bonded to totally porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

[^348]L27-Porous silica particles, 30 to $50 \mu \mathrm{~m}$ in diameter.
L28-A multifunctional support, which consists of a high purity, $100 \AA$, spherical silica substrate that has been bonded with anionic exchanger, amine functionality in addition to a conventional reversed phase C 8 functionality.

L29-Gamma alumina, reverse-phase, low carbon percentage by weight, alumina-based polybutadiene spherical particles, $5 \mu \mathrm{~m}$ in diameter with a pore volume of $80 \AA$.

L30-Ethyl silane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter.

L31-A strong anion-exchange resin-quaternary amine bonded on latex particles attached to a core of $8.5-\mu \mathrm{m}$ macroporous particles having a pore size of $2000 \AA$ and consisting of ethylvinylbenzene cross-linked with $55 \%$ divinylbenzene.

L32-A chiral ligand-exchange packing-L-proline copper complex covalently bonded to irregularly shaped silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L33-Packing having the capacity to separate dextrans by molecular size over a range of 4000 to $500,000 \mathrm{Da}$. It is spherical, silica-based, and processed to provide pH stability. ${ }^{6}$

L34-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the lead form, about $9 \mu \mathrm{~m}$ in diameter.

L35-A zirconium-stabilized spherical silica packing with a hydrophilic (diol-type) molecular monolayer bonded phase having a pore size of $150 \AA$.

L36-A 3,5-dinitrobenzoyl derivative of L-phenylglycine covalently bonded to $5-\mu \mathrm{m}$ aminopropyl silica.

L37-Packing having the capacity to separate proteins by molecular size over a range of 2,000 to $40,000 \mathrm{Da}$. It is a polymethacrylate gel.

L38-A methacrylate-based size-exclusion packing for watersoluble samples.

L39-A hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin.

L40-Cellulose tris-3,5-dimethylphenylcarbamate coated porous silica particles, 5 to $20 \mu \mathrm{~m}$ in diameter.

L41-Immobilized $\alpha_{1}$-acid glycoprotein on spherical silica particles, $5 \mu \mathrm{~m}$ in diameter.

L42-Octylsilane and octadecylsilane groups chemically bonded to porous silica particles, $5 \mu \mathrm{~m}$ in diameter.

L43-Pentafluorophenyl groups chemically bonded to silica particles $\square_{\text {by }}$ a propyl spacer, $\mathbf{m S}_{1 S}$ (USP27) 5 to $10 \mu \mathrm{~m}$ in diameter.

L44-A multifunctional support, which consists of a high purity, $60 \AA$, spherical silica substrate that has been bonded with a cationic exchanger, sulfonic acid functionality in addition to a conventional reversed phase C8 functionality.

L45-Beta cyclodextrin bonded to porous silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter.

L46-Polystyrene/divinylbenzene substrate agglomerated with quaternary amine functionalized latex beads,

■about $_{\square 15}$ (USP28)
$10 \mu \mathrm{~m}$ in diameter.
L47-High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, $8 \mu \mathrm{~m}$ in diameter. ${ }^{7}$
L48-Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion-exchange microbeads, $15 \mu \mathrm{~m}$ in diameter.

[^349]L49-A reversed-phase packing made by coating a thin layer of polybutadiene onto spherical porous zirconia particles, 3 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{8}$
L50-Multifunction resin with reversed-phase retention and strong anion-exchange functionalities. The resin consists of ethylvinylbenzene, $55 \%$ cross-linked with divinylbenzene copolymer, 3 to $15 \mu \mathrm{~m}$ in diameter, and a surface area not less than $350 \mathrm{~m}^{2}$ per $g$. Substrate is coated with quaternary ammonium functionalized latex particles consisting of styrene cross-linked with divinylbenzene. ${ }^{9}$

L51-Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{10}$

L52-A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{11}$

L53-Weak cation-exchange resin consisting of ethylvinylbenzene, $55 \%$ cross-linked with divinylbenzene copolymer, 3 to 15 $\mu \mathrm{m}$ diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than $500 \mu \mathrm{Eq} /$ column. ${ }^{12}$

L54-A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 $\mu \mathrm{m}$ in diameter. ${ }^{13}$
${ }^{\mathbf{\Delta}}$ L55-A strong cation-exchange resin made of porous silica coated with polybutadiene-maleic acid copolymer, about $5 \mu \mathrm{~m}$ in diameter. ${ }^{14}$ பUSP27
${ }^{\mathbf{\Delta}}$ L56-Propyl silane chemically bonded to totally porous silica particles, 3 to $10 \mu \mathrm{~m}$ in diameter. ${ }^{15} \Delta U S P 27$
-L57-A chiral-recognition protein, ovomucoid, chemically bonded to silica particles, about $5 \mu \mathrm{~m}$ in diameter, with a pore size of $120 \AA$. $\mathbf{m}_{2 S}$ (USP27)

■58-Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, about 7 to $11 \mu \mathrm{~m}$ in diameter. ${ }^{16}{ }^{\mathbf{2 S}}$ (USP27)
${ }^{\text {® }}$ L57 \#\# (Nevirapine, Supelcosil ABZ)—Spherical, porous silica gel, 3 or $5 \mu \mathrm{~m}$ in diameter, the surface of which has been covalently modified with palmitamidopropyl groups and endcapped with acetamidopropyl groups to a ligand density of about $6 \mu$ moles per $\mathrm{m}^{2}{ }^{\mathrm{a}} \mathbf{\Delta}^{\mathrm{\Delta}}$ USP28

[^350]${ }^{\text {st5 }}$ \#\# (Albumin Human, Antithrombin III Human, TSKgel G3000 SW) -Packing having the capacity to separate proteins by molecular weight over the range of 10 to 500 kDa . It is spherical ( $10 \mu \mathrm{~m}$ ), silica-based, and processed to provide hydrophilic characteristics and pH stability. ${ }^{\mathrm{b}}$ USPP28
-L64 \#\# (Lycopene, Lycopene Preparation, YMC 30)C30 silane bonded phase on a fully porous spherical silica, 3
to $15 \mu \mathrm{~m}$ in diameter. IS (USP28) L\#\# (Enoxaparin Solitinn Injection, IomPac AG11) [TO eome.?

eome.]
E\#\# (Enoxaparin Soditm, Dowex 1X8) [Tocome.]
L\#\# (Enoxaparin Sodium, Dowex 50WX2) [Te
come. $]$
-L\#\# (Dalteparin Sodium, anion-exchange Dowex 1X8)-[To come.]
L\#\# (Dalteparin Sodium, cation-exchange Dowex
50WX2)-[To come.] $]_{\text {2S (USP28) }}$

## Phases

G1-Dimethylpolysiloxane oil.
G2-Dimethylpolysiloxane gum.
G3-50\% Phenyl-50\% methylpolysiloxane.
G4-Diethylene glycol succinate polyester.
G5-3-Cyanopropylpolysiloxane.
G6-Trifluoropropylmethylpolysiloxane.
G7-50\% 3-Cyanopropyl-50\% phenylmethylsilicone.
G8-80\% Bis(3-cyanopropyl)-20\% 3-cyanopropylphenylpoly-
siloxane (percentages refer to molar substitution).
G9-Methylvinylpolysiloxane.
G10-Polyamide formed by reacting a $\mathrm{C}_{36}$ dicarboxylic acid with 1,3-di-4-piperidylpropane and piperidine in the respective mole ratios of $1.00: 0.90: 0.20$.

G11—Bis(2-ethylhexyl) sebacate polyester.
G12—Phenyldiethanolamine succinate polyester.
G13-Sorbitol.
G14-Polyethylene glycol (av. mol. wt. of 950 to 1050).
G15-Polyethylene glycol (av. mol. wt. of 3000 to 3700).
G16-Polyethylene glycol compound (av. mol. wt. about 15,000 ). A high molecular weight compound of polyethylene glycol with a diepoxide linker. Available commercially as Polyethylene Glycol Compound 20M, or as Carbowax 20M, from suppliers of chromatographic reagents.

[^351]G17-75\% Phenyl-25\% methylpolysiloxane.
G18-Polyalkylene glycol.
G19-25\% Phenyl-25\% cyanopropyl-50\% methylsilicone.
G20-Polyethylene glycol (av. mol. wt. of 380 to 420).
G21-Neopentyl glycol succinate.
G22-Bis(2-ethylhexyl) phthalate.
G23-Polyethylene glycol adipate.
G24-Diisodecyl phthalate.
G25-Polyethylene glycol compound TPA. A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with terephthalic acid. Available commercially as Carbowax 20M-TPA from suppliers of chromatographic reagents.

G26-25\% 2-Cyanoethyl-75\% methylpolysiloxane.
G27-5\% Phenyl-95\% methylpolysiloxane.
G28-25\% Phenyl-75\% methylpolysiloxane.
G29-3,3'-Thiodipropionitrile.
G30--Tetraethylene glycol dimethyl ether.
G31-Nonylphenoxypoly(ethyleneoxy)ethanol (av. ethyleneoxy chain length is 30); Nonoxynol 30.

G32-20\% Phenylmethyl-80\% dimethylpolysiloxane.
G33-20\% Carborane-80\% methylsilicone.
G34-Diethylene glycol succinate polyester stabilized with phosphoric acid.

G35-A high molecular weight compound of a polyethylene
glycol and a diepoxide that is esterified with nitroterephthalic acid.
G36-1\% Vinyl-5\% phenylmethylpolysiloxane.
G37-Polyimide.
G38-Phase G1 containing a small percentage of a tailing inhibitor. ${ }^{17}$

G39-Polyethylene glycol (av. mol. wt. about 1500).
G40-Ethylene glycol adipate.
G41—Phenylmethyldimethylsilicone ( $10 \%$ phenyl-substituted).
G42-35\% phenyl-65\% dimethylpolysiloxane (percentages refer to molar substitution).

G43-6\% cyanopropylphenyl-94\% dimethylpolysiloxane (percentages refer to molar substitution).

G44-2\% low molecular weight petrolatum hydrocarbon grease and $1 \%$ solution of potassium hydroxide.

G45-Divinylbenzene-ethylene glycol-dimethylacrylate.
G46-14\% Cyanopropylphenyl-86\% methylpolysiloxane.
G47-Polyethylene glycol (av. mol. wt. of about 8000).
G48-Highly polar, partially cross-linked cyanopolysiloxane.
G49_Proprietary derivatized phenyl groups on a polysiloxane backbene. ${ }^{+8}$
-G50 \#\# (Docosahexaenoic Acid)—Polyethylene glycol,
cross-linked (av. mol. wt. of more than 20,000). ${ }^{\mathrm{c}}$ 1S (USP28)
neutral, but not base-washed. The siliceous earth may be silanized by treating with an agent such as dimethyldichlorosilane ${ }^{19}$ to mask surface silanol groups.

S1AB-The siliceous earth as described above is both acid- and base-washed. ${ }^{19}$

S1C-A support prepared from crushed firebrick and calcined or burned with a clay binder above $900^{\circ}$ with subsequent acidwash. It may be silanized.

S1NS-The siliceous earth is untreated.
S2-Styrene-divinylbenzene copolymer having a nominal surface area of less than $50 \mathrm{~m}^{2}$ per g and an average pore diameter of 0.3 to $0.4 \mu \mathrm{~m}$.

S3-Copolymer of ethylvinylbenzene and divinylbenzene having a nominal surface area of 500 to $600 \mathrm{~m}^{2}$ per $g$ and an average pore diameter of $0.0075 \mu \mathrm{~m}$.

S4-Styrene-divinylbenzene copolymer with aromatic - O and N groups, having a nominal surface area of 400 to $600 \mathrm{~m}^{2}$ per g and an average pore diameter of $0.0076 \mu \mathrm{~m}$.

S5-40- to $60-\mathrm{mesh}$, high-molecular weight tetrafluorethylene polymer.

S6-Styrene-divinylbenzene copolymer having a nominal surface area of 250 to $350 \mathrm{~m}^{2}$ per g and an average pore diameter of $0.0091 \mu \mathrm{~m}$.

S7-Graphitized carbon having a nominal surface area of $12 \mathrm{~m}^{2}$ per g .

S8-Copolymer of 4-vinyl-pyridine and styrene-divinylbenzene.

S9-A porous polymer based on 2,6-diphenyl-p-phenylene oxide.

S10-A highly polar cross-linked copolymer of acrylonitrite and divinylbenzene.

S11—Graphitized carbon having a nominal surface area of 100 $\mathrm{m}^{2}$ per g modified with small amounts of petrolatum and polyethylene glycol compound. ${ }^{20}$

S12-Graphitized carbon having a nominal surface area of 100 $\mathrm{m}^{2}$ per g .

## GENERAL CHAPTERS

## General Information

## Supports

NOTE-Unless otherwise specified, mesh sizes of 80 to 100 or, alternatively, 100 to 120 are intended.

S1A-Siliceous earth for gas chromatography has been flux-calcined by mixing diatomite with $\mathrm{Na}_{2} \mathrm{CO}_{3}$ flux and calcining above $900^{\circ}$. The siliceous earth is acid-washed, then water-washed until

[^352]
## Briefing

$\langle 1072\rangle$ Disinfectants and Antiseptics, page 726 of PF 29(3) [May-June 2003]. On the basis of comments received, it is proposed to clarify this general information chapter and to eliminate Table 3: Biocidal Activity, Organic Inactivation, Residual Activity, and Application of Some Common Disinfectants.

$$
\text { (AMB: D. Porter) } \quad \text { RTS }-41771-1
$$

[^353]
## Add the following:

## ■ $\langle 1072\rangle$ DISINFECTANTS AND ANTISEPTICS

## INTRODUCTION

A sound cleaning and sanitization program is needed $\ddagger$ prevent the mierobial contamination of Pharmacopeial artieles in controlled environments used for manufacture. for controlled environments used in the manufacture of pharmacopeial articles to prevent the microbial contamination of these articles. Sterile drug products may be contaminated via their pharmaceutical ingredients, process water, packaging components, manufacturing environment, processing equipment, and manufacturing operators. Current Good Manufacturing Practices (cGMPs) emphasize the size, design, construction, and location of buildings and construction materials, and the appropriate material flow to facilitate cleaning, maintenance, and proper operations for the manufacture of drug products. When disinfectants are used in a manufacturing environment, care must should be taken to prevent the drug product from becoming contaminated with chemical disinfectants as a result of the inherent toxicity of the disinfectants. The requirements for aseptic processing include readily cleanable floors, walls, and ceilings that have smooth and nonporous surfaces; particulate, temperature, and humidity controls; and cleaning and disinfecting procedures to produce and maintain aseptic conditions. The cleaning and sanitization program menst should achieve specified cleanliness standards, control microbial contamination of products, and be designed to prevent the chemical contamination of pharmaceutical ingredients,
product-contact surfaces and/or equipment, packaging materials, and ultimately the drug products. These principles also apply to nonsterile dosage forms where the microbial contamination is controlled by the selection of appropriate pharmaceutical ingredients, utilities, manufacturing environments, sound equipment cleaning procedures, products especially formulated to control water activity, inclusion of suitable preservatives, and product packaging design.
In addition to disinfectants, antiseptics are used to decontaminate human skin and exposed tissue and may be used by personnel prior to entering the manufacturing area. Chemical sterilants may be used to decontaminate surfaces in manufacturing and sterility testing areas. Furthermore, sterilants may be used for the sterilization of Pharmacopeial articles, and UV irradiation may be used as a surface sanitizer.

This general information chapter will discuss the selection of suitable chemical disinfectants and antiseptics; the demonstration of their bactericidal, fungicidal, and sporicidal efficacy; the application of disinfectants in the sterile pharmaceutical manufacturing area; and regulation and safety considerations. Biofilm formation and its relationship to disinfectants are outside the scope of this chapter. Additional information not covered in the chapter may be obtained from standard texts on disinfectants and antiseptics. ${ }^{1}$

## DEFINITIONS

Antiseptic-An agent that inhibits or destroys microorganisms on living tissue including skin, oral cavities, and open wounds.

[^354]Chemical Disinfectant-A chemical agent used on inanimate surfaces and objects to destroy infectious fungi, viruses, and bacteria, but not necessarily their spores. Sporicidal and antiviral agents are may be considered a special elasses class of disinfectants. Disinfectants are often categorized as high-level, intermediate-level and low-level by medically oriented groups based upon their efficacy against various microorganisms.

Cleaning Agent-An agent for the removal from facility and equipment surfaces of product residues that may inactivate sanitizing agents or harbor microorganisms.

Decontamination-The removal of microorganisms by disinfection or sterilization.

Disinfectant—A chemical or physical agent that destroys or removes vegetative forms of harmful microorganisms when applied to a surface.

Sanitizing Agent-An agent for reducing, on inanimate surfaces, the number of all forms of microbial life including fungi, viruses, and all forms of bacteria and their spores.

Sporicidal Agent-An agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

Sterilant—An agent that destroys all forms of microbial life including fungi, viruses, and all forms of bacteria and their spores. Sterilants are liquid or vapor-phase agents.

Microorganisms differ greatly in their resistance to disinfection agents. The order of resistance of clinically significant microorganisms to chemical disinfectants from most to least resistant is listed in Table 1.

Table 1. The Resistance of Some Clinically Important Microorganisms to Chemical Disinfectants (Listed in Order of Decreasing Resistance)

| Type of |  |
| :---: | :---: |
| Microorganisms | Examples |
| Bacterial spores | Bacillus subtilis and Clostridium |
|  | sporogenes |
| Mycobacteria | Myeobacteria <br> Mycobacterium <br> tuberculosis |
| Nonlipid-coated viruses | Poliovirus and rhinovirus |
| Fungi Fungal spores and vegetative molds and yeast | Trichophyton, Cryptococcus, and Candida spp. |
| Vegetative bacteria | Pseudomonas aeruginosa, <br> Staphylococcus aureus, and Salmonella spp. |
| Lipid-coated viruses | Herpes simplex virus, hepatitis B virus, and human immunodeficiency virus |

## CLASSIFICATION OF DISINFECTANTS

Chemical disinfectants are classified by their chemical type. This includes aldehydes, alcohols, halogens, peroxides, quaternary ammonium compounds, and phenolic compounds (see Table 2).

Table 2. General Classification of Antiseptics, Disinfectants, and Sporicidal Agents

| Chemical |  |  |
| :--- | :---: | :---: |
| Fype Entity | Classification | Example |
| Aldehydes | Sporicidal agent | $2 \%$ Glutaldehyde |
| Alcohols | General purpose | $70 \%$ Isopropyl |
|  | disinfectant, | alcohol, 70\% |
|  | antiseptic, <br> antiviral agent | alcohol |
|  |  |  |

Table 2. General Classification of Antiseptics, Disinfectants, and Sporicidal Agents (Continued)

| Chemical Type Entity | Classification | Example |
| :---: | :---: | :---: |
| Chlorine and sodium hypochlorite | Sporicidal agent | $0.5 \%$ Sodium hypochlorite |
| Phenolics | General purpose disinfectant | $500 \mu \mathrm{~g}$ per g <br> Chlorocresol, $500 \mu \mathrm{~g}$ per g chloroxylenol |
| Ozone | Sporicidal agent | 8\% Gas by weight |
| Hydrogen peroxide | Vapor phase sterilant, liquid sporicidal agent, antiseptic | $4 \mu \mathrm{~g}$ per $\mathrm{g} \mathrm{H}_{2} \mathrm{O}_{2}$ <br> vapor, $10 \%-25 \%$ <br> solution, 3\% <br> solution |
| Substituted diguanides | Antiseptic agent | 0.5\% Chlorhexidine gluconate |
| Peracetic acid | Liquid sterilant, vapor phase sterilant | $0.2 \%$ peracetic acid, $1 \mu \mathrm{~g}$ per g peracetic acid |
| Ethylene oxide | Vapor-phase sterilant | $600 \mu \mathrm{~g}$ per g ethylene oxide |

Table 2. General Classification of Antiseptics, Disinfectants, and Sporicidal Agents (Continued)

| Chemical |  |  |
| :---: | :---: | :---: |
| جype Entity | Classification | Example |
| Quaternary | General purpose | $200 \mu \mathrm{~g}$ per g |
| ammonium | disinfectant, | benzalkonium |
| compounds | antiseptic | chloride |
| $\beta$-Propiolac- | Sporicidal agent | $100 \mu \mathrm{~g}$ per g |
| tone |  | $\beta$-propiolactone |

The effectiveness of a disinfectant depends on its intrinsic biocidal activity, the concentration of the disinfectant, the contact time, the nature of the surface disinfected, the hardness of water used to dilute the disinfectant, the amount of organic materials present on the surface, and the type and the number of microorganisms present. Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Environmental Protection Agency (EPA) registers chemical disinfectants marketed in the United States and requires manufacturers to supply product information on the use dilution, type of microorganisms killed, and the necessary contact time (Table 3). Certain liquid chemical sterilizers intended for use on critical or semicritical medical devices are defined and regulated by the U.S. Food and Drug Administration (FDA).

Table 3. Biocidal Activity, Organic Inactivation, Residual-Activity, and Applications of Some-Common-Disinfectants

| Class Entity | Bacterici- <br> dat | Fungieidat | Sperieidal | Inactivated by | Residat <br> Activity | Application |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | Organies |  |  |
| Aleohels | yes | yes | n | HO | n | antiseptic, removing disinfectant residues |
| Aldehydes | yes | yes | yes | A | yes | disinfecting instruments |
| Chlorines (hypechlo rites) | yes | yes | yes | yes | m | disinfecting surfaces |

Fable 3. Biocidal-Aetivity, Organie Inactivation, Residual Activity, and-Applieations of Some-Common-Disinfeetants (Continued)

| Chemieal | Bacterici | Fungieidat | Spericidat | Inactivated | Residtat | Applieation |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Class Entity | dat |  |  | by | Aetivity |  |
|  | Organies |  |  |  |  |  |
| Hydrogen peroxide | yes | yes | yes | yes | A | antiseptic, vaper phase-sterilant |
| Phenolies | yes | yes | ne | weakly | yes | disinfecting surfaces |
| Peracetic acid | yes | yes | yes | n | yes | vaper phase sterilant |
| Quaternay ammeni | yes | weak | f | yes | yes | antiseptic, disinfecting suffaces |
| um compeunds |  |  |  |  |  |  |
| Substitated digut | yes | yes | m | m | yes | antiseptic; disinfecting instrut |
| nides (chlorhexi |  |  |  |  |  | ments |
| dine) |  |  |  |  |  |  |
| Iedophors (provi- | yes | yes | n | n® | yes | antiseptic |
| done iodine) |  |  |  |  |  |  |
| Ethylene dioxide | yes | yes | yes | H | n | *aper phase-sterilant |
| oxide |  |  |  |  |  |  |

## SELECTION OF AN ANTISEPTIC FOR HAND AND SURGICAL SITE DISINFECTION

Hands and surgical sites are disinfected in a hospital setting to reduce the resident flora and to remove transient flora (e.g., Streptococcus pyogenes) and methicillin-resistant $S$. aureus and P. aeruginosa that have been implicated in hos-pital-associated infection. Use of antiseptics to disinfect hands has been shown to be more effective than soap and water in reducing the counts of bacteria on the skin; repeated antiseptic use further reduces these counts. These principles may be applied to clean-room operators in the pharmaceutical industry.

Common antiseptics include 4\% chlorhexidine, $10 \%$ propidine povidone-iodine, $3 \%$ hexachlorophene, $70 \%$ isopropyl alcohol, and $0.5 \%$ chlorhexidine in $95 \%$ ethanel alcohol.

## SELECTION OF A DISINFECTANT FOR USE IN A PHARMACEUTICAL MANUFACTURING

## ENVIRONMENT

When selecting a disinfectant for use in a pharmaceutical manufacturing area, the following points ment should be considered: the number and types of microorganisms to be controlled; the spectrum of activity of commercially available disinfectants; the reputation of the disinfectant supplier; the claims as a sterilant; the disinfectant or sanitizer supported by the EPA registrations; the concentration, application method, and contact time of the disinfectant; the nature of the surface material being disinfected and its compatibility with the disinfectant; the amount of organic compounds on the surface that may inactivate a disinfectant; the possible need to maintain a residual bactericidal activity of the disin-
fectant on the surface; the corrosiveness of the disinfectant to equipment with repeated application; the safety considerations for operators applying the disinfectant; the compatibility of the disinfectant with cleaning agents and other disinfectants; the planned disinfectant rotation; and the steps that need to be taken to avoid the contamination of pharmaceutical products by a disinfectant. ${ }^{2}$

## THEORETICAL DISCUSSION OF DISINFECTANT ACTIVITY

Plots of the $\log$ of the number of microorganisms per mL surviving in a disinfectant solution indicate that first-order kinetics can be applied as a rable gross approximation to the reduction in microbial count with respect to time. In practice, the plots show a more sigmoid curve with a slower initial reduction in numbers followed by an increasing rate with respect to time.

The rate constant, $K$, for the disinfection process can be calculated by the formula:

$$
(1 / t)\left(\log N_{\mathrm{o}} / N\right),
$$

in which $t$ is the time, in minutes, for the microbial count to be reduced from $N_{\mathrm{o}}$ to $N$; $N_{\mathrm{o}}$ is the initial number of organisms, in cfu per mL; and $N$ is the final number, in cfu per mL , of organisms.

As with a first-order chemical reaction, the same concentration of disinfectant reduces the number of organisms more rapidly at elevated temperatures. This can be ex-

[^355]pressed as a temperature, $T$, coefficient per $10^{\circ}$ rise in temperature, $Q_{10}$, calculated by the formula:

Time to decontamination at $T /$
Time to decontamination at $T$,
in which $T$ is $T^{\circ}-10$.
Further evidence that a first-order reaction is an inadequate description of disinfection is that the $Q_{10}$ values for chemical and enzyme reactions are 2 to 3 , while the common disinfectants phenol and alcohol have a $Q_{10}$ of 4 and 45 , respectively.

Critical to the successful employment of disinfectants is an understanding of the effect of disinfectant concentration on microbial reduction. A plot of the $\log$ of the time to reduce the microbial population in a standard inoculum to zero against the $\log$ of the disinfectant concentration is a straight line with the slope of the line termed the concentration exponent, $n$. The relationship can be expressed as follows:
$n=\left(\log\right.$ of the kill time at concentration $\left.C_{2}\right)-(\log$ of the kill time at concentration $\left.C_{1}\right) /\left(\log C_{1}-\log C_{2}\right)$,
in which $C_{1}$ and $C_{2}$, are the higher and lower disinfectant concentrations, respectively.

The wide differences in concentration exponents, $n$, have practical consequences in picking the use dilution of different disinfectants and in using dilution to neutralize a disinfectant in disinfectant-effectiveness testing and routine microbial monitoring of the manufacturing environment. For example, mercuric chloride has a concentration exponent of 1 , so a 3 -fold dilution will reduce the disinfectant activity by $3^{1}$ (or by one-third), while phenol with a concentration exponent of 6 will have a $3^{6}$ (or a 729 -fold) reduction in disinfectant activity. Disinfectants with a larger concen-
tration exponent or dilution coefficient rapidly lose activity when diluted. The concentration exponents for some disinfectants are listed in Table 3.

Table 3. Concentration Exponents of Common Antiseptics, Disinfectants, and Sterilants

| Disinfectant | Concentration Exponents |
| :--- | :---: |
| Hydrogen peroxide | 0.5 |
| Sodium hypochlorite | 0.5 |
| Mercuric chloride | 1 |
| Chlorhexidine | 2 |
| Formaldehyde | 1 |
| Ethan Alcohol | 9 |
| Phenol | 0.8 to 2.5 |
| Quaternary ammonium | 6.0 to 12.7 |
| $\quad$ compounds | 4 to 9.9 |
| Aliphatic alcohols |  |
| Phenolic compounds |  |

Another important consideration may be the pH of the disinfectant. Many disinfectants are more active in the ionized form, while others are more active in the nonionized form. The degree of ionization will depend on the $\mathrm{p} K_{\mathrm{a}}$ of the agent and the pH of the disinfection environment. For example, phenol, with a $\mathrm{p} K_{\mathrm{a}}$ of 10 , will be more effective at a pH below 7 where it is nonionized, while acetic acid will be more effective at a pH below 4 where it is ionized.

## MECHANISM OF DISINFECTANT ACTIVITY

Table 4 lists the sites and modes of action of some representative disinfectants.

Table 4. Mechanism of Disinfectant Activity Against Microbial Cells

| Target | Disinfectant |
| :---: | :---: |
| Cell wall | Formaldehyde, hypochlorite, and mercurials |
| Cytoplasmic membrane, action on membrane potential | Anilides and hexachlorophene |
| Membrane enzymes, action on electrontransport chain | Hexachlorophene |
| Action on ATP | Chlorhexidine and ethylene oxide |
| Action on enzymes with - SH groups | Ethylene oxide, glutaraldehyde, hydrogen peroxide, hypochlorite, iodine, and mercurials |
| Action on general membrane permeability | Alcohols, chlorhexidine, and quaternary ammonium compounds |
| Cell contents, general coagulation | Chlorhexidine, aldehydes, hexachlorophene, and quaternary ammonium compounds |
| Ribosomes | Hydrogen peroxide and mercurials |
| Nucleic acids | Hypochlorites |
| Thiol groups | Ethylene oxide, glutaraldehyde, hydrogen peroxide, hypochlorite, mercurials |
| Amino groups | Ethylene oxide, glutaraldehyde and hypochlorite |
| General oxidation | Ethylene oxide, glutaraldehyde, and hypochlorite |

## MICROBIAL RESISTANCE TO DISINFECTANTS

The development of microbial resistance to antibiotics is a well-described phenomenon. The development of microbial resistance to disinfectants is less likely, as disinfectants are more powerful biocidal agents than antibiotics and are applied in high concentrations against low populations of microorganisms usually not growing actively, so the selective pressure for the development of resistance is less profound. However, the most frequently isolated microorganisms from an environmental monitoring program may be periodically subjected to use dilution testing with the agents used in the disinfection program to confirm their susceptibility.

## DISINFECTANT CHALLENGE TESTING

Under FIFRA, the EPA requires companies that register public health antimicrobial pesticide products including disinfectants, sanitization agents, sporicidal agents, and sterilants to ensure the safety and effectiveness of their products before they are sold or distributed. Companies registering these products must address the chemical composition of their product, include toxicology data to document that their product is safe if used as directed on the label, include efficacy data to document their claims of effectiveness against specific organisms and to support the directions for use provided in the labeling, and provide labeling that reflects the required elements for safe and effective use. While these directions provide valuable information, they may not be helpful in terms of the products' use as disinfectants in a manufacturing environment.

In the United States, the official disinfectant testing methods are published by AOAC International ${ }^{3}$ and include the Phenol-Coefficient Test, Use-Dilution Method Test, Hand Surface Carrier Method and Sporicidal Carrier Test. A scientific study submitted for EPA review in support of disinfectant registration must be conducted at a laboratory facility that follows the Good Laboratory Practices (GLP) regulations ( 21 CFR 58). To demonstrate the efficacy of a disinfectant within a pharmaceutical manufacturing environment, it may be deemed necessary to conduct the following tests: (1) use-dilution tests (screening disinfectants for their efficacy at various concentrations and contact times against a wide range of standard test organisms and environmental isolates); (2) surface challenge tests (using standard test microorganisms and microorganisms that are typical environmental isolates, applying disinfectants to surfaces at the selected use concentration with a specified contact time, and determining the log reduction of the challenge microorganisms); and (3) a statistical comparison of the frequency of isolation and numbers of microorganisms isolated prior to and after the implementation of a new disinfectant. This is considered necessary because critical process steps like disinfection of aseptic processing areas, as required by GMP regulations, need to be validated, and the EPA registration requirements do not address how disinfectants are used in the pharmaceutical, biotechnology, and medical device industries. For the surface challenge tests, the test organisms are enumerated using swabs, surface rinse, or contact plate methods. Neutralizers that inactivate the disinfectants must should be included in either the diluent or microbiological media used for microbial enumeration or both (see Table 5).

[^356]Additional information on disinfectant neutralization may be found in Validation of Microbial Recovery from Pharmacopeial Articles $\langle 1227\rangle$.

Table 5. Neutralizing Agents for Common Disinfectants

| Disinfectant | Neutralizing Agent |
| :--- | :--- |
| Alcohols | Dilution or polysorbate 80 |
| Glutaraldehyde | Glycine and sodium <br> bisulfite |
| Sodium hypochlorite | Sodium thiosulfate |
| Chlorhexidine <br> Mercuric chloride and <br> other mercurials | Thioglycolic acid |
| Quaternary ammonium <br> compounds | Polysorbate 80 and lecithin |
| Phenolic compounds | Dilution or polysorbate 80 |
|  | and lecithin |

Universal neutralizer broths may be formulated to contain a range of neutralizing agents. For example, Đay Dey/Engley (D/E) broth contains $0.5 \%$ polysorbate $80,0.7 \%$ lecithin, $0.1 \%$ sodium thioglycolate, $0.6 \%$ sodium thiosulfate, $0.25 \%$ sodium bisulfite, $0.5 \%$ tryptone, $0.25 \%$ yeast extract, and $1.0 \%$ dextrose; letheen broth contains $0.5 \%$ polysorbate $80,0.07 \%$ lecithin, $1.0 \%$ peptamin, $0.5 \%$ beef extract, and $0.5 \%$ sodium chloride; and Tryptone-Azolectin-Tween (TAT) broth base + tween 20 contains $4.0 \%(\mathrm{v} / \mathrm{v})$ polysorbate $20,0.5 \%$ lecithin, and $2.0 \%$ tryptone.

In practice, sufficient organisms need to be inoculated on a 2 -inch $\times 2$-inch square of the surface being decontaminated, i.e., a coupon, to demonstrate at least a 2 (for bacterial spores) to 3 (for vegetative bacteria) log reduction during a predetermined contact time (i.e., 10 minutes over and above the recovery observed with a control disinfectant application). The efficacy of the neutralizers and their ability to
recover inoculated microorganisms from the material ment should be demonstrated during the use-dilution or surfacechallenge studies. Points to remember are that disinfectants are less effective against the higher numbers of microorganisms used in laboratory challenge tests than they are against the numbers that are found in clean rooms (see Microbiological Evaluation of Clean Rooms and Other Controlled Environments $\langle 1116\rangle$ ); that inocula from the $\log$ growth phase that are typically employed in laboratory tests are more resistant, with the exception of spores formed during the static phase, than those from a static or dying culture or stressed organisms in the environment; and that microorganisms may be physically removed during actual disinfectant application in the manufacturing area.
Fypieat Although not all inclusive, typical challenge organisms that may be employed are listed in Table 6.

Table 6. Typical Challenge Organisms

| AOAC Challenge | Typical Environmental |
| :---: | :---: |
| Organisms | Isolates |
| Bactericide: Escherichia coli, | Bactericide: Micrococcus |
| ATCC 11229; | luteus, S. epidermdis, |
| S. aureus, ATCC 6538; | Coynebacterium |
| P. aeruginosa, ATCC | jeikeium, P. vesiclaris |
| 15442 |  |
| Fungicide: C. albicans, | Fungicide: P. chryso- |
| ATCC 10231 or 2091; | genum, A. niger |
| Penicillium chrysogenum, |  |
| ATCC 11709; Aspergillus |  |
| niger, ATCC 16404 |  |
| Sporicide: B. subtilis, | Sporicide: B. sphaericus, |
| ATCC 19659 | B. thatrensis B. |
|  | thuringiensis |

Because a wide range of different materials of construction are used in clean rooms and other controlled areas, each material needs to be evaluated separately to validate the efficacy of a given disinfectant. Table 7 contains a list of common materials used in clean room construction.

Table 7. Typical Surfaces to be Decontaminated by Disinfectants in a Pharmaceutical Manufacturing Area

| Material | Application |
| :--- | :--- |
| Stainless steel 305 304L | Work surfaces, filling |
| and 316L grades | equipment, tanks, etc. |
| Glass | Windows and vessels |
| Plastic, vinyl | Curtains |
| Plastic, polycarbonate | Insulation coating |
| Lexan ${ }^{\circledR}$ (plexiglass) | Shields |
| Epoxyl coated gypsum | Walls and ceilings |
| Fiberglass reinforced | Wall paneling |
| $\quad$ plastic $^{\text {Tyvek }}{ }^{\circledR}$ |  |
| Terrazzo tiles | Equipment wraps |

## DISINFECTANTS IN A CLEANING AND SANITIZATION PROGRAM

The selection of suitable disinfectants and the verification of their effectiveness in surface challenge testing is critical in the development of a cleaning and sanitization program.

Issues associated with the successful implementation of such a program are the development of written procedures, staff training, the decisions on disinfectant rotation, institution of application methods and contact times, environmental monitoring to demonstrate efficacy, and personnel safety.

The cGMP 21 CFR 211.67, Equipment Cleaning and Maintenance, details the requirements for written procedures for cleaning, maintenance, and sanitization of pharmaceutical manufacturing equipment. These procedures must
should address the assignment of responsibility, establishment of schedules, details of cleaning operations, protection of clean equipment prior to use, inspection for cleanliness immediately prior to use, and maintenance of cleaning and sanitization records.

Involved staff require training in mierobiology, industry practices for cleaning and sanitization, safe handling of concentrated disinfeetants, the preparation and disposal of dis infectants, and the appropriate applieation methods. It must be emphasized that the preparation of the eorrect dilutions is eritical since many disinfectant failures are attributable to use of excessively diluted disinfectant solutions. Typically, disinfectants used in aseptic filling areas are diluted with Water for Injection and are prepared aseptically. Since it is theoretically possible for the selective presstre of the con tinmous use of a single disinfectant to result in the presence of disinfectant resistant mieroorganisms in a mantufacturing area, regulatory agencies advoeate the rotation of disinfec tants. Commen practices inelude the daily use of a phenolic empend and weekly use of a sperieidal agent or the rota tion of daily use of phenolic and quaternary ammonium empounds and weekly use of sporicidal agent. Other options may also be supported. Disinfectants applied on petent tial product contact suface are typieally removed with $70 \%$ aleohel wipes. The use of a sperieidal agent is frequently limited to weekly application, since they are com monly oxidizing agents and may corrode stainless steel equipment and degrade other materials used in facility construetion. Facilities must be periodieally cleaned to remove any disinfectant residues.

Staff involved in disinfection require training in microbiology, industry practices for cleaning and sanitization, safe handling of concentrated disinfectants, the preparation and disposal of disinfectants, and appropriate application methods. It should be emphasized that the preparation of the cor-
rect dilutions is critical because many disinfectant failures can be attributed to use of disinfectant solutions that are too dilute. Typically disinfectants used in aseptic processing and filling areas are diluted with Sterile Purified Water, and are prepared aseptically. Alternately, the disinfectant may be diluted with Purified Water, and then sterile filtered to eliminate microorganisms that may potentially persist in a disinfectant. Diluted disinfectants must have an assigned expiration dating justified by effectiveness studies.

Because it is theoretically possible that the selective pressure of the continuous use of a single disinfectant could result in the presence of disinfectant-resistant microorganisms in a manufacturing area, in some quarters the rotation of disinfectants has been advocated. However, the literature supports the belief that the exposure of low numbers of microorganisms on facility and equipment surfaces within a clean room where they are not actively proliferating will not result in the selective pressure that may be seen with the antibiotics. It is prudent to augment the daily use of a bactericidal disinfectant with weekly (or monthly) use of a sporicidal agent. The daily application of sporicidal agents is not generally favored because of their tendency to corrode equipment and because of the potential safety issues with chronic operator exposure. Other disinfection rotation schemes may be supported on the basis of a review of the historical environmental monitoring data. Disinfectants applied on potential product contact surfaces are typically removed with $70 \%$ alcohol wipes. The removal of residual disinfectants should be monitored for effectiveness as a precaution against the possibility of product contamination.

The greatest safety concerns are in the handling of concentrated disinfectants and the mixing of incompatible disinfectants. For example, concentrated sodium hypochlorite solutions (at a concentration of more than $5 \%$ ) are strong
oxidants and will decompose on heating, on contact with acids, and under the influence of light, producing toxic and corrosive gases including chlorine. In contrast, dilute solutions (at a concentration of less than $0.5 \%$ ) are not considered as hazardous. Under no circumstances should disinfectants of different concentrations be mixed. Material Safety Data Sheets for all the disinfectants used in a manufacturing area mest should be available to personnel handling these agents. Appropriate safety equipment such as face shields, safety glasses, gloves, and uniforms must be issued to personnel handling the disinfectant preparation, and personnel must be trained in the proper use of this equipment. Safety showers and eye wash stations must be situated in the work area where disinfectant solutions are

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prepared.m2S (USP28)
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## BRIEFING

$\langle 1079\rangle$ Good Storage and Shipping Practices. The previous proposal that appeared on page 1612 of $P F 29(5)$ [Sept.-Oct. 2003] is hereby canceled and replaced with a new proposal for this general information chapter, which is intended to provide guidance to manufacturers, repackagers, distributors, shippers, and pharmacists on practices designed to maintain the integrity of pharmaceuticals during storage and shipment. Some sections of the previously proposed chapter Packaging, Storage, and Distribution of Pharmacopeial Articles $\langle 1141\rangle$, page 493 of PF 26(2) [Mar.-Apr. 2000] are incorporated into this current proposal. Additional information from $\langle 1141\rangle$ related to packaging can also be found in the proposed Good Packaging Practices $\langle 1177\rangle$, also appearing in this number of $P F$.
Other official chapters referred to in the text for this currently proposed chapter include Pharmaceutical Calculations in Prescription Compounding $\langle 1160\rangle$, Pharmaceutical Stability $\langle 1150\rangle$, a renamed section of Pharmaceutical Dosage Forms $\langle 1151\rangle$, and a proposed chapter Environmentally Sensitive Preparations $\langle 386\rangle$, PF 30(5) [Sept.-Oct. 2004]. Although cold-chain management is a timely topic, the PSD Expert Committee is awaiting industrial initiatives before including it in this currently proposed chapter, or it may be proposed as a separate new chapter. Because the text has undergone many edits and revisions, it is presented afresh here to facilitate review. Comments should be addressed to: Dr. Claudia Okeke, Department of Standards Development.

This Committee reports with great sadness the passing of Leonard Bailey, Ph.D., the driving force for this chapter (see Policies and Announcements).
(PSD: C. Okeke) RTS-41145-1

## Add the following:

## <1079 GOOD STORAGE AND SHIPPING PRACTICES

This general information chapter is intended to provide general guidance concerning storing, distributing, and shipping of Pharmacopeial preparations. It describes procedures to maintain proper storage environments for individual articles and to ensure a preparation's integrity, including its appearance, until it reaches the user. There is no change to any applicable requirements under Current Good Manufacturing Practices, approved labeling, state laws governing pharmacies, the USP General Notices and Requirements, or monographs. The section Preservation, Packaging, Storage, and Labeling under General Notices and Requirements provides definitions for storage conditions. All equipment used for recording, monitoring, and maintaining temperatures and humidity conditions should be calibrated on a regular basis. This calibration should be based on NIST or international standards (see Monitoring Devices-Time, Temperature, and Humidity $\langle 1118\rangle$ ). A Pharmacopeial preparation may follow several potential routes from the original manufacturer to the patient. Figure 1 documents present-day routes and the associated risks. These risks include exposure to temperature excursions, humidity, light, and oxygen. For a discussion of climates, stability, and mean kinetic temperature, see Pharmaceutical Stability $\langle 1150\rangle$. Temperature- or
humidity-sensitive articles are to be handled in accordance with General Notices and Environmentally Sensitive Preparations 〈386〉.

## PACKAGING AND STORAGE STATEMENT IN MONOGRAPHS

Most articles have storage conditions identified by their labeling. Otherwise, it is expected that the conditions for storing the article are specified in the monograph according to definitions provided by the General Notices and Requirements in the section Storage Temperature and Humidity under Preservation, Packaging, Storage, and Labeling. In cases where additional information on packaging and storage is desired, a specific statement can be provided in the Packaging and storage or the Labeling section of the individual monograph.

## STORAGE IN WAREHOUSES, PHARMACIES, TRUCKS, SHIPPING DOCKS, AND OTHER LOCATIONS

Pharmacopeial articles are to be stored in locations that adhere to conditions established by the manufacturer. Where the desired conditions are not established, use storage conditions described in the General Notices and Requirements or in the applicable monograph.

## Warehouses

Observation of the temperature variations in a warehouse should be made over a period of time to establish a meaningful temperature profile, including the temperature variations and conditions in the different parts of the warehouse. Such observations provide data and information as to where various products should and should not be stored.

## ESTABLISHING TEMPERATURE PROFILES

Temperature profiles can be compiled by using a suitable number of thermometers or other temperature recording instruments. They should be placed throughout the warehouse in divided sections and should record the maximum and minimum temperatures during a 24 -hour period for a total of three consecutive 24 -hour periods. The following factors, some of which may give rise to extreme temperatures, should be considered during the process of temperature profiling: the size of the space, location of space heaters, sunfacing walls, low ceilings or roofs, and geographic location of the warehouse. Temperature profiling for warehouses already in use should be done at known times of external temperature extremes, e.g., for a period of not less than 3 hours when air temperatures are higher than $25^{\circ}$ or less than $15^{\circ}$. Profiling should be conducted in both summer and winter. A mean kinetic temperature (MKT) should be obtained for any separate areas within the warehouse (see Pharmaceutical Calculations in Prescription Compounding $\langle 1160\rangle$ for samples of MKT calculations). The temperature profile report should provide recommendations for the use of each area and identification of any areas that are found unsuitable for storage of Pharmacopeial articles.

## CONTROLLED ROOM TEMPERATURE

The General Notices provide a definition for Controlled Room Temperature. A temperature profiling study should demonstrate suitability for storing Pharmacopeial articles in areas determined to be at room or controlled room temperature. A suitable number of temperature and humidity recording instruments should be installed to record temperatures and to provide temperature and humidity profiles. Temperature recording should be conducted to meet the recommendations for establishing mean kinetic temper-
ature and to comply with the warehouse's written procedures. These written procedures should have a reporting mechanism in place whereby a management tree is informed in the event that predefined high or low temperatures or humidity limits have been exceeded. Records can be reviewed as determined by the management system in accordance with established guidelines. Suitable training should be provided to persons who record temperatures, and proper quality accountability and tracking systems should be maintained.

## STORAGE AT "COOL," "COLD," "REFRIGERATOR," AND "FREEZING" CONDITIONS

The General Notices provide definitions for cool, cold, refrigerator, and freezer temperatures. A temperature profiling study can be used to establish suitable areas for storing Pharmacopeial articles designated to be stored under these conditions. Equipment used for storing Pharmacopeial articles at these low temperatures should be qualified according to written procedures provided by the management system. Recording devices can be installed within the equipment and used to enable both air and product temperatures to be recorded at regular intervals. The number and location of monitoring devices should be determined based on the result of the temperature profile. Temperature records should be examined at least once every 24 hours or as provided in the equipment protocol. Cool or cold conditions are moisture-condensing conditions. Humidity-monitoring devices should be used in cases where the repackaged Pharmacopeial article is humidity-sensitive or labeled to avoid moisture. Additionally, there can be installed temperaturemonitoring, and where necessary, humidity-monitoring alarm devices that have the capability of alerting personnel in the event that control is compromised. There should be protocols in place to address procedures for responding to
failed temperature and humidity ranges both for normal working hours and outside normal working hours. Temperature and humidity should be reviewed at the times designated by the established protocol. The calibration and functioning of all temperature and humidity monitoring devices, including alarms and other associated equipment, should be checked on an annual or semiannual basis. Regular maintenance protocols should be in place for refrigeration equipment. There should be written agreements in place for all maintenance and evaluation procedures, and this may include an emergency situation protocol.

## PERSONNEL TRAINING

Suitable training should be provided for personnel who handle Pharmacopeial articles with special storage temperature requirements. Personnel should know how to monitor temperatures and how to react to situations where adverse temperatures are identified. There should be written procedures in place such that the adverse temperatures are recorded and a report provided to the parties designated in the protocol.

## VALIDATION OF "COLD" EQUIPMENT OR STORES

Only climate control equipment for which a contractor has provided documentation to assure its suitability for temperature and humidity requirements should be considered for use in cold storage. Qualification procedures on a regular basis should be independently conducted on equipment in
cold stores to guarantee suitability and proper functioning. The procedure should demonstrate the temperature profile throughout the proposed equipment for both air and product temperatures when empty as well as when loaded. The procedure should also demonstrate the time taken for temperatures to exceed the maximum temperature in the event of a power failure. Qualification should consider thermal fluctuations that occur during stock replenishment and order removal. The results of the qualification should demonstrate the ability of the equipment to maintain the required temperature range in all areas, defining any zones which should not be used for storage such as those areas in close proximity to cooling coils, cold air streams from equipment ventilation, or doors. The variability of the system can be characterized by using the relative standard deviation. Thermal monitoring should establish that the system is rugged in that its temperature profile is consistent and reliable.

## DISTRIBUTION AND SHIPMENT OF PHARMACOPEIAL ARTICLES

As indicated in Figure 1, a drug can take a variety of paths from the manufacturer to the patient. In the simplest form of the distribution system, the manufacturer ships directly to the customer, such as a doctor's office, clinic, or hospital. However, more often, the article leaves the manufacturer's chain of control and enters a complex system of handoffs that involve the distribution chain to the patient.

## Drug Product Distribution



Figure 1

Figure 1. Drug product distribution.

Shippers and distributors are to follow the proper storage and shipping requirements as indicated by the manufacturer. For particular cases, such as shipment of vaccines or other special care products, manufacturers may require special shipping and storage conditions generally referred to as "cold-chain management". For example, manufacturers may attach temperature-monitoring devices and/or ship under specified controlled conditions to ensure that the desired temperature is maintained during distribution (see Monitoring Devices-Time, Temperature, and Humidity $\langle 1118\rangle$ ). Validated, available temperature- and/or humidity-monitor-
ing technologies can be used to monitor the overall environmental effect on compendial articles during shipment and distribution. In these cases, the shipping conditions of the package are recorded. In general, extreme temperature conditions (i.e., excessive heat, freezing) should be avoided. Distribution systems chosen to deliver pharmaceutical products from the manufacturer to the consumer should take into account basic operational parameters, including timeliness and accountability. The manufacturer's FDA-approved storage conditions, printed in the labeling of the product, should be observed carefully at each destination of the distribution
chain (see Figure 1), unless specifically instructed otherwise in the immediate label of a shipping container. This may be the case for certain pallet-sized shipping containers where the amount of refrigerant contained (e.g., dry ice, gel packs) is based on an anticipated exterior condition approximating controlled room temperature. In such cases, placing the shipping container in a refrigerator could lead to the product inside freezing, potentially affecting its quality. Items requiring special handling conditions will have those conditions clearly indicated in the labeling for the product. The Prescription Drug Marketing Act of 1987 and the ensuing regulations in 21 CFR Part 203, Prescription Drug Marketing, and Part 205, Guidelines for State Licensing of Wholesale Prescription Drug Distributors, provide the necessary regulations and guidance for several legs of the distribution chain for the prescription drug. The manufacturers and distributors should work together to establish proper distribution and product-handling requirements for the purpose of ensuring appropriate product maintenance in transit. Pharmacists and physicians should educate patients regarding proper storage of products to ensure product integrity at the patient level. Information that may be considered in determining the ability of pharmaceutical articles to maintain their Pharmacopeial requirements of identity, strength, quality, and purity through the distribution channel may include, but is not limited to the following: ICH stability studies, temperature cycling studies, stability shipping studies, ongoing regulatory stability commitment studies, market experience portfolio (i.e., product complaint files, historical product performance data, product development data), and product labeling commitments.

## Qualification Protocol

Operational and performance testing should be parts of a formal qualification protocol that may use controlled environments or actual field testing based on the projected transportation channel. These should reflect actual load configurations, conditions, and expected environmental extremes. Temperature and humidity monitors should be placed into the product or a representative thereof. Testing consists of consecutive replicate field transportation tests using typical loads, according to an established protocol.

## Physical Challenges

Most products are sufficiently robust to withstand distribution with minimal protection from routine, well-understood physical and environmental hazards. Several standard test methods are available for evaluating package performance factors under well-documented shock, vibration, and other transit elements. The American Society for Testing and Materials document, "Standard Practice for Performance Testing of Shipping Containers and Systems" (ASTM D4169-98), and the International Safe Transit Association's (ISTA) specifications have similar methods for evaluation of shipping performance for various types of transit modes such as less-than-truckload (LTL), small package, rail car, air freight, etc. From the manufacturer's perspective, these tests are very useful in evaluating the product and package durability and fragility. The tests are usually performed on shipping carton quantities of a specific stock keeping unit (SKU) as an unbroken whole. Fragility problems can be corrected with package modifications, which could include placing cotton or rayon coilers in bot-
tles or placing top and bottom pads in the shipping case to reduce package breakage. Not all protective packaging elements follow the SKU through the system.

Basic packaging principles are observed when separating the contents of the manufacturer's shipping container or pallet load into smaller quantities or when shipping mixed product loads. For example, glass containers are wrapped in a bubble wrap or other shock-absorbent material, and the void spaces are filled with dunnage (e.g., foam "peanuts," shredded or tightly crumpled paper, bubble wrap) to protect the contents from shifting and drop impact. Large-volume liquid containers may be bagged in plastic and kept isolated to prevent leakage to, or damage of, adjacent packages. "Skin packaging," a term describing a heat-shrink film that anchors the load to fiberboard and prevents load shift, can be an excellent method of protecting some products, but it may be inappropriate for heat-sensitive products. The shipping carton should have correct Edge Crush Test (ECT) characteristics for freight being shipped according to Item 222 of the National Motor Freight Classification and Rule 41 of the Uniform Freight Classification.

## Temperature Challenges

Shipping of temperature-sensitive articles requiring ther-
carrier type (e.g., small package carrier or integrator, freight forwarder, U.S. Postal Service). The shippers should know and understand the systems they use and should design the protective package accordingly. Storage temperature ranges may not be indicative of the allowable tolerances during shipping. Articles labeled for special storage conditions (between $2^{\circ}$ and $8^{\circ}$ ) vary widely in their tolerance of short-term exposure to heat and cold. Some, such as soft gelatin capsules and suppositories, carry specific upper limits on both shipping containers and SKUs. A temperature cycling study intended to identify those articles affected by multiple, short-term excursions beyond the storage temperature limits should be performed. These data provide wholesalers and distributors with clearer identification of those drug products that may require special handling during particular climate conditions.

## Materials

Two commonly used types of refrigerant are dry ice (frozen carbon dioxide gas) and wet ice (frozen water), which appears as crushed ice or in various refrigerant packs containing water mixtures with specific freezing points. Phasechange materials are also available for specialized needs. Refrigerant packs should have the correct freezing point and be cooled to the proper surface temperature prior to use. Articles harmed by accidental freezing may require a barrier between the refrigerant and the product or some other special packaging. Insulating materials commonly available include foil laminates, bubble pack, corrugated, fabricated, and molded expanded polystyrene (EPS) cartons, and fabricated or molded urethane foam cartons, with or without additional interior components. Recognized standard test methods for evaluating insulated containers are currently limited to ASTM D3103-92, Standard Test Method for Thermal Insulation Quality of Packages and a method
under development by ISTA. Neither one fully addresses all of the issues involved, but both include useful information on testing procedures. The tests should be modified based on the specific system adopted by the shipper. The manufacturer may be able to supply helpful data on specific articles and their requirements.

## SPECIAL HANDLING

Certain classes of Pharmacopeial articles may require special handling. Such articles include products classified as dangerous goods under the Department of Transportation (DOT), state, local, or carrier rules; or products classified as controlled substances by the Drug Enforcement Administration (DEA) or by individual states.

## Receipt of Pharmacopeial Articles

Upon arrival of Pharmacopeial articles to warehouse loading docks, premises, and other arrival areas, the Pharmacopeial articles are to be transferred to their manufacturerdesignated storage environment within 2 hours of receipt. Limitation of the time spent in the uncontrolled environments of the loading dock is important to ensure that the integrity of the preparation is maintained. This is particularly important for temperature-sensitive items. The delivery document should be reviewed at receiving sites to ensure that the Pharmacopeial articles have not been subjected to any delays during shipment that could result in exposure of the article to extremes of temperature, or to any other extreme or undesirable conditions. In addition, to the extent possible, the receiving personnel should ensure that the ruggedness requirements in shipment have been met. For Pharmacopeial articles requiring extreme caution, special handling, or refrigerator temperature storage conditions,
those who supply the articles (e.g., wholesalers and manufacturers) and delivery contractors should provide documented evidence to show that the required temperature range has been maintained during transportation. In the event that a deviation from the required temperature range has been observed during shipment of an article requiring such a shipping condition, the supplier or delivery contractors should document the temperature and the length of time the compendial article was not within the designated storage temperature. The pharmaceutical manufacturer may be contacted to determine the significance of unusual variances.

## Distribution or Shipping Vehicles

Vehicles used for shipping or distribution of Pharmacopeial articles designated for storage at controlled room temperature should be suitably equipped to ensure that the temperature excursions encountered are within those allowed under the definition of controlled room temperature. Steps should be taken so that extremes of temperature, whether above or below the specified temperatures, should not be encountered during delivery procedures.

## Vehicle Qualification

Where practical, suitable monitoring devices, as determined by the manufacturer and vehicle supplier, should be placed in different areas of the truck to establish a temperature profile of the truck over a 24 -hour period during a hot summer day, average high, and a cold winter day, average low, and during a normal or typical day. The derived temperature of the different parts of the truck may be used to determine the location on the truck where Pharmacopeial articles can be stored appropriately during shipping (see Monitoring Devices-Time, Temperature, and Humidity $\langle 1118\rangle$ ).

## Pharmaceutical Delivery Staff

As part of the contractual agreement between the delivery contractors and the manufacturers, the delivery staff should receive appropriate training to ensure that they are aware of the correct procedures to follow in maintaining products at the correct temperature. There may be written procedures that should be documented. In addition, the transportation personnel should have proper knowledge of the temperature profile of the vehicle to ensure proper placement of the Pharmacopeial articles in the vehicle. Pharmacopeial articles requiring special handling (e.g., refrigeration) or environmentally sensitive preparations should be transported in a suitably equipped vehicle to ensure that the articles are maintained at the correct temperature during distribution, shipping, and delivery and up to the point of receipt. Special arrangements should be made to inform receiving personnel, pharmacists, or other appropriate customers that the package includes articles with special storage and handling specifications and are to be transferred immediately to the appropriate storage location. The manufacturer, shipper, or delivery agency should provide appropriate evidence to show that the required temperature has been maintained throughout shipment and distribution.

## SHIPMENT FROM MANUFACTURER TO WHOLESALER

## Wholesaler

The wholesaler receiving the pharmaceutical articles should ensure that on arrival, the pharmaceutical articles are transferred to the correct environment without delay, as directed by the manufacturer, ideally within 2 hours of receipt. The wholesaler should examine the delivery documentation to ensure that the products have not been subject-
ed to any delays during shipping and distribution that could result in products being exposed to extreme temperatures (see also the previous section, Pharmaceutical Delivery Staff, for staff expectations). The vehicles used for shipping of Pharmacopeial articles to the wholesaler, especially products requiring storage at low temperatures, should be suitably equipped to ensure that products are maintained at the correct temperature during shipping and distribution and up to the point of receipt. The receiving wholesaler staff should be informed that the articles are transferred to appropriate storage locations without delays. The vehicles used for shipping of Pharmacopeial articles requiring storage at room or controlled room temperatures should be suitably equipped to ensure that extremes of temperature, either above or below the specified temperature, do not occur during delivery procedures. Warehouse staff may receive appropriate training to ensure that the correct procedures are followed to maintain required temperature conditions (see Pharmaceutical Delivery Staff). Where necessary, a monitoring device for temperature and/or humidity should be used during shipping and distribution.

## Compromised Temperature Conditions

A procedure should be in place in the warehouse to define the action that should be taken in the event of deviation from required storage conditions. Suitable records should be maintained to explain the reason for deviation and the resulting action that is taken. The product in question should then be placed in a quarantine status. Advice on the suitability of the product for use should be sought from the manufacturer or supplier of the product. The manufacturer's response should be documented prior to issuing the product to the customer, if that product is to be issued to the customer.

## SHIPMENT FROM MANUFACTURER OR <br> WHOLESALER TO PHARMACY

## Pharmacy

The pharmacy receiving the pharmaceutical articles should ensure that on arrival, the pharmaceutical articles are transferred to the correct environment without delay, as directed by the manufacturer, ideally within 2 hours of receipt. The pharmacy personnel should examine the delivery documentation to ensure that the products have not been subjected to any delays during shipping and distribution, which could result in the products being exposed to extreme temperatures (see also the section, Pharmaceutical Delivery Staff, for staff expectations). The vehicles used for shipping of Pharmacopeial articles to the pharmacy, especially products requiring storage at low temperatures, should be suitably equipped to ensure that products are maintained at the correct temperature during shipping and distribution and up to the point of receipt. Receiving pharmacy staff should be informed that the articles are to be transferred to appropriate storage without delays. The vehicles used for shipping of Pharmacopeial articles requiring storage at room or controlled room temperatures should be suitably equipped to ensure that extremes of temperature, either above or below the specified temperature, do not occur during delivery procedures. Pharmacy staff may receive appropriate training to ensure that the correct procedures are followed to maintain required temperature conditions (see Pharmaceutical Delivery Staff). Where necessary, a monitoring device for temperature and/or humidity may be used during shipping and distribution.

## Compromised Temperature Conditions

The pharmacy should maintain appropriate procedures to define action that should be taken in the event of deviation from the required storage conditions. Suitable records should be maintained to explain the reason for deviation and the resulting action taken (including whether the product is issued to the patient or customer). Advice on the suitability of the product for use as an acceptable drug article should be sought from the manufacturer or supplier of the product.

## SHIPMENT FROM PHARMACY TO PATIENT OR CUSTOMER

The pharmacy should provide an appropriate label on the package sent through air or surface routes so that the deliverer does not place the package in a mailbox exposed to extremes in temperature. In the event that no one is available to receive the package, the deliverer should return the package to the post office or service office, and store it in a cool or air-conditioned area until the patient can receive the medication. In the event that the package has not been delivered for more than 2 days, the package may be returned to the pharmacy (see Environmentally Sensitive Preparations $\langle 386\rangle$ ). For temperature-sensitive articles, it is important that proper arrangements be made to protect the drug from exposure to high temperatures, or in some cases, from freezing conditions. Such arrangements may include the following: insulating the packaging, or packaging with coolant included; overnight shipping; and pre-arranged pick-up. In such cases, the pharmacy should provide on the external package a statement of an acceptable period of delay for de-
livery. The patient or customer should examine the delivery documentation to ensure that the package has not been subjected to any unacceptable delays during shipping and distribution. The patient or customer receiving the pharmaceutical articles, either by mail, delivery vehicle from the pharmacy, or directly from the physician or pharmacy, should be advised that upon receipt the articles are to be transferred to appropriate storage conditions without delay, as directed by the pharmacy, ideally within 2 hours of receipt. The vehicle used for air or surface shipping and distribution of pharmaceutical packages to the patient or customer, especially those requiring low temperatures, should contain the article suitably packaged in containers that maintain the desired storage conditions until the article reaches the patient or customer. The vehicles used for shipping and distribution of pharmaceutical articles to patient or customer, especially those requiring storage at room or controlled room temperatures, should be suitably equipped during extreme temperature conditions such that the packages are not exposed to extremes of temperature either in winter or summer months. In the event that the vehicle is not adequately equipped with air conditioning or heating to protect the product, the time that the article is exposed to ambient conditions should be strictly limited, ideally not more than 2 hours. Where appropriate, a monitoring device may be used to ensure that required temperatures are maintained until the package reaches the patient or customer. If stability studies for the Pharmacopeial preparation indicate that it is particularly sensitive to environmental insults or if appropriate shipping safeguards described in this section are not feasible, then the preparation should be shipped by a different method whereby environmental control can be maintained.

## Compromised Temperature Conditions

There should be appropriate procedures in the pharmacy that ships the article to the patient or customer defining the action that should be taken in the event that a patient reports that there has been a deviation from required storage conditions for an article, including any environmentally sensitive preparations, prior to the point of receipt. Advice on the suitability of the product for use should be provided to the patient or customer after the manufacturer or supplier's advice has been sought by the pharmacy. If the patient is advised to use the article, such advice should be documented and noted appropriately by the pharmacy. Otherwise, appropriate arrangements should be made to promptly replace the suspect article. For mail order items, replacement from local pharmacies may be an option to ensure an uninterrupted supply of medication.

## RETURNS OF PHARMACEUTICAL ARTICLES FROM PATIENTS OR CUSTOMERS

The wholesaler, manufacturer, and pharmacy personnel should evaluate the validity of the request for return, and maintain an auditable account of the return receipt. For products in unopened manufacturer's containers that have been at variance during shipment, arrangement may be made to return the products to the manufacturer, wholesaler, or pharmacy preferably within 3 working days of receipt. The supplier may request records or written confirmation by the patient to show that the product was stored properly while in possession of the customer.

## STORAGE OF PHYSICIAN SAMPLES HANDLED

 BY SALES REPRESENTATIVES IN AUTOMOBILESStorage of physician samples by sales representatives is regulated under 21CFR 203.34(b)(4); each manufacturer or distributor is to have appropriate policies in place to ensure that proper storage is maintained. The following suggestions may be considered in response to this need and are of interest to practitioners who may observe actual practices. Automobile trunks or passenger cabins used for the storage and distribution of physician samples should be monitored to determine the temperature profile of the trunk or passenger cabin. Suitable monitoring devices as determined by the sales representative may be placed in different areas of the trunk or passenger cabin on a hot summer and a cold winter day. Measurements should also be made during typical 24-hour periods, and the derived temperature should be used for calculation of the mean kinetic temperature at which the sample is stored (see Pharmaceutical Calculations in Prescription Compounding $\langle 1160\rangle$ for examples of MKT calculations). If the Pharmacopeial article designated for storage requires storage at controlled room temperature, then suitable measures should be taken to maintain the sample within the allowable limits of the storage parameters. Environmentally-sensitive preparations should not be stored in automobile trunks or passenger cabins. Medications stored in automobile trunks or passenger cabins should be removed at the end of 3 days. Sales representatives should consider parking automobiles in shaded areas to avoid extreme heat during the summer and in garages to avoid freezing temperatures during the winter. The use of vouchers from the manufacturer that patients could use to obtain medication samples from participating pharmacies is an alternative way of providing drug samples.

## STORAGE OF DRUGS IN EMERGENCY MEDICAL

 SERVICES (EMS) VEHICLESSee Emergency Medical Services Vehicles and Ambu-lances-Storage of Preparations $\langle 1070\rangle$.

## STABILITY, STORAGE, AND LABELING

The design of stability studies of Pharmacopeial articles is based on knowledge of the behavior, properties, and stability of the drug substance and experience gained from clinical formulation studies. ${ }^{1}$ The length of the studies and the storage conditions for a Pharmacopeial article should be sufficient to cover storage, shipment, distribution, and subsequent use of a Pharmacopeial article. The data gathered from ICH accelerated testing or from testing at an ICH intermediate condition may be used to evaluate the effect of short-term excursions outside the label storage conditions such as those that might occur during shipping. See Pharmaceutical Stability $\langle 1150\rangle$.

## STATEMENTS/LABELING OF THE IMMEDIATE CONTAINERS OR PACKAGE INSERT

Storage statements should be based on the stability evaluations of the Pharmacopeial drug substances and in accordance with national and international requirements.

Room Temperature Storage Statements-For products with a storage statement reading, "Store at controlled room temperature," the labeling should read as follows on the package insert: "Store at $20^{\circ} \mathrm{C}$ to $25^{\circ} \mathrm{C}\left(68^{\circ} \mathrm{F}\right.$ to $\left.77^{\circ} \mathrm{F}\right)$, excursions permitted between $15^{\circ} \mathrm{C}$ and $30^{\circ} \mathrm{C}$ (between $59^{\circ} \mathrm{F}$ and $86^{\circ} \mathrm{F}$ ). Brief exposure to temperatures up to $40^{\circ} \mathrm{C}$

[^357]$\left(104^{\circ} \mathrm{F}\right)$ may be tolerated provided the mean kinetic temperature does not exceed $25^{\circ} \mathrm{C}\left(77^{\circ} \mathrm{F}\right)$; however, such exposure should be minimized."

On the immediate container label, the following may read for controlled room temperature (CRT): "Store at $20^{\circ} \mathrm{C}$ to $25^{\circ} \mathrm{C}\left(68^{\circ} \mathrm{F}\right.$ to $\left.77^{\circ} \mathrm{F}\right)$, excursions permitted between $15^{\circ} \mathrm{C}$ and $30^{\circ} \mathrm{C}$ (between $59^{\circ} \mathrm{F}$ and $86^{\circ} \mathrm{F}$ )."

Cool Storage Statement-The storage statement for labeling may be as follows: "Store in a cool place, $8^{\circ} \mathrm{C}$ to $15^{\circ} \mathrm{C}\left(46^{\circ} \mathrm{F}\right.$ to $\left.59^{\circ} \mathrm{F}\right) .{ }^{\prime \prime}$

Refrigerator Storage Statement-The storage statement for labeling may be as follows: "Store in a refrigerator, $2^{\circ} \mathrm{C}$ to $8^{\circ} \mathrm{C}\left(36^{\circ} \mathrm{F}\right.$ to $\left.46^{\circ} \mathrm{F}\right)$."

Freezer Storage Statement-The storage statement for labeling may be as follows: "Store in a freezer, $-25^{\circ} \mathrm{C}$ to $-10^{\circ} \mathrm{C}\left(-13^{\circ} \mathrm{F}\right.$ to $\left.14^{\circ} \mathrm{F}\right)$."

See the General Notices for all other applicable storage conditions, such as Storage Under Nonspecific Conditions and store in a Dry Place. Additional cautionary statements to protect the Pharmacopeial drug product from extreme temperature and humidity conditions may be included on the container label and package insert, as the manufacturer desires. ${ }^{\text {2S }}$ (USP28)

## BRIEFING

$\langle\mathbf{1 0 8 7}\rangle$ Intrinsic Dissolution, USP 27 page 2512. It is proposed to revise the current name and content of this general information chapter in order to accommodate the inclusion of a stationary disk dissolution method. Sections for Experimental Procedure and Data Analysis and Interpretation are also included.
(BPC: H. Pappa) RTS-21026-1

## Change to read:

## <1087 $\rangle$ INTRINSIC DISSOLUTION

## rotating disk and stationary DISK DISSOLUTION TESTING 

This chapter diseusses determination of the rate of intrinsic dissolution.

The measurement of intrinsic dissolution rates is a tool in the functionality and characterization of bulk drug substanees andexeipients. The intrinsie dissolution rate is defined as the dissolution rateof pure substance under the eondition of constant surface area. The dissolution rate and bieavailability of a drug substanee are influeneed by its solid-state properties: crystallinity, amorphism, polymorphism, hydration, solvation, particle size, and particle surface area. The measured intrinsic dissolution rate is dependent on these solid-state properties. The dissolution rate is also influeneed by extrinsic factors, such as hydrodynamies (e.g., test apparatus, and-disk rotation speedor fluid flow) and test conditions (e.g., temperature, fluid viseosity, pH , and buffer strength in the case of ionizable compernds). By expesing the surface are of a material to an appropriate dissolution medium while maintaining constamt temperature, stirring rate, and pH , the intrinsic dissolution rate ean be determined. Typieally the intrinsic dissolution is expressed in terms of me per minte per $\mathrm{cm}^{2}$ :
Apparatus A yppieal apparates-consists of a punch and die fabrieated out of hardened steel. The base of the die has three threaded holes for the attachment of a surface plate made of pol ished steel, providing a mirrer smouth base for the compacted pet tet. The die has a 0.1 em to 1.0 em diameter cavity into whieh is placed a meastred amernt of the material whese intrinsic dissolut tion rate is to be determined. The punch is then inserted in the die eavity and the test material is compressed with a benchtop tablet press. [NOTE-A hole threugh the head of the puneh allows insertion of the metal rod to facilitate removal from the die after the test.] A compacted pellet of the material is formed in the eavity with a single face of defined area expesed on the bettom of the die (see manying figute). The bettom of the die eavity is threaded so that at least $50 \%$ to $75 \%$ of the compacted pellet cam dissolve witheut its falling out of the die. The top of the die has a threaded shoulder that allows it to be attached to a holder. The holder is mounted on a laboratory stirring deviee, and the entire die, with the compacted pellet still in place, is immersed in the dis solution medium and rotated by the stirring deviee (see Dissolution $\langle 714\rangle$ ).


Test Preparation-Weigh the material to be testento a piece of tared weighing paper. Attach the surface plate to the underside of the die, and secure it with the three serews provided. Transfer the aceurately weighed portion of the materiat under test into the die eavity. Place the punch int the ehamber, and secure the metal plate on top of the assembly. Compress the powder on a hydraulic press for 1 minte at the minimum compression pressure necessary to form a nondisintegrating compacted pellet. Detach the surface plate, and serew the die with punch still in place inte the holder. Tighten securely. Remove all loose powder from the surface of the die by blowing compressed air or nitrogen.

Procedure Slide the die holder assembly into the dissolution test chuck, and tighten. Position the shaft in the spindle-so that when the tested head is lowered, the expesed surface of the com pacted pellet will be 3.8 cm from the bottom of the vessel. The disk assembly should be aligned to minimize wobble, and air bubbles should not be allowed to form on the compacted pellet or die sur face as this could alter fluid flow. [NOTE-Air bubbles may be avided by using an apparatus with a different configuration, sueh as a die holder that holds the compacted pellet in a fixed vertieal position with agitation provided by a paddle positioned 6 mm from the surface of the pellet.] Perform the analysis as directed in the individual menegraph. If possible, sink conditions should be maintained threughout the test. The data for the cumulative amount dis solved a ach time point should be corrected for sampling losses. To caleulate the intrinsic dissolution rate, plot the eumalative a mount of test specimen dissolved per unit area of the compacted pellet against time until $10 \%$ is dissolved. The emmulative amount dissolved per unit area is given by the cumulative amount dissolved at each time point divided by the surface area expesed $\left(0.5-\mathrm{cm}^{2}\right)$. Linear regression should then be performed on data peints up to and ineluding the time point beyond which-10\% is
dissolved. The intrinsic dissolution rate of the test specimen, in my per mintte per $\mathrm{em}^{2}$, is determined from the slope of the regres sion line.
-This chapter discusses the determination of dissolution rates from nondisintegrating compacts held in a fixed position in a tablet die of known dimensions. Compacts, as used here, are understood to be a nondisintegrating mass resulting from the compression of the material under test using appropriate pressure conditions. A single surface having specified physical dimensions is presented for dissolution. The determination of the rate of dissolution can be important during the course of the development of new chemical entities because it sometimes permits prediction of potential bioavailability problems and may also be useful to characterize compendial articles such as excipients or drug substances.

Dissolution rate is influenced by intrinsic solid-state properties such as crystalline state including polymorphs and solvates, as well as degree of noncrystallinity. In addition, there are numerous methods available for modifying the physicochemical properties of chemical entities such that their solubility and dissolution properties can be modified. Among these are co-precipitates and the use of racemates and enantiomeric mixtures. The effect of impurities associated with a material can also significantly alter its dissolution properties. It is also influenced by extrinsic factors such as surface area, hydrodynamics, and dissolution medium properties, including solvent (typically water), presence of surfactants, temperature, fluid viscosity, pH , buffer type, and buffer strength. Dissolution rate generally is expressed as the mass of solute appearing in the dissolution media per unit time (e.g., mass sec ${ }^{-1}$ ) while dissolution flux is expressed as the rate per unit area (e.g., mass $\mathrm{cm}^{-2} \mathrm{sec}^{-1}$ ). Reporting dissolution flux is preferred as it is normalized for surface area.

The rotating disk and stationary disk dissolution systems provide methodologies that are versatile enough to study the characteristics of compounds of pharmaceutical interest under a variety of test conditions. Characteristics common to both systems include the following:
(1) They are adaptable to use with standard dissolution testing stations, and both use a tablet die to hold the nondisintegrating compact during the dissolution test.
(2) They rely on being able to compress the test compound into a compact that does not flake or fall free during the dissolution test.
(3) A single surface of known geometry and physical dimension is presented for dissolution.
(4) The die is located at a fixed position in the vessel which decreases the variation from hydrodynamic conditions.

A difference between the two systems is the source of fluid flow over the dissolving surface. In the case of the rotating disk system, fluid flow is generated by the rotation of the die in a quiescent fluid while fluid flow is generated by a paddle or other stirring device for the stationary disk system.

## EXPERIMENTAL PROCEDURE

The procedure for carrying out dissolution studies with this type of equipment consists of preparing a nondisintegrating compact of material using a suitable compaction apparatus, placing the compact and surrounding die assembly in a suitable dissolution medium, subjecting the compact to the desired hydrodynamics near the compact surface, and measuring the amount of dissolved solute as a function of time.

Compacts are typically prepared using an apparatus that consists of a die, an upper punch, and a lower surface plate fabricated out of hardened steel or other material that allows the compression of material into a nondisintegrating compact. An alternative compaction apparatus consists of a die and two punches. Other configurations that achieve a nondisintegrating compact of constant surface area also may be used. The nondisintegrating compact typically has a diameter of 0.2 cm to 1.5 cm .

## Compact Preparation

Attach the smooth lower surface plate to the underside of the die, or alternatively, insert the lower punch using an appropriate clamping system. Accurately weigh a quantity of material necessary to achieve an acceptable compact and transfer to the die cavity. Place the upper punch into the die cavity and compress the powder on a hydraulic press at a compression pressure required to form a nondisintegrat-
ing compact that will remain in the die assembly for the length of the test. Compression for 1 minute at 15 MPa usually is sufficient for many organic crystalline compounds, but alternative compression conditions that avoid the formation of capillaries should be evaluated.

Changes in crystalline form may occur during compression, therefore confirmation of solid state form should be performed by powder X-ray diffraction or other similar technique. Remove the surface plate or lower punch. Remove loose powder from the surface of the compact and die by blowing compressed air or nitrogen over the surface.

## Dissolution Media

Dissolution may be run in the physiological pH range at $37^{\circ}$ to approximate in-vivo conditions. Whenever possible, it also is appropriate to perform the test under sink conditions. Dissolution media should be deaerated immediately prior to use to avoid air bubbles forming on the compact or die surface. ${ }^{1}$

Dissolution media temperature and pH must be controlled, especially when dealing with ionizable compounds and salts. In those cases, the dissolution rate may depend strongly on the pH , buffer species, and buffer concentration.

Where possible, testing should be carried out under the same conditions that are used to determine the intrinsic solubility of the solid state form being tested. A simplifying assumption in constant surface area dissolution testing is that the pH at the surface of the dissolving compact is the same as the pH of the bulk dissolution medium. For nonionizable compounds, this is relatively simple as no signifi-

[^358]cant pH dependence of dissolution rate is expected. For acids and bases, the solute can alter the pH at and near the surface of the compact as it dissolves. Under these conditions, the pH at the surface of the compact may be quite different from the bulk pH due to the self-buffering capacity of the solute. To assess intrinsic solubility, experimental conditions should be chosen to eliminate the effect of solute buffering, alteration of solution pH , and precipitation of other solid state forms at the surface of the compact. For weak acids, the pH of the dissolution media should be one to two pH units below the pKa of the dissolving species. For weak bases, the pH of the dissolution medium should be one to two pH units above the pKa of the dissolving species.

## Test Apparatus

## METHOD 1 (ROTATING DISK)

A typical apparatus (Figure 1) consists of a punch and die fabricated out of hardened steel. The base of the die has three threaded holes for the attachment of a surface plate made of polished steel, providing a mirror-smooth base for the compacted pellet. The die has a cavity into which is placed a measured amount of the material whose intrinsic dissolution rate is to be determined. The punch is then inserted in the die cavity and the test material is compressed with a hydraulic press. [NOTE-A hole through the head of the punch allows insertion of a metal rod to facilitate removal from the die after the test.] A compacted pellet of the material is formed in the cavity with a single face of defined area exposed on the bottom of the die.


Figure 1

The die assembly is then attached to a shaft constructed of an appropriate material (typically steel). The shaft holding the die assembly is positioned so that when the die assembly is lowered into the dissolution media (Figure 2), the exposed surface of the compact will be not less than 1.0 cm
from the bottom of the vessel and nominally in a horizontal position. The die assembly should be aligned to minimize wobble, and air bubbles should not be allowed to form on the compact or die surface.


Figure 2
A rotating disk speed of 300 rpm is recommended. Typical rotation speeds may range from 60 rpm to 500 rpm . The dissolution rate depends on the rotation speed used. This parameter should be selected in order to admit at least five sample points during the test, but excessive stirring speeds may create shear patterns on the surface of the dissolving material that could cause aberrant results (i.e., nonlinearity). Typically, the concentration of the test specimen is measured as a function of time, and the amount dissolved is then calculated. The sampling interval will be determined by the speed of the dissolution process. If samples are removed from the dissolution medium, the cumulative amount dissolved at each time point should be corrected for losses due to sampling.

## METHOD 2 (STATIONARY DISK)

The apparatus (Figure 3) consists of a steel punch, die, and a base plate. The die base has three holes for the attachment of the base plate. The three fixed screws on the base
plate are inserted through the three holes on the die and then fastened with three washers and nuts. The test material is placed into the die cavity. The punch is then inserted into the cavity and compressed, with the aid of a bench top press. The base plate is then disconnected from the die to expose a smooth compact pellet surface. A gasket is placed around the threaded shoulder of the die and a polypropylene cap is then screwed onto the threaded shoulder of the die.


Figure 3
The die assembly is then positioned at the bottom of a specially designed dissolution vessel with a flat bottom (Figure 4). The stirring unit (e.g., paddle) is positioned at an appropriate distance (typically 2.54 cm ) from the compact surface. The die assembly and stirring unit should be aligned to ensure consistent hydrodynamics, and air bubbles should not be present on the compact surface during testing. Alternative configurations may be utilized if adequate characterization and control of the hydrodynamics can be established.


Figure 4
The dissolution rate depends on the rotation speed and precise hydrodynamics that exist. Typically, the concentration of the test specimen is measured as a function of time and the amount dissolved then calculated. The sampling interval will be determined by the speed of the dissolution process (see Method 1). If samples are removed from the dissolution media, the cumulative amount dissolved at each time point should be corrected for losses due to sampling.

## DATA ANALYSIS AND INTERPRETATION

The dissolution rate is determined by plotting the cumulative amount of solute dissolved against time. Linear regression analysis is performed on data points in the initial linear region of the dissolution curve. The slope corresponds to the dissolution rate (mass sec${ }^{-1}$ ).

The amount versus time profiles may show significant curvature. When this occurs, it is important that only the initial linear portion of the profile is used to determine the dissolution rate. If curvature is observed, it may be valuable to assess the crystalline form of the compact by removing it from the media and examining it by powder X-ray diffraction or another similar technique to determine if the exposed surface area is changing.

The constant surface area dissolution rate is reported in units of mass sec ${ }^{-1}$ while the dissolution flux is reported in units of mass $\mathrm{cm}^{-2} \mathrm{sec}^{-1}$. Test conditions, typically a description of the apparatus, rotation speed, temperature, buffer species and strength, pH , and ionic strength should also be reported with the analyses. The dissolution flux is calculated by dividing the dissolution rate by the surface area of the compact.

Under ideal conditions, dissolution flux may be used to estimate solubility. When hydrodynamic conditions are well-defined, the appropriate hydrodynamic equations can be solved taking into account that dissolution is determined by both diffusive and convective components.

Ratios of the flux, measured under varying conditions of pH , stirring speeds, buffer species, buffer concentrations, or ionic strengths, yield values that are useful to determine the relative dependence of the normalized dissolution rate on these variables. These ratios are especially useful for ionizable solutes where the flux is strongly dependent on pH , buffer species, and buffer concentration. They are also useful to determine relative stirring speed dependence.
In both Method 1 and Method 2, the functional relationship between the experimental flux and the physicochemical characteristics of the drug (solubility and diffusion coefficient) as well as the convective components (stirring speed and kinematic viscosity of the medium) are known. Therefore, a comparison between the experimental and the calcu-
lated flux values can be made. It is also possible to use the experimental flux value to calculate the solubility of the compound when all other variables are known a priori. With a more complex analysis, it is useful to compare the pH at the dissolving surface of ionizable solute with the bulk pH , which is an important consideration when setting conditions for dissolution testing.

Upward curvature (positive second derivative) of the concentration versus time data is typically indicative of a systematic experimental problem. Possible problems include physical degradation of the compact by cracking, delaminating, or disintegration.

Downward (negative second derivative) curvature of the dissolution profile is often indicative of a transformation of the solid form of the compact at the surface or when saturation of the dissolution medium is inadvertently being approached. This often occurs when a less thermodynamically stable crystalline form converts to a more stable form. Examples include conversion from an amorphous form to a crystalline form or from an anhydrous form to a hydrate form, or the formation of a salt or a salt converting to the corresponding free acid or free base. $\mathbf{\omega S S}^{2 S}$ (USP28)

## BRIEFING

$\langle\mathbf{1 1 0 1}\rangle$ Medicine Dropper, USP 27 page 2559. The proposed revisions are intended to update and clarify this general information chapter.
(PDF: W. Paul) RTS-41712-1

## Change to read:

The Pharmacopeial medicine dropper consists of a tube made of glass or other suitable transparent material that generally is fitted with a collapsible bulb and, while varying in capacity, is constrict-
ed at the delivery end to a round opening having an external diameter of about 3 mm . The dropper, when held vertically, delivers water in drops each of which weighs between 45 mg and 55 mg .

In using a medicine dropper, one should keep in mind that few

- most.. ${ }^{2 S}$ (USP28)
medicinal liquids
$\mathbf{- d o}^{\text {not }}{ }_{\mathbf{2 S}}$ (USP28)
have the same surface
tension $_{\text {2S }}$ (USP28)
and flow
$\square_{\text {viscosity }}^{\text {2S (USP28) }}$
characteristics as water, and therefore the size of drops tially
$\square_{\text {will vary }}{ }^{2 S}$ (USP28)
from one preparation to another.
Where accuracy of dosage is important, a dropper that has been calibrated eially
$\square_{\text {specifically }}^{\mathbf{m}_{2 S}}{ }_{\text {(USP28) }}$
for the preparation with which it is supplied should be employed. The volume error incurred in measuring any liquid by means of a calibrated dropper should not exceed $15 \%$ under normal use conditions.


## BRIEFING

〈1119〉 Near-Infrared Spectrophotometry, USP 27 page 2569 and page 3337 of the Second Supplement. The unavailability of NIST SRM 1920a NIR wavelength calibration standard has prompted the USP to establish an equivalent USP Near-Infrared Calibrator Reference Standard (see Test Details under Instrumentation in this general information chapter). Also, it is proposed to replace the NIST SRM 2034 with the recommended NIST SRM 2036 for transmission wavelength and NIR diffuse reflectance wavelength qualification because this standard contains a piece of sintered polytetrafluoroethylene (PTFE) that provides a nearly ideal diffuse reflector.
(PA6: L. Evans, G. Ritchie) RTS-41187-1

## Change to read:

## INSTRUMENTATION

## Apparatus

All NIR measurements are based on passing light radiation through or into a sample and measuring the attenuation of the emerging (transmitted, scattered, or reflected) beam. There are a variety of spectrophotometers available based on different operating principles.

Some examples of currently available spectrophotometers are the following: filter and grating-based dispersive, acousto-optical tunable filter (AOTF), Fourier-transform (FT-NIR), and liquid crystal tunable filters (LCTF) systems. Silicon, lead sulfide, indium gallium arsenide and deuterated triglycine sulphate are commonly used detector materials. Conventional cuvette sample holders, fi-ber-optic probes, transmission dip cells, and spinning or traversing sample holders are some of the more common sampling arrangements.

The selection of the equipment should be based on the intended application, with particular attention being paid to the suitability of the sampling device for the type of sample to be analyzed.

## Near-Infrared Reflectance References

NIR references, by providing a known stable measurement against which other measurements can be compared, are used to eliminate instrumental variations that would affect the measurements.

Transmittance Mode-The measurement of transmittance is dependent on a background transmittance spectrum for its calculation. A transmittance reference can be air, an empty cell, a solvent blank, or in special cases, a reference sample.

Reflectance Mode-The measurement of reflectance is dependent on a background reflectance spectrum for its calculation. Most measurements are performed in single-beam instruments; the reflectance of a background reference is scanned to obtain a baseline, and then the reflectance of one or more analytical samples is measured. Common reflectance references are ceramic, perfluorinated polymers and gold; other suitable materials may be used. Only spectra measured against a background possessing the same optical properties can be directly compared with one another.

## Qualification of NIR Instruments

Elements of Qualification-The qualification of an NIR instrument can be divided into three elements:

- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

Installation Qualification-The IQ requirements help ensure that the hardware and software are installed according to vendor and safety specifications at the desired location.

Operational Qualification-In operational qualification, the instrument's performance is controlled with respect to external certified standards to verify that the system operates within target specifications. The purpose of operational qualification is to ensure that an instrument is suitable for its intended application. Because there are so many different approaches to measuring NIR spectra, operational qualification with traceable external standards that can be used on any instrument is desired. The most important property of a reference material is its stability. For example, the commonly employed internal polystyrene-film reference may be subject to aging and attack by solvents and vapors in the laboratory environment. The use of external traceable reference standards does not imply the omission of the instrument's internal quality control procedures. Similiar to any spectrophotometric device, NIR instruments need to be qualified for both wavelength and photometric scale. Maximum and reduced light-flux noise tests are also included.

Performance Qualification-In performance qualification, a quality of fit to an initial scan or group of scans included in the operational qualification is employed. In such an analysis, it is as-
sumed that reference standard spectra collected on a new or a newly repaired, properly operating instrument represent the best ones available. Comparisons of spectra taken over time on the identical reference standards form the basis for evaluating the long-term stability of an NIR measurement system. The objective is to ensure that no wavelength calibration shift or change in sensitivity occurs during ongoing analysis.

Previous operational qualification has shown that the equipment is acceptable for use; therefore, a single performance qualification standard can be used to reverify performance on a continuing basis. The user may have a method-specific reference sample to perform this kind of control, providing the sample is stable.

Test Details-The specific tests and how frequently they are performed for each level of qualification is dependent on the instrument and intended application.

Wavelength Uncertainty-Potential problems with internal calibration schemes are avoided by specifying appropriate independent external wavelength standards. For the reflectance mode, NHST SRM-1920a+

- USP Near-Infrared Calibrator $\mathrm{RS}^{1}{ }^{1}{ }^{2 S}$ (USP28) and NIST SRM $2035^{2}$ used in the transflectance mode are available. The nature and type of background reference standard must be specified. In transmittance measurements, NIST SRM 2035 rare earth oxide in glass standard, or Holmizm oxide solution NIST SRM 2034 ${ }^{3}$
- NIST SRM $2036^{3}{ }^{3}$ 2S (USP28)
are available. Alternative standards may be used with appropriate justification.

Take one spectrum (with the same spectral resolution used to obtain the certified value) and measure the position of at least three peaks to cover the entire available range. The acceptance limits for SRM 1920a are reported in Table 1.
${ }^{1}$ USP Near-Infrared Calibrator RS is a mixture of dysprosium, holmium, erbium, and talc and may be obtained from USP. "Accurate Wavelength Measurements of a Putative Standard for Near-Infrared Diffuse Reflection Spectrometry," by Tomas Isaksson, Husheng Yang, Gabor J. Kemeny, Richard S. Jackson, Qian Wang, M. Kathleen Alam, and Peter R. Griffiths (Department of Chemistry, University of Idaho, Moscow, Idaho 838442343, USA) Appl Spectrosc 2003, 57(2) 176-185. This reference material exhibits peaks in both the $700-$ to $1100-\mathrm{nm}$ and $1100-$ to $2500-\mathrm{nm}$ ranges.
${ }^{2}$ SRM 2035, a rare earth oxide in glass, is intended for transmission wavelength qualification and has been certified recently by NIST.
-This standard consists of samarium, ytterbium, holmium, and neodymium rare earth oxide (REO). $\begin{aligned} & \text { 2S } \\ & \text { (USP28) }\end{aligned}$
"Production and Verification of SRM 2035. Near Infrared Transmission Wavelength Standard", NIST Special Publication 1999, 260-102 (in preparation). This standard may be used in transflectance mode, but it is not currently certified for such use.
${ }^{3}$ Helmitm oxide-selution, NHST SRM 2034, (wavelength-standard frem $240-650 \mathrm{~mm})$ may be used eurrently in the 650 to -1100 nm regien at theugh bands are net certified in this region. "Holmium-Oxide-Solution wavelength Standard from 240-640 mm-SPM-2034", NBS Special Pub-am-Oxide in-Perchloric Acid" $J$ Rec. Natl Bur Stdc 1985-90(2) 115 125.
${ }^{3}$ SRM 2036, a rare earth oxide in glass, is intended for NIR diffuse reflectance wavelength qualification and is available from NIST. This standard also consists of samarium, ytterbium, holmium, and neodymium rare earth oxide (REO). In addition, SRM 2036 contains a piece of sintered polytetrafluoroethylene (PTFE) that provides a nearly ideal diffuse reflector.

Table 1. Recommended Near-IR Instrument Specifications ${ }^{\mathrm{a}}$

| Wavelength Uncertainty | SRM-1920a |
| :---: | :---: |
|  | -USP Near-Infrared Calibrator $\mathrm{RS}_{\mathbf{\bullet 2 S}}$ (USP28) peaks ${ }^{\text {b }}$ occur at 1261, 1681, and 1935 nm |
| Tolerances | $\pm 1 \mathrm{~nm}$ at 1200 nm or $\pm 8 \mathrm{~cm}^{-1}$ at $8300 \mathrm{~cm}^{-1}$ |
|  | $\pm 1 \mathrm{~nm}$ at 1600 nm or $\pm 4 \mathrm{~cm}^{-1}$ at $6250 \mathrm{~cm}^{-1}$ |
|  | $\pm 1.5 \mathrm{~nm}$ at 2000 nm or $\pm 4 \mathrm{~cm}^{-1}$ at $5000 \mathrm{~cm}^{-1}$ |
| Photometric Linearity | $A_{O B S}$ vs $A_{\text {REF }}$ at 1200,1600 , and $2000 \mathrm{~nm} ;{ }^{c}$ <br> slope $=1.0+0.05$; intercept $=0.0+0.05$ |
| Spectrophotometric Noise | measured for $100-\mathrm{nm}\left(300 \mathrm{~cm}^{-1}\right)$ segments between 1200 and 2200 nm ( 8300 and 4500 $\mathrm{cm}^{-1}$ ) |
| Average RMS for measurements at high-light flux | less than $0.3 \times 10^{-3} ;$ no RMS noise greater than $0.8 \times 10^{-3}$ |
| Average RMS for measurements at low-light flux | less than $1 \times 10^{-3}$; no RMS noise greater than $2.0 \times 10^{-3}$ |

${ }^{\text {a }}$ A maximum nominal instrument bandwidth of 10 nm at 2500 nm or $16 \mathrm{~cm}^{-1}$ at $4000 \mathrm{~cm}^{-1}$ is appropriate for most applications.
${ }^{\mathrm{b}}$ The nominal $1935-\mathrm{nm}$ peak is sensitive to instrument bandwidth. Use the wavelength value supplied with SRM 1920a

- USP Near-Infrared Calibrator RS ${ }_{\text {■2S (USP28) }}$.
at the appropriate instrument bandwidth to determine wavelength uncertainty.
${ }^{\mathrm{c}} A_{O B S}$ is the observed absorbance, and $A_{\text {REF }}$ is the tabulated absorbance of the reference reflectors at each of the three specified wavelengths.

Photometric Linearity-Verification of photometric linearity is demonstrated with a set of transmission standards of known relative transmittance or reflectance standards of known relative reflectance, usually expressed as percent transmittance or reflectance. For reflectance measurements, traceable carbon-doped polymer standards are available. Spectra obtained from reflectance standards are subject to variability as a result of the difference between the experimental conditions under which they were factory-calibrated and those under which they are subsequently put to use. Hence, the percent reflectance values supplied with a set of calibration standards may not be useful in the attempt to establish an "absolute" calibration for a given instrument. Provided that (1) the standards do not change chemically or physically, (2) the same reference background is used as was used to obtain the certified values, and (3) the instrument measures each standard under identical conditions (including precise sample positioning), the reproducibility of the photometric scale will be established over the range of standards used. Subsequent measurements on the identical set of standards give information on long-term stability. Use at least four reference standards in the range $10 \%$ to $90 \%$. [NOTE-A typical set of four reflectance references might be $10 \%, 20 \%, 40 \%$, and $80 \%$ with $1.0,0.7,0.4$, and 0.1 as their respective absorbances.] If the system is used for analytes with absorbances higher than 1.0 , add a $2 \%$ or a $5 \%$ standard, or both, to the set. The specifications are reported in Table 1.

Spectrophotometric Noise-NIR instrument software may include built-in procedures to automatically determine system noise and to provide a statistical report of noise or signal-to-noise ratio over its operating range. As previously discussed, it is desirable to supplement such checks with measurements that do not rely directly on manufacturer-supplied procedures. If the qualification procedures in the NIR software do not comply with the contents of this chapter, it is recommended to supplement such checks with measurements that do not rely directly on manufacturer-supplied procedures. The method involves measuring spectra of high- and low-
reflectance traceable reference materials. For transmittance modules there are no standards for the low-flux noise test at this time, so it is only possible to perform the high-flux noise test.

HIGH-FLUX NOISE-The instrument noise is evaluated at highlight flux by measuring reflectance or transmittance of the reference standard, with the reference material (e.g., $99 \%$, reflectance standard) acting as both the sample and the background reference. The analysis is performed by tabulating RMS noise levels in successive nominal $100-\mathrm{nm}\left(300 \mathrm{~cm}^{-1}\right)$ spectral segments across the instrument's range. The limits are reported in Table 1.

LOW-FLUX NOISE-The same procedure may be used with a low-er-reflectivity reference material (e.g., $10 \%$ reflectance standard) to determine system noise at reduced light flux. The source, optics, detector, and electronics make significant contributions to the noise under these conditions. The limits are reported in Table 1.

## BRIEFING

$\langle 1120\rangle$ Raman Spectrophotometry. A new general chapter, designated $\langle 1120\rangle$ Raman Spectrophotometry, is proposed. It is recognized that Raman spectrophotometry is being used in the pharmaceutical industry in a variety of settings, both as a laboratory and as a process-measuring tool. As such, in the production of pharmaceuticals, this technique has many potential uses for controlling product consistency, homogeneity, and final product quality. A chapter on Raman spectrophotometry is being added to provide general information on this technique, which may have application in certain cases as a manufacturing real-time control technique.
(PA6: L. Evans, G. Ritchie) RTS-41439-1

## Add the following:

## ■ $\langle 1120\rangle$ RAMAN SPECTROPHOTOMETRY

## INTRODUCTION

Raman spectroscopy shares many of the principles that apply to other spectroscopic measurements discussed in Spectrophotometry and Light-Scattering $\langle 851\rangle$. Raman is a vibrational spectroscopic technique and is therefore related to infrared (IR) and near-infrared (NIR) spectroscopy. The Raman effect itself arises as a result of a change in the polarizability of a molecular bond and is measured as inelastically scattered radiation.
A Raman spectrum is generated by exciting the sample of interest to a virtual state with a monochromatic source, typically a laser. Light elastically scattered (no change in wavelength) is known as Rayleigh scatter and is not of analytical interest. However, if the sample relaxes to a vibrational energy level differing from the initial state, the scattered radiation is shifted in energy. The shift is commensurate with the energy difference between the initial and final vibrational states. This "inelastically scattered" light is referred to as Raman scatter. Only about one in $10^{8}$ photons incident to the sample undergoes Raman scattering. If the Raman scattered photon is of lower energy, it is referred to as Stokes scattering. If it is of higher energy, it is referred to as antiStokes scattering. In practice, nearly all analytically useful Raman measurements make use of Stokes-shifted Raman scatter.

The appearance of a Raman spectrum is much like an absorption Fourier transform-IR (FT-IR) spectrum. The intensities, or the number of Raman photons counted, are plotted against the shifted energies. The $x$-axis is generally labeled "Raman Shift/cm ${ }^{-1}$ " or "Wavenumber/cm-1". The
shift position is usually expressed in frequency and represents the frequency of the peak relative to the laser frequency. The spectrum is interpreted in the same manner as the commensurate absorption FT-IR spectrum. The positions of the shift frequencies for a given bond in an analyte are similar to their respective absorption frequencies in an IR spectrum. However, the peaks emphasized in a Raman spectrum are often de-emphasized in an IR spectrum and viceversa. This is why the two spectroscopic techniques are often said to be complementary.

Raman spectroscopy is advantageous because quick and accurate measurements can often be made without destroying the sample (solid, semi-solid, liquid, or gas) and with minimal or no sample preparation. The signal is typically in the visible or near-IR (NIR) range, allowing efficient coupling to fiber optics. This also means that a signal can be obtained from any medium transparent to the laser, such as glass, plastics, or samples in aqueous media. From an instrumental point of view, modern systems are easy to use, provide fast analysis times (seconds to several minutes), and are reliable. The Raman spectrum contains information on fundamental vibrational modes of the sample that can yield both sample and process understanding. Finally, the analysis modeling may be simpler than that associated with other spectroscopic techniques. (Both univariate and multivariate methods and calibrations can be used).
In addition to normal Raman spectroscopy, there are a number of more specialized Raman techniques. These include resonance Raman (RR), surface-enhanced Raman spectroscopy (SERS), Raman optical activity (ROA), coherent anti-Stokes Raman spectroscopy (CARS), Raman gain or loss spectroscopy, and hyper-Raman spectroscopy. These techniques are not widely implemented currently, and are not addressed in this general information chapter.

## QUALITATIVE AND QUANTITATIVE RAMAN MEASUREMENTS

There are two general classes of commonly performed Raman measurements: qualitative and quantitative.

## Qualitative Raman Measurements

Qualitative Raman measurements yield accurate spectral information about the vibrational bands present in the sample. Because the Raman spectrum is specific for a given compound, qualitative Raman measurements may be used as a compendial ID test, as well as for structural elucidation.

## Quantitative Raman Measurements

Quantitative Raman measurements follow a relationship comparable to Beer's law:

$$
I_{V}=K L C I_{0}
$$

in which $I_{V}$ is the peak intensity at a given wavelength, $K$ represents instrument and sample constants, $L$ is the pathlength, $C$ is the molar concentration of a particular component in the sample, and $I_{0}$ is the laser intensity. In practice, path length is more accurately described as sampling volume, which is an instrumental variable described by the focus of the laser and the collection optics. From the equation, it is apparent that peak intensity is directly correlated to concentration. It is this relationship that is the basis for the majority of quantitative Raman applications.

## FACTORS AFFECTING QUANTITATION

## Sample-Based Factors

The most important sample-based factors are fluorescence, sample heating, and matrix absorption. Fluorescence is typically observed as a broad sloping background underlying the Raman spectrum. The effect on quantitation is therefore that of an unstable baseline and decreased sig-nal-to-noise ratio. The exact wavelength and intensity is dependent on the identity and concentration of the fluorescing material. Because fluorescence is generally a much more efficient process, even very minor amounts of fluorescent impurities can lead to significant Raman signal degradation. Fluorescence can be minimized by using longer wavelength excitation sources such as 785 nm or 1064 nm . However, the intensity of the Raman signal is proportional to $\nu^{-4}$, where $\nu$ is the excitation wavelength. The optimum sig-nal-to-noise ratio will be obtained by balancing fluorescence rejection, signal strength, and detector response.

Fluorescence in solids can also be mitigated by exposing the sample to the laser source for a period of time before measurement. This process is called photobleaching, and operates by degrading the highly absorbing species. Photobleaching is less effective in liquids, where the sample is mobile, or if the amount of fluorescent material is more than a trace.
Sample heating can cause a variety of issues, such as physical form change (melting), polymorph conversion, or sample burning. This is usually an issue for colored, highly absorbing species, or very small particles that have low heat transfer. The effects of sample heating are usually observable either as changes in the Raman spectrum over time or by visual inspection of the sample. Besides decreasing the laser flux, a variety of methods can be employed to diminish
heating, such as moving the sample or laser during the measurement or improving the heat transfer of the sample with thermal contact or liquid immersion.

Absorption of the Raman signal by the matrix can also occur. This problem is more prevalent with long wavelength FT-Raman systems where the Raman signal can overlap with a NIR overtone absorption. This effect will be dependent on the optics of the system as well as on the sample presentation. Associated with this effect is variability from scattering in solids as a result of packing and particle size differences. The magnitude of all of these effects, however, is typically less severe than in NIR because of the limited depth of penetration and the relatively narrower wavelength region sampled in Raman spectroscopy.

## Sampling Factors

Quantitative Raman spectroscopy differs from many other spectroscopic techniques in that it is a single beam measurement with no background. Careful instrument design and sampling can minimize this variation but not entirely remove it. Thus the absolute Raman signal intensity is very difficult to use for direct quantitation of an analyte. Among the potential sources of variation are changes in sample opacity, sample heterogeneity, changes in laser power at the sample, and changes in optical collection geometry or sample position. These effects can be minimized by sampling in a reproducible, representative manner.

Use of an internal reference is the most common and robust method of eliminating variations due to absolute intensity fluctuations. There are several choices for this approach. An internal standard can be deliberately added, and isolated peaks from this standard can be employed. In a solution, an isolated solvent band can be employed because the solvent will remain relatively unchanged from sample to sample. Also, in a formulation, an excipient peak can be used if it
is in substantial excess compared to the analyte. The entire spectrum can also be used as a reference, with the assumption that laser and sample orientation changes will affect the entire spectrum equally.

A second important sampling-based factor to consider is spectral contamination. Raman is a weak effect that can be masked by a number of external sources. Common contamination sources include sample holder artifacts (container or substrate) and ambient light. Typically, these issues can be identified and resolved by careful experimentation.

## APPARATUS

## Components

All modern Raman measurements involve irradiating a sample with a laser, collecting the scattered radiation, rejecting the Rayleigh scattered light, differentiating the Raman photons by wavelength, and detecting the resulting Raman spectrum. All commercial Raman instruments therefore share the following common features to perform these functions:

1. Excitation source (Laser)
2. Sampling device
3. Device to filter/reject light scattered at the laser wavelength
4. Wavelength processing unit
5. Detector and electronics

## EXCITATION SOURCE (LASER)

Table 1 identifies several common lasers used for pharmaceutical applications. UV lasers have also been used for specialized applications but have various drawbacks that severely limit their utility for general analytical measurements.

Table 1. Typical Lasers Used in Pharmaceutical Applications

| Laser $\lambda, \mathrm{nm}$ (nearest whole number) | Type | Typical Power at Laser | Wavelength Range, nm (Stokes Region, 100 $\mathrm{cm}^{-1}$ to $3000 \mathrm{~cm}^{-1}$ shift) | Comments |
| :---: | :---: | :---: | :---: | :---: |
| NIR Lasers |  |  |  |  |
| 1064 | Solid state (Nd:YAG) | Up to 3W | 1075-1563 | Commonly used in Fourier transform instruments |
| 785 | Diode | Up to 500 mW | 791-1027 | Most ubiquitous dispersive Raman laser |
| Visible Lasers |  |  |  |  |
| 488-632.8 | Ion gas and solid state frequency doubled lasers | Up to 1W | 488-781 | Fluorescence risks |

## SAMPLING DEVICE

A wide variety of sampling arrangements are possible, including direct optical interfaces, microscopes, fiber opticbased probes (either noncontact or immersion optics), and sample chambers (including specialty sample holders and automated sample changers). The sampling optics may also be designed to obtain the polarization-dependent Raman spectrum, which often contains additional information. Selection of the sampling device will often be dictated by the analyte. However, considerations such as sampling volume, speed of the measurement, laser safety, reproducibility of sample presentation, etc., should be evaluated to optimize the sampling device for any given application.

## FILTERING DEVICE

Scattered light at the laser wavelength (Rayleigh) is many orders of magnitude greater than the Raman signal and must be rejected prior to the detector. Notch filters are almost uni-
versally used for this purpose and provide excellent rejection and stability combined with small size. The traditional use of multistage monochromators for this purpose, although still viable, is now rare. In addition, various filters or physical barriers to shield the sample from external radiation sources (e.g., room lights, laser plasma lines) may be required depending on the collection geometry of the instrument.

## WAVELENGTH PROCESSING UNIT

The wavelength may be processed either by dispersion or interferometry (Fourier transform). The specific benefits and drawbacks of each of the dispersive designs compared to the FT instrument are beyond the scope of this chapter. Any properly qualified instruments should be suitable for qualitative measurements. However, care must be taken when selecting an instrument for quantitative measurements, as
dispersion and response linearity may not be uniform across the full spectral range (for example, when using an echelle spectrograph).

## DETECTOR

The silicon-based charge-coupled device (CCD) is the most common detector for dispersive instruments. The cooled array detector allows fast, full-spectrum measurements with low noise. It also has peak wavelength responsivity when matched to the commonly used $785-\mathrm{nm}$ diode laser. Fourier transform instruments typically use singlechannel germanium or indium-gallium-arsenide (InGaAs) detectors responsive in the NIR to match neodymium:yt-trium-aluminum-garnet (Nd:YAG) 1064-nm excitation.

## Calibration

Raman instrument calibration consists of three components: primary wavelength ( $x$-axis), laser wavelength, and intensity ( $y$-axis).

## PRIMARY WAVELENGTH (X-AXIS)

In the case of FT-Raman instruments, primary wave-length-axis calibration is maintained with an internal $\mathrm{He}-$ Ne laser. Most dispersive instruments utilize atomic emission lamps for primary wavelength-axis calibration. In all Raman systems suitable for analytical Raman measurements, the vendor will offer a procedure of $x$-axis calibration that can be performed by the user. For dispersive Raman instruments, a calibration based on multiple atomic emission lines is preferred. The validity of this calibration approach can be verified subsequent to laser wavelength calibration using a suitable Raman shift standard. For scanning disper-
sive instruments, calibration may need to be performed more frequently and precision in both a scanning and static operation mode may need to be verified. ${ }^{1}$

## LASER WAVELENGTH

Laser wavelength variation can impact both the wavelength precision and the photometric (intensity) precision of a given instrument. Even the most stable current lasers can vary slightly in their measured wavelength output. The laser wavelength must therefore be confirmed to assure that the Raman shift positions are accurate for both FT-Raman or dispersive Raman instruments. A reference Raman shift standard material such as those outlined in ASTM E1840-96(2002) ${ }^{1}$ or other suitably verified materials can be utilized for this purpose. [NOTE-Reliable Raman shift standard values for frequently used liquid and solid reagents, required for wavenumber calibration of Raman spectrometers, are provided in the ASTM Standard Guide cited. These values can be used in addition to the highly accurate and precise low-pressure arc lamp emission lines that are also available for use in Raman instrument calibration.] Spectrophotometric grade material can be purchased from appropriate suppliers for this use. Certain instruments may use an internal Raman standard separate from the primary optical path. External calibration devices exactly reproduce the optical path taken by the scattered radiation. [NOTEWhen chemical standards are used, care must be taken to avoid standard contamination and to confirm standard stability.]

Unless the instrument is of a continuous calibration type, the primary wavelength axis calibration should be performed, as per vendor procedures, just prior to measuring

[^359]the laser wavelength. For external calibration, the Raman shift standard should be placed at the sample location and measured using appropriate acquisition parameters. The peak center of a strong, well-resolved band in the spectral region of interest should be evaluated. The position can be assessed manually or with a suitable, valid peak-picking algorithm. The software provided by the vendor may measure the laser wavelength and adjust the laser wavelength appropriately so that this peak is at the proper position. If the vendor does not provide this functionality, the laser wavelength should be adjusted manually.

## INTENSITY (Y-AXIS)

Calibration of the photometric axis can be critical for successful quantitation using certain analytical methods (chemometrics) and method transfer between instruments. Both FT-Raman units and dispersive Raman units should undergo similar calibration procedures. The tolerance of photometric precision acceptable for a given measurement should be assessed during the method development stage.

To calibrate the photometric response of a Raman instrument, a broad-band emission source should be used. There are two accepted methods: Method $A$, which utilizes an NIST-traceable tungsten white light source ${ }^{2}$ (and is applicable to all common laser excitation wavelengths listed in Ta ble 1) and Method B, which utilizes NIST SRM 2241, ${ }^{3}$ a doped-glass fluorescence source that is currently available only for systems with $785-\mathrm{nm}$ nominal excitation.

[^360]Method A-The NIST-traceable source should be placed at the sample location with the laser off and the response of the detector measured (using parameters appropriate for the instrument). The output for the source used for calibration should be known. The ratio of the measured response to the true response should be determined and a correction file generated. This correction should be applied to all spectra acquired with the instrument. Most manufacturers will provide both appropriate calibration sources and software for this approach. If the manufacturer does not provide a procedure or method, the user may accomplish the task using a source obtained from NIST and appropriate software. If using a manufacturer's method, attention must be paid to the calibration procedure and source validity. The user should obtain appropriate documentation from the manufacturer to ensure a qualified approach.

Method B-The NIST SRM 2241 should be placed at the sample location. With the laser on, a spectrum of the SRM should be obtained (using parameters appropriate for the instrument). The output for the source used for calibration should be known. The ratio of the measured response to the true response should be determined and a correction file generated. This correction should be applied to all spectra acquired with the instrument. Most manufacturers will provide both appropriate calibration sources and software for this approach. If the manufacturer does not provide a procedure or method, the user may accomplish the task using a source obtained from NIST and appropriate software. If using a manufacturer's method, attention must be paid to the calibration procedure and source validity. The user should obtain appropriate documentation from the manufacturer to ensure a qualified approach. [NOTE-Meth$\operatorname{od} B$ is currently appropriate only for a system with $785-\mathrm{nm}$ laser excitation. NIST is currently producing other SRM
materials that will be wavelength-specific for 1064-, 632.8-, 532-, and 514-nm excitation (and available in the 20042006 timeframe).]

## EXTERNAL CALIBRATION

Detailed functional validation employing external reference standards is recommended to demonstrate instrumental suitability for laboratory instruments, even for instruments possessing an internal calibration approach. The use of external reference standards does not negate the need for internal quality control procedures; rather, it provides independent documentation of the fitness of the instrument to perform the specific analysis/purpose. For instruments installed in a process location or in a reactor where positioning of an external standard routinely is not possible, including those instruments possessing an internal calibration approach, periodic checking of the relative performance of an internal vs. external calibration approach should be made. The purpose of this test is to check for change in components that may not be included in the internal calibration method (process lens, fiber-optic probe, etc.), e.g., photometric calibration of the optical system.

## QUALIFICATION AND VERIFICATION OF RAMAN INSTRUMENTS

its intended application and, when requalified periodically, continues to function properly over extended time periods. When the device is used for a specific qualitative or quantitative analysis, regular performance verifications are made. Because there are many different approaches to measuring Raman spectra, instrument operational qualification and performance verification often employ external standards that can be used on any instrument. As with any spectrophotometric device, a Raman instrument needs to be qualified for both wavelength ( $x$-axis and shift from the excitation source) and photometric (intensity axis) precision.
In performance verification, a quality of fit to an initial scan or group of scans (often referred to in nonscanning instruments as an accumulation) included in the instrumental qualification can be employed. In such analysis, it is assumed that reference standard spectra collected on a new or a newly repaired, properly operating instrument represent the best available spectra. Comparison of spectra taken over time on identical reference standards [either the original standard or identical new standards (if stability of the reference standards is a concern)] form the basis for evaluating the long-term stability of a Raman measurement system.

## Frequency of Testing

Instrumental qualification is performed at designated intervals or following a repair or significant optical reconfiguration, such as a laser replacement or changing excitation wavelengths. Full instrument requalification may not be necessary when changing between sampling accessories such as a microprobe, a sample compartment, or a fixed fiber-optic probe. Performance verification tests may be sufficient in these cases; instrument-specific guidance from the vendor on qualification requirements should be followed. Tests include wavelength ( $x$-axis and shift from the
excitation source) and photometric (intensity axis) precision. Instrument qualification tests require that specific ap-plication-dependent tolerances be met.

Performance verification is carried out on the instrument configured for the analytical measurements and is done more frequently than instrument qualification. Performance verification includes wavelength uncertainty and intensityscale precision. Wavelength precision and intensity-scale precision tests may be needed prior to any data collection on a given day. Performance is verified by matching the current spectra to those collected during the previous instrument qualification.

## Instrument Operational Qualification

It is important to note that the acceptance specifications given in both the Instrument Operational Qualification and Performance Qualification sections are applicable for general use; specifications for particular instruments and applications may vary depending on the analysis method used and the desired accuracy of the final result. ASTM standard reference materials are also specified, with the understanding that under some circumstances (specifically remote online applications) calibration using one of these materials may be impractical, and other suitably verified materials may be employed. At this juncture it is important to note that specific parameters such as spectrometer noise, limits of detection (LOD), limits of quantification (LOQ), and acceptable spectral bandwidth for any given application should be developed as part of the analytical method development. Specific values for tests such as spectrometer noise and bandwidth will be dependent on the instrument chosen and the purpose required. In view of this, specific instrument tests for these parameters are not dictated in this information chapter.

## WAVELENGTH (X-AXIS) PRECISION

It is important to ensure the precision of the wavelength axis via calibration to maintain the integrity of Raman peak positions. Wavelength calibration of a Raman spectrometer consists of two parts: primary wavelength axis and laser wavelength calibration. After calibrating both the primary wavelength axis and the laser wavelength, instrument wavelength uncertainty can be determined. This can be accomplished using a Raman shift standard such as the ASTM shift standards or other suitably verified material. Selection of a standard with bands present across the full Raman spectral range is recommended so that instrument wavelength uncertainty can be evaluated at multiple locations within the spectrum. The tolerance of wavelength precision that is required for a given measurement should be assessed during the method-development stage. [NOTE-For scanning dispersive instruments, calibration may need to be performed more frequently, and precision in both a scanning and static operation mode may need to be verified.]

## PHOTOMETRIC PRECISION

Laser variation in terms of the total emitted photons occurring between two measurements can give rise to changes in the photometric precision of the instrument. Unfortunately, it is very difficult to deconvolute changes in the photometric response associated with variations in the total emitted laser photons from the sample and sampling-induced perturbations. This is one of the reasons why absolute Raman measurements are strongly discouraged and why the photometric precision specification is set relatively loosely. The tolerance of photometric precision required for a given measurement should be assessed during the method-development stage.

## Performance Qualification

The objective of performance qualification is to ensure that the instrument is performing within specified limits with respect to wavelength precision, intensity axis precision, and sensitivity. In certain cases when the instrument has been set up for a specific measurement (for example, installed in a process reactor), it may no longer be possible or desirable to measure the wavelength and photometric (intensity) qualification reference standards identified above. Provided instrument operational qualification has shown that the equipment is fit for use, a single external performance verification standard can be used to reverify function on a continuing basis (for example, a routinely used process solvent signal, for both wavelength and photometric precision, following reactor cleaning). The performance verification standard should match the format of the samples in the current analysis as closely as possible and use similar spectral acquisition parameters. Quantitative measurements of an external performance verification standard spectrum checks both the wavelength ( $x$-axis and laser wavelength) and the photometric (intensity) precision. Favorable comparison of a series of performance verification spectra demonstrates proper continued operation of the instrument.

## WAVELENGTH PRECISION

The wavelength precision should be measured by collecting data for a single spectrum of the selected Raman shift standard for a period equal to that used in the photometric consistency test. Peak positions across the spectral range of interest are used to calculate precision. Performance is verified by matching the current peak position to those collected during the previous instrument qualification and should
not vary by more than $\pm 0.3 \mathrm{~cm}^{-1}$, although this specification may be adjusted according to the required accuracy of the measurement.

## PHOTOMETRIC CONSISTENCY

The photometric consistency should be measured by collecting data for a single spectrum of a suitably verified reference standard material for a specified time. The areas of a number of bands across the spectral range of interest should be calculated using an appropriate algorithm. The most intense band area is set to an intensity of 1 , and all other envelopes are normalized to this band. Performance is verified by matching the current band areas to their respective areas collected during the previous instrument qualification. The areas should vary by no more than $10 \%$, although this specification may be adjusted according to the required accuracy of the measurement.

## LASER POWER OUPUT PRECISION AND ACCURACY

This test is applicable only to Raman instruments with automatic, internal laser power meters. Instruments without laser power measurement should utilize a calibrated laser power meter from a reputable supplier. The laser output should be set on a representative output, dictated by the requirements of the analytical measurement and the laser power measured. The output should be measured and checked against the output measured at instrument qualification. The power (in milliwatts or watts) should vary by no more than $25 \%$ compared to the qualified level. If the power varies by more than this amount, the instrument should be serviced (as this variation may indicate, among other things, a gross misalignment of the system or the onset of failure of the laser).

For instruments with an automatic, internal laser power meter, the accuracy of the values generated from the internal power meter should be compared to a calibrated external laser power meter at an interval of not more than 12 months. The internally calculated value should be compared to that generated by the external power meter. Performance is verified by matching the current value to that generated during the previous instrument qualification. The manufacturer may provide software to facilitate this analysis. If the instrument design prevents the use of an external power meter, then the supplier should produce documentation to ensure the quality of the instrument and provide a recommended procedure for the above analysis to be accomplished during a scheduled service visit.

## METHOD VALIDATION

Validation of Raman methods will follow the same protocols described in Validation of Compendial Methods $\langle 1225\rangle$ in terms of accuracy, precision, etc. However, several of these criteria are affected by variables specific to Raman.

Fluorescence is the primary variable that can affect the suitability of a method. The presence of fluorescent impurities in samples can be quite variable and have little effect on the acceptability of a material. The method must be flexible enough to accommodate different sampling regimes that may be necessary to minimize the effects of these impurities.

Detector linearity must be confirmed over the range of possible signal levels. Fluorescence may drive the signal baseline higher than that used in the validation, in which case the fluorescence must be decreased, or the method validated to accommodate the higher fluorescence levels. This is also true for the precision, LOD, and LOQ of the method, as increased baseline noise will negatively impact all of these values. Because fluorescence may also affect quantita-
tion due to baseline shifts, confirmation of acceptable quantitation at different levels of photobleaching, when used, should also be obtained.

The impact of the laser on the sample must be determined. Visual inspection of the sample and qualitative inspection of the Raman spectrum for measurements with differing laser powers and exposure times will confirm that the sample is not being altered (other than by photobleaching). Specific variables to confirm in the spectrum are shifts in peak position, changes in peak intensity and band width, and unexpected changes in background intensity.

Method precision must also encompass sample position. The sample presentation is a critical factor for both solids and liquids, and must be either tightly controlled or accounted for in the calibration model. Sample position sensitivity can often be minimized by appropriate sample preparation or sample holder geometry, but will vary from instrument to instrument based on excitation and collection optical configuration.

## DEFINITION OF TERMS AND SYMBOLS

Calibration model is a mathematical expression to relate the response from an analytical instrument to the properties of samples.

Instrument bandwidth is a measure of the ability of a spectrometer to separate radiation of similar wavelengths.
Multiple linear regression is a calibration algorithm used to relate the response from an analytical instrument to the properties of samples. The distinguishing feature of this algorithm is the use of a limited number of independent variables. Linear-least-squares calculations are performed to establish a relationship between these independent variables and the properties of the samples.

Multivariate curve resolution (MCR) is a curve deconvolution technique that separates spectral components on the basis of their linear contributions to the overall spectrum.

Operational qualification is the process by which it is demonstrated and documented that the instrument performs according to specifications, and that it can perform the intended task. This process is required following any significant change such as instrument installation, relocation, major repair, etc.

Partial least squares (PLS) is a calibration algorithm used to relate instrument responses to the properties of samples. The distinguishing feature of this algorithm is that, although similar to PCR, this algorithm includes data concerning the properties of the samples used for calibration in the calculation of the factors used to describe the instrument responses.

Performance qualification is the process of using one or more well-characterized and stable reference materials to verify consistent instrument performance. Qualification may employ the same or different standards for different performance characteristics.
Principal component analysis and regression (PCA and $P C R)$ is a calibration algorithm used to relate the response from an analytical instrument to the properties of samples. This algorithm, which expresses a set of independent variables as a linear combination of factors, is a method of relating those factors to the properties of the samples for which the independent variables were obtained.

Raman spectrum ${ }^{4}$ is a graph of the radiant energy, or number of photons, scattered by the sample through the indirect interaction between the molecular vibrations in the sample and monochromatic radiation of frequency much higher than that of the vibrations. The abscissa is usually the difference in wavenumber between the incident and scattered radiation.

[^361](Normal) Raman scattering ${ }^{4}$ is Raman scattering that occurs through the polarizability, not the hyper-polarizabilities, and is excited by radiation that is not in resonance with electronic transitions in the sample. The scattering, in fact, occurs through the derived polarizability tensors, i.e., through changes in the polarizability during the vibrations. Raman wavenumber shift ${ }^{4}$,
$\Delta \tilde{v}$
is the wavenumber of the exciting line minus the wavenumber of the scattered radiation. SI unit: $\mathrm{m}^{-1}$. Common unit: $\mathrm{cm}^{-1}=100 \mathrm{~m}^{-1}$.
$\Delta \tilde{v}$
is positive for Stokes scattering and negative for anti-Stokes scattering.

## APPENDIX: CHEMOMETRIC APPLICATIONS

 AND MODEL BUILDINGChemometrics can legitimately be used with Raman data to create models that can be used for qualitative and/or quantitative analysis.

## Data Pretreatments

Pretreatments are mathematical manipulations of the spectra performed prior to the primary modeling step. The goal of pretreatments is to reduce the amount of irrelevant information, eliminating it from the model prior to the application of the primary technique. There are several data pretreatments that are typically used for removal of baseline anomalies. These include multiplicative scatter correction
(MSC), standard normal variate (SNV), and derivatives. Pearson's method, an iterative approach to baseline decurvature, works well for the correction of some sets of data.

## Library Construction and Use

Raman libraries are often used for compound identification. The test material can be tentatively known to the user or not. Libraries used for the purpose of raw material, intermediate, or formulation identity confirmation are best constructed from real production materials. This is particularly prudent in light of the fact that materials differing in crystallinity or polymorphic constitution will yield varying Raman spectra. Raman libraries purchased from a third party should be used judiciously.

Qualitative algorithms vary, and the appropriate choice is application dependent. For simple identifications, correlation algorithms often work well. These algorithms can be based on a variety of mathematical manipulations. Principal component-based methods such as discriminant analysis can also be used for qualitative analysis.

## Quantitative Calibration Approach

Raman spectroscopy can be used for quantitative analysis both for in-line and off-line work. There are some unique aspects concerning the use of quantitative Raman spectra that should be noted.

## ALGORITHMS FOR QUANTITATION

As in the case of NIR spectroscopy (see Near-Infrared Spectrophotometry $\langle 1119\rangle$ ), multivariate methods may be used to model Raman data. However, univariate analyses are often appropriate because of the resolution of information that Raman affords.

Both peak areas and peak heights can appropriately be used for Raman quantitation when univariate models are employed. Peaks should be reasonably well resolved when this approach is employed. As described above, peak ratios, as a rule, should be employed to account for peak intensity changes not related to the analyte. The judicious choice for a reference band is critical in such cases. Multivariate methods are also viable for Raman quantitation.
Multivariate curve resolution (MCR), which attempts to deconvolute the spectral data as a linear sum of its contributions, is a particularly effective means of dealing with Raman data that exhibit substantial change. This algorithm can potentially isolate the contribution from the analyte of interest and quantify the level of this contribution from sample to sample. The method is often employed in a non-negative mode making the resulting factors potentially interpretable.
Principal components analysis (PCA) can be used similarly to MCR. The contribution of each component generated can be used to semiquantitatively estimate the level of the analyte. Related to PCA, principal component regression (PCR) can also be used. This provides an opportunity for reference data to be employed and is thus truly quantitative.
In many circumstances, multiple linear regression (MLR) can be very effective for Raman quantitation. MLR gives the user the capability of using denominator data points, which can be very useful for Raman data. As with other types of data, the ability to choose multiple numerators can also work synergistically in a quantitative analysis.
Partial least squares (PLS) regression remains one of the more popular choices for Raman quantitation. PLS uses the reference data to orient the factor generation. This can be very effective, especially for the quantitation of low-level analytes.

The choice of appropriate quantitation tools varies from project to project. Both pretreatment methods and quantitative algorithms should be chosen wisely according to the goals. If isolated analyte and reference bands are available, univariate models are often a good choice. If quantitative estimates are all that are necessary or the sample set is a closed set (no future predictions will be made), then MCR or PCA are good choices. For reasonably extensive data sets with available reference data, MLR, PCR, or PLS can be used.■2S (USP28)

## BRIEFING

〈1177〉 Good Packaging Practices, page 1630 of $P F$ 29(5) [Sept.-Oct. 2003]. This chapter, which appeared in In-Process Revision, is published again, with minor editorial changes, for public comment.
(PSD: C. Okeke) RTS-41087-2

## Add the following:

## ■ $\langle 1177\rangle$ GOOD PACKAGING PRACTICES

This chapter provides general guidance on packaging considerations for Pharmacopeial preparations that may be stored, transported, and distributed. It describes procedures that should be considered to ensure that proper packaging practices are maintained. It does not affect any applicable requirements under good manufacturing practices, state laws governing pharmacy, the USP General Notices and Requirements or monographs, or provisions under approved labeling.

Definitions for storage conditions and packaging are provided in Preservation, Packaging, Storage, and Labeling under General Notices and Requirements. All equipment used for recording, monitoring, and maintaining these temperature and humidity conditions should be calibrated on a regular basis. This calibration should be traceable to national or international standards (see also the general information chapter Monitoring Devices-Time, Temperature, and Humidity $\langle 1118\rangle$ ).

## CONTAINERS

The monograph packaging and storage statement specifies that the container (primary package) should meet the requirements under Containers $\langle 661\rangle$ and ContainersPermeation $\langle 671\rangle$, which include the stipulations for determining if a container is "tight" or "well-closed." In most cases, compendial preparations are expected to be packaged in "tight" containers, especially if the article is moisture sensitive. In addition, where necessary, the packaging component should protect the preparation from light, reactive gases, solvent loss, microbial contamination, etc. "Tight" and "well-closed" containers are clearly defined in General Notices and Requirements (see Containers under Preservation, Packaging, Storage, and Labeling), whereas testing protocol and moisture permeation limits to determine if the container meets either of these definitions can be found in Containers $\langle 661\rangle$ and Containers-Permeation $\langle 671\rangle$ for single-unit and multiple-unit containers.

A packaging system is composed of a container system with its closure. This system may include several layers of protection for the Pharmacopeial preparation along with any sealing devices, delivery devices, labeling, and package inserts. The General Notices section also provides definitions for types of packaging systems that contain and protect a Pharmacopeial preparation (e.g., single-unit containers,
unit-dose containers, etc.). Stability testing is conducted on the dosage forms packaged in the container-closure system proposed for marketing.

One type of permeation test for multiple-unit containers is described in Containers-Permeation $\langle 671\rangle$. This test is intended for drug products being dispensed on prescription in vials with a container-closure system. The results of the test reflect the water vapor permeation through the container and through the closure. Limits have been established to define whether a container for dispensing has tight or well-closed characteristics with regard to water vapor permeation. FDA recommends that manufacturers perform this test on the container-closure system, although it is not specified in USP. In this particular test, the inner seal of the manufacturer's container-closure system is removed prior to testing.

Single-unit containers for capsules and tablets under Con-tainers-Permeation $\langle 671\rangle$ are measured for water vapor permeation according to the criteria for the four classes of containers (classes A-D).

The $U S P$ recognizes several official container materials that can be selected on the basis of their properties. Most containers are made of glass or plastic. Glass containers must be evaluated for chemical resistance and light transmission (if indicated) as described in Containers $\langle 661\rangle$. In addition, injectable medication containers should be reviewed according to the section Packaging under Injections $\langle 1\rangle$. Elastomeric closures should be evaluated separately as described in Elastomeric Closures for Injection $\langle 381\rangle$. Plastic containers should be assessed using different criteria for the three types of plastics as described in the following sections under Containers $\langle 661\rangle$ : Polyethylene Containers (PE) for dry oral solid dosage forms, Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Bottles (PET, PETG) for liquid oral dosage forms, and Polypropylene Containers (PP) for dry solid and liquid oral dosage
forms. As articulated in these sections, plastics should undergo testing for light transmission (if appropriate), water vapor permeation (see also Containers-Permeation $\langle 671\rangle$ ), extraction physiochemical testing, and biological testing (see also Biological Reactivity Tests, In Vitro $\langle 87\rangle$ and Biological Reactivity Tests, In Vivo $\langle 88\rangle$ ). For example, testing water vapor permeation for a PE container is conducted by sealing the container with heat-sealed foil laminate and measuring the water permeation in a humid atmosphere. Given that water vapor does not permeate the foil laminate, this test assesses only the properties of the container. The level of protection provided by a packaging system marketed with a heat-sealed foil laminate inner seal (prior to removal of the foil) is approximated by this test. However, in the case of a PET bottle for liquid preparations, water vapor permeation testing is done by filling containers with water and measuring the water loss rate in a dry atmosphere. Additional testing may be required for certain pharmaceutical dosage forms as well.

The container-closure system for the storage or shipment of a bulk liquid drug substance is typically plastic, stainless steel, a glass-lined metal container, or an epoxy-lined metal container with a rugged, tamper-resistant closure. Qualification of the container-closure system for these types of preparations includes evaluation for solvent and gas permeation, light transmittance, closure integrity, ruggedness in shipment, protection against microbial contamination through the closure, and compatibility and safety of the packaging components as appropriate (see Containers $\langle 661\rangle$ ).
Other information on container-closure systems may be found in FDA's Guidance for Industry: Container Closure System for Packaging Human Drugs and Biologics, www.fda.gov.

## PACKAGING

Packaging for Pharmacopeial articles can be divided into categories according to terminology generally accepted by industry. As mentioned earlier, the General Notices section provides some definitions for different types of containers classified by their characteristics and uses. In addition, the ASTM Committee D10 on packaging publishes terminology, practices, test methods, specifications, guides, and classifications for testing and evaluating packaging (see ASTM D99695, "Standard Terminology of Packaging and Distribution Environments"). Under certain rules and guidelines (e.g., such as 49 CFR, Dangerous Goods, and others), however, alternate terminology is used for the components described below. For terminology pertaining to repackaging processes, refer to Packaging Practice-Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container〈1146〉.

Primary Container-This container is in direct contact with the Pharmacopeial preparation. The purpose of a primary container, also referred to as an immediate container, is to protect the preparation from environmental hazards during storage and handling. In some cases, the primary container is also a specialized delivery system, such as an aerosol or a metered-dose dispenser (see Pharmaceutical Dosage Forms $\langle 1151\rangle$ ). For the majority of oral dosage forms, the primary container consists of a cap and a bottle or a blister or pouch package that can be made from many different materials, including glass, plastic, single or laminated flexible materials, and metal. All components of the primary container must meet the requirements under 21 CFR for direct food contact and, where applicable, the USP requirements under Containers $\langle 661\rangle$ and Con-tainers-Permeation $\langle 671\rangle$. A full description of the primary container is included under the "Container/Closure

System" section of the New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or other classes of FDA submissions.

Critical Secondary Container-This container is not in direct contact with the article, but it provides essential product stability protection. For example, a primary container may be packed inside a critical secondary container such as a pouch to provide moisture, gas, light, or microbial protection not afforded by the primary container. A description of the critical secondary container is included under the "Container/Closure System" section of the NDA, ANDA, or other classes of FDA submissions.

Secondary Container-This container encloses one or more primary containers. A secondary container is not always present. If used, it is usually designed for the final market presentation. Secondary containers are often used simply to carry required labeling or to keep individual primary containers together with delivery systems or other add-on features. Secondary containers can also provide protection against damage in the handling and distribution system. The most common secondary container is the standard folding carton. Some products, such as syringes, may be placed in trays prior to packing in a carton. Secondary container materials are not included in the container and closure description and require neither stability studies nor prior approval when making a change in the materials used.

Additional Packaging-A wide variety of additional packaging, such as trays and display cartons, may be used to hold primary containers.

Unit of Sale-This may be an individual bottle, a carton containing one or more bottles, or a tray with multiple primary containers. A unit of sale may contain more than one item for individual sale. For example, a display tray may have multiples of a single article or a variety of related articles from a single manufacturer, each intended for individ-
ual sale. The individual item intended for sale is referred to as a stock-keeping-unit (SKU). SKUs are distinguished by a discrete National Drug Code (NDC). Over-the-counter (OTC) articles contain a Universal Product Code (UPC) for all SKUs. A prescription SKU may be intended for final consumer use and may not be repackaged by a pharmacy. Such packages, often called "unit of issue" or "unit of use," require child-resistant (CR) packaging as described under 16 CFR 1700, "Poison Prevention Packaging," except for packages exempted by the Consumer Product Safety Commission. The CR feature is typically incorporated by the manufacturer (see Packaging-Unit of Use $\langle 1136\rangle$ ). OTC articles are regulated under the same rule, but only if they contain certain active ingredients above specified limits. Any regulated product shipped via the United States Postal Service (USPS) must meet the USPS rules under 39 CFR 111.

Final Exterior Package-This is typically a corrugated fiberboard box (case) or a wrapper. The shipping case label is affixed to this outermost layer and incorporates all of the bar codes required by the National Wholesale Druggists' Association (NWDA). This final package is normally shipped on pallets to distribution centers, wholesalers, and other large-volume customers. The manufacturer may or may not intend that this package enter the small-packageshipping environment as an individual unit without further protection.

Especially with fiberboard boxes, relative humidity (RH) may have a negative effect on the compression strength of the box, causing loads to shift and potentially damage the article or the outer and inner packaging. Articles stored in refrigerators or freezers, which are environments with high RH, are prone to this type of damage when stacked. The problem may be exacerbated by carton design, stacking pat-
tern, or use of low edge-crush-test corrugated fiberboard. Computer programs are available to determine the acceptable stack height and patterns on the basis of carton weight, style, size, and material. If problems occur, the product manufacturer should be contacted. Source materials and reference information on corrugated fiberboard boxes can be found in the "Fiber Box Handbook" published by the Fiber Box Association.
A wholesaler or other reshipper should not assume that the package received from the manufacturer is suitable for reuse. Many packages are customized for very specific routes and modes of transportation and are not suitable for other applications. Like any other shipping container, insulated cartons and inner protective packaging can be damaged during transit, thus affecting package performance and possibly allowing damage to contents if reused.

## ENVIRONMENTAL ISSUES

Packaging materials are regulated by a variety of federal, state, and local rules. In general, most pharmaceutical packaging containers can be recycled within local programs. The use of recycled material in primary containers is governed by the FDA, but it is generally not allowed. Pharmaceutical manufacturers commonly follow the most current Coalition of Northeastern Governors' rules (e.g., Model Toxics in Packaging Legislation) regarding heavy metals in packaging and other environmental issues.
Certain classes of Pharmacopeial articles may require special handling. Such articles include products classified as (1) Dangerous Goods under the Department of Transportation (DOT), state, local, or carrier rules; (2) controlled drugs under the Drug Enforcement Administration (DEA); or (3) scheduled substances under state regulations.

## LABELING

The labeling of shipping containers by manufacturers must be in compliance with the pertinent sections of FDA and DOT rules.

Dangerous Goods-The labeling of shipments classified as Dangerous Goods, including all information on the bill of lading or airway bill, must follow the instructions provided by the DOT, the International Air Transport Association (IATA), and the carrier. The exterior package must carry all of the required standard symbols for the class of goods, and the shipping container must comply with the performance standards for the articles enclosed. The shipper of record is responsible for compliance with the Dangerous Goods requirements.

Controlled Substances-When Pharmacopeial preparations that contain DEA-scheduled controlled substances are distributed to a patient directly via the USPS, these articles must be marked and labeled in accordance with USPS Domestic Mail Manual, Regulation Article C023, Section 7.2.■2S (USP28)

## Briefing

$\langle 1178\rangle$ Good Repackaging Practices, page 1219 of $P F$ 29(4) [July-Aug. 2003]. This proposed general chapter is being revised to eliminate references to "prepackager" and to address comments received. Editorial revisions have also been made.
(PSD: C. Okeke) RTS-40651-1

## Add the following:

## - $\langle 1178\rangle$ GOOD REPACKAGING PRACTICES

This chapter is intended to provide guidance to those engaged in repackaging of drug products in accordance with 21 CFR 10.90. A pharmacist who repackages under the state law needs to apply (1) the principal information provided in the USP general information chapter Packaging PracticeRepackaging a Single Solid Oral Drug Product Into a UnitDose Container $\langle 1146\rangle$ and (2) other beyond-use date references in the Expiration Dating section under General Notices and Requirements.

This chapter provides information to any person who removes drugs from their original manufacturer's container and repacks them into a different container-closure system for resale or for distribution to hospitals or other pharmacies. It does not apply to repackaging of any radioactive drug products, including oral solids.

A repackager referred to here may also be a contract packager or a contract repackager., or antract prepackager. The words "repackager" and "repacker" are the same in this text and may be used interchangeably. These functions are beyond the regular practice of a pharmacist. A repackager or prepacker is required to register with the FDA and comply with current Good Manufacturing Practices (cGMPs) regulations in 21 CFR 210 and 211.

A repackager is expected to meet the requirements of packaging practice under 21 CFR 210 through 226. Because the packaging practice relates to packaging, processing, or holding a drug product intended for administration to humans or animals, the repackager is expected to comply with regulations such as those relating to the sections pertaining to quality control, personnel qualifications, building and fa-
cilities, equipment, production and process controls, packaging and labeling controls, laboratory controls, master production record, batch records and reprints, distribution records, storage control records, and complaint files.

## DEFINITIONS

For the purposes of this chapter repackager, contract packager, and contract repackager prepacker, and prepackager are defined as follows:

A REPACKAGER is one who purchases and removes a drug product from the manufacturer's market container or bulk dosage container and places the product into a different container for distribution for human or animal use. A repackager may or may not take ownership from the manufacturer. A repackager is engaged in the repackaging of drugs (see also Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container $\langle 1146\rangle$ for more definitions of a repackager).
A CONTRACT PACKAGER is one who is contracted by original drug manufacturers to package or repackage their product into a single- or multi-unit container chosen by the manufacturer. These containers should meet all the applicable requirements in this chapter, pertinent sections in general test chapters Containers $\langle 661\rangle$ and ContainersPermeation $\langle 671\rangle$, and comply with 21 CFR food additive requirements.

AN EQUIVALENT CONTAINER-CLOSURE SYSTEM refers to a container-closure system that yields the same, or better, moisture vapor transmission rate (MVTR), oxygen transmission, and light transmission as the original market container. These values may be determined by the repackager, or they may be obtained from the container-closure vendor for the specific container-closure system under consideration.

BEYOND-USE DATE (BUD) AND DISCARD-AFTER DATE are equivalent and are assigned using the criteria stated in the relevant section below.

EXPIRATION DATE is determined using stability studies and is not the same as beyond-use date or discard-after date.

## FACILITIES

The facility in which repackaging is practiced should be operated in conformity with cGMPs. The environmental conditions during the packaging and storage operation of the drug product should comply with the controlled room temperature (see General Notices), storage in a dry place, and other requirements as directed by the manufacturer or supplier, especially if the drug requires storage at special temperature and humidity conditions (see Good Storage and Shipping Practices $\langle 1079\rangle$ ).

## ACQUISITION PROCESS

The repackager is expected to perform appropriate analytical testing for all pertinent specifications, such as identity and strength of each active ingredient, and any other finished product tests to establish valid analytical data. The repackager is expected to maintain records of such analyses on a batch-by-batch basis for the repackaged product that is either transferred to the repackager by the manufacturer or independently maintained by the repackager.
"Bulk" in this text refers to the quantity of either drug product or dosage form. The following criteria should be considered by the repackager upon receipt of bulk prior to repackaging.
(a) The bulk article should be distributed to the repackager by the manufacturer in accordance with all regulatory requirements and accompanied by appropriate labeling and a valid expiration date. The repackager should also
receive Material Safety Data Sheets (MSDS), Certificates of Analysis, and sample market labeling, including inserts from the drug product manufacturer.
(b) The bulk article should be received intact and undamaged and in properly labeled containers with the Certificate of Analysis.
(c) The bulk article should undergo definitive organoleptic evaluations to confirm its identity (e.g., physical appearance, marking, color, and odor) and to confirm the labeling as described by the manufacturer.
(d) Records should be maintained to verify the identity and quantity of each shipment received and to verify the lot number and bar coded information for each article of the bulk shipment received. This record should also include the name of the manufacturer or supplier and its lot numbers and the date of receipt.
(e) The repackager should store and maintain the bulk under storage conditions specified by the manufacturer, and/or as directed under controlled room temperature (see General Notices).

## REPACKAGING PROCESS

The following criteria should be observed.
(a) The repackaging operations should be conducted under conditions that meet specified storage temperature definitions (see General Notices). Conditions of operation include maintenance of controlled room temperature in the area where the repackaging operation is conducted or other conditions as instructed by the manufacturer.
(b) The manufacturer should include, in the package insert or in other appropriate literature supplied to the repackager, the following information about the packaging: materials of construction of the market package, its

MVTR (see USP general chapter $\langle 671\rangle$ ), as well as oxygen transmission and light transmission characteristics in order to enable the repackager to properly select an equivalent container-closure system. If the repackager does not use a container-closure system equivalent to the manufacturer's market package, then the repackager must generate stability data for the drug product in the new container-closure system to justify the expiration date or BUP assigned.
(c) The repackaging containers are labeled with the same labeling information as the market label that is used by the manufacturer. The conditions on the labeling should meet those required under 21 CFR 201, 211.122, 211.125, and 211.130.
(d) Written procedures should be maintained to ensure that correct labels, labeling, and packaging materials are used for drug products.
(e) All requirements for repackaging of bulk products should meet 21 CFR 211.
(f) The packaging materials should meet the test requirements provided in 21 CFR in direet food additives or additives that have been approved as foodeontact sub staces. Semeral comply with 21 CFR food additives regulations and all applicable requirements in USP general chapters $\langle 661\rangle,\langle 671\rangle$, and $\langle 1146\rangle$.

## LABELING

A repackager should provide appropriate labeling of the product identical to the manufacturer's approved market container. All repackaged products should be labeled with an appropriate BUD in the absence of stability data, or with an expiration date in cases where suitable stability studies, determined in CFR 211.166 (for recommended conditions
see International Conference on Harmonization ICH Q1A Stability Testing of New Drug Substances and Products), have been performed on the product using the repackager's container. The expiration date will ensure that the products meet applicable standards of identity, strength, quality, and purity at the time of use.

## EXPIRATION DATE/BEYOND-USE DATE

## Expiration Date

Stability studies are performed on the drug product in the original manufacturer's containers to establish an expiration date. When a drug is repackaged into a different container, the product's expiration date is altered or interrupted.
(a) The repackager may perform stability studies on the repackaged products to establish an expiration date for the product based on scientific evaluation of the drug product in the container-closure system in which it is to be marketed.
(b) A repackager may use the manufacturer's original expiration date without additional stability testing if the drug product is repackaged into an equivalent contain-er-closure system that is at least as protective as, or more protective than, the original system and complies with criteria established for equivalency. Establishment of system equivalency means (1) that the requirements of USP general test chapters $\langle 661\rangle$ and $\langle 671\rangle$ are met and (2) that the specifications such as light transmission, seals, or desiccants associated with the original container-closure system, or special protective materials in which the drug product is marketed, are the same. Comparison of container-closure systems may be done through stress testing of the product after storage under exaggerated conditions of temperature and
humidity. If the repackager does not use a containerclosure system equivalent to the manufacturer's market package, then the repackager must generate stability data for the drug product in the new container-closure system to justify the expiration date or BUD assigned.
(c) A repackager should not use the equivalency contain-er-closure system criteria to repackage drug products where such products have been identified by the manufacturer to have stability problems or if the manufacturer specifically states that the product should not be repackaged using the equivalency container-closure system criteria. For example, "This product is labile (e.g., moisture sensitive) and therefore should be dispensed only in the original manufacturer's container". In this case, a repackager needs to demonstrate the stability of the drug product in the repackager's containerclosure system.
(d) Establishing the expiration date in the case listed in (c) is applicable for unit-dose containers, mul-tiple-unit containers, and unit-of-use container types.

## Beyond-Use Date or Discard-After Date

In the absence of stability data, where a repackager repackages a product into a unit-dose or multiple-unit container without conducting appropriate stability studies to support expiration dates used, the period of use of the product is limited by the BUD for the repackaged product, which must be less than the expiration date.

## UNIT-DOSE PACKAGING

For unit-dose packaging, the following criteria should be considered.
(1) The original bulk container of the drug product to be used for repackaging has not been previously opened.
(2) The contents of the original bulk drug product to be repackaged are repackaged at one time.
(3) The unit-dose container meets USP general test chapter $\langle 671\rangle$ testing requirements for either Class A or Class B containers.
(4) The unit-dose container meets or exceeds the manufacturer's specification for light resistance.
(5) The conditions of storage meet the storage specifications provided in the General Notices and as described in the labeling by the manufacturer of the bulk product. Where no specific storage conditions are specified, the product should be maintained at controlled room temperature and in a dry place during repackaging.
(6) The BUD used for the repackaged product does not exceed 6 months from the date of repackaging.
(7) The BUD does not exceed the manufacturer's expiration date.
(8) The BUD does not exceed $25 \%$ of the time between the date of repackaging and the expiration date shown on the manufacturer's bulk article container of the drug being repackaged.
(9) Documentation should be in place to show that the preceding criteria (items $1-8$ ) are met. Documentation to show the type of packaging material used and the testing for these materials is also kept on file.
(10) The repackager may not repackage if the manufacturer specifically states "Do not repackage." However, the repackager may affix the repackager's labeling if it is
in accordance with FDA requirements and in agreement with the manufacturer of the drug product.
(11) The repackager may not use the expiration date and BUD interchangeably because they imply the presence or absence of stability testing, respectively.

## MULTIPLE-UNIT PACKAGING

The General Notices define multiple-unit packaging as a package that contains more than one single-dosage unit. For multiple-unit packaging, the following criteria should be considered in assigning a BUD.
(1) The original bulk container of drug product to be used for repackaging has not been previously opened.
(2) The contents of the original bulk drug product to be packaged are repackaged at one time.
(3) The conditions of storage meet the storage specifications in the General Notices and as described in the labeling of the manufacturer's bulk product. Where no specific storage conditions are specified, the product should be maintained at controlled room temperature and in a dry place during repackaging.
(4) The type of container used for repackaging should be the same type used by the manufacturer as the market container, and the product container should comply with the requirements for containers as directed under USP general test chapters $\langle 661\rangle$ and $\langle 671\rangle$, as well as the requirements of 21 CFR for food additives, or the container should be composed of an approved food contact substance. For example, if the manufacturer packages in glass, the repackager should repackage in glass of the same type used by the manufacturer or in chemical-resistant glass containers.
(5) Where the original container is a material other than glass or high density polyethylene (HDPE), the repackager may use a container demonstrated to be equivalent to, or exceed, the protective properties of the manufacturer's multiple-unit market container when performing the applicable tests as described in USP general test chapters $\langle 661\rangle$ and $\langle 671\rangle$.
(6) Where the original container is polyethylene, the repackager may repackage in a chemical-resistant glass container or a polyethylene container. These containers should meet the appropriate tests and specifications in 21 CFR and USP general test chapters $\langle 661\rangle$ and $\langle 671\rangle$.
(7) The container meets or exceeds the test results of the manufacturer's multiple-unit market container for light transmission.
(8) The container meets or exceeds the manufacturer's container in special protective features: methods used to prevent leaching of container materials or the use of desiccants to maintain low moisture content. [NOTEDesiccants should always be packaged on top of the drug product.]
(9) The container meets or exceeds the manufacturer's container test results for "tight" as provided in USP general test chapters $\langle 661\rangle$ and $\langle 671\rangle$.
(10) For all products, if the repackager uses a container that is equivalent in MVTR to the manufacturer's container or one that has a higher barrier, then the BUD should be 12 months or the manufacturer's expiration date, whichever is less. (See USP general information chapter $\langle 1146\rangle$ for a description of low- and high-barrier packaging.)
(11) The repackager may not repackage the original bulk container of the drug product if the manufacturer specifically states "Do not repackage." However, the repackager may affix the repackager's labeling if this is in accordance with FDA requirements or the specifications of the drug product manufacturer.

## MINIMUM REQUIREMENTS

The following represents the minimum requirements a repackager must meet in order to engage in repackaging drugs from their original manufacturer's container.
(a) A repackager is expected to comply with cGMPs and 21 CFR 211.170(b) for retained samples of repackaged drug products. Any alteration or manipulation of the repackaging process should be documented in accordance with the requirements in 21 CFR 211.
(b) A repackager is expected to repack penicillins, or products such as penicillins, in facilities separate from those facilities used for drug products as described in 21 CFR 211.42 and 21 CFR 211.46.

## SHIPPING AND DISTRIBUTION

For products identified by the manufacturer as moistureand temperature-sensitive, the repackager must follow the specifications provided by the manufacturer during repackaging, shipping, and distribution.
(a) A repackager may not repackage a moisture- and tem-perature-sensitive product if the manufacturer so instructs, except if the repackager is only altering the labeling in accordance with FDA requirements.
(b) The repackaging container should show the equivalent of or be better in protective properties than the manufacturer's original container. For moisture-sensitive
products, a higher-barrier container should be used for repackaging.
(c) The repackager should have proper documentation in place to show the equivalency in protection of the container used.
(d) The storage and handling of the drug product should meet the conditions specifically instructed by the manufacturer of the product.
(e) The repackager should label the container "Contains moisture-sensitive product."

For all other products, the repackager should follow the same guidelines provided in Good Storage and Shipping Practices $\langle 1079\rangle$ that are applicable to a manufacturer. ${ }^{2 S}$ (USP28)

## Briefing

$\langle 1208\rangle$ Sterility Testing-Validation of Isolator Systems, USP 27 page 2613. The proposed revision of this general information chapter includes the replacement of references to sterilization with references to decontamination, thereby reflecting more accurately what is accomplished by treating the inside of an isolator with a process that eliminates viable bioburden. Other changes reflect the new ISO standards $14644-1,-2,-3$, and -7 .
(AMB: D. Porter) RTS-41772-1

## Change to read:

This chapter provides guidelines for the validation of isolator systems for use in sterility testing of compendial articles. [NOTE-In the context of this chapter, sterilized

■"decontaminated" ${ }^{\text {as (USP28) }}$
refers to an item or surface that has been subjected to a process that eliminates viable bioburden.]

Isolators-devices that create controlled environments in which to conduct Pharmacopeial sterility tests-have been used since the mid-1980s. An isolator is either sealed or supplied with air through a mierobial retentive
$\square^{-}$HEPA or better air $_{\text {■2S (USP28) }}$
filter and is able to be reproducibly sterilized. When closed, it uses enly sterilized interfaces or a specialized rapid transfer pert for the transfer of materials. When open, it allows the egress of materials threugh a define opening that has been designed and validated to preclude the entry of contamination. Isolaters are construeted of flexible plasties (such as polyrinyl chleride), rigid plasties, glass, Or stainless steel.
-decontaminated. Closed isolators, which are systems with no direct opening to the external environment, are normally used for sterility testing, although open isolators which allow the egress of materials through a defined opening that precludes the entry of contamination by means of air overpressure may be used. Closed isolators use only decontaminated interfaces or a rapid-transfer port for the transfer of materials. Isolators are constructed of flexible plastics (such as polyvinyl chloride), rigid plastics, glass, or stainless steel. 2 2S (USP28)

Isolator systems protect the test article and supplies from contamination during handling by essentially eliminating direct contact between the analyst and the test articles. All transfers of material into
-and out of ${ }_{\text {n2S }}$ (USP28)
the isolator are accomplished in an aseptic fashion while maintaining complete environmental separation. Aseptic manipulations within the isolator are made with half-suits, which are flexible components of the isolator wall that allow the operator a full range of motion within the isolator, or by gloves and sleeves. Operators are not required to wear special clean-room clothing for conducting sterility tests within isolators; standard laboratory clothing is adequate,

■although a pair of sterile gloves is frequently worn under the isolator gloves as an added precaution against contamination entering the isolator enclosure and for hygiene pur-
poses.m2S (USP28)
The interior of the isolator is treated with sporicidal chemicals that result in the elimination of all viable bioburden

- on exposed surfaces. $\quad$ 2S (USP28)


## Change to read:

## ISOLATOR DESIGN AND CONSTRUCTION

## Air Handling Systems

An isolator used for sterility testing is equipped with microbial retentive filters (HEPA filters
$\mathbf{- o r}$ better $_{\text {2S (USP28) }}$
are required). At rest, the isolator meets the particulate air-quality requirements for Class 100 area as defined in U.S. Federal Stan dard-209E

■an ISO Class 5 area as defined in ISO 14644-1 through $-3^{*}$ 2S (USP28)
(see Microbio
(see Microbiological Evaluation of Clean Rooms and Other Controlled Environments $\langle 1116\rangle$ ). However, the isolator need not meet Glass 100 conditions during operation, and ne requirements for air velocity or air exehange rate exist. The isolator system is leak proof, however, it is not generally impermeable to gas exchange with the strrounding environment.
-Class 5 conditions during an operation that may generate particulates, and no requirements for air velocity or air exchange rate exist. The isolator should be sealed well enough during decontamination that the dissemination of sporicidal vapors or gases into the surrounding environment is kept to
appropriately low levels.■2S (USP28)
When direct openings to the outside environment exist, constant air overpressure conditions maintain sterile conditions within the isolator.
-In general, both open and closed isolators are maintained at positive pressure relative to the surrounding environment,
and overpressures of 20 to 40 Pa are typical. $\quad$ 2S (USP28)
Airflow within isolators used for sterility testing is
■ither $_{\text {n2S (USP28) }}$
unidirectional or turbulent.

## Transfer Ports and Doors

Isolaters are attached to a "pass through" sterilizer to enable the direet transfer of sterile media, sterile dilution fluids, and-sterile supplies from the sterilizer into the isolater system. Specially designed rapid transfer perts or doers (RTPs) enable isolaters to be connected to one another, so that supplies ean be moved aseptically from one isolator to mother. Aseptic connections between two isolators or an isolator and a container can be made in unelassified enviremments using RTPs.
-Isolators may be attached to a "pass-through" decontaminator or transfer isolator to enable the direct transfer of sterile media, sterile dilution fluids, and sterile supplies from the decontaminator into the isolator system. Rapid transfer ports (RTPs) enable two isolators, i.e., the work station and transfer isolator, to be connected to one another, so that supplies can be moved aseptically from one isolator to another. Aseptic connections between two isolators or an isolator and an RTP-equipped container can be made in unclassified environments using RTPs.■2S (USP28)

[^362]The nonsterile surfaces of the RTP are connected using locking rings or flanges. A compressed gasket assembly provides an airtight seal, thereby preventing the ingress of microorganisms.

When the two RTP flanges are linked to form an airtight passage, a narrow band of gasket remains that could harbor microbial contamination. This exposed gasket is
$\square_{\text {should }} \mathrm{be}_{\text {п2S }}$ (USP28)
treated with a sporicidal agent immediately after the connection is made, and before materials are transferred through the RTP. Good aseptic technique is used when transferring materials and care is taken not to touch the gasket with the materials being transferred or with the gloved hands.

Preventive maintenance and lubrication of the gasket assemblies on the flanges is performed according to the RTP manufacturer's recommendations. The RTP gaskets are changed at the recommended frequency and periodically checked for damage, since cut or torn gaskets cannot make a truly airtight seal.

## Selection of a Location for the Isolator

Isolators for sterility testing need not be installed in a classified clean room, but it is important to place the isolator in an area that provides limited access to nonessential staff. The appropriate location provides adequate space around the isolator for moving transfer isolators, staging of materials, and general maintenance. No environmental monitoring of the surrounding room is required.

Temperature and humidity control in the room is important to operator safety and comfort and is critical for the effective utilization of certain sterilization-or

- $\quad$ 2S (USP28)
decontamination technologies. If an-isolater is directly in the flow path of an air supply grille, it could cool sections of the isolator's walls and result in condensation during vaper sterilization.
-n2S (USP28)
Uniform temperature conditions in the room are desirable when temperature-sensitive sterilization
-decontamination $_{\text {■2S (USP28) }}$ methods are employed.
- Care should be taken in locating the isolator so that cold spots are avoided that might result in excessive condensation when condensing vapors are used for decontamination. ${ }^{2 S}$ (USP28)


## Change to read:

## VALIDATION OF THE ISOLATOR SYSTEM

The isolator system must be validated before its use in sterility testing as part of a batch release procedure. To verify that the isolator system and all associated equipment are suitable for sterility tests, validation studies are performed in three phases: installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). The following sections contain points to consider in the validation of isolator systems for sterility testing. The assignment of test functions to a particular phase of the validation program (i.e., IQ, OQ, and PQ) is not critical, as long as proper function of the isolator is demonstrated and documented before its use in compendial Assays.

## Installation Qualification (IQ)

The IQ phase includes a detailed description of the physical aspects of the system, such as the dimensions, internal configuration, and materials of construction. The unit layout is diagrammed with interfaces and transfer systems clearly and dimensionally indicated. Compliance with design specifications for utility services, such as air supply, vacuum, external exhaust, and temperature and humidity control, is verified. Other equipment used with the isolator system is also described in detail; if any revisions to design specifications are made, these are included. Equipment manuals and copies are catalogued and stored where they can be retrieved and reviewed. Compliance of drawings to design specifications is verified. All drawings and process and instrumentation diagrams are catalogued, stored, and are retrievable.

All documentation is reviewed to verify that it precisely reflects the key attributes of the installed system. This establishes a general benchmark for the isolator system's compliance with design specifications and installation requirements.

Potential process-control or equipment problems that could cause system failure during operation are identified and documented during failure-mode analysis and hazard analysis. The system is modified, if necessary, to minimize the risk of failure, and critical control point methods are established.

The results of the IQ are summarized in an Installation Qualification Report. The following documentation is suggested.

Equipment-The equipment is listed with its relevant design specifications. The IQ verifies that equipment meeting the appropriate design specifications was received and that it was installed according to the manufacturer's requirements.

Construction Materials-The construction materials of critical system components are checked for compliance with design specifications. The compatibility of the intended sterilization

- decontamination $_{\mathbf{m}_{2 S} \text { (USP28) }}$
method with the construction materials is verified.
Instruments-System instruments are listed with their calibration status.

Utility Specifications-All utilities required for operation-as defined in the operating manuals and process and instrumentation diagrams-are checked for availability and compliance with design specifications. Any connection between utility systems and the isolator system is inspected and conformance of these connections to specifications is verified.

Filter Certification-HEPA filters and other microbial retentive filters are tested and certified; copies of test results and certificates are included in the IQ summary. Purchase orders are reviewed and conformance of the air filtration system to specifications is verified.

Computer Software-All computer software associated with the isolator system is listed with its name, size, and file revision number. The master computer disks are checked for proper labeling and stored securely.

## Operational Qualification (OQ)

The OQ phase verifies that the isolator system operates in conformance to functional specifications.

Operational Performance Check-This test verifies that all alert and alarm functions comply with their functional specifications. The system's ability to comply with all set points and adjustable parameters is verified.

Isolator Integrity Check-The integrity of the isolator is maintained during all normal operating conditions. A leak test is performed to verify the compliance with the manufacturer's functional specifications and to ensure safety prior to charging the isolator with a sterilizing

- decontaminating sporicidal $_{\mathbf{m}_{2 S} \text { (USP28) }}$
chemical. To safeguard against adventitious contamination, isolators are operated at a positive pressure differential of about 20-40 Pa during normal operation. If constantorpressure is needed, va tidation studies must show that the
-Validation studies must show that the air pressure ${ }_{\text {nes }}$ (USP28) set point can be maintained and controlled during operation.


## Sterilization

■Decontamination ■2S (USP28)
Cycle Verification A sterilization eyele is performed to verify that all actual values conform to cyele steps and set points.

- A decontamination cycle that is the function of the decontamination equipment in concert with the isolator(s) is verified. $\mathbf{D S S}^{\text {S }}$ (USP28)


## Different sterilization

- decontamination ${ }_{\text {W2S (USP28) }}$
methods can be used to eliminate bioburden from isolator systems and supplies. Among the chemicals that have been used to treat isolators are peracetic acid, chlorine dioxide, ozone, and hydrogen peroxide; each has different requirements for exposure conditions and process control. It is critical to comply with the manufacturer's operational requirements for the selected sterilization
- decontamination ${ }_{\text {n2S }}$ (USP28).
method and to describe them in the functional specifications. Temperature and humidity control within the room is critical when hy drogen peroxide vaper is used in sterilization.

■ ${ }^{-1 S}$ (USP28)
The temperature inside the isolator is also important, particularly for hydrogen peroxide vapor sterilization
-decontamination, ${ }^{2 S}$ (USP28)
where it is critical to maintain the concentration
-relative to ${ }_{\text {■2S }}$ (USP28)
the condensation point. Some sterilization chemicals, such as chlorine dioxide and ozone, require the addition of moisture to the isolator prior to stilizan

- decontamination. 2SS (USPP8) $^{2}$

When elevated relative humidity is required, the ability to control it must be verified during OQ.
It is also important to verify the concentration and distribution of the sterilizing

- decontaminating ${ }_{\text {n2S }}$ (USP28)
chemical. When applied in gaseous or vapor form, the tien is measured using chemicalindicaters, spectrescepic metheds, or electrenic sensors. Distribution may atso be tested using chem iealindieaters.
- distribution may be evaluated using chemical indicators,
spectroscopic methods, or electronic sensors. $\mathbf{Q 2 S}^{\text {S }}$ (USP28)
[NOTE Chemical indieators provide qualitative, but not quantita-
tive, information.]
■ ${ }^{\text {n }}$ (USP28)
Gas and vapor sterilization
- decontamination $\mathbf{■ 2 S ~ ( U S P 2 8 ) ~}^{\text {( }}$
methods require fans in the isolator to distribute the chemical evenly. The location and orientation of these fans are adjusted to ensure optimum air distribution.
-If the isolator utilizes a recirculating unidirectional airflow system, distribution fans may not be required, but this should be evaluated on a case-by-case basis. $\quad$ 2S (USP28) Because shelving units, equipment, glove-and-sleeve assemblies, and half-suits have an impact on distribution patterns, distribution checks are done with the isolator fully loaded with equipment and supplies, and the setup of these units is defined and documented.

Many installations use smaller transfer isolators as portable surface sterilization

- decontamination $_{\text {ne }_{2 S}}{ }_{\text {(USP28) }}$
units. In these transfer isolators, test articles and supplies are treated chemically to eliminate bioburden before transfer through an RTP into the testing isolator. Its loading configuration is defined, and configuration drawings are reviewed and verified during the OQ. [NOTE-The sterilizing
- decontaminating $_{\text {M2S (USP28) }}$
chemicals used in isolators work on the surfaces of materials; therefore, any surface that is occluded will not be treated and could contain viable bioburden.
-Special precautions should be in place for treating surfaces known to be occluded with a sporicide if such surfaces may be revealed during the conduct of sterility tests.] $\mathbf{m}_{\text {2S (USP28) }}$


## Sterilization

- Decontamination ${ }_{\text {■2S }}$ (USP28)
agents need to be removed from the isolator after the exposure period, which is accomplished by a current of fresh air provided either by the sterilization
- decontamination $_{\text {® }_{2 S} \text { (USP28) }}$
equipment or by semether means
-utilizing the isolator air handling system. ${ }^{2 S}$ (USP28)
Aeration is accomplished either in an open loop, in which the gas is exhausted through a vent to the atmosphere, or in a closed loop, in which the chemical is removed and destroyed by the sterilization
- decontamination ${ }_{\text {■2S (USP28) }}$
equipment. The aeration system is checked; if an open-loop configuration is used, the external exhaust system's flow and safety are checked.


## Sterilization

-Decontamination ${ }_{\text {m2S }}$ (USP28)
Cycle Development - When the OQ is completed, serilizat

- decontamination $_{\mathbf{m}_{2 S} \text { (USP28) }}$
cycle development is performed to establish the parameters necessary for process control during routine sterilization
- decontamination $_{\text {■ }^{2 S} \text { (USP28) }}$
cycles. Any of the methods generally used in the industry for the validation of sterilization
- decontamination $_{\mathbf{m}_{2 S} \text { (USP28) }}$
processes-including bioburden-based,
- fractional cycle, $\mathbf{m}_{2 S}$ (USP28)
and overkill methods-are adequate. The sterilization
- decontamination $_{\mathbf{m}_{2 S}(\text { USP28) }}$
process is challenged with biological indicators (BIs). The spore population and resistance of the BIs to the serilization
- decontamination $_{\mathbf{m}_{2 S}(\text { USTP28) }}$
conditions being applied is
-are $_{\text {n2S }}$ (USP28)
known. Wherever possible, atre- $D$ value-is oblaned for the B system
-a D value or survivor curve for the BI system is estima-


## $\operatorname{ted}_{\mathbf{2 S}}$ (USP28)

(see Biological Indicators—Resistance Performance Tests $\langle 55\rangle$ ); it is acceptable to obtain the D value from the BI vendor. When it is impossible determine an aceurate $D$ walue and no means to ver ify the eoncentration of the sterilizing agent are available, the half eyele appreach to cyele development and verifieation is employed.
-n2S (USP28)

## Performance Qualifications (PQ)

The PQ phase verifies that the system is functioning in compliance with its operator requirement specifications. At the completion of the PQ phase, the efficacy of the sterilization

- decontamination ${ }_{\text {2S }}$ (USP28) cycle and, if appropriate, the adequacy of sterilizing
-decontaminating ${ }_{\text {n2S }}$ (USP28)
chemical venting are verified. All PQ data are adequately summarized, reviewed, and archived.
Cleaning Verification-In general, cleaning is not critical for sterility testing applications. However, residual products are a concern in multiproduct testing, particularly for aggressive antimicrobial agents, because these materials could interfere with the ability of subsequent tests to detect low levels of contamination in the product. Concerns about contamination with the product are heightened when it is an inherently antimicrobial powder, because powders are more readily disseminated. Cleaning to a level at which no visible contamination is present is adequate for sterility test isolator systems and is a suitable operator requirement specification. The cleaning method, frequency, equipment, and materials used to clean the isolator are documented.


## Sterilization

-Decontamination. ${ }_{\text {2S (USP28) }}$
Validation-The interior surfaces of the isolator, the equipment within the isolator, and the materials brought into the isolator are treated to eliminate all bioburden. The strilizan

- decontamination $_{\mathbf{Q 2 S}^{\text {(USP28) }}}$
of isolator surfaces, sterility testing supplies, and test articles is different from the sterilization
- decontamination $\mathbf{D V S S}_{\text {(USP28) }}$
of product contact parts or drug components used in product manufacturing. The methods used to sterilize
- decontaminate $_{\text {. } 2 \mathrm{~S}}$ (USP28)
an isolator may be able to achieve log reduction values of production overkill processes. This level of assurance of sterility eanmet be gutranteed over time.
$\square_{\text {of six }}$ logs or greater; however, this does not mean that an isolator enclosure and materials within that enclosure can be
maintained free of bioburden. $\mathbf{m}_{2 S}$ (USP28)
Upon completion of the sterilization
- decontamination $_{\text {m }_{2 S} \text { (USP28) }}$
process, asepsis within the isolator is maintained primarily by the air filtration system, by the appropriate materials transfer operations, and, most importantly, by the integrity of gloves,

■leeves, and half-suits $_{\mathbf{m}_{\text {2S }} \text { (USP28) }}$
used to conduct aseptic manipulations.
The sterilization

- decontamination $_{\text {■ } 2 \text { S (USP28) }}$
methods used to treat isolators, test articles, and sterility testing supplies are capable of reproducibly yielding a-six log kill
- greater than a three-log reduction $_{\mathbf{m}_{2 S} \text { (USP28) }}$
against an appropriate,
-m2S (USP28)
highly resistant biological indicators (see Biological Indicators for Sterilization $\langle 1035\rangle$ ), as verified by the fraction negative or total kill analysis methods. Total kill analysis studies are suitable for BIs with a population of $1 \theta^{4}$
$-10^{3}$ 2S (USP28)
spores per unit, while fraction negative studies are suitable for BIs with a population of $10^{5}$ or greater. A sufficient number of BIs are used to prove statistical reproducibility and adequate distribution of the sterilizing
- decontaminating $_{\text {■2S }}$ (USP28) .
agent. Particular attention is given to areas that pose problems relative to the concentration of the agent. A larger number of BIs are used
$\mathbf{m}_{\text {may }}$ be required ${ }_{\text {m2S (USP28) }}$
in isolators that are heavily loaded with equipment and materials. Also, when it is not pessible to use one or mere calibrated sensers to direetly meastre the concentration of the sterilizing agent, the placement of additional BIs is considered.

■ 2S (USP28)
The ability of the process to reproducibly deliver a six log

kill is confirmed in three consecutive validation studies.
The operator establishes a frequency for resterilization
$\square_{\text {re-decontamination }}^{\mathbf{m}_{2 S} \text { (USP28) }}$
of the isolator. The frequency may be as short as a few days or as long as several weeks, depending on the sterility maintenance effort (see Maintenance of Asepsis within the Isolator Environment).

## Change to read:

## PACKAGE INTEGRITY VERIFICATION

Some materials are adversely affected by sterilizing

- decontaminating $_{\text {■ }_{2 S}}$ (USP28) $^{\text {d }}$
agents, which can result in inhibition of microbial growth. Of concern are the penetration of sterilizing
- decontaminating $_{\text {■2S (USP28) }}$
agents into product containers; accessory supplies such as filter sets and tubing; or any material that could come in contact with product, media, or dilution fluids used in the sterility test. It is the responsibility of the operator to verify that containers, media, and supplies are unaffected by the reemmended sterilization
- decontamination $_{\text {■2S }}$ (USP28)
process. Screw-capped tubes, bottles, or vials sealed with rubber stoppers and crimp overseals have proven very resistant to the penetration of commonly used sterilizing
- decontaminating ${ }_{\text {as }}{ }^{2 S}$ (USP28)
agents. Wrapping materials in metal foil or placing them in a sealed container will prevent contact with the sterilizing
- decontaminating $_{\text {■2S (USP28) }}$
agent; however, these procedures may also result in some surfaces not being sterilized
- decontaminated. In some cases, the use of shorter duration decontamination cycles and reduced concentrations may be necessary to minimize penetration of decontaminating agents into the package or container. Cycles that provide a less than three-log kill of resistant BIs may be acceptable provided microbiological analysis of the environment proves that the isolator(s) are free of recoverable biobur-


## den.m2S (USP28)

In many cases, the operator will choose to treat the surfaces of product containers under test with the sterilizing

- decontaminating ${ }_{\text {men }}$ (USP28)
agent in order to minimize the likelihood of bioburden entering the isolator. It is the responsibility of the operator to demonstrate, via validation studies, that exposure of product containers to the ster illzing
- decontaminating $_{\mathbf{a}^{2 S} \text { (USP28) }}$
agent does not adversely affect the ability of the sterility test to detect low levels of contamination within these test articles. It is suggested that the ability of the package to resist contamination be examined using both chemical and microbiological test procedures. Bacteriostasis and fungistasis validation tests must be performed using actual test articles that have been exposed to all phases of the sterilization
- decontamination $_{\text {■2S }}$ (USP28)
process (see Sterility Tests $\langle 71\rangle$ ). This applies to medicinal device packages as well as pharmaceutical container and closure systems.

Validation studies determine whether both sterility test media and environmental control media meet the requirements for Growth Promotion Test of Aerobes, Anaerobes, and Fungi under Sterility Tests $\langle 71\rangle$.

## Change to read:

## MAINTENANCE OF ASEPSIS WITHIN THE ISOLATOR ENVIRONMENT

The ability of the isolator system to maintain an aseptic environment throughout the defined operational period must be validated. In addition, a microbiological monitoring program must be implemented to detect malfunctions of the isolator system or the presence of adventitious contamination within the isolator. Microbiological monitoring usually involves a routine sampling program, which may include, for instance, sampling following sterilization

- decontamination $_{\text {■2S (USTP28) }}$
on the first day of operation and sampling on the last day of the projected maintenance of asepsis period. Intermediat sampling is
-Periodic sampling throughout the use period can be $_{\text {m2S (USP28) }}$
performed to demonstrate maintenance of asepsis within the isolator.

The surfaces within the isolator can be monitored using either contact plates for flat surfaces or swabs for irregular surfaces. However, because media residues could impose a risk on isolator asepsis, these tests are generally best done at the end of the test period. If performed concurrently with testing, care is used to ensure that any residual medium is removed from isolator surfaces,

■and that those surfaces are carefully cleaned and disinfec-

## ted.■2S (USP28)

Active air samples and settling plates may be used, but they may not be sufficiently sensitive to detect the very low levels of contamination present within the isolator enclosure.

The most likely route

- A potential route ${ }_{\text {2S }}$ (USP28)
for contamination to enter the isolator is during the introduction of supplies and samples into the enclosure. Validating that all materials taken into the isolator enclosure are free of microbial contamination is critical, as is periodic inspection of gaskets to detect imperfections that could allow ingress of microorganisms. Gloves and half-suit assemblies are another tikely
$\square_{\text {potential }}^{\text {n2S (USP28) }}$
source of microbial contamination. Gloves are of particular concern because they are used to handle both sterility testing materials and test articles.
-Resistance to puncture and abrasion should be considered in the selection of gloves and sleeves. Hypalon materials are resistant to both chemical sporicides used in the decontamination of isolators and to punctures and are available in several thicknesses to provide adequate tactile feel through the gloves while maintaining their integrity.■2S (USP28)

Very small leaks in gloves are difficult to detect until the glove is stretched during use. There are several commercially available glove leak detectors; the operator ensures that the detectors test the glove under conditions as close as possible to actual use conditions. Microbiological tests are used to supplement or substitute physical tests. [NOTE-Standard "finger dab plates" may not be sensitive enough to detect low levels of contamination. Submer-
sion of the gloves in $0.1 \%$ peptone water followed by filtration of the diluent and plating on growth media can detect loss of integrity in the gloves that would otherwise go unnoticed.]

Continuous nonviable particulate monitoring within the isolator's enclosure is ideal, because it can quickly detect filter failure. A second choice is periodic monitoring using a portable particle counter. Sampling for particles must be done in a manner that poses no risk to the maintenance of asepsis within the isolator.

## Change to read:

## INTERPRETATION OF STERILITY TEST RESULTS

A sterility test resulting in a false positive in a properly functioning and validated isolator is very unlikely if bioburden is eliminated from the isolator interior with a high degree of assurance; if persenmel is not in diree contat with the work area, and if the integrity of the transfer perts is validated.
-if gloves, sleeves, and half-suits are free of leaks; and if the RTPs are functioning properly. $\mathrm{m}_{2 \text { S }}$ (USP28)
Nevertheless, isolators are mechanical devices and good aseptic techniques are still required. A decision to invalidate a false positive is made only after fully complying with the requirements of Observation and Interpretation of Results under Sterility Tests $\langle 71\rangle$.

## Change to read:

## TRAINING AND SAFETY

As with sterility testing conducted in conventional clean rooms, operators are trained in procedures that are specific to their isolator.
-Use of proper aseptic techniques is vital to the conduct of sterility tests in isolators, just as it is in clean rooms. Therefore, training in proper aseptic techniques is required for all sterility testing technicians.■2S (USP28)
All training sessions and the evaluation of the operator's performance are documented in the individual's training record. Training of all personnel in the appropriate safety procedures necessary for the operation and maintenance of the isolation system is imperative.

Personnel safety in the use of a sterilizing agent must be assessed. Material Safety Data Sheets, or equivalent documents, are available in the immediate area where the sterilizing
-decontaminating ■2S (USP28)
agent is being used. All storage and safety precautions are followed. An operational readiness inspection of the safety of the isolator and all associated equipment is performed and documented prior to placing the unit in service.

# REAGENTS, INDICATORS, AND SOLUTIONS Reagent Specifications 


#### Abstract

BRIEFING

4-Chlorophenol, USP 27 page 2677 and page 1045 of $P F$ 30(3) [May-June 2004]-See briefing under Triclosan.


(HDQ: M. Marques) RTS-41691-1

## Delete the following:

## -4-Chlorophenol

: (p-Chlorophenol), ars (uspze)
$\mathrm{E}_{6} \mathrm{H}_{5} \mathrm{El}$ 128.56-Off white to light tan solid.
Asseay Injeet an appropriate volume into a gas chromatograph (see-Chrematography $(624)$ ) equipped with a flame ienization detector, helium being used as the carrier gas. The following conditions have been found suitable: a $0.25 \mathrm{~mm} \times 30 \mathrm{~m}$ capillary columm coated with a $1-\mu \mathrm{m}$ layer of phase G2; the injection port temperature is maintained at $230^{\circ}$; the detector temperature is maintained at $300^{\circ}$; and the column temperature is maintained at $130^{\circ}$ and programmed to rise $10^{\circ}$ per mintete to $280^{\circ}$. The area of the $\mathrm{C}_{6} \mathrm{H}_{5} \mathrm{ClO}$ peak is not less than $99.0 \%$ of the total peak arear.

Bre a suitable grade with a content of not less than $99.0 \%$. 0 (USP28)

Briefing

2,8-Dichlorodibenzo-p-dioxin, USP 27 page 2680—See briefing under Triclosan.
(HDQ: M. Marques) RTS-41691-1

## Delete the following:

-2,8-Dichlorodibenzo-p-dioxin, $\mathrm{G}_{42} \mathrm{H}_{6} \mathrm{Cl}_{2} \mathrm{O}_{2}-\mathbf{2 5 3 . 0 8}$ [67478 04-0] Use -suitable grade.
ENOTE-A suitable grade is available- ${ }^{-1}$ as a mixture of the 2,7 and 2,8 isomers, catalog nmber ED-926, mys, frem, from Cambridge Isotope Laboratories, Inc., ${ }^{\text {P/ Www.isotope. }}$


## Briefing

2,8-Dichlorodibenzofuran, USP 27 page 2680 —See briefing under Triclosan.
(HDQ: M. Marques) RTS-41691-1

## Delete the following:

-2,8-Dichlorodibenzofuran, $\mathrm{G}_{42} \mathrm{H}_{5} \mathrm{Cl}_{2} \mathrm{O} \quad \mathbf{2 3 6 . 0 7}$ Off white fibers.

Assay
м 20).

PROCEDURE-Inject $20 \mu \mathrm{H}$ into a suitable liquidehromate graph (see Chromatography $\langle 624$ ) ) equipped with 2254 nm detec tor and a $-4.6 \mathrm{~mm} \times 15 \mathrm{~cm}$ columm that contains packing $L 1$. The flow rate is about 1.5 mL per minute. The area of the $\mathrm{C}_{12} \mathrm{H}_{5} \mathrm{Cl}_{2} \mathrm{O}$ peak is not less than 99.9\% of the peak area-m2S (USP28)

## Briefing

2,4-Dichlorophenol, USP 27 page 2680—See briefing under Triclosan.
(HDQ: M. Marques) RTS-41691-1

## Delete the following:

-2,4-Diehlorephenol, $\epsilon_{6} \mathrm{H}_{4} \mathrm{Cl}_{2} \mathrm{O} \quad \mathbf{1 6 3 . 0 0}$. White off white erystalline-solid.
Assety Inject an appropriate volume into a gas chromatograph (see-Chrematography (624)) equipped with a flame-ienization detector, helium being used as the carrier gas. The following eonditions have been found suitable: a $0.25 \mathrm{~mm} \times 30 \mathrm{~m}$ capillary column eoted with a $1 \mu \mathrm{~m}$ layer of phase $\mathbf{G 2}$; the injection pert
temperature is maintained at $230^{\circ}$, the detector temperature is maintaine at $300^{\circ}$; the column temperature is maintained at $130^{\circ}$ and programmed to rise $10^{\circ}$ per minute to $280^{\circ}$. The area of the $\mathrm{C}_{6} \mathrm{H}_{4} \mathrm{CH}_{2} \mathrm{O}$ peak is not less than $98.5 \%$ of the peak area-■2S (USP28)

## BRIEFING

Heptakis-(2,6-di- $\boldsymbol{O}$-methyl)- $\beta$-cyclodextrin. It is proposed to add this new reagent used in the test for Enantiomeric purity in the new monograph for Ropivacaine Hydrochloride, published elsewhere in this issue of $P F$.
(HDQ: M. Marques) RTS-41751-1

## Add the following:

■Heptakis-(2,6-di-O-methyl)- $\beta$-cyclodextrin (2,6-Di-O-meth$y l-\beta$-cyclodextrin; Dimethyl- $\beta$-cyclodextrin) $\mathrm{C}_{56} \mathrm{H}_{98} \mathrm{O}_{35}-$ 1331.36 [51166-71-3]—Use a suitable grade.■2S (USP28)

## BRIEFING

1,3,7-Trichlorodibenzo-p-dioxin, USP 27 page 2718 and page 1392 of PF 30(4) [July-Aug. 2004]-See briefing under Triclosan.
(HDQ: M. Marques) RTS-41691-1

## Delete the following:

-1,3,7 Triehlorodibenzop-dioxin, $\mathrm{G}_{21} \mathrm{H}_{3} \mathrm{Cl}_{3} \mathrm{O}_{2}-\mathbf{2 8 7 . 5 3}$ [67028-17-5] Use atritable grade.

EFNOTE-A suitable grade-is avaitable frem Cambridge Isotope Laboratories, www.isotope.com, catalog number


## Briefing

2,4,8-Trichlorodibenzofuran, USP 27 page 2718—See briefing under Triclosan.
(HDQ: M. Marques) RTS-41691-1

## Delete the following:

-2,4,8-Trichlorodibenzofuran, $\mathrm{C}_{42} \mathrm{H}_{5} \mathrm{Cl}_{3} \mathrm{O}$ 271.53 Off white fibers.
Assely
MOBHE PHASE-Prepare a mixture of acetenitrile and water (80: 20).

PROCEDURE-Inject bout $20 \mu \mathrm{~L}$ into a suitable liquidehrematograph (see Chromatography $\langle 624$ ) ) equipped with a 254 nm detec tor and a $4.6 \mathrm{~mm} \times 15 \mathrm{~cm}$ column that contains packing L1. The flow rate is about 1.5 mL per minute. The area of the $\mathrm{C}_{12} \mathrm{H}_{5} \mathrm{Cl}_{3} \mathrm{O}$ peak is not less than $99.9 \%$ of the total peak area.

Melting range $\langle 741\rangle$ - between $152^{\circ}$ and $156^{\circ} \cdot \mathbf{\square}$ 2S (USP28)

## Briefing

Vinyl Acetate, page 3348 of the Second Supplement. It is proposed to correct the temperature of the column in the Assay test.
(HDQ: M. Marques) RTS-41765-1

## Change to read:

■Vinyl Acetate, $\mathrm{CH}_{3} \mathrm{COOCH}=\mathrm{CH}_{2}-\mathbf{8 6 . 0 9}$ —Liquid.
Assay-Inject an appropriate volume into a gas chromatograph (see Chromatography $\langle 621\rangle$ ) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a $0.25-\mathrm{mm} \times 30-\mathrm{m}$ capillary column coated with a $1-\mu$ m layer of G2; the injection port temperature is maintained at $100^{\circ}$; the detector temperature is maintained at $300^{\circ}$; and the column temperature is maintained at $\theta^{\circ}$
$-100^{\circ}$ ■2S (USP28)
and programmed to rise $10^{\circ}$ per minute to $150^{\circ}$. The area of the $\mathrm{CH}_{3} \mathrm{COOCH}=\mathrm{CH}_{2}$ peak is not less than $99 \%$ of the total peak area.■2S (USP27)

## Volumetric Solutions

BRIEFING

Volumetric Solutions, USP 27 page 2732, page 3162 of the First Supplement, and page 1393 of PF 30(4) [July-Aug. 2004]. It is proposed to correct the formula used to calculate the normality of the Ceric Sulfate, Tenth Normal $(0.1 \mathrm{~N})$ volumetric solution.
(HDQ: M. Marques) RTS-41720

## Change to read:

## Ammonium Thiocyanate, Tenth-Normal (0.1 N) $\mathrm{NH}_{4} \mathrm{SCN}, 76.12$ <br> 7.612 g in 1000 mL

Dissolve about 8 g of ammonium thiocyanate in 1000 mL of water, and standardize the solution as follows.

Accurately measure about 30 mL of 0.1 N silver nitrate VS into a glass-stoppered flask. Dilute with 50 mL of water, then add 2 mL of nitric acid and 2 mL of ferric ammonium sulfate TS, and titrate with the ammonium thiocyanate solution to the first appearance of a red-brown color. Galeulate the normality.

$$
\mathrm{N}=\frac{\mathrm{mL} \mathrm{AgNO}}{3} \times \mathrm{NAgNO}_{3} \mathrm{~mL} \mathrm{NH}_{4} \mathrm{SCN} \text { Solution } \quad \text { 1S (USP28) }
$$

If desirable, 0.1 N ammonium thiocyanate may be replaced by 0.1 N potassium thiocyanate where the former is directed in various tests and assays.

## Change to read:

$$
\begin{gathered}
\text { Bromine, Tenth-Normal }(\mathbf{0 . 1 ~ \mathbf { ~ N }}) \\
\mathrm{Br}, 79.90 \\
7.990 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
\end{gathered}
$$

Dissolve 3 g of potassium bromate and 15 g of potassium bromide in water to make 1000 mL , and standardize the solution as follows.

Accurately measure about 25 mL of the solution into a $500-\mathrm{mL}$ iodine flask, and dilute with 120 mL of water. Add 5 mL of hydrochloric acid, insert the stopper in the flask, and shake it gently. Then add 5 mL of potassium iodide TS, again insert the stopper, shake the mixture, allow it to stand for 5 minutes, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Galeutate the nomality.

Preserve in dark amber-colored, glass-stoppered bottles.

$$
{ }^{\square} \mathrm{N}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{\mathrm{~mL} \mathrm{Br}} \mathrm{Br}_{2} \text { Solution } \quad \mathrm{m}_{1 \mathrm{~S}(U S P 28)}
$$

## Change to read:

Ceric Ammonium Nitrate, Twentieth-Normal ( 0.05 N )

$$
\mathrm{Ce}\left(\mathrm{NO}_{3}\right)_{4} \cdot 2 \mathrm{NH}_{4} \mathrm{NO}_{3}, \mathbf{5 4 8 . 2 2}
$$

$$
2.741 \mathrm{~g} \text { in } 100 \mathrm{~mL}
$$

Dissolve 2.75 g of ceric ammonium nitrate in 1 N nitric acid to obtain 100 mL of solution, and filter. Standardize the solution as follows.

Accurately measure 10 mL of freshly standardized 0.1 N ferrous ammonium sulfate VS into a flask, and dilute with water to about 100 mL . Add 1 drop of nitrophenanthroline TS, and titrate with the ceric ammonium nitrate solution to a colorless endpoint. From the volume of 0.1 N ferrous ammenium sulfate VS taken and the volume of ceric ammonitm nitrate solution consumed, caleulate the nermality.

$$
\square \mathrm{N}=\frac{\mathrm{mLFe}\left(\mathrm{NH}_{4}\right)_{2}\left(\mathrm{SO}_{4}\right)_{2} \times \mathrm{N} \mathrm{Fe}\left(\mathrm{NH}_{4}\right)_{2}\left(\mathrm{SO}_{4}\right)_{2}}{\mathrm{~mL} \mathrm{Ce}^{2}\left(\mathrm{NO}_{3}\right)_{4} \cdot 2 \mathrm{NH}_{4} \mathrm{NO}_{3}} \quad 1 \mathrm{~S}(U S P 28)
$$

## Change to read:

> Ceric Sulfate, Tenth-Normal $(\mathbf{0 . 1} \mathrm{N})$
> $\mathrm{Ce}\left(\mathrm{SO}_{4}\right)_{2}, \mathbf{3 3 2 . 2 4}$
> 33.22 g in 1000 mL

Transfer 59 of of ceric ammenium nitrate to a beaker, add 31 mL of sulfuric acid, mix, and cautiously add water, in 20 - mL pertions, until solution is complete. Cover the beaker, allow to stand overfight, filter through a fine peresity, sintere glass crucible, dilute with water to 1000 mL , and miv.
-Use commercially available volumetric standard solu-

## tion. 1 1S (USP28)

Standardize the solution as follows. FNOTE-Prepare the-osmitm tetroxide solution used in this procedure in a well ventilated hood, as peiseneus vapers are given off by this compeund.] Weigh ac eurately 200 mg of arsenic trioxide, previously dried at $105^{\circ}$ for 4 hour, and transfer to a 500 mL conieal flack. Wash down the inner walls of the flask with 25 mL of sodium hydroxide solution ( 2 im 25), swinl to dissolve the substance, and when solution is complete, add 100 mL of water, and mix. Add 10 mL of dilute oulfuric neid $(1$ in-3), then add 2 dreps each of orthophenanthroline TS and a - 1 in 400 solution of esmitm tetroxide in 0.1 N sulftrie acid, and slewly titrate with the cerie sulfate solution until the pink color is changed to a very pale blue. Caleulate the nermality. Each 4.946 mg of ar senic trioxide is equivalent to 1 mL of 0.1 Necric sulfate.

- Accurately weigh about 0.2 g of sodium oxalate, primary standard, previously dried for 2 hours at $105^{\circ}$, and dissolve in 75 mL of water. Add, with stirring, 2 mL of sulfuric acid that has previously been mixed with 5 mL of water, mix well, add 10 mL of hydrochloric acid, and heat to between $70^{\circ}$ and $75^{\circ}$. Titrate with 0.1 N ceric sulfate to a permanent slight yellow color. Each 6.700 mg of sodium oxalate is equivalent to 1 mL of 0.1 N ceric sulfate.


$$
\mathbf{E}_{\mathrm{N}}=\frac{\mathrm{mg} \mathrm{Na}}{2} \mathrm{C}_{2} \mathrm{O}_{4} \mathbf{m}_{2 \mathrm{~S}(\text { USP28) }}
$$

## Change to read:

> Cupric Nitrate, Tenth-Normal (0.1 N)
> $\mathrm{Cu}\left(\mathrm{NO}_{3}\right)_{2} \cdot 2.5 \mathrm{H}_{2} \mathrm{O}, \mathbf{2 3 2} .59$ 23.26 g in 1000 mL
> $\mathrm{Cu}\left(\mathrm{NO}_{3}\right)_{2} \cdot 3 \mathrm{H}_{2} \mathrm{O}, \mathbf{2 4 1 . 6 0}$ 24.16 g in 1000 mL

Dissolve 23.3 g of cupric nitrate 2.5 hydrate, or 24.2 g of the trihydrate, in water to make 1000 mL . Standardize the solution as follows.

Transfer 20.0 mL of the solution to a $250-\mathrm{mL}$ beaker. Add 2 mL of 5 M sodium nitrate, 20 mL of ammonium acetate TS, and sufficient water to make 100 mL . Titrate with 0.05 M edetate disodium VS. Determine the endpoint potentiometrically using a cupric iondouble junction reference electrode system. Perform a blank determination, and make any necessary correction. Galeulate the nor mality by the formula:

$$
+M / 20.0,
$$

in which $V$ is the volume, in mL , of edetate disodium consumed, M is the molarity of the detate disodimm, and 20.0 is the number of mL of eupric nitrate solution taken.

## Change to read:

## Standard Dichlorophenol-Indophenol Solution

To 50 mg of 2,6-dichlorophenol-indophenol sodium that has been stored in a desiccator over soda lime add 50 mL of water containing 42 mg of sodium bicarbonate, shake vigorously, and when the dye is dissolved, add water to make 200 mL . Filter into an amber glass-stoppered bottle.
-Use within 3 days, and standardize immediately before

## USE.■1S (USP28)

Standardize the solution as follows.
Accurately weigh 50 mg of USP Ascorbic Acid RS, and transfer to a glass-stoppered, $50-\mathrm{mL}$ volumetric flask with the aid of a sufficient volume of metaphosphoric-acetic acids TS to make 50 mL . Immediately transfer 2 mL of the ascorbic acid solution to a $50-\mathrm{mL}$ conical flask containing 5 mL of the metaphosphoric-acetic acids TS, and titrate rapidly with the dichlorophenol-indophenol solution until a distinct rose-pink color persists for at least 5 seconds. Perform a blank titration by titrating 7 mL of the metaphosphoric-acetic acids TS plus a volume of water equal to the volume of the dichlorophenol solution used in titrating the ascorbic acid solution. Express the concentration of the standard solution in terms of its equivalent in mg of ascorbic acid.

## Change to read:

> Edetate Disodium, Twentieth-Molar $(\mathbf{0 . 0 5} \mathbf{~ M})$ $\mathrm{C}_{10} \mathrm{H}_{14} \mathrm{~N}_{2} \mathrm{Na}_{2} \mathrm{O}_{8} \cdot 2 \mathrm{H}_{2} \mathrm{O}, \mathbf{3 7 2 . 2 4}$
> 18.61 g in 1000 mL

Dissolve 18.6 g of edetate disodium in water to make 1000 mL , and standardize the solution as follows.

Accurately weigh about 200 mg of chelometric standard calcium carbonate, previously dried at $110^{\circ}$ for 2 hours and cooled in a desiccator, transfer to a $400-\mathrm{mL}$ beaker, add 10 mL of water, and swirl to form a slurry. Cover the beaker with a watch glass, and introduce 2 mL of diluted hydrochloric acid from a pipet inserted between the lip of the beaker and the edge of the watch glass. Swirl the contents of the beaker to dissolve the calcium carbonate. Wash down the sides of the beaker, the outer surface of the pipet, and the watch glass with water, and dilute with water to about 100 mL . While stirring the solution, preferably with a magnetic stirrer, add about 30 mL of the edetate disodium solution from a $50-\mathrm{mL}$ buret. Add 15 mL of sodium hydroxide TS and 300 mg of hydroxy naphthol blue, and continue the titration with the edetate disodium solution to a blue endpoint. Galeulate the molarity taken by the formula:
W/(100.09٪),
in which Wis the weight, in mg, of $\mathrm{CaCO}_{3}$ in the portion of caleimm earbenate taken, and $V$ is the volume, in mL, of edetate disoditm solution consumed.

$$
\mathbf{m}^{\mathbf{m}}=\frac{\left(\mathrm{g} \mathrm{CaCO}_{3}\right)(1000)}{100.09 \times \mathrm{mL} \text { EDTA }} \boldsymbol{\square}_{1 \mathrm{~S}(U S P 28)}
$$

${ }^{\mathbf{■}} \mathrm{N}=\frac{\text { mL edetate disodium (corrected for the blank) } \times \mathrm{M} \text { edetate disodium }}{20.0} \mathbf{m}_{1 \mathrm{~S} \text { (USP28) }}$

## Change to read:

## Ferric Ammonium Sulfate, Tenth-Normal (0.1 N) <br> $\mathrm{FeNH}_{4}\left(\mathrm{SO}_{4}\right)_{2} \cdot 12 \mathrm{H}_{2} \mathrm{O}, 482.19$ <br> 48.22 g in 1000 mL

Dissolve 50 g of ferric ammonium sulfate in a mixture of 300 mL of water and 6 mL of sulfuric acid, dilute with water to 1000 mL , and mix. Standardize the solution as follows:

Accurately measure about 40 mL of the solution into a glassstoppered flask, add 5 mL of hydrochloric acid, mix, and add a solution of 3 g of potassium iodide in 10 mL of water. Insert the stopper, allow to stand for 10 minutes, then titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Correct for a blank run on the same quantities of the same reagents. and caleulate the nermality.

- $\quad$ 1S (USP28)

Store in tight containers, protected from light.

$$
\mathrm{N}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{\mathrm{~mL} \mathrm{FeNH}_{4}\left(\mathrm{SO}_{4}\right)_{2}} \square_{1 \mathrm{~S}(\text { USP28) }}
$$

## Change to read:

Ferrous Ammonium Sulfate, Tenth-Normal ( $0.1 \mathbf{N}$ )

$$
\mathrm{Fe}\left(\mathrm{NH}_{4}\right)_{2}\left(\mathrm{SO}_{4}\right)_{2} \cdot 6 \mathrm{H}_{2} \mathrm{O}, \mathbf{3 9 2 . 1 4}
$$

$$
39.21 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
$$

Dissolve 40 g of ferrous ammonium sulfate in a previously cooled mixture of 40 mL of sulfuric acid and 200 mL of water, dilute with water to 1000 mL , and mix. On the day of use, standardize the solution as follows.

Accurately measure 25 to 30 mL of the solution into a flask, add 2 drops of orthophenanthroline TS, and titrate with 0.1 N ceric sulfate VS until the red color is changed to pale blue. From the volume of 0.1 N ceric sulfate consumed, caleulate the normality.

$$
\mathbf{m}^{\mathbf{N}}=\frac{\mathrm{mL} \mathrm{Ce}^{\mathrm{IV}} \times \mathrm{N} \mathrm{Ce}^{\mathrm{IV}}}{\mathrm{~mL} \mathrm{Fe}^{\mathrm{II}} \text { Solution }}
$$

Each 121.14 mg of tromethamine is equivalent to 1 mL of 1 N hydrochloric acid.

$$
\mathbf{m}=\frac{m g \text { tromethamine }}{121.14 \times \mathrm{mL} \mathrm{HCl}}_{\mathbf{\square} 1 \mathrm{~S}(U S P 28)}
$$

## Add the following:

-Hydrochloric Acid, Half-Normal ( $\mathbf{0 . 5} \mathbf{N}$ )

$$
\mathrm{HCl}, \mathbf{3 6 . 4 6}
$$

$$
18.23 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
$$

To a $1000-\mathrm{mL}$ volumetric flask containing 40 mL of water slowly add 43 mL of hydrochloric acid. Cool, and add water to volume. Standardize the solution as follows.

Accurately weigh about 2.5 g of tromethamine, previously dried at $105^{\circ}$ for 3 hours. Proceed as directed under Hy drochloric Acid, Normal ( 1 N ), beginning with "Dissolve in 50 mL of water."

$$
\mathrm{N}=\frac{\mathrm{mg} \text { tromethamine }}{121.14 \times \mathrm{mLHCl}} \mathbf{■ 1 S}(U S P 28)^{1 \mathrm{~m}_{(\text {P }}}
$$

## Change to read:

Hydrochloric Acid, Half-Normal ( $\mathbf{0 . 5} \mathbf{N}$ ) in Methanol
$\mathrm{HCl}, 36.46$
18.23 g in 1000 mL

To a $1000-\mathrm{mL}$ volumetric flask containing 40 mL of water slowly add 43 mL of hydrochloric acid. Cool, and add methanol to volume. Standardize the solution as follows.

Accurately weigh about 2.5 g of tromethamine, previously dried at $105^{\circ}$ for 3 hours. Proceed as directed under Hydrochloric Acid, Normal ( 1 N ), beginning with "Dissolve in 50 mL of water."

$$
\mathbf{~} \mathrm{N}=\frac{\mathrm{mg} \text { tromethamine }}{121.14 \times \mathrm{mL} \mathrm{HCl}} \boldsymbol{\square}_{1 \mathrm{~S}(\text { USP28) }}
$$

Dilute 85 mL of hydrochloric acid with water to 1000 mL . Standardize the solution as follows.

Accurately weigh about 5.0 g of tromethamine, previously dried at $105^{\circ}$ for 3 hours. Dissolve in 50 mL of water, and add 2 drops of bromocresol green TS. Titrate with 1 N hydrochloric acid to a pale yellow endpoint. Galeulate the normality.

[^363]
## Add the following:

-Hydrochloric Acid, Alcoholic, Tenth-Molar (0.1 M)

$$
\mathrm{HCl}, \mathbf{3 6 . 4 6}
$$

Dilute 9.0 mL with aldehyde free alcohol of hydrochloric acid to 1000 mL . ${ }^{1 \mathrm{~S}}$ (USP28)

## Change to read:

## ■Iodine, Tenth-Normal ( 0.1 N ) <br> I, 126.90 <br> 12.69 g in 1000 mL

Dissolve about 14 g of iodine in a solution of 36 g of potassium iodide in 100 mL of water, add 3 drops of hydrochloric acid, dilute with water to 1000 mL , and standardize the solution as follows.

Transfer 25.0 mL of the iodine solution to a $250-\mathrm{mL}$ flask, dilute with water to 100 mL , add 1 mL of 1 N hydrochloric acid, swirl gently to mix, and titrate with 0.1 N sodium thiosulfate VS until the solution has a pale yellow color. Add 2 mL of starch TS and continue titrating until the solution is colorless. Galeulate the nor mality.

■1S (USP28)
Preserve in amber-colored, glass-stoppered bottles. $\quad 1 \mathrm{~S}$ (USP27)

$$
{ }^{\boldsymbol{m}}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{25} \mathbf{■} 1 \mathrm{~S}(\text { USP28) }
$$

## Change to read:

## ■Iodine, Hundredth-Normal (0.01 N) I, 126.90 <br> 1.269 g in 1000 mL

Dissolve about 1.4 g of iodine in a solution of 3.6 g of potassium iodide in 100 mL of water, add 3 drops of hydrochloric acid, dilute with water to 1000 mL , and standardize the solution as follows.

Transfer 100.0 mL of iodine solution to a $250-\mathrm{mL}$ flask, add 1 mL of 1 N hydrochloric acid, swirl gently to mix, and titrate with 0.1 N sodium thiosulfate VS until the solution has a pale yellow color. Add 2 mL of starch TS, and continue titrating until the solution is colorless. Ealeulate the nermality.

■1S (USP28)
Preserve in amber-colored, glass-stoppered bottles.■1S (USP27)

## Add the following:

-Lead Perchlorate, Tenth-Molar (0.1 M)

$$
\begin{gathered}
\mathrm{Pb}\left(\mathrm{ClO}_{4}\right)_{2} \cdot 3 \mathrm{H}_{2} \mathrm{O}, 460.15 \\
46.01 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
\end{gathered}
$$

Dissolve 46 g of lead perchlorate in water, and dilute with water to 1000.0 mL . Accurately weigh about 150 mg of sodium sulfate, previously dried at $105^{\circ}$ for 4 hours, and dissolve in 50 mL of water. Add 50 mL of a mixture of water and formaldehyde ( $1: 1$ ), and stir for about 1 minute. Determine the endpoint potentiometrically using a lead ion selective electrode. Perform a blank determination, and make any necessary corrections. Each 14.204 mg of sodium sulfate is equivalent to 1 mL of 0.1 M lead perchlorate.

$$
\mathrm{M}=\frac{\mathrm{mg} \text { sodium sulfate }}{142.04 \times \mathrm{mL} \text { lead perchlorate }} \mathbf{m}_{1 \mathrm{~S}(\text { USP28) }}
$$

## Change to read:

## Lead Perchlorate, Hundredth-Molar (0.01 M)

$\mathrm{Pb}\left(\mathrm{ClO}_{4}\right)_{2} 406.10$
Accurately pipet 100 mL of commercially available 0.1 M lead perchlorate solution into a $1000-\mathrm{mL}$ volumetric flask, add a sufficient quantity of water to make 1000 mL , and standardize the solution as follows.

Accurately pipet 50 mL of 0.01 M lead perchlorate solution, as prepared above, into a $250-\mathrm{mL}$ conical flask. Add 3 mL of aqueous hexamethylenetetramine solution ( 2.0 g per 100 mL ) and 4 drops of $0.5 \%$ xylenol orange indicator prepared by adding 500 mg of xylenol orange to 10 mL of alcohol and diluting with water to 100 mL . (Omit the alcohol if the sodium salt of the indicator is used). Titrate with 0.05 M edetate disodium VS to a yellow endpoint. Galeulate the melarity.

$$
{ }^{\mathbf{\square}} \mathrm{M}=\frac{\mathrm{mL} \text { edetate disodium } \times \mathrm{M} \text { edetate disodium }}{50.0} \mathbf{\square 1 S}(U S P 28)
$$

## Change to read:

Lithium Methoxide, Fiftieth-Normal ( $0.02 \mathbf{N}$ ) in Methanol $\mathrm{CH}_{3} \mathrm{LiO}, 37.97$
759.6 mg in 1000 mL

Dissolve 0.12 g of freshly cut lithium metal in 150 mL of methanol, cooling the flask during addition of the metal. When the reaction is complete, add 850 mL of methanol, and mix. Store the solution preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution by titration against benzoic acid as described under Sodium Methoxide, Tenth-Normal ( 0.1 N ) (in Toluene), but use only 100 mg of benzoic acid. Each 2.442 mg of benzoic acid is equivalent to 1 mL of 0.02 N lithium methoxide.

NOTE-Restandardize the solution frequently.

$$
\boldsymbol{N}=\frac{\mathrm{mg} \text { benzoic acid }}{122.1 \times \mathrm{mL} \text { lithium methoxide (corrected for the blank) } \boldsymbol{\square}_{1 \mathrm{~S}(\text { USP28) }}}
$$

## Change to read:

Lithium Methoxide, Tenth-Normal (0.1 N) in Benzene

$$
\begin{gathered}
\text { Toluene }_{\mathbf{1}} \text { S } \text { (USP28) } \\
\mathrm{CH}_{3} \mathrm{OLi}, \mathbf{3 7 . 9 7} \\
3.798 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
\end{gathered}
$$

Dissolve 0.6?

- $500 \mathrm{mg}_{\text {■1S (USP28) }}$
of freshly cut lithium metal in 150 mL of methanol, cooling the flask during addition of the metal. When reaction is complete, add 850 mL of benzene
-toluene.■1S (USP28)
If cloudiness or precipitation occurs, add sufficient methanol to clarify the solution. Store preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution by titration against benzoic acid as described under Sodium Methoxide, Tenth-Normal ( 0.1 N ) (in Toluеne).

NOTE-Restandardize the solution frequently.
$\square \mathrm{n}=\frac{\mathrm{mg} \text { benzoic acid }}{122.1 \times \mathrm{mL} \text { lithium methoxide (corrected for the blank) }} \square_{1 \mathrm{~S} \text { (USP28) }}$

## Change to read:

Lithium Methoxide, Tenth-Normal ( 0.1 N ) in Chlorobenzene $\mathrm{CH}_{3} \mathrm{OLi}, 37.97$
3.798 g in 1000 mL

Dissolve 0.7 g
${ }^{-500} \mathrm{mg}_{\text {■1S }}$ (USP28) $^{\text {( }}$
of freshly cut lithium metal in 150 mL of methanol, cooling the flask during addition of the metal. When reaction is complete, add 850 mL of chlorobenzene. If cloudiness or precipitation occurs, add sufficient methanol to clarify the solution. Store preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution by titration against benzoic acid as described under Sodium Methoxide, Tenth-Normal ( 0.1 N ) (in Toluene).

NOTE-Restandardize the solution frequently.


## Change to read:

$$
\begin{gathered}
\text { Mercuric Nitrate, Tenth-Molar }(\mathbf{0 . 1 ~ M}) \\
\mathrm{Hg}\left(\mathrm{NO}_{3}\right)_{2}, \mathbf{3 2 4 . 6 0} \\
32.46 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
\end{gathered}
$$

Dissolve about 35 g of mercuric nitrate in a mixture of 5 mL of nitric acid and 500 mL of water, and dilute with water to 1000 mL . Standardize the solution as follows.

Transfer an accurately measured volume of about 20 mL of the solution to a conical flask, and add 2 mL of nitric acid and 2 mL of ferric ammonium sulfate TS. Cool to below $20^{\circ}$, and titrate with 0.1 N ammonium thiocyanate VS to the first appearance of a permanent brownish color. Ealeulate the molarity.

$$
\mathbf{M}=\frac{\mathrm{mL} \mathrm{NH}_{4} \mathrm{SCN} \times \mathrm{N} \mathrm{NH}_{4} \mathrm{SCN}}{\mathrm{~mL} \mathrm{Hg}\left(\mathrm{NO}_{3}\right)_{2}} \square_{1 \mathrm{~S}(\text { USP28) }}
$$

## Delete the following:

$$
\begin{gathered}
\text { Morpholine, Half Normal }(0.5 \mathrm{~N}) \text { in Methanel } \\
\in_{4} \mathrm{H}_{2} \mathrm{NO}, \mathbf{8 7 . 1 2} \\
43.56 \mathrm{~g} \text { in } 1000 \mathrm{mE}
\end{gathered}
$$

Transfer 44 mL of reeently distilled morpholine to a-1 liter reagent bottle, and add methanol to make about 1 liter. Protect from absorption of earbon dioxide during withdrawal of aliquots. It is not necessary to standardize this solution:■1S (USP28)

## Change to read:

Oxalic Acid, Tenth-Normal ( $0.1 \mathbf{N}$ )
$\mathrm{H}_{2} \mathrm{C}_{2} \mathrm{O}_{4} \cdot 2 \mathrm{H}_{2} \mathrm{O}, 126.07$
6.303 g in 1000 mL

Dissolve 6.45 g of oxalic acid in water to make 1000 mL . Standardize by titration against freshly standardized 0.1 N potassium
permanganate VS as directed under Potassium Permanganate, Tenth-Normal ( 0.1 N ).

Preserve in glass-stoppered bottles, protected from light.

$$
\mathbf{m}^{\mathrm{N}}=\frac{\mathrm{mL} \mathrm{KMnO}_{4} \times \mathrm{N} \mathrm{KMnO}_{4}}{\mathrm{~mL} \mathrm{H}_{2} \mathrm{C}_{2} \mathrm{O}_{4}}
$$

## Change to read:

Perchloric Acid, Tenth-Normal ( 0.1 N ) (in Glacial Acetic Acid)

$$
\mathrm{HClO}_{4}, \mathbf{1 0 0 . 4 6}
$$

10.05 g in 1000 mL

NOTE-Where called for in the tests and assays, this volumetric solution is specified as " 0.1 N perchloric acid." Thus, where 0.1 N or other strength of this volumetric solution is specified, the solution in glacial acetic acid is to be used, unless the words "in dioxane" are stated. [See also Perchloric Acid, Tenth-Normal ( 0.1 N ) in Dioxane.]

Mix 8.5 mL of perchloric acid with 500 mL of glacial acetic acid and 21 mL of acetic anhydride, cool, and add glacial acetic acid to make 1000 mL . Alternatively, the solution may be prepared as follows. Mix 11 mL of 60 percent perchloric acid with 500 mL of glacial acetic acid and 30 mL of acetic anhydride, cool, and add glacial acetic acid to make 1000 mL .

Allow the prepared solution to stand for 1 day for the excess acetic anhydride to be combined, and determine the water content by Method I (see Water Determination $\langle 921\rangle$ ), except to use a test specimen of about 5 g of the 0.1 N perchloric acid that is expected to contain approximately 1 mg of water and the Reagent (see Reagent under Method Ia in Water Determination $\langle 921\rangle$ ) diluted such that 1 mL is equivalent to about 1 to 2 mg of water. If the water content exceeds $0.5 \%$, add more acetic anhydride. If the solution contains no titratable water, add sufficient water to obtain a content of between $0.02 \%$ and $0.5 \%$ of water. Allow the solution to stand for 1 day, and again titrate the water content. The solution so obtained contains between $0.02 \%$ and $0.5 \%$ of water, indicating freedom from acetic anhydride.

Standardize the solution as follows.
Accurately weigh about 700 mg of potassium biphthalate, previously crushed lightly and dried at $120^{\circ}$ for 2 hours, and dissolve it in 50 mL of glacial acetic acid in a $250-\mathrm{mL}$ flask. Add 2 drops of crystal violet TS, and titrate with the perchloric acid solution until the violet color changes to blue-green. Deduct the volume of the perchloric acid consumed by 50 mL of the glacial acetic acid. and caleulate the normality.

- $\quad 1$ (USP28)

Each 20.42 mg of potassium biphthalate is equivalent to 1 mL of 0.1 N perchloric acid.

$$
\mathrm{N}=\frac{\mathrm{g} \mathrm{KHC}_{8} \mathrm{H}_{4} \mathrm{O}_{4}}{0.20423 \times \mathrm{mL} \mathrm{HClO}_{4} \text { solution (corrected for the blank) }} \quad \begin{array}{|l|l} 
\\
\text { (USP28) }
\end{array}
$$

## Change to read:

## Perchloric Acid, Tenth-Normal (0.1 N) in Dioxane

Mix 8.5 mL of perchloric acid with sufficient dioxane to make 1000 mL . Standardize the solution as follows.
Accurately weigh about 700 mg of potassium biphthalate, previously crushed lightly and dried at $120^{\circ}$ for 2 hours, and dissolve in 50 mL of glacial acetic acid in a $250-\mathrm{mL}$ flask. Add 2 drops of crystal violet TS, and titrate with the perchloric acid solution until the violet color changes to bluish green. Dedue the volume of the perehloric acid consumed by 50 mL of the glacial acetic acid, and ealeulate the normality.
-Carry out a blank determination. 1 (USP28).
Each 20.42 mg of potassium biphthalate is equivalent to 1 mL of 0.1 N perchloric acid.

$$
\mathrm{N}=\frac{\mathrm{g} \mathrm{KHC}_{8} \mathrm{H}_{4} \mathrm{O}_{4}}{0.20423 \times \mathrm{mL} \mathrm{HClO}_{4} \text { solution (corrected for the blank) }} \quad \text { 1S (USP28) }
$$

## Change to read:

Potassium Bromate, Tenth-Normal ( 0.1 N )
$\mathrm{KBrO}_{3}, \mathbf{1 6 7 . 0 0}$
2.784 g in 1000 mL

Dissolve 2.784 g of potassium bromate in water to make 1000 mL , and standardize the solution as follows.

Transfer an accurately measured volume of about 40 mL of the solution to a glass-stoppered flask, add 3 g of potassium iodide, and follow with 3 mL of hydrochloric acid. Allow to stand for $5 \mathrm{~min}-$ utes, then titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Correct for a blank run on the same quantities of the same reagents, and calculate the normality.

$$
\mathbf{m}^{\mathbf{N}}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{\mathrm{~mL} \mathrm{KBrO}_{3} \text { Solution }} \mathbf{m}_{1 \mathrm{~S}(\text { USP28) }}
$$

## Change to read:

## Potassium Bromide-Bromate, Tenth-Normal (0.1 N)

Dissolve 2.78 g of potassium bromate $\left(\mathrm{KBrO}_{3}\right)$ and 12.0 g of potassium bromide $(\mathrm{KBr})$ in water, and dilute with water to 1000 mL . Standardize by the procedure set forth for Potassium Bromate, Tenth-Normal ( 0.1 N ).

$$
\mathrm{N}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{\mathrm{~mL} \mathrm{KBrO}} / \mathrm{KBr} \quad \text { 1S (USP28) }
$$

## Change to read:

$$
\begin{gathered}
\text { Potassium Dichromate, Tenth-Normal }(\mathbf{0 . 1} \mathbf{~ N}) \\
\mathrm{K}_{2} \mathrm{Cr}_{2} \mathrm{O}_{7}, \mathbf{2 9 4 . 1 8} \\
4.903 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
\end{gathered}
$$

Dissolve about 5 g of potassium dichromate in 1000 mL of water. Standardize the solution as follows.

Transfer 25.0 mL of this solution to a glass-stoppered, $500-\mathrm{mL}$ flask, add 2 g of potassium iodide (free from iodate), dilute with 200 mL of water, add 5 mL of hydrochloric acid, allow to stand for 10 minutes in a dark place, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Correct for a blank rumon the same quantities of the same reagents, and caleulate the nommality.
-Carry out a blank determination.

$$
\mathrm{N}=\frac{\mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \times \mathrm{N} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}}{25.0} \square_{1 \mathrm{~S}(\text { USP28) }}
$$

## Change to read:

Potassium Ferricyanide, Twentieth-Molar (0.05 M)
$\mathrm{K}_{3} \mathrm{Fe}(\mathrm{CN})_{6}, 329.24$
16.46 g in 1000 mL

Dissolve about 17 g of potassium ferricyanide in water to make 1000 mL . Standardize the solution as follows.

Transfer 50.0 mL of this solution to a glass-stoppered, $500-\mathrm{mL}$ flask, dilute with 50 mL of water, add 10 mL of potassium iodide TS and 10 mL of dilute hydrochloric acid, and allow to stand for 1 minute. Then add 15 mL of zinc sulfate solution ( 1 in 10 ), and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Galeulate metarity.

## - $\quad$ IS (USP28)

Protect from light, and restandardize before use.

## Change to read:

Potassium Hydroxide, Normal (1 N)
$\mathrm{KOH}, \mathbf{5 6 . 1 1}$
56.11 g in 1000 mL

Dissolve 68 g of potassium hydroxide in about 950 mL of water. Add a freshly prepared saturated solution of barium hydroxide until no more precipitate forms. Shake the mixture thoroughly, and allow it to stand overnight in a stoppered bottle. Decant the clear
liquid, or filter the solution in a tight, polyolefin bottle, and standardize by the procedure set forth for Sodium Hydroxide, Normal (1N).

$$
\boldsymbol{\square}^{\mathrm{N}}=\frac{\mathrm{g} \mathrm{KHC}_{8} \mathrm{H}_{4} \mathrm{O}_{4}}{0.20423 \times \mathrm{mL} \mathrm{NaOH}} \quad \text { ■1S (USP28) }
$$

## Change to read:

Potassium Hydroxide, Alcoholic, Half-Normal ( 0.5 N) 28.06 g in 1000 mL

Dissolve about 34 g of potassium hydroxide in 20 mL of water, and add aldehyde-free alcohol to make 1000 mL . Allow the solution to stand in a tightly stoppered bottle for 24 hours. Then quickly decant the clear supernatant into a suitable, tight container, and standardize the solution as follows.

Accurately measure about 25 mL of 0.5 N hydrochloric acid VS. Dilute with 50 mL of water, add 2 drops of phenolphthalein TS, and titrate with the alcoholic potassium hydroxide solution until a permanent, pale pink color is produced. Galeulate the normality.

- 1 (USP28)

NOTE-Store in tightly stoppered bottles, protected from light.

$$
\mathrm{N}=\frac{\mathrm{mL} \mathrm{HCl} \times \mathrm{N} \mathrm{HCl}}{\mathrm{~mL} \mathrm{KOH}} \square_{1 \mathrm{~S}(U S P 28)}
$$

## Add the following:

-Potassium Hydroxide, Alcoholic, Tenth-Molar (0.1 M)
KOH,56.11
Dilute 20 mL of 0.5 M alcoholic potassium hydroxide with aldehyde-free alcohol to 100.0 mL .■1S (USP28)

## Change to read:

Potassium Hydroxide, Methanolic, Tenth-Normal (0.1 N) 5.612 g in 1000 mL

Dissolve about 6.8 g of potassium hydroxide in 4 mL of water, and add methanol to make 1000 mL . Allow the solution to stand in a tightly stoppered bottle for 24 hours. Then quickly decant the clear supernatant into a suitable, tight container, and standardize the solution as follows.

Measure accurately about 25 mL of 0.1 N hydrochloric acid VS. Dilute with 50 mL of water, add 2 drops of phenolphthalein TS,
and titrate with the methanolic potassium hydroxide solution until a permanent, pale pink color is produced. Galeulate the normality.

## ■1S (USP28)

NOTE-Store in tightly stoppered bottles, protected from light.

$$
{ }^{\mathbf{m}}=\frac{\mathrm{mL} \mathrm{HCl} \times \mathrm{N} \mathrm{HCl}}{\mathrm{~mL} \mathrm{KOH}} \quad \mathrm{~m}_{\mathrm{S}(U S P 28)}
$$

## Change to read:

Potassium Permanganate, Tenth-Normal (0.1 N)<br>$\mathrm{KMnO}_{4}, 158.03$<br>3.161 g in 1000 mL

Dissolve about 3.3 g of potassium permanganate in 1000 mL of water in a flask, and boil the solution for about 15 minutes. Insert the stopper in the flask, allow it to stand for at least 2 days, and filter through a fine-porosity, sintered-glass crucible. If necessary, the bottom of the sintered-glass crucible may be lined with a pledget of glass wool. Standardize the solution as follows.

Accurately weigh about 200 mg of sodium oxalate, previously dried at $110^{\circ}$ to constant weight, and dissolve it in 250 mL of water. Add 7 mL of sulfuric acid, heat to about $70^{\circ}$, and then slowly add the permanganate solution from a buret, with constant stirring, until a pale pink color, which persists for 15 seconds, is produced. The temperature at the conclusion of the titration should be not less than $60^{\circ}$. Calculate the normality. Each 67.00 mg
$\mathbf{■}_{6.700} \mathrm{mg}_{\mathbf{■}_{1 S}(\text { USP28) }}$
of sodium oxalate is equivalent to 1 mL of 0.1 N potassium permanganate.

Because potassium permanganate is reduced on contact with organic substances such as rubber, the solution must be handled in apparatus entirely of glass or other suitably inert material. It should be frequently restandardized. Store in glass-stoppered, amber-colored bottles.

$$
\mathrm{N}=\frac{\mathrm{g} \mathrm{Na}_{2} \mathrm{C}_{2} \mathrm{O}_{4}}{\mathrm{~mL} \mathrm{KMnO}} 4 \text { solution } \times 0.06700 \quad \square 1 \mathrm{~S}(\text { USP28) }
$$

## Change to read:

Silver Nitrate, Tenth-Normal, ( $0.1 \mathbf{N}$ )
$\mathrm{AgNO}_{3}, 169.87$
16.99 g in 1000 mL

Dissolve about 17.5 g of silver nitrate in 1000 mL of water, and standardize the solution as follows.

Transfer about 100 mg , accurately weighed, of reagent-grade sodium chloride, previously dried at $110^{\circ}$ for 2 hours, to a $150-\mathrm{mL}$ beaker, dissolve in 5 mL of water, and add 5 mL of acetic acid, 50 mL of methanol, and about 0.5 mL of eosin Y TS. Stir, preferably with a magnetic stirrer, and titrate with the silver nitrate solution. Galeulate the normality.

$$
\mathrm{N}=\frac{\mathrm{mg} \mathrm{NaCl}}{\mathrm{~mL} \mathrm{AgNO}_{3} \times 58.44} \square_{1 \mathrm{~S}(U S P 28)}
$$

## Change to read:

Sodium Hydroxide, Normal (1 N)<br>$\mathrm{NaOH}, 40.00$<br>40.00 g in 1000 mL

Dissolve 162 g of sodium hydroxide in 150 mL of carbon diox-ide-free water, cool the solution to room temperature, and filter through hardened filter paper. Transfer 54.5 mL of the clear filtrate to a tight, polyolefin container, and dilute with carbon dioxide-free water to 1000 mL .

Accurately weigh about 5 g of potassium biphthalate, previously crushed lightly and dried at $120^{\circ}$ for 2 hours, and dissolve in 75 mL of carbon dioxide-free water. Add 2 drops of phenolphthalein TS, and titrate with the sodium hydroxide solution to the production of a permanent pink color. Each 204.2 mg of potassium biphthalate is equivalent to 1 mL of 1 N sodium hydroxide.

$$
\mathbf{■}^{\mathrm{N}}=\frac{\mathrm{g} \mathrm{KHC}_{8} \mathrm{H}_{4} \mathrm{O}_{4}}{0.20423 \times \mathrm{mL} \mathrm{NaOH} \text { solution }} \quad \begin{aligned}
& \text { 1S }(U S P 28) \\
& \hline
\end{aligned}
$$

NOTES-(1) Solutions of alkali hydroxides absorb carbon dioxide when exposed to air. They should be preserved in bottles having well-fitted, suitable stoppers, provided with a tube filled with a mixture of sodium hydroxide and lime (soda-lime tubes) so that air entering the container must pass through this tube, which will absorb the carbon dioxide. (2) Prepare solutions of lower concentration (e.g., $0.1 \mathrm{~N}, 0.01 \mathrm{~N}$ ) by quantitatively diluting accurately measured volumes of the 1 N solution with sufficient carbon diox-ide-free water to yield the desired concentration.

Restandardize the solution frequently.

## Change to read:

## Sodium Hydroxide, Alcoholic, Tenth-Normal (0.1 N) $\mathrm{NaOH}, 40.00$

To 250 mL of alcohol add 2 mL of a $50 \%(\mathrm{w} / \mathrm{w})$ solution of sodium hydroxide.

Dissolve about 200 mg of benzoic acid, accurately weighed, in 10 mL of alcohol and 2 mL of water. Add 2 drops of phenolphthalein TS, and titrate with the alcoholic sodium hydroxide solution until a permanent pale pink color is produced. Ealeulate the ner mality as follows:-

$$
W / 122.12 \mathrm{~V}
$$

in which $W$ is the weight, in mg, of benzoic acid taken, $V$ is the volume, in mL, of alcoholic sodium hydroxide consumed, and 122.12 is the molecular weight of benzoic acid.

$$
\mathbf{N}=\frac{\mathrm{mg} \text { benzoic acid }}{122.1 \times \mathrm{mL} \text { sodium hydroxide }} \mathbf{\square} \text { 1S (USP28) }
$$

## Change to read:

Sodium Methoxide, Tenth-Normal ( $0.1 \mathbf{N}$ ) (in Toluene) $\mathrm{CH}_{3} \mathrm{ONa}, 54.02$
5.402 g in 1000 mL

Cool in ice-water 150 mL of methanol contained in a $1000-\mathrm{mL}$ volumetric flask, and add, in small portions, about 2.5 g of freshly cut sodium metal. When the metal has dissolved, add toluene to make 1000 mL , and mix. Store preferably in the reservoir of an automatic delivery buret suitably protected from carbon dioxide and moisture. Standardize the solution as follows.

Accurately weigh about 400 mg of primary standard benzoic acid, and dissolve in 80 mL of dimethylformamide in a flask. Add 3 drops of a 1 in 100 solution of thymol blue in dimethylformamide, and titrate with the sodium methoxide to a blue endpoint. Correct for the volume of the sodium methoxide solution consumed by 80 mL of the dimethylformamide. andealeulate the normality.
-■1S (USP28)
Each 12.21 mg of benzoic acid is equivalent to 1 mL of 0.1 N sodium methoxide.

$$
\mathrm{N}=\frac{\mathrm{mg} \text { benzoic acid }}{122.1 \times \mathrm{mL} \text { sodium methoxide }(\text { corrected for the blank) }} \square_{1 \mathrm{~S}(\text { USP28) }}
$$

addition of the methanol so that the vapors are condensed and do not escape through the top of the condenser. After addition of the methanol is complete, connect a drying tube to the top of the condenser, and allow the solution to cool. Transfer the solution to a 1-L volumetric flask, dilute with anhydrous methanol to volume, and mix. Standardize the solution as follows.

Accurately measure about 20 mL of freshly standardized 1 N hydrochloric acid VS into a $250-\mathrm{mL}$ conical flask, add 0.25 mL of phenolphthalein TS, and titrate with the sodium methoxide solution to the first appearance of a permanent pink color. Ealeulate the normality.

$$
\mathrm{N}=\frac{\mathrm{mLHCl} \times \mathrm{N} \mathrm{HCl}}{\mathrm{~mL} \text { sodium methoxide }} \quad \text { 1S (USP28) }
$$

## Change to read:

> Sodium Nitrite, Tenth-Molar $(\mathbf{0 . 1 ~ M})$
> $\mathrm{NaNO}_{2}, \mathbf{6 9 . 0 0}$
> 6.900 g in 1000 mL

Dissolve 7.5 g of sodium nitrite in water to make 1000 mL , and standardize the solution as follows.
Accurately weigh about 500 mg of USP Sulfanilamide RS, previously dried at $105^{\circ}$ for 3 hours, and transfer to a suitable beaker. Add 20 mL of hydrochloric acid and 50 mL of water, stir until dissolved, and cool to $15^{\circ}$. Maintaining the temperature at about $15^{\circ}$, titrate slowly with the sodium nitrite solution, placing the buret tip below the surface of the solution to preclude air oxidation of the sodium nitrite, and stir the solution gently with a magnetic stirrer, but avoid pulling a vortex of air beneath the surface. Use the indicator specified in the individual monograph, or, if a potentiometric procedure is specified, determine the endpoint electrometrically, using platinum-calomel or platinum-platinum electrodes. When the titration is within 1 mL of the endpoint, add the titrant in $0.1-\mathrm{mL}$ portions, and allow 1 minute between additions. Galeulate the melarity.

- $\quad$ 1S (USP28)

Each 17.22 mg of sulfanilamide is equivalent to 1 mL of 1000 M
$\square^{-} 0.1000 \mathrm{M}_{1 \mathrm{IS} \text { (USP28) }}$
sodium nitrite.

NOTES- (1) To eliminate any turbidity that may form following dilution with toluene, add methanol ( 25 to 30 mL usually suffices) until the solution is clear. (2) Restandardize the solution frequently.

## Change to read:

## Sodium Methoxide, Half-Normal ( 0.5 N) in Methanol $\mathrm{CH}_{3} \mathrm{ONa}, 54.02$ <br> $$
27.01 \mathrm{~g} \text { in } 1000 \mathrm{~mL}
$$

Weigh 11.5 g of freshly cut sodium metal, and cut into small cubes. Place about 0.5 mL of anhydrous methanol in a round-bottom, $250-\mathrm{mL}$ flask equipped with a ground-glass joint, add 1 cube of the sodium metal, and, when the reaction has ceased, add the remaining sodium metal to the flask. Connect a water-jacketed condenser to the flask, and slowly add 250 mL of anhydrous methanol, in small portions, through the top of the condenser. Regulate the

## Change to read:

## Sodium Tetraphenylboron, Fiftieth-Molar (0.02 M)

 $\mathrm{NaB}\left(\mathrm{C}_{6} \mathrm{H}_{5}\right)_{4}, \mathbf{3 4 2 . 2 2}$ 6.845 g in 1000 mLDissolve an amount of sodium tetraphenylboron, equivalent to 6.845 g of $\mathrm{NaB}\left(\mathrm{C}_{6} \mathrm{H}_{5}\right)_{4}$, in water to make 1000 mL , and standardize the solution as follows.

Pipet two $75-\mathrm{mL}$ portions of the solution into separate beakers, and to each add 1 mL of acetic acid and 25 mL of water. To each beaker add, slowly and with constant stirring, 25 mL of potassium biphthalate solution (1 in 20), and allow to stand for 2 hours. Filter one of the mixtures through a filtering crucible, and wash the precipitate with cold water. Transfer the precipitate to a container, add 50 mL of water, shake intermittently for 30 minutes, filter, and use the filtrate as the saturated potassium tetraphenylborate solution in the following standardization procedure. Filter the second mixture through a tared filtering crucible, and wash the precipitate with three $5-\mathrm{mL}$ portions of saturated potassium tetraphenylborate solution. Dry the precipitate at $105^{\circ}$ for 1 hour. Each g of potassium tetraphenylborate is equivalent to 955.1 mg of sodium tetraphenylboron. From the weight of sodimm tenaphenylboron obtained, eat eulate the molarity of the soditm tetraphenylboren solution.

■.1S (USP28)
NOTE-Prepare this solution fresh
■just before use.■1S (USP28)

## Change to read:

## Sodium Thiosulfate, Tenth-Normal (0.1 N) <br> $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3} \cdot 5 \mathrm{H}_{2} \mathrm{O}, 248.19$ <br> 24.82 g in 1000 mL

Dissolve about 26 g of sodium thiosulfate and 200 mg of sodium carbonate in 1000 mL of recently boiled and cooled water. Standardize the solution as follows.

Accurately weigh about 210 mg of primary standard potassium dichromate, previously pulverized and dried at $120^{\circ}$ for 4 hours, and dissolve in 100 mL of water in a glass-stoppered, $500-\mathrm{mL}$ flask. Swirl to dissolve the solid, remove the stopper, and quickly add 3 g of potassium iodide, 2 g of sodium bicarbonate, and 5 mL of hydrochloric acid. Insert the stopper gently in the flask, swirl to mix, and allow to stand in the dark for exactly 10 minutes. Rinse the stopper and the inner walls of the flask with water, and titrate the liberated iodine with the sodium thiosulfate solution until the solution is yellowish-green in color. Add 3 mL of starch TS, and continue the titration until the blue color is discharged. Perform a blank determination. Galeulate the nermatity.

## ■1. (USP28)

Restandardize the solution as frequently as supported by laboratory stability data. In the absence of such data, restandardize the solution weekly.

$$
\mathbf{■}^{\mathrm{N}}=\frac{\mathrm{mg} \mathrm{~K}_{2} \mathrm{Cr}_{2} \mathrm{O}_{7}}{49.04 \times \mathrm{mL} \mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}} \boldsymbol{\square}_{1 \mathrm{~S}(\text { USP28) }}
$$

## Change to read:

> Sulfuric Acid, Half-Normal $(\mathbf{0 . 5} \mathrm{N})$ in Alcohol $\mathrm{H}_{2} \mathrm{SO}_{4}, \mathbf{9 8 . 0 8}$
> 24.52 g in 1000 mL

Add slowly, with stirring, 13.9 mL of sulfuric acid to a sufficient quantity of dehydrated alcohol to make 1000 mL . Cool, and stan-
dardize against tromethamine as described under Hydrochloric Acid, Half-Normal ( 0.5 N ) in Methanol.

$$
{ }^{\mathbf{n}}=\frac{\mathrm{mg} \text { tromethamine }}{121.14 \times \mathrm{mL} \mathrm{H}_{2} \mathrm{SO}_{4}} \quad \mathrm{■}_{1 \mathrm{~S}(U S P 28)}
$$

## Change to read:

Tetrabutylammonium Hydroxide, Tenth-Normal (0.1 N)
$\left(\mathrm{C}_{4} \mathrm{H}_{9}\right)_{4} \mathrm{NOH}, \mathbf{2 5 9 . 4 7}$
25.95 g in 1000 mL

Dissolve 40 g of tetra- $n$-butylammonium iodide in 90 mL of anhydrous methanol in a glass-stoppered flask. Place in an ice bath, add 20 g of powdered silver oxide, insert the stopper in the flask, and agitate vigorously for 60 minutes. Centrifuge a few mL , and test the supernatant for iodide (see Iodide $\langle 191\rangle$ ). If the test is positive, add an additional 2 g of silver oxide, and continue to allow to stand for 30 minutes with intermittent agitation. When all of the iodide has reacted, pass through a fine-porosity, sintered-glass funnel. Rinse the flask and the funnel with three $50-\mathrm{mL}$ portions of anhydrous toluene, adding the rinsings to the filtrate. Dilute with a mixture of three volumes of anhydrous toluene and 1 volume of anhydrous methanol to 1000 mL , and flush the solution for $10 \mathrm{~min}-$ utes with dry, carbon dioxide-free nitrogen. [NOTE-If necessary to obtain a clear solution, further small quantities of anhydrous methanol may be added.] Store in a reservoir protected from carbon dioxide and moisture, and discard after 60 days. Alternatively, the solution may be prepared by diluting a suitable volume of commercially available tetrabutylammonium hydroxide solution in methanol with a mixture of 4 volumes of anhydrous toluene and 1 volume of anhydrous methanol. [NOTE-If necessary to obtain a clear solution, further small quantities of methanol may be added.]

Standardize the solution on the day of use as follows. Dissolve about 400 mg of primary standard benzoic acid, accurately weighed, in 80 mL of dimethylformamide, add 3 drops of a 1 in 100 solution of thymol blue in dimethylformamide, and titrate to a blue endpoint with the tetrabutylammonium hydroxide solution, delivering the titrant from a buret equipped with a carbon dioxide absorption trap. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N tetrabutylammonium hydroxide is equivalent to 12.21 mg of benzoic acid.

$$
\mathbf{■}^{\mathrm{N}}=\frac{\mathrm{mg} \text { benzoic acid }}{122.1 \times \mathrm{mL}\left(\mathrm{C}_{4} \mathrm{H}_{9}\right)_{4} \mathrm{NOH}} \square_{1 \mathrm{~S}(\text { USP28) }}
$$

## Change to read:

${ }^{\Delta}$ Tetrabutylammonium Hydroxide in Methanol/Isopropyl Alcohol, 0.1 N

Prepare as described for Tetrabutylammonium Hydroxide, Tenth-Normal ( 0.1 N ), using isopropyl alcohol instead of toluene, and standardize as described. Alternatively, the solution may be prepared by diluting a suitable volume of commercially available
tetrabutylammonium hydroxide solution in methanol with 4 volumes of anhydrous isopropyl alcohol.

$$
{ }^{■} \mathrm{~N}=\frac{\mathrm{mg} \text { benzoic acid }}{122.1 \times \mathrm{mL}_{\left(\mathrm{C}_{4} \mathrm{H}_{9}\right)_{4} \mathrm{NOH}}^{\square} 1 \mathrm{~S}(U S P 28) \Delta U S P 28}
$$

## Change to read:

Tetramethylammonium Bromide, Tenth-Molar (0.1 M) $\left(\mathrm{CH}_{3}\right)_{4} \mathrm{NBr}, 154.05$
15.41 g in 1000 mL

Dissolve 15.41 g of tetramethylammonium bromide in water to make 1000 mL , and standardize the solution as follows.

Transfer an accurately measured volume of about 40 mL of the solution to a beaker, add 10 mL of diluted nitric acid and 50.0 mL of 0.1 N silver nitrate VS , and mix. Add 2 mL of ferric ammonium sulfate TS, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS. Galeulate the molarity.


## Change to read:

Tetramethylammonium Chloride, Tenth-Molar (0.1 M)
$\left(\mathrm{CH}_{3}\right)_{4} \mathrm{NCl}, 109.60$
10.96 g in 1000 mL

Dissolve 10.96 g of tetramethylammonium chloride in water to make 1000 mL , and standardize the solution as follows.

Transfer an accurately measured volume of about 40 mL of the solution to a flask, add 10 mL of diluted nitric acid and 50.0 mL of 0.1 N silver nitrate VS , and mix. Add 5 mL of nitrobenzene and 2 mL of ferric ammonium sulfate TS, shake, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS. Ealeulate the melarity.

## Change to read:

Titanium Trichloride, Tenth-Normal (0.1 N) $\mathrm{TiCl}_{3}, \mathbf{1 5 4 . 2 3}$<br>15.42 g in 1000 mL

Add 75 mL of titanium trichloride solution (1 in 5) to 75 mL of hydrochloric acid, dilute to 1000 mL , and mix. Standardize the solution as follows, using the special titration apparatus described.

Apparatus-Store the titanium trichloride solution in the reservoir of a closed-system titration apparatus in an atmosphere of hydrogen.

Use a wide-mouth, $500-\mathrm{mL}$ conical flask as the titration vessel, and connect it by means of a tight-fitting rubber stopper to the titration buret, an inlet tube for carbon dioxide, and an exit tube. Arrange for mechanical stirring. All joints must be airtight. Arrange to have both the hydrogen and the carbon dioxide pass through wash bottles containing titanium trichloride solution (approximately 1 in 50 ) to remove any oxygen.

If the solution to be titrated is to be heated before or during titration, connect the titration flask with an upright reflux condenser through the rubber stopper.

Standardization-Place an accurately measured volume of about 40 mL of 0.1 N ferric ammonium sulfate VS in the titration flask, and pass in a rapid stream of carbon dioxide until all the air has been removed. Add the titanium trichloride solution from the buret until near the calculated endpoint (about 35 mL ), then add through the outlet tube 5 mL of ammonium thiocyanate TS , and continue the titration until the solution is colorless. Galeulate the nermality.

$$
■ \mathrm{~N}=\frac{\mathrm{mL} \mathrm{FeNH}_{4}\left(\mathrm{SO}_{4}\right)_{2} \times \mathrm{N} \mathrm{FeNH}_{4}\left(\mathrm{SO}_{4}\right)_{2}}{\mathrm{~mL} \mathrm{TiCl}_{3}} \llbracket 1 \mathrm{~S}(\text { USP28) }
$$

## Change to read:

Zinc Sulfate, Twentieth-Molar ( 0.05 M )
$\mathrm{ZnSO}_{4} \cdot 7 \mathrm{H}_{2} \mathrm{O}, 287.56$
14.4 g in 1000 mL

Dissolve 14.4 g of zinc sulfate in water to make 1 L . Standardize the solution as follows.

Accurately measure about 10 mL of 0.05 M edetate disodium VS into a $125-\mathrm{mL}$ conical flask, and add, in the order given, 10 mL of acetic acid-ammonium acetate buffer TS, 50 mL of alcohol, and 2 mL of dithizone TS. Titrate with the zinc sulfate solution to a clear, rose-pink color. Gateulate the molarity.
NOTE- FOr many of the reagents mentioned in the foregoing section, the eorrespending standards of the 6 th edition (1980) of Reagent Chemieals, published by the Amerienn-Chemieal Society, should be consulted. For a limited number of other reagents, the standards are adapted from these appearing in Reagent Chemicats and Standards, 5 th edition, by Joseph Rosin and copyrighted by the publisher, D. Van Nestrand Co., Ine.
$\square \mathbf{m}=\frac{\mathrm{mL} \text { edetate disodium } \times \mathrm{M} \mathrm{edetate} \mathrm{disodium}_{\mathrm{mL} \mathrm{ZnSO}}^{4}}{} \quad$ 1S (USP28)

## REFERENCE TABLES

## Briefing

Container Specifications for Capsules and Tablets, USP 27 page 2741, page 3352 of the Second Supplement, and page 1821 of PF 30(5) [Sept.-Oct. 2004].
(HDQ) RTS—39932-1; 40720-1; 40720-2; 40844-2; 40844-3

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the Packaging and storage requirements set forth in the individual monographs. It lists the capsules and tablets that are, or will be, official in the United States Pharmacopeia and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

Monograph Title | Container |
| :---: |
| Specification |

## Add the following:

-Acetaminophen Tablets, Extended-
Release
$\mathrm{T}_{\text {■1S (USP28) }}$

## Add the following:

${ }^{\Delta}$ Alendronate Sodium Tablets

> Alendronic Acid Tablets
$\mathrm{T}_{\mathbf{\Delta U S P 2 8}}$

## Add the following:

| ■Benazepril Tablets | $\mathrm{W}_{\text {■1S (USP28) }}$ |
| :---: | :---: |
| Add the following: |  |
| - Bismuth Subsalicylate Tablets | $\mathrm{T}_{\mathbf{\square 1 S} \text { (USP28) }}$ |
| Add the following: |  |
| ${ }^{\text {- Cefaclor Tablets }}$ | $\mathrm{T}_{\mathbf{\square 1 S} \text { (USP28) }}$ |

Container Specifications for Capsules and Tablets (Continued)
Container
Monograph Title

## Add the following:

-Chromium Picolinate Tablets
$\mathrm{W}_{\mathbf{\square} 2 \mathrm{~S}}$ (USP28)
Add the following:
-Clarithromycin Tablets, ExtendedRelease
$\mathrm{W}_{\text {■1S (USP28) }}$

## Add the following:

-Black Cohosh Tablets
$\mathrm{T}, \mathrm{LR}_{\mathbf{■ 1 S}(U S P 28)}$
Add the following:

- Desogestrel and Ethinyl Estradiol

Tablets
$\mathrm{W}_{\text {■1S (USP28) }}$

## Add the following:

- Diethylstilbestrol Diphosphate Tablets $\quad \mathrm{W}_{\boxed{\square}}$ (USP28)


## Add the following:

■Estradiol and Norethindrone Acetate
Tablets

Add the following:
-Fexofenadine Hydrochloride Tablets

## Add the following:

■Fluoxetine Capsules, Delayed-Release

## Add the following:

-Fosinopril Sodium Tablets

## Add the following:

-Fosinopril Sodium and Hydrochlorothiazide Tablets

Add the following:
-Gabapentin Capsules
$\mathrm{W}_{\text {■2S (USP28) }}$

$\mathrm{T}_{\mathbf{■} 2 \mathrm{~S} \text { (USP28) }}$
$\mathrm{W}_{\mathbf{\square} 2 \mathrm{~S}(\text { USP28) }}$

■1S (USP28)
$\mathrm{T}_{\text {■2S (USP28) }}$
$\mathrm{W}_{\mathbf{I}}$ (USP28)


Description and Relative Solubility of USP and NF Articles, USP 27 page 2747, page 3166 of the First Supplement, page 3352 of the Second Supplement, page 7017 of PF 24(5) [Sept.-Oct. 1998], page 8589 of $P F$ 25(4) [July-Aug. 1999], page 8917 of PF 25(5) [Sept.-Oct. 1999], page 9254 of $P F 25(6)$ [Nov.-Dec. 1999], page 1135 of $P F$ 26(4) [July-Aug. 2000], page 1385 of $P F$ 26(5) [Sept.-Oct. 2000], page 1542 of $P F$ 28(5) [Sept.-Oct. 2002], page 1953 of $P F$ 28(6) [Nov.-Dec. 2002], page 266 of $P F$ 29(1) [Jan.-Feb. 2003], page 509 of $P F$ 29(2) [Mar.-Apr. 2003], page 812 of $P F$ 29(3) [May-June 2003], page 1262 of $P F$ 29(4) [July-Aug. 2003], page 1684 of $P F 29(5)$ [Sept.-Oct. 2003], page 2057 of $P F$ 29(6) [Nov.-Dec. 2003], page 317 of $P F$ 30(1) [Jan.-Feb. 2004], page 650 pf $P F$ 30(2) [Mar.-Apr. 2004], page 1050 of $P F 30(3)$ [May-June 2004], page 1405 of PF 30(4) [July-Aug. 2004], and page 1822 of PF 30(5) [Sept.Oct. 2004].
(HDQ) RTS-41670-1; 41341-1; 41613-5; 38281-2; 402825; 41471-1; 41471-2; 41365-1

## Change to read:

Alginic Acid: White to yellowish white, fibrous powder. Is odorless, or practically odorless, and is tasteless. Insoluble in water and in organic solvents; soluble in alkaline solutions. NF category:
■Suspending and/or viscosity-increasing agent; $\quad$ 2S (USP28) tablet binder; tablet disintegrant.

## Change to read:

Almond Oil: Clear, pale straw-colored or colorless, oily liquid, having a bland taste. Remains clear at $-10^{\circ}$, and does not congeal until cooled to almost $-20^{\circ}$. Slightly soluble in alcohol; miscible with ether, with chloroform, with benzene, and with solvent hexane. NF category: Flavors and perfumes;
$■_{\text {vehicle (oleaginous). }} \mathbf{m}^{2 S}$ (USP28)

## Change to read:

Aromatic Elixir: NF category: Flavored and/or sweetened wehicle.

■Vehicle (flavored and/or sweetened).■2S (USP28)

## Change to read:

Activated Attapulgite: Cream-colored, micronized, nonswelling powder, free from gritty particles. The high heat treatment used in its preparation causes it to yield only moderately viscous aqueous suspensions, its dispersion consisting mainly of particle groups. Insoluble in water.

$$
\begin{aligned}
& \text { NF category: Suspending and/or viscosity-increasing } \\
& \text { agent. } \quad 2 \text { S (USP28) }
\end{aligned}
$$

## Change to read:

Colloidal Activated Attapulgite: Cream-colored, micronized, nonswelling powder, free from gritty particles. Yields viscous aqueous suspensions, as a result of dispersion into its constituent ultimate particles. Insoluble in water.

- NF category: Suspending and/or viscosity-increasing
agent.■2S (USP28)


## Change to read:

Purified Bentonite: Odorless, tasteless, fine (micronized) powder or small flakes that are creamy when viewed on their flat surfaces and tan to brown when viewed on their edges. Insoluble in water and in alcohol. Swells when added to water or glycerin.
-NF category: Suspending and/or viscosity-increasing

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agent.m2S (USP28)
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agent.m2S (USP28)
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agent.m2S (USP28)
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agent.m2S (USP28)
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## Add the following:

-Budesonide: White to off-white, ordorless, crystalline powder. Freely soluble in chloroform; sparingly soluble in alcohol; practically insoluble in water and in heptane. ${ }^{2 S}$ (USP28)

## Change to read:

Calcium Carbonate: Fine, white, odorless, tasteless, microcrystalline powder. Is stable in air. Practically insoluble in water. Its solubility in water is increased by the presence of any ammonium salt or of carbon dioxide. The presence of any alkali hydroxide reduces its solubility. Insoluble in alcohol. Dissolves with effervescence in 1 N acetic acid, in 3 N hydrochloric acid, and in 2 N nitric acid.
-NF category: Tablet and/or capsule diluent. ${ }^{2 S}$ (USP28)

## Add the following:

-Carboxymethylcellulose Sodium 12: Colorless or white to off-white powder or granules. Is odorless. Water solubility depends on degree of substitution (easily dispersed in water at all temperatures, forming a clear, colloidal solution). Insoluble in acetone, in alcohol, in ether, and in toluene. NF category: Suspending and/or viscosity-increas-
ing agent. ${ }^{2 S}$ (USP28)

## Change to read:

Cellulose Acetate: Fine, white powder or free-flowing pellets. Available in a range of viscosities and acetyl contents. High viscosity, which reflects high molecular weight, decreases solubility slightly. High acetyl content cellulose acetates generally have more
limited solubility in commonly used organic solvents than low acetyl content cellulose acetates, but are more soluble in methylene chloride. All acetyl content cellulose acetates are insoluble in alcohol and in water; soluble in dioxane and in dimethylformamide. $N F$ category:

- Coating agent; ${ }^{\mathbf{n} 2 \text { S (USP28) }}$
polymer membrane.


## Change to read:

Chlorocresol: Colorless or practically colorless crystals or crystalline powder, having a characteristic, nontarry odor. Is volatile in steam. Slightly soluble in water and more soluble in hot water; very soluble in alcohol; soluble in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides.
-NF category: Antimicrobial preservative.■2S (USP28)

## Change to read:

Dextrin: Free-flowing, white, yellow, or brown powder. Its solubility in water varies; it is usually very soluble, but often contains an insoluble portion.

- NF category: Tablet binder; tablet and/or capsule diluent.■2S (USP28)


## Change to read:

Dextrose: Colorless crystals or white, crystalline or granular powder. Is odorless, and has a sweet taste. Freely soluble in water; very soluble in boiling water; soluble in boiling alcohol; slightly soluble in alcohol. NF category: Sweetening agent; tonicity agent;
$■_{\text {vehicle (flavored and/or sweetened). }}^{\boldsymbol{\square}}$ 2S (USP28)

## Change to read:

Dimethicone: A clear, colorless, and odorless liquid. Insoluble in water, in methanol, in alcohol, and in acetone; very slightly soluble in isopropyl alcohol; soluble in chlorinated hydrocarbons, in benzene, in toluene, in xylene, in $n$-hexane, in petroleum spirits, in ether, and in amyl acetate.

- NF category: Antifoaming agent; water repelling
agent.■2S (USP28)


## Change to read:

Edetate Calcium Disodium: White, crystalline granules or white, crystalline powder. Is odorless, is slightly hygroscopic, and has a faint, saline taste. Is stable in air. Freely soluble in water.
-NF category: Chelating agent; complexing agent.п2s (USP28)

## Change to read:

Edetate Disodium: White, crystalline powder. Soluble in water. NF category: Chelating agent;

## - complexing agent.п2S (USP28)

## Change to read:

Edetic Acid: White, crystalline powder. Melts above $220^{\circ}$, with decomposition. Very slightly soluble in water; soluble in solutions of alkali hydroxides. NF category: Chelating agent;
$\square_{\text {complexing agent. }}^{\text {■2S (USP28) }}$

## Change to read:

Ethyl Acetate: Transparent, colorless liquid, having a fragrant, refreshing, slightly acetous odor, and a peculiar, acetous, burning taste. Soluble in water. Miscible with alcohol, with ether, with fixed oils, and with volatile oils. NF category: Flavors and perfumes;
$\square_{\text {solvent. }}$ [2S (USP28)

## Change to read:

Ethyl Oleate: Mobile, practically colorless liquid, having an agreeable taste. Insoluble in water. Miscible with vegetable oils, with mineral oil, with alcohol, and with most organic solvents. $N F$ category: Vehicle
-(oleaginous)..n2S (USP28)

## Change to read:

Glaze, Pharmaceutical:
-Denatured alcohol solution.■2S (USP28)
NF category: Coating agent.

## Change to read:

Hexylene Glycol: Clear, colorless, viscous liquid. Absorbs moisture when exposed to moist air. Miscible with water and with many organic solvents, including alcohol, ether, chloroform, acetone, and hexanes.
-NF category: Humectant; solvent.п2S (USP28)

## Change to read:

Low-Substituted Hydroxypropyl Cellulose: White to yellowish white, practically odorless and tasteless, fibrous or granular powder. Is hygroscopic. Practically insoluble in alcohol and in ether. Dissolves in a solution of sodium hydroxide ( 1 in 10), and produces a viscous solution. Swells in water, in sodium carbonate TS, and in 2 N hydrochloric acid. The pH of the suspension, obtained by shaking 1.0 g with 100 mL of water, is between 5.0 and 7.5. NF category:Fablet disintegrant and/or tablet binder.
-Tablet binder; tablet disintegrant.■2S (USP28)

## Add the following:

■Lactitol: A white or light brown, ordorless crystal. Has a mild, sweet taste, and no aftertaste. NF category: Flavors and perfumes; tablet and/or capsule diluent.■2S (USP28)

## Add the following:

-Lansoprazole: White to brownish-white powder. Freely soluble in dimethylformamide; practically insoluble in water. Melts at about $166^{\circ}$, with decomposition.п2S (USP28)

## Change to read:

Maltodextrin: White, hygroscopic powder or granules. Freely soluble or readily dispersible in water; slightly soluble to insoluble in anhydrous alcohol. NF category: Coating agent;
$\square_{\text {Suspending and/or viscosity-increasing agent; }{ }^{\text {2S }} \text {.(USP28) }}$ tablet binder; tablet and/or capsule diluent. iseosity inereasing agent.


## Change to read:

Methylparaben Sodium: White, hygroscopic powder. Freely soluble in water; sparingly soluble in alcohol; insoluble in fixed oils.

- NF category: Antimicrobial preservative.■2S (USP28)


## Change to read:

Monoethanolamine: Clear, colorless, moderately viscous liquid, having a distinctly ammoniacal odor. Miscible with water, with acetone, with alcohol, with glycerin, and with chloroform. Immiscible with ether, with solvent hexane, and with fixed oils, although it dissolves many essential oils.

- NF category: Emulsifying and/or solubilizing agent.■2S (USP28)


## Add the following:

-Monoglyceride Citrate: Soft white to ivory-colored, waxy solid with a lard-like consistancy and bland odor. Dispersible in most common fat solvents and in alcohol; insoluble in water. $\quad$ 2S (USP28)

## Add the following:

-Morantel Tartrate: A white or pale yellow, crystalline powder. Very soluble in water and in alcohol; practically insoluble in ethyl acetate. $\quad$ 2S (USP28)

## Change to read:

Nonoxynol 9: Clear, colorless to light yellow, viscous liquid. Soluble in water, in alcohol, and in corn oil.
-NF category: Wetting and/or solubilizing agent.■2S (USP28)

## Change to read:

Octyldodecanol: Clear water-white, free-flowing liquid. Insoluble in water; soluble in alcohol and in ether.

- $N F$ category: Vehicle (oleaginous).■2S (USP28)


## Add the following:

-Ondansetron: White to off-white powder. Very soluble in acid solutions; sparingly soluble in water.■2S (USP28)

## Change to read:

Oxyquinoline Sulfate: Yellow powder. Melts at about $185^{\circ}$. Very soluble in water; freely soluble in methanol; slightly soluble in alcohol; practically insoluble in acetone and in ether.

- NF category: Complexing agent.■2S (USP28)


## Add the following:

-Peppermint Spirit: A clear, colorless liquid with a peppermint fragrance. Completely soluble in water; easily soluble in methanol and in diethyl ether. NF category: Flavors and perfumes.■2S (USP28)

## Change to read:

Peppermint Water: NF category: Flavered and/er sweened wehicle.

- Vehicle (flavored and/or sweetened)...n2S (USP28)


## Change to read:

Poloxamer: NF category: Emulsifying and/or solubilizing agent;
$\boldsymbol{m}_{\text {Wetting }}$ and/or solubilizing agent. $\mathbf{m}_{\text {2S }}$ (USP28)
Poloxamer 124: Colorless liquid, having a mild odor. When solidified, it melts at about $16^{\circ}$. Freely soluble in water, in alcohol, in isopropyl alcohol, in propylene glycol, and in xylene.

Poloxamer 188: White, prilled or cast solid. Is odorless, or has a very mild odor. Melts at about $52^{\circ}$. Freely soluble in water and in alcohol.

Poloxamer 237: White, prilled or cast solid. Is odorless, or has a very mild odor. Melts at about $49^{\circ}$. Freely soluble in water and in alcohol; sparingly soluble in isopropyl alcohol and in xylene.

Poloxamer 338: White, prilled or cast solid. Is odorless, or has a very mild odor. Melts at about $57^{\circ}$. Freely soluble in water and in alcohol; sparingly soluble in propylene glycol.

Poloxamer 407: White, prilled or cast solid. Is odorless, or has a very mild odor. Melts at about $56^{\circ}$. Freely soluble in water, in alcohol, and in isopropyl alcohol.

## Change to read:

Polyethylene Oxide: Polyethylene oxide resins are high molecular weight polymers having the common structure:

$$
\left(-\mathrm{O}-\mathrm{CH}_{2} \mathrm{CH}_{2}-\right)_{n}
$$

in which $n$, the degree of polymerization, varies from about 2000 to over 100,000 . Polyethylene oxide, being a polyether, strongly hydrogen, bonds with water. It is nonionic and undergoes salting-out effects associated with neutral molecules in solutions of high dielectric media. Salting-out effects manifest themselves in depressing the upper temperature limit of solubility, and in reducing the viscosity of both dilute and concentrated solutions of the polymers. All molecular weight grades are powdered or granular solids. They are soluble in water but, because of the high solution viscosities obtained (see table), solutions over $1 \%$ in water may be difficult to prepare. The water solubility, hygroscopicity, solubility in organic solvents, and melting point do not vary in the specified molecular weight range. At room temperature polyethylene oxide is miscible with water in all proportions. At concentrations of about $20 \%$ polymer in water, the solutions are nontacky, reversible, elastic gels. At higher concentrations, the solutions are tough, elastic materials with the water acting as a plasticizer. Polyethylene oxide is also freely soluble in acetonitrile, in ethylene dichloride, in trichloroethylene, and in methylene chloride. Heating may be required to obtain solutions in many other organic solvents. It is insoluble in aliphatic hydrocarbons, in ethylene glycol, in diethylene glycol, and in glycerol.

- NF category: Suspending and/or viscosity-increasing agent; tablet binder. $\quad$ 2S (USP28)

| Approximate <br> Molecular Weight | Typical Solution Viscosity (cps), 25 ${ }^{\circ}$ |  |
| :---: | :---: | :---: |
|  | $5 \%$ Solution | $1 \%$ Solution |
| 100,000 | 40 |  |
| 200,000 | 100 |  |
| 300,000 | 800 |  |
| 400,000 | 3000 |  |
| 600,000 | 6000 |  |
| 900,000 | 15000 |  |
| $4,000,000$ |  | 3500 |
| $5,000,000$ |  | 5500 |

## Change to read:

Polyoxyl 10 Oleyl Ether: White, soft semisolid, or pale yellow liquid, having a bland odor. Soluble in water and in alcohol; dispersible in mineral oil and in propylene glycol, with possible separation on standing. NF category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; ${ }^{\text {2S }}$ (USP28) wetting and/or solubilizing agent.

## Change to read:

Polyoxyl 20 Cetostearyl Ether: Cream-colored, waxy, unctuous mass, melting, when heated, to a clear brownish-yellow liquid. Soluble in water, in alcohol, and in acetone; insoluble in solvent hexane. NF category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; $\mathbf{m}_{2 \text { S (USP28) }}$ wetting and/or solubilizing agent.

## Change to read:

Polyoxyl 35 Castor Oil: Yellow, oily liquid, having a faint, characteristic odor and a somewhat bitter taste. Very soluble in water, producing a practically odorless and colorless solution; soluble in alcohol and in ethyl acetate; insoluble in mineral oils. NF category: Emulsifying and/or solubilizing agent;

- tablet and/or capsule lubricant; $\quad$ 2S (USP28) wetting and/or solubilizing agent.


## Change to read:

Polyoxyl 40 Hydrogenated Castor Oil: White to yellowish paste or pasty liquid, having a faint odor and slight taste. Very soluble in water, producing a practically tasteless, odorless, and colorless solution; soluble in alcohol and in ethyl acetate; insoluble in mineral oils. NF category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; $\quad$ 2S (USP28) wetting and/or solubilizing agent.

## Change to read:

Polyoxyl 40 Stearate: Waxy, white to light tan solid. Is odorless or has a faint, fat-like odor. Soluble in water, in alcohol, in ether, and in acetone; insoluble in mineral oil and in vegetable oils. NF category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; $\mathbf{m}_{2 \text { S }}$ (USP28) wetting and/or solubilizing agent.

## Change to read:

Polysorbate 20: Lemon to amber liquid having a faint characteristic odor. Soluble in water, in alcohol, in ethyl acetate, in methanol, and in dioxane; insoluble in mineral oil. NF category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; $\quad$ 2S (USP28) wetting and/or solubilizing agent.

## Change to read:

Polysorbate 40: Yellow liquid having a faint, characteristic odor. Soluble in water and in alcohol; insoluble in mineral oil and in vegetable oils. NF category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; ${ }^{2 S}$ (USP28) wetting and/or solubilizing agent.

## Change to read:

Polysorbate 60: Lemon- to orange-colored, oily liquid or semi-gel having a faint, characteristic odor. Soluble in water, in ethyl acetate, and in toluene; insoluble in mineral oil and in vegetable oils. NF category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; $\quad$ 2S (USP28) wetting and/or solubilizing agent.

## Change to read:

Polysorbate 80: Lemon- to amber-colored, oily liquid having a faint, characteristic odor and a warm, somewhat bitter taste. Very soluble in water, producing an odorless and practically colorless solution; soluble in alcohol and in ethyl acetate; insoluble in mineral oil. NF category: Emulsifying and/or solubilizing agent;

- tablet and/or capsule lubricant; $\mathbf{m}_{2 S}$ (USP28)
wetting and/or solubilizing agent.


## Change to read:

Potassium Benzoate: White, odorless, or practically odorless, granular or crystalline powder. Is stable in air. Freely soluble in water; sparingly soluble in alcohol and somewhat more soluble in $90 \%$ alcohol.
-NF category: Antimicrobial preservative.■2S (USP28)

## Change to read:

Potassium Citrate: Transparent crystals or white, granular powder. Is odorless, has a cooling, saline taste, and is deliquescent when exposed to moist air. Freely soluble in water; almost insoluble in alcohol.

- NF category: Buffering agent.■2S (USP28)


## Change to read:

Propionic Acid: Oily liquid having a slight pungent, rancid odor. Miscible with water and with alcohol and various other organic solvents.
-NF category: Acidifying agent.■2S (USP28)

## Change to read:

Propylene Glycol Alginate: White to yellowish fibrous or granular powder. Practically odorless and tasteless. Soluble in water, in solutions of dilute organic acids, and, depending on the degree of esterification, in hydroalcoholic mixture containing up to $60 \%$ by weight of alcohol to form stable, viscous colloidal solutions at a pH of 3 .

■ NF category: Suspending and/or viscosity-increasing
agent.п2S (USP28)

## Change to read:

Propylparaben Sodium: White powder. Is odorless and hygroscopic. Freely soluble in water; sparingly soluble in alcohol; insoluble in fixed oils.
-NF category: Antimicrobial preservative.■2S (USP28)

## Add the following:

■Ropivacaine Hydrochloride: White, crystalline powder. Soluble in water.■2S (USP28)

## Change to read:

Simethicone: Translucent, gray, viscous fluid. Insoluble in water and in alcohol. The liquid phase is soluble in chloroform, in ether, and in benzene, but silicon dioxide remains as a residue in these solvents.

- NF category: Antifoaming agent; water repelling
agent.■2S (USP28)


## Change to read:

## Sodium Bisulfite:

-White, crystalline powder. Freely soluble in cold water and
in hot water; sparingly soluble in alcohol.■2S (USP28) NF category: Antioxidant.

## Change to read:

Sodium Lauryl Sulfate: Small, white or light yellow crystals having a slight, characteristic odor. Freely soluble in water, forming an opalescent solution. NF category: Emulsifying and/or solubilizing agent;

- tablet and/or capsule lubricant; $\quad$ 2S (USP28) wetting and/or solubilizing agent.


## Change to read:

Sodium Stearyl Fumarate: Fine, white powder. Slightly soluble in methanol; practically insoluble in water.

- NF category: Tablet and/or capsule lubricant.■2S (USP28)


## Change to read:

Sorbitan Monolaurate: Yellow to amber-colored oily liquid, having a bland, characteristic odor. Insoluble in water; soluble in mineral oil; slightly soluble in cottonseed oil and in ethyl acetate. NF category: Emulsifying and/or solubilizing agent;

- tablet and/or capsule lubricant; $\quad$ 2S (USP28) wetting and/or solubilizing agent.


## Change to read:

Sorbitan Monooleate: Viscous, yellow to amber-colored, oily liquid, having a bland, characteristic odor. Insoluble in water and in propylene glycol. Miscible with mineral and vegetable oils. $N F$ category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; $\mathbf{m}_{2 \text { S }}$ (USP28) wetting and/or solubilizing agent.

## Change to read:

Sorbitan Monopalmitate: Cream-colored, waxy solid having a faint fatty odor. Insoluble in water; soluble in warm absolute alcohol; soluble, with haze, in warm peanut oil and in warm mineral oil. NF category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; $\mathbf{m}_{2 \text { S (USP28) }}$ wetting and/or solubilizing agent.

## Change to read:

Sorbitan Monostearate: Cream-colored to tan, hard, waxy solid, having a bland odor and taste. Insoluble in cold water and in acetone; dispersible in warm water; soluble, with haze, above $50^{\circ}$ in mineral oil and in ethyl acetate. NF category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; ${ }^{\text {2S }}$ (USP28) wetting and/or solubilizing agent.

## Change to read:

Sorbitan Sesquioleate: Viscous, yellow to amber-colored, oily liquid. Insoluble in water and in propylene glycol; soluble in alcohol, in isopropyl alcohol, in cottonseed oil, and in mineral oil. NF category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; $\mathbf{m}_{2 \text { S (USP28) }}$
wetting and/or solubilizing agent.

## Change to read:

Sorbitan Trioleate: Yellow to amber-colored, oily liquid. Insoluble in water, in ethylene glycol, and in propylene glycol; soluble in methyl alcohol, in alcohol, in isopropyl alcohol, in corn oil, in cottonseed oil, and in mineral oil. NF category: Emulsifying and/or solubilizing agent;
-tablet and/or capsule lubricant; $\mathbf{m}_{2 \text { S (USP28) }}$ wetting and/or solubilizing agent.

## Change to read:

Starch: Irregular, angular, white masses or fine powder. Is odorless, and has a slight, characteristic taste. Insoluble in cold water and in alcohol. NF category: Tablet and/or capsule diluent; tablet disintegrant;
-tablet and/or capsule lubricant.■2S (USP28)

## Change to read:

Purified Stearic Acid: Hard, white or faintly yellowish, somewhat glossy and crystalline solid, or white or yellowish-white powder. Its odor and taste are slight, suggesting tallow. Freely soluble in chloroform and in ether; soluble in alcohol; practically insoluble in water.
-NF category: Tablet and/or capsule lubricant.■2S (USP28)

## Change to read:

Sucrose: White, crystalline powder or lustrous, dry, colorless or white crystals. Very soluble in water; slightly soluble in alcohol; practically insoluble in dehydrated alcohol.
-NF category: Coating agent; sweetening agent; tablet and/ or capsule diluent. $\quad$ 2S (USP28)

## Change to read:

Sugar Spheres: Hard, brittle, free-flowing, spherical masses ranging generally in size from $10-$ to 60 -mesh. Usually white, but may be colored. Solubility in water varies according to the su-gar-to-starch ratio.
$\mathbf{■}^{-}$NF category: Vehicle (solid carrier).■2S (USP28)

## Change to read:

Syrup: NF category: Sweetening agent; tablet binder; fla vored and/or sweetened vehiele.
$■_{\text {vehicle }}$ (flavored and/or sweetened).п2S (USP28)

## Change to read:

## Tocopherol:

- Clear, colorless to yellow, yellowish-brown, or greenishyellow, viscous oil. Is odorless. Soluble in oils, in fats, in acetone, in alcohol, in chloroform, in ether, and in alcohol;
insoluble in water. $\quad$ 2S (USP28)
NF category: Antioxidant.


## Change to read:

Zein: White to yellow powder. Soluble in aqueous alcohols, in glycols, in ethylene glycol ethyl ether, in furfuryl alcohol, in tetrahydrofurfuryl alcohol, and in aqueous alkaline solutions of pH 11.5 or greater. Insoluble in water and in acetone; readily soluble in ace-tone-water mixtures between the limits of $60 \%$ and $80 \%$ of acetone by volume; insoluble in all anhydrous alcohols except methanol.

- NF category: Coating agent.■2S (USP28)

Items from Earlier Numbers of PF that Have Not Yet Appeared in a Supplement, and are Therefore Candidates for Subsequent Supplements.

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$\dagger$ New cancellations in PF 30(6).

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## HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps (Stages).

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In $P F$, this stage appears as OFFICIAL INQUIRY STAGE 4 in the Harmonization section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

## Stage 5: Consensus

## A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

## B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.
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## GENERAL CHAPTERS

## General Tests and Assays

## Physical Tests and Determinations

## BRIEFING

〈776〉 Optical Microscopy，USP 27 page 2332 and page 606 of PF 28（2）［Mar．－Apr．2002］．The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of compendial standards for this chapter．The revisions presented in this proposal represent the ADOPTION STAGE 6 draft and have been accepted by the members of the Pharmacopeial Discussion Group．The range of particle sizes to which this chapter should ap－ ply is modified to include all particles above $1 \mu \mathrm{~m}$ ．References to other USP general chapters are omitted，as they are not appropriate for a harmonized document．The reference to ASTM standards is replaced with a reference to the applicable ISO standards．The sec－ tion on Number of Particles to Characterize has been omitted，be－ cause the statistical parameters are not suited to this chapter，but may be incorporated into a general information chapter at another time．Other minor changes and editorial changes are included．
（ETM：J．Lane）RTS－41721－1

## Change to read：

## 〈776〉－OPTICAL MICROSCOPY

[^364]eroscopy is partieularly useful for characterizing particles that are net spherical．This method may alse serve as a base for the calibra tion of faster and more routine methods that may be developed．

Apparatus Use a mierescope that is stable and protected frem vibration．The mieroseope magniffention（product of the objective magnification，ocular magniffeation，and additional magnifying eompenents）must be sufficient to allow adequate characterization of the smallest particles to be classified in the test specimen．The greatest numerieal aperture of the objective should be sought for each magnification range．Polarized light may be used in conjunc tion with suitable analyzers and retardation plates．Coler filters of relatively narrow spectral transmission should be used with achre－ matic objectives and are preferable with apochromats and are re－ quired for appropriate color rendition in photomicrography． Gondensers corrected for at least spherieal aberration－should be used in the mieroscope substage and with the lamp．The numerical aperture of the substage condenser should mateh that of the objec tive under the conditions of use；this is affected by the actual ap exture of the condenser diaphragm and the presence of immersion eils．
Adjustment The precise alignment of all elements of the op－ tieal system and proper fousing are essential．The fousing of the elements should be done in accordance with the recommendations of the mierescope mantufacturer．Critieal axial alignment is reeom－ mended．

Hlumination A requirement for good illumination is a uni－ form and adjustable intensity of light over the entire field of view； Kohler illumination is preferred．With colored particles，choose the eolor of the filters used so as to control the contrast and detailof the image．
Vistal－Charaeterization－The magnifieation and numerical aperture should be sufficiently high to allow adequate resolution of the edges of the images of the particles to be characterized．De termine the actual magnification using a calibrated stage miereme－ ter to calibrate an ocular mieremeter．Errers can be minimized if the magnification is oufficient that the image of the partiele is at least 10 －ceular divisions．Each objective must be calibrated separately． To calibrate the ocular seale，the stage mierometer seale and the ecular seale should be aligned．In this way，a precis detemmination of the distane be weenoeular stag divisions ean be made．Severat different magnifications may be necessary to characterize materials having a wide particle size distribution．

Photographic Characterization－If particle size is to be deter－ mined by photographic methods，take care to ensure that the object is sharply foeused at the plane of the photographic emmlsion．De－ termine the aetual magniffeation by photographing a calibrated stage micrometer，using photographic film of sufficient speed，re solving power，and contrast．Expesure and proeessing should be identieal for photographs of beth the test specimen and the deter mination of magnifieation．The apparent size of a photographic im age is influenced by the exposure，development，and printing process as well as by the resolving power of the miereseope．

Preparation of the Mount The meunting medium will vary recording to the physieal properties of the test specimen．Suffl eient，but not excessive，contrast between the specimen and the mounting medimm is required to ensure adequate detailof the spec imen edge．The particles should rest in one plane and be adequately dispersed to distinguish individual particles of interest．Further more，the partieles must be representative of the distribution of siz es in the material and must not be altered during preparation of the mount．Care should be taken to ensure that this impertant require－ ment is met．Selection of the mounting medium must inelude a eemsideration of the analyte solubility．

Grystallinity Characterization－Therystallinity of amateriat may be characterized to determine complianee with the erystallin－ ity requirement where stated in the individual menegraph of a drug substance．Unless otherwise specified in the individual mone－ graph，mount a few particles of the specimen in mineral oil on a
elean glass slide. Examine the mixture using a polarizing mieroseope: the particles show birefringence (interference colors) and extinction positions when the mieroscope stage is revolved.

Limit Test of Partiele Size by Mieroseopy Unless otherwise specified in the individual menegraph, use the following method. Weigh a suitable quatity of the powder to be examined (for example, 10 to 100 mg ), and suspend it in 10 mL of a suitable medium in which the powder does not dissolve, adding, if necessary, a wetting agent. $A$ homogeneous suspension of particles ean be achieved by matching the density of the meditm and the particles, and by providing adequate agitation. Introduce a pertion of the hemegeneeus suspension int a suitable counting cell, and sean under a miero seope an are correspending to not less than $10 \mu$ go f the powder to be examined. Count all the particles having a maximum dimension greater than the preseribe size limit. The size limit and the permit ted number of particles exceeding the limit are stated in the monograph.

Number of Particles to-Characterize-The number of partieles characterized must be sufficient to ensure an acceptable level of uncertainty in the measured parameter. Suecessively higher magnification may be necessary to ensure proper dispersion of the specimen. An estimate of the number of particles, $n$, to be mea stred that will provide an aceeptable level of uneertainty in the mean particle diameter can be obtained frem the statistical theory of normal populations. For a sufficiently large population ( $n>30$ ), the uncertainty in the estimate for the mean particle diameter, $d$, is given in the formula:

in which $z_{\text {e correspends to }}$ the desired eonfidence coeffient ands is the standard deviation of the test specimen. For $n>30, z_{e}$ is about 1.96 at the $95 \%$ confidence level. Other confidence coeffleients can be obtained from reference books on statistics, and, if necessary, small population statisties ean be similarly applied. From this equation, it can be seen that the uneertainty in the mea stred diameter decreases as the number of particles increases. As an example, to obtain an uncertainty of $\pm 5 \mu \mathrm{~m}$ in a specimen that has a standard deviation of $20 \mathrm{\mu m}$ would require that 61 particles be aceurately measured.

An estimate of the uneertainty in the standard deviation of a specimen ean be obtained in a similar fashion. The standard devi ation of the population, $\sigma$, is estimated to lie in the interval:-
where $s$ is the standard deviation of the specimen, and $\chi_{*}{ }^{2}$ and $\chi_{*}{ }^{2}$ are the confidence coefficients obtained from the $\chi^{2}$-distribution. $\chi{ }^{2}$ - and $\chi_{t}{ }^{2}$ ean be obtained from standard statistics references or approximate by the following expressions at the-95\% ennfidence level where $x^{2}{ }^{2}$ and $x_{\Delta}{ }^{2}$ represent the 97.5 and 2.5 pereentile values, respectively:


In general, a larger sample must be aequired to obtain a good estimate of the standard deviation or distribution of the population. For the example population deseribed above, if the mean particle diameter was $50 \mu \mathrm{~m}$, only 61 particles would have to be measured tobtain an uncertainty of $10 \%$ in the diameter (e.g., $d-50 \pm 5$ $\mu \mathrm{m})$, but about 200 particles would have to be meastred to obtaina similar confidence of $\pm 10 \%$ in the standard deviation (e.g., $18.3<s<22.3)$.

For a material that conforms more closely to a log normal dis tribution, the logarithm of the individual particle diameters can be eomputed, and the mean and the standard deviation of the log partiele diameter directly substituted in the above quations. The antilogs correspend to the geometric mean and geometric standarde deviation, respectively.

Particle-SizeCharacterization-The meacurement of particle size varies in complexity depending on the shape of the partiele. For spherieal particles, size is defined by the diameter. For irregular particles, a variety of definitions of particle size exist. In seneral, for irregularly shaped particles, characterization of particle-size must also inelude information on the type of diameter measured as well as information on partiele shape. Several commenly used measurements of particle size are defined below (see Figute 1):


Fig. 1. Commenly used measurements of particle-size.

Feret's Diameter. The-distanee between-imaginary paralle 4 lines tangent to a randomly oriented particle and perpendicular to the ocular seale.

Matin's Bitameter. The diameter of the particle at the peint that divides a randomly oriented partiele into equal projected areas.

Projectar Dicmeter. The diameter of acirele that has the same projected area the particle.

Length The lengest dimension from edge to edge of a particle eriented parallel to the oeular seale-

Width The longest dimension of the particle measured at right angle to the length.

Partiele Shape-Characterization-For irregularly shaped par tieles, characterization of particle-size must also include informar tionen particle shape. The following defines some ommenly used descriptors of particle shape (see Figute 2):


Fig. 2. Commenly used descriptions of particle-shape.

Aeicultar Slender, needle like paricle of similar width and thickness.

Golumnat Leng, thin pariele with a width and thiekness that are greater than these of an acieular particle.

Flate Thin, flat particle of similar length and width.
Plate Flat particles of similar length and width but with greater thickness than flakes.
tath Long, thin, and blade like particle.

Equant Particles of similar length, width, and thickness; both eubical and spherieal particles are ineluded.

General-Observations A partiele is generally considered to be the smallest discrete unit. A particle may be a liequid or semisolid droplet; a single erystal or polyerystalline; amorphous or an as glomerate. Particles may be associated. This degree of association may be described by the following terms:

Lamellat Stacked plates.
Agspegate Mass of adhered parieles.

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    Agglomerate Fused or cemented particles.
    Genglemerate Mixture of two or more types of particles.
Spherulite Radial-cluster.
Drusy Particle covered with tiny particles.
Particle condition may be deseribed by the following terms:
Edges Angular, reunded, smooth, sharp, fractured.
Optical Color (using proper color balaneing flters), tramspar
ent, translueent, opaque.
Defeets Oeelusions, imelusions.
Surface characteristies may be described as:
Gracked Partial-split, break, or fissure-
Smeoth Free of inregularities, reughness, or projections.
Poreus Having openings or passageways.
Rough Bumpy, uneven, not smooth.
Pitted Smallindentations.
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## ■ $\langle 776\rangle$ OPTICAL MICROSCOPY

Optical microscopy for particle characterization can generally be applied to particles $1 \mu \mathrm{~m}$ and greater. The lower limit is imposed by the resolving power of the microscope. The upper limit is less definite and is determined by the increased difficulty associated with the characterization of larger particles. Various alternative techniques are available for particle characterization outside the applicable range of optical microscopy. Optical microscopy is particularly useful for characterizing particles that are not spherical. This method may also serve as a base for the calibration of faster and more routine methods that may be developed.

Apparatus-Use a microscope that is stable and protected from vibration. The microscope magnification (product of the objective magnification, ocular magnification, and additional magnifying components) must be sufficient to allow adequate characterization of the smallest particles to be classified in the test specimen. The greatest numerical aperture of the objective should be sought for each magnification range. Polarizing filters may be used in conjunction with suitable analyzers and retardation plates. Color filters of relatively narrow spectral transmission should be used with achromatic objectives, are preferable with apochromats, and are required for appropriate color rendition in
photomicrography. Condensers corrected at least for spherical aberration should be used in the microscope substage and with the lamp. The numerical aperture of the substage condenser should match that of the objective under the conditions of use and is affected by the actual aperture of the condenser diaphragm and by the presence of immersion oils.

Adjustment-The precise alignment of all elements of the optical system and proper focusing are essential. The focusing of the elements should be done in accordance with the recommendations of the microscope manufacturer. Critical axial alignment is recommended.

Illumination-A requirement for good illumination is a uniform and adjustable intensity of light over the entire field of view; Kohler illumination is preferred. With colored particles, choose the color of the filters used so as to control the contrast and detail of the image.

Visual Characterization-The magnification and numerical aperture should be sufficiently high to allow adequate resolution of the images of the particles to be characterized. Determine the actual magnification using a calibrated stage micrometer to calibrate an ocular micrometer. Errors can be minimized if the magnification is sufficient that the image of the particle is at least 10 ocular divisions. Each objective must be calibrated separately. To calibrate the ocular scale, the stage micrometer scale and the ocular scale should be aligned. In this way, a precise determination of the distance between ocular stage divisions can be made. Several different magnifications may be necessary to characterize materials having a wide particle size distribution.

Photographic Characterization-If particle size is to be determined by photographic methods, take care to ensure that the object is sharply focused at the plane of the photographic emulsion. Determine the actual magnification by photographing a calibrated stage micrometer, using photo-
graphic film of sufficient speed, resolving power, and contrast. Exposure and processing should be identical for photographs of both the test specimen and the determination of magnification. The apparent size of a photographic image is influenced by the exposure, development, and printing processes as well as by the resolving power of the microscope.

Preparation of the Mount-The mounting medium will vary according to the physical properties of the test specimen. Sufficient but not excessive contrast between the specimen and the mounting medium is required to ensure adequate detail of the specimen edge. The particles should rest in one plane and be adequately dispersed to distinguish individual particles of interest. Furthermore, the particles must be representative of the distribution of sizes in the material and must not be altered during preparation of the mount. Care should be taken to ensure that this important requirement is met. Selection of the mounting medium must include a consideration of the analyte solubility.

Crystallinity Characterization-The crystallinity of a material may be characterized to determine compliance with the crystallinity requirement where stated in the individual monograph of a drug substance. Unless otherwise specified in the individual monograph, mount a few particles of the specimen in mineral oil on a clean glass slide. Examine the mixture using a polarizing microscope: the particles show birefringence (interference colors) and extinction positions when the microscope stage is revolved.

Limit Test of Particle Size by Microscopy—Weigh a suitable quantity of the powder to be examined (for example, 10 to 100 mg ), and suspend it in 10 mL of a suitable medium in which the powder does not dissolve, adding, if necessary, a wetting agent. A homogeneous suspension of particles can be maintained by suspending the particles in a medium of similar or matching density and by providing adequate agitation. Introduce a portion of the homogeneous suspension into a suitable counting cell, and scan under a microscope an area corresponding to not less than $10 \mu \mathrm{~g}$ of the powder to be examined. Count all the particles having a maximum dimension greater than the prescribed size limit. The size limit and the permitted number of particles exceeding the limit are defined for each substance.

Particle Size Characterization-The measurement of particle size varies in complexity depending on the shape of the particle, and the number of particles characterized must be sufficient to ensure an acceptable level of uncertainty in the measured parameters. Additional information on particle size measurement, sample size, and data analysis is available, for example, in ISO 9276. For spherical particles, size is defined by the diameter. For irregular particles, a variety of definitions of particle size exist. In general, for irregularly shaped particles, characterization of particle size must also include information on the type of diameter measured as well as information on particle shape. Several commonly used measurements of particle size are defined below (see Figure 1):


Fig. 1. Commonly used measurements of particle size.

Feret's Diameter-The distance between imaginary parallel lines tangent to a randomly oriented particle and perpendicular to the ocular scale.

Martin's Diameter-The diameter of the particle at the point that divides a randomly oriented particle into two equal projected areas.

Projected area Diameter-The diameter of a circle that has the same projected area as the particle.

Length-The longest dimension from edge to edge of a particle oriented parallel to the ocular scale.

Width-The longest dimension of the particle measured at right angles to the length.

Particle Shape Characterization-For irregularly shaped particles, characterization of particle size must also include information on particle shape. The homogeneity of the powder should be checked using appropriate magnification. The following defines some commonly used descriptors of particle shape (see Figure 2):


Equant



Columnar


Plate


Fig. 2. Commonly used descriptions of particle shape.

Acicular-Slender, needle-like particle of similar width and thickness.

Columnar-Long, thin particle with a width and thickness that are greater than those of an acicular particle.

Flake-Thin, flat particle of similar length and width.
Plate-Flat particles of similar length and width but with greater thickness than flakes.

Lath-Long, thin, and blade-like particle.
Equant-Particles of similar length, width, and thickness; both cubical and spherical particles are included.

General Observations-A particle is generally considered to be the smallest discrete unit. A particle may be a liquid or semisolid droplet; a single crystal or polycrystalline; amorphous or an agglomerate. Particles may be associated. This degree of association may be described by the following terms:

Lamellar-Stacked plates.
Aggregate-Mass of adhered particles.

Agglomerate-Fused or cemented particles.
Conglomerate-Mixture of two or more types of particles.

Spherulite-Radial cluster.
Drusy-Particle covered with tiny particles.
Particle condition may be described by the following terms:

Edges-Angular, rounded, smooth, sharp, fractured.
Optical-Color (using proper color-balancing filters), transparent, translucent, opaque.

Defects-Occlusions, inclusions.
Surface characteristics may be described as:
Cracked-Partial split, break, or fissure.
Smooth-Free of irregularities, roughness, or projections.
Porous-Having openings or passageways.
Rough-Bumpy, uneven, not smooth.
Pitted-Small indentations.■2S (USP28)

## Briefing

<786〉 Particle Size Distribution Estimation by Analytical Sieving, USP 27 page 2335 and page 1581 of $P F 28(5)$ [Sept.Oct. 2002]. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of compendial standards for this chapter. The revisions presented in this proposal represents the ADOPTION STAGE 6 draft and have been accepted by the members of the Pharmacopeial Discussion Group. Major changes from the current USP General Chapter include the omission of the section on the Wet Sieving Method, because it is not adequate or practical for pharmaceutical powders. Other minor changes and editorial changes are included.
(ETM: J. Lane) RTS-41729-2

Change to read:

## 〈786) PARTICLE SIZE <br> DISTRIBUTION ESTIMATION BY ANALYTICAL SIEVING

Sieving is one of the oldest metheds of elassifying powders by particle size distribution. Sieving is most suitable where the major ity of the particles are larger than about $75 \mu \mathrm{~m}$, although it can be used for some powders having smaller particle sizes where the methed ean be validated. In pharmaceutical terms, sieving is usuat ly the methed of choiee for classifieation of the coarser grades of single powders. It is a partieularly attractive method in that pow ders are classiffed only on the basis of partiele-size, and in most eases the analysis can be carried out in the dry state-

Ameng the limitations of the sieving method are the need for an appreciable amount of sample (normally at least 25 g ) and diffient ty in sieving oily or other cohesive powders that tend to clog the
sieve openings. The method is essentially a dwo dimensional estimate of size because passage through the sieve aperture is frequent ly more dependent on maximum width and thiekness than on length.
This method is intended for estimation of the total partiele-size distribution of a single material. It is not intended for detemination of the propertion of partieles passing or retained on one-or two sieves.

Estimate the particle size distribution as described under Method I, unless otherwise specified in the individual menegraph. Method $I$ is the dry sieving method. Where diffieulty is experienced in reaching the endpeint (i.e., material doe not readily pass through the sieves) or when it is neeessary to use the finer end of the sieving fange (below $75 \mathrm{\mu m}$ ), Method II, which is a wet sieving technique, may be used; however, in the latter case serious consideration should be given to the use of an altemative partiele-sizing method.

Principles of Analytical-Sieving Analytical test sieves are eonstructed from a woven wire mesh, which is of simple weave that is assumed to give nearly square apertures and is sealed inte the base of an open cylindrieal container. The basic analytieal methed involves stacking the sieves on top of one another in as eending degrees of coarseness, and then placing the test powder on the top-sieve.

The nest of sieves is subjected to a standardized period of agitation, and then the weight of material retained on each sieve is ac eurately determined. The test gives the weight pereentage of powder in each sieve size range.

This sieving process for estimating the particle size distribution of a single pharmaentieal powder is generally intended for use where at least $80 \%$ of the partieles are larger than $75 \mu \mathrm{~m}$. The size parameter involved in determining particle size distribution by analytieal sieving is the length of the side fo the minimum square apexture through which the particle will pass.

## TEST SHEVES

Test sieves suitable for pharmacopeial tests conform to the most eurrent edition of International-Organization for Standardization Speciffeation ISO 3310-1: Test sieves Technieal requirements and Testing ${ }^{+}$(see Table 1). Unless otherwise speeified in the menograph, use these ISO sieves listed as principal sizes in Table 1.

[^365]Table 1. Sizes of Standard-Sieve-Series in-Range of Interest ${ }^{\mathbf{z}}$

| ISO Neminal Aperture |  |  | $\begin{aligned} & \text { US-Sieve } \\ & \text { No. } \\ & \hline \end{aligned}$ | Recemmended USP Sieves | Erropean Sieve Ne . | Japan Sieve No. |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Prineipalsizes R 2013 | $\begin{aligned} & \mathrm{Supp} \\ & \mathrm{R} 20^{\mathrm{sun}} \end{aligned}$ | sizes R-40/3 |  |  |  |  |
| 14.20 mm | $\begin{aligned} & 14.20 \mathrm{~mm} \\ & 10.00 \mathrm{~mm} \end{aligned}$ | 41.20 mm |  |  | 14200 |  |
|  |  | 9.50 mm |  |  |  |  |
| 8.00 mm | 9.00 mm |  |  |  |  |  |
|  | 8.00 mm | 8.00 mm |  |  |  |  |
|  | 7.10 mm | 6.70 mm |  |  |  |  |
| 5.60 mm | 6.30 mm |  |  |  |  |  |
|  | 5.60 mm | 5.60 mm |  |  | 5600 | 3.5 |
|  | 5.00 mm |  |  |  |  |  |
| 4.00 mm |  | 4.75 mm |  |  |  | 4 |
|  | 4.50 mm |  |  |  |  |  |
|  | 4.00 mm | 4.00 mm | 5 | 4000 | 4000 | 4.7 |
|  | 3.55 mm |  |  |  |  |  |
|  |  | 3.35 mm | 6 |  |  | 5.5 |
| 2.80 mm | 3.15 mm |  |  |  |  |  |
|  | 2.80 mm | 2.80 mm | 7 | 2800 | 2800 | 6.5 |
|  | 2.50 mm |  |  |  |  |  |
| 2.00 mm |  | 2.36 mm | 8 |  |  | 7.5 |
|  | 2.24 mm |  |  |  |  |  |
|  | 2.00 mm | 2.00 mm | 10 | 2000 | 2000 | 8.6 |
|  | 1.80 mm |  |  |  |  |  |
|  |  | 1.70 mm | 12 |  |  | 10 |
| 1.40 mm | 1.60 mm |  |  |  |  |  |
|  | 1.40 mm | 1.40 mm | 14 | 1400 | 1400 | 12 |
|  | 1.25 mm |  |  |  |  |  |
|  |  | 1.18 mm | 16 |  |  | 14 |
| 1.00 mm | 1.12 mm |  |  |  |  |  |
|  | 1.00 mm | 1.00 mm | 18 | 1000 | 1000 | 16 |
|  | $900 \mu \mathrm{~m}$ |  |  |  |  |  |
|  |  | 850 - mm | 20 |  |  | 48 |
| 710 - | $800 \mu \mathrm{~m}$ |  |  |  |  |  |
|  | $710 \mu \mathrm{~m}$ | $710 \mu \mathrm{~m}$ | 25 | 710 | 710 | 22 |
|  | $630 \mu \mathrm{~m}$ |  |  |  |  |  |
| $500 \mu \mathrm{~m}$ |  | $600 \mu \mathrm{~m}$ | 30 |  |  | 26 |
|  | 560 - |  |  |  |  |  |
|  | $500 \mathrm{\mu m}$ | $500-\mathrm{mm}$ | 35 | 500 | 500 | 30 |
|  | $450 \mathrm{\mu m}$ |  |  |  |  |  |
|  |  | $425 \mu \mathrm{~mm}$ | 40 |  |  | 36 |
| $355 \mu \mathrm{~m}$ | $400-\mathrm{mm}$ |  |  |  |  |  |
|  | $355 \mu \mathrm{~m}$ | $355 \mu \mathrm{~m}$ | 45 | 355 | 355 | 42 |
|  | $315 \mu \mathrm{~m}$ |  |  |  |  |  |
|  |  | $300 \mu \mathrm{~m}$ | 50 |  |  | 50 |
| $250 \mu \mathrm{~m}$ | 280 - mm |  |  |  |  |  |
|  | $250 \mu \mathrm{~m}$ | $250 \mu \mathrm{~m}$ | 69 | 250 | 250 | 69 |
|  | 224 ¢m | $212 \mu \mathrm{~m}$ | 70 |  |  | 70 |
| $180 \mu \mathrm{~m}$ | $200-\mu \mathrm{m}$ |  |  |  |  |  |
|  | 180 - $\mathrm{mm}^{\text {m }}$ | 180- mm | 80 | 180 | 180 | 83 |
|  | $160 \mu \mathrm{~m}$ |  |  |  |  |  |
| 125 $\mu \mathrm{m}$ |  | $150 \mu \mathrm{~m}$ | 100 |  |  | 100 |
|  | 140 ¢m |  |  |  |  |  |
|  | $125 \mathrm{\mu m}$ | $125 \mu \mathrm{~m}$ | 120 | 125 | 125 | 44 |
|  | 112 $\mu \mathrm{m}$ | $106 \mu \mathrm{~mm}$ | 140 |  |  | 140 |
| $90 \mu \mathrm{~m}$ |  |  |  |  |  |  |
|  | 90- mm | $90 \mu \mathrm{~m}$ | 170 | 98 | 98 | 166 |
|  | $80 \mu \mathrm{~m}$ |  |  |  |  |  |
|  |  | $75 \mu \mathrm{~m}$ | 200 |  |  | 200 |
| 63 mm | $\begin{aligned} & 71 \mathrm{\mu m} \\ & 63 \mathrm{\mu m} \end{aligned}$ | 63 mm | 230 | 63 | 63 | 235 |
|  | $\begin{aligned} & 63 \mu \mathrm{~m} \\ & 56 \mu \mathrm{~mm} \end{aligned}$ | $63 \mu \mathrm{~m}$ | 230 | 63 | 63 | 235 |
|  |  | 53 mm | 270 |  |  | 282 |
|  | $50 \mu \mathrm{~m}$ |  |  |  |  |  |

Fable 1. Sizes of Standard Sieve Series in-Range of Interest ${ }^{\text {r }}$ (Continued)

| ISO Neminal Aperture |  |  | US-Sieve No . | Recommended USP Sieves | Emropean Sieve Ne. | Japan Sieve No. |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Principal-sizes R20/3 | Supplementay sizes |  |  |  |  |  |
| $45 \mu \mathrm{~m}$ | $\begin{aligned} & 45 \mathrm{\mu m} \\ & 40 \mathrm{\mu m} \end{aligned}$ | 45 нm | 325 | 45 | 45 | 330 |
|  |  | 38 mm |  |  | 38 | 394 |

${ }^{2}$ The-speeifieations for standard sieves in Eurepe, Japan, and the US are all identieal to ISO-3310-1: 2000(E). The-lists-of Eurepean-and Japanese-standard sieves are included for informational purpeses.

Sieves are selected to cover the entire range of particle-sizes present in the test specimen. This nest of sieves is completed by a well fitting collecting pan at its base and lidat its top. Use mierometers or millimeters in denoting test sieve openings. [NOTE-Mesh nembers are provided in the table for conversion purposes only.] Test sieves are made from stainless steel or, less preferably, from brass or other suitable nomreactive wire.

Galibration and recalibration of test sieves is in accordance with the most current dition of ISO-3310-1. Sieves sheuld be careftlly examined for gross distortions and fractures, especially at their sereen frame joints, before use. Sieves may be ealibrated optieally to estimate the average opening size, and opening variability, of the sieve mesh. Altematively, for the evaluation of the effective opening of test sieves in the size range of 212 to $850 \mu \mathrm{~m}$, Standard Glass Spheres are available frem the National Institute of Standards and Fechnology as Standard Reference Material 1018. Unless other wise speciffed in the individual menograph, perform the sieve anat ysis at controlled room temperature and a relative humidity beven 20\% and 70\%.

Eleaning Test Sieves. Ideally, test sieves should be cleanedusing only an air jet or a liquid stream. If some apertures remain blocked by test particles, careful gentle brushing may be used as a last resort. Washing sieves in hot water is not recemmended since the sieve an distort and rupture during heating and cooling. If it is neeessary to use water, it should be used at ambient temperature and the sieve dried by first using a volatile water miscible-solvent to remove the water and then a low pressure air jet to remove the solvent. This procedure should be carried out in a fume hood or eabinet hat conforms to local regulations.

Test Specimen-If the test specimen weight is not given in the monegraph for a particular material, use a test specimen having a weight be 25 and 100 or , depending on the bulk density of the material, and test sieves haring a 200 mm diameter. Determine the most appropriate weight for a given material by test sieving aceurately weighed specimens of different weights, sueh as 25,50, and 100 g, for the same time period on a mechanieal shaker. [NOTE-If the test results are similar for the 25 -g and 50 - s speei mens, but the 100 s specimen shows a lower percentage through the finest sieve, the 100 हु specimen size is to large.] Where only $a$ specimen of 10 to 25 g is available, smaller diameter test sieves eonforming to the same ISO mesh specifieations may be substitut ed, but the endpeint must be redetermined.

If the test material is prone to pieking up-or losing significant amounts of water with varying humidity, the test must be carried out in an appropriately controlled envirenment. Similarly, if the test material is known to develop an electrostatic charge, carefut observation must be made to ensure that such charging is net in flueneing the analysis. If both of the above effeets cannot be eliminated, an alternative partiele-sizing technique must be selected.

Agitation Methods Use a mechanieal device that imparts et ther a retating tap ( 200 to 300 horizontal revolutions and 140 to 300 taps per minute) or vibratory ( 1 to 2 mm amplitude) motion to the sieves as the reference method of agitating test sieves, unless etherwise stated in the individual menograph. Methods utilizing entrainment of the parieles in an air stream may also be used. The results must indieate the ype sieving method used.
Endpoint Determination-The test sieving analysis is eomplete when the weight on any of the test sieves does not change by more than $5 \%$ ( $10 \%$ in the ease 76 mm sieves) of the previ eus weight on that sieve. If less than $5 \%$ of the total specimen weight is present on a given sieve, the endpeint for that sieve is increase to a weight change of not more than $20 \%$ of the previous weight on that sieve.

If mere than 50\% of the total specimen weight is found on any ene-sieve, the test should be repeated, but with the addition to the sieve nest of the nex coarsest sieve to that carying the exeessive weight, i.e., addition of the ISO series sieve omitted from the USP series in Table 1. Fer example, if mere than 50\% of the spec imen weight is found on the $180 \mu \mathrm{~m}$ sieve, the ISO $212 \mu \mathrm{~m}$ sieve should be placed be ween the 180 Hm and 250 رm sieves in the sieve nest.

## SHEVING METHODS

Method I (Dry Sieving Methed). Tare ench test sieve the nearest 0.1 g. Place an aceurately weighed quantity of test speei menon the top (coarsest) sieve, and replace the lid. Agitate the nest of sieves for 5 minutes. Then carefully remove from the nest without loss of material. Reweigh each sieve, and determine the weight of material on each sieve. Determine the weight of materiat in the colleeting pan in a similar manner. Reassemble the nest of sieves, and agitate for 5 minetes. Remove and weigh each sieve as previously described. Repeat these steps untill the endpoint eriteria are met (see Endpoint Determination under Test Sieves). Upen emmpletion of the analysis, reeoncile the weights of material. Totat lesses must not exceed $5 \%$ of the weight of the original test spec imen.

Repent the analysis with a fresh specimen, but using a single sieving time equal to that of the combined times used above. Con frm that this sieving time conforms to the requirements for end point determination. When this endpoint has been validated for a speeific material, then a single fixed time of sieving may be used for future analyses, providing the partiele size distribution does not ehange-signifiently.

If there is evidence that the particles retained on any sieve are aggregater rather than single particles, the use of dry sieving is un likely to give good reproducibility, and Methed II should be een sidered as one preferred teehnique.

MethodH(Wet Sieving Method) Modify the lid and colleet ing pan of the sieve nest to permit addition of a liquident the sur face of the top sieve and collection of the liquid from the pan. Dry a sufficient quantity of the test material to constant weight at a tem-
perature that will not have a detrimental effect on the material, e.g., if it is a solvate. Select a liquid in which the test specimen is insol uble, and modify the sieving method as indicated below. Ther eughly disperse the dried test material in the liquid by gentle agitation, and perm this dispersion ont the top sieve. Rinse the dis persion equipment with fresh liquid, and add the rinsings to the top sieve. Feed the sieving liquid through a suitable pumping mechafism the nozzle(s) in the lid, and collect the sieving liguid from the pan in a stitable container. Continte the wet sieving process until the emerging liquid appears free of partieles.

Remove ach sieve from the sieve nest, and dry each sieve-to eonstant weight at the same temperature as that used above. Deter mine the weight of dried material on each sieve.

Air Jet and-Sonie Sifter Sieving Differentypes of commer eial equipment that use moving air eurrent are available for siev ing. A system that uses a single sieve at a time is referred to as air je sieving. It uses the same general sieving methodology as that described under Method $I$, but with a standardized air jet replacing the nermal agitation mechanism. It requires sequential analyses on individual sieves to provide a partiele size distribution. This teehnique is more suitable where only oversize or undersize fractions are needed.

In the senic sifting method, a nest of sieves is used, and the test specimen is carried in a vertically oseillating column of air that lifts the specimen and then carries it back against the mesh openings at a given number of pulses per mintte. The air jet sieving and sonie sieving methods may be usefut when the standard dry and wet siev ing techniqutes are ineapable of giving a meaningful analysis.

These methods are highly dependent upen proper dispersion of the powder in the air current. This requirement may be hard to a ehieve if the methed is used at the lower end of the sieving range (i.e., below $75 \mu \mathrm{~m}$ ), when the particles tend to be more cohesive, and especially if there is any tendency for the material to develep an electrostatic charge. In the latter ease an antistatic agent, such as silicen dioxide or alumintmoxide, may be added at the $0.5 \%$ (wh W) level to minimize this effect. For the above reasons endpoint determination is particularly eritieal, and it is very important to eonflim that the oversize material is in fact single particles and is not composed of aggregates.

## INTERPRETATION

The raw data metst include the weight of test specimen, the total sieving time, and the precise-sieving methodology, in addition to the weights on the individtal sieves and in the pan. It may beent venient to convert the raw data into a cemmative weight distribut tion, and if it is desired to express the distribution in terms of a eumulative weight undersize, the range of sieves used should in elude a sieve through which all the material passes. If there is evi dence on any of the test sieves that the material remaining on it is ermposed of aggregates formed during the sieving process, the a malysis is invalid.

## 〈786〉 PARTICLE SIZE <br> DISTRIBUTION ESTIMATION BY ANALYTICAL SIEVING

Sieving is one of the oldest methods of classifying powders and granules by particle size distribution. When using a woven sieve cloth, the sieving will essentially sort the particles by their intermediate size dimension (i.e., breadth or width). Mechanical sieving is most suitable where the majority of the particles are larger than about $75 \mu \mathrm{~m}$. For smaller particles, the light weight provides insufficient force during sieving to overcome the surface forces of cohesion and adhesion that cause the particles to stick to each other and to the sieve, and thus cause particles that would be expected to pass through the sieve to be retained. For such materials other means of agitation such as air-jet sieving or sonic sifting may be more appropriate. Nevertheless, sieving can sometimes be used for some powders or granules having median particle sizes smaller than $75 \mu \mathrm{~m}$ where the method can be validated. In pharmaceutical terms, sieving is usually the method of choice for classification of the coarser grades of single powders or granules. It is a particularly attractive method in that powders and granules are classified only on the basis of particle size, and in most cases the analysis can be carried out in the dry state.

Among the limitations of the sieving method are the need for an appreciable amount of sample (normally at least 25 g , depending on the density of the powder or granule, and the diameter of test sieves) and difficulty in sieving oily or other cohesive powders or granules that tend to clog the sieve openings. The method is essentially a two-dimensional estimate of size because passage through the sieve aperture is frequently more dependent on maximum width and thickness than on length.

This method is intended for estimation of the total particle size distribution of a single material. It is not intended for determination of the proportion of particles passing or retained on one or two sieves.

Estimate the particle size distribution as described under Dry Sieving Method, unless otherwise specified in the individual monograph. Where difficulty is experienced in reaching the endpoint (i.e., material does not readily pass through the sieves) or when it is necessary to use the finer end of the sieving range (below $75 \mu \mathrm{~m}$ ), serious consideration should be given to the use of an alternative particle-sizing method.

Sieving should be carried out under conditions that do not cause the test sample to gain or lose moisture. The relative humidity of the environment in which the sieving is carried out should be controlled to prevent moisture uptake or loss by the sample. In the absence of evidence to the contrary, analytical test sieving is normally carried at ambient humidity. Any special conditions that apply to a particular material should be detailed in the individual monograph.

Principles of Analytical Sieving-Analytical test sieves are constructed from a woven-wire mesh, which is of simple weave that is assumed to give nearly square apertures and is sealed into the base of an open cylindrical container. The
basic analytical method involves stacking the sieves on top of one another in ascending degrees of coarseness, and then placing the test powder on the top sieve.

The nest of sieves is subjected to a standardized period of agitation, and then the weight of material retained on each sieve is accurately determined. The test gives the weight percentage of powder in each sieve size range.

This sieving process for estimating the particle size distribution of a single pharmaceutical powder is generally intended for use where at least $80 \%$ of the particles are larger than $75 \mu \mathrm{~m}$. The size parameter involved in determining particle size distribution by analytical sieving is the length of the side of the minimum square aperture through which the particle will pass.

## TEST SIEVES

Test sieves suitable for pharmacopeial tests conform to the most current edition of International Organization for Standardization Specification ISO 3310-1: Test SievesTechnical Requirements and Testing (see Table 1). Unless otherwise specified in the monograph, use those ISO sieves listed as principal sizes in Table 1. Unless otherwise specified in the monograph, use those ISO sieves listed in Table 1 as recommended in the particular region.

Table 1. Sizes of Standard Sieve Series in Range of Interest

| ISO Nominal Aperture |  |  |  | Recommended USP Sieves (mesh) | European <br> Sieve No. | Japan <br> Sieve No. |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Principal Sizes | Supplementary Sizes |  | US Sieve |  |  |  |
| R 20/3 | R 20 | R 40/3 | No. |  |  |  |
| 11.20 mm | 11.20 mm | 11.20 mm |  |  | 11200 |  |
|  | 10.00 mm |  |  |  |  |  |
|  |  | 9.50 mm |  |  |  |  |
|  | 9.00 mm |  |  |  |  |  |
| 8.00 mm | 8.00 mm | 8.00 mm |  |  |  |  |

Table 1. Sizes of Standard Sieve Series in Range of Interest (Continued)


Table 1. Sizes of Standard Sieve Series in Range of Interest (Continued)

| ISO Nominal Aperture |  |  | Recommended |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Principal Sizes | Supplementary Sizes |  | US Sieve <br> No. | USP Sieves (mesh) | European <br> Sieve No. | Japan <br> Sieve No |
| R 20/3 | R 20 | R 40/3 |  |  |  |  |
| $500 \mu \mathrm{~m}$ | $560 \mu \mathrm{~m}$ |  |  |  |  |  |
|  | $500 \mu \mathrm{~m}$ | $500 \mu \mathrm{~m}$ | 35 | 500 | 500 | 30 |
|  | $450 \mu \mathrm{~m}$ |  |  |  |  |  |
|  |  | $425 \mu \mathrm{~m}$ | 40 |  |  | 36 |
| $355 \mu \mathrm{~m}$ | $400 \mu \mathrm{~m}$ |  |  |  |  |  |
|  | $355 \mu \mathrm{~m}$ | $355 \mu \mathrm{~m}$ | 45 | 355 | 355 | 42 |
|  | $315 \mu \mathrm{~m}$ |  |  |  |  |  |
|  |  | $300 \mu \mathrm{~m}$ | 50 |  |  | 50 |
| $250 \mu \mathrm{~m}$ | $280 \mu \mathrm{~m}$ |  |  |  |  |  |
|  | $250 \mu \mathrm{~m}$ | $250 \mu \mathrm{~m}$ | 60 | 250 | 250 | 60 |
|  | $224 \mu \mathrm{~m}$ |  |  |  |  |  |
|  |  | $212 \mu \mathrm{~m}$ | 70 |  |  | 70 |
| $180 \mu \mathrm{~m}$ | $200 \mu \mathrm{~m}$ |  |  |  |  |  |
|  | $180 \mu \mathrm{~m}$ | $180 \mu \mathrm{~m}$ | 80 | 180 | 180 | 83 |
|  | $160 \mu \mathrm{~m}$ |  |  |  |  |  |
|  | $140 \mu \mathrm{~m} \quad 150 \mu \mathrm{~m}$ |  | 100 |  |  | 100 |
| $125 \mu \mathrm{~m}$ |  |  |  |  |  |  |
|  | $125 \mu \mathrm{~m}$ | $125 \mu \mathrm{~m}$ | 120 | 125 | 125 | 119 |
|  | $112 \mu \mathrm{~m}$ |  |  |  |  |  |
|  | $100 \mu \mathrm{~m}$ |  | 140 |  |  | 140 |
| $90 \mu \mathrm{~m}$ |  |  |  |  |  |  |
|  | $90 \mu \mathrm{~m}$ | $90 \mu \mathrm{~m}$ | 170 | 90 | 90 | 166 |
|  | $80 \mu \mathrm{~m}$ |  |  |  |  |  |
|  | $71 \mu \mathrm{~m}$ | $75 \mu \mathrm{~m}$ | 200 |  |  | 200 |
| $63 \mu \mathrm{~m}$ |  |  |  |  |  |  |
|  | $63 \mu \mathrm{~m}$ | $63 \mu \mathrm{~m}$ | 230 | 63 | 63 | 235 |
|  | $56 \mu \mathrm{~m}$ |  |  |  |  |  |
|  |  | $53 \mu \mathrm{~m}$ | 270 |  |  | 282 |
|  | $50 \mu \mathrm{~m}$ |  |  |  |  |  |
| $45 \mu \mathrm{~m}$ | $45 \mu \mathrm{~m}$ | $45 \mu \mathrm{~m}$ | 325 | 45 | 45 | 330 |

Table 1. Sizes of Standard Sieve Series in Range of Interest (Continued)

| ISO Nominal Aperture |  |  | Recommended |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Principal Sizes | Supplementary Sizes |  | US Sieve <br> No. | USP Sieves (mesh) | European <br> Sieve No. | Japan <br> Sieve No. |
| R 20/3 | R 20 | R 40/3 |  |  |  |  |
| $40 \mu \mathrm{~m}$ |  |  |  |  |  |  |
|  |  | $38 \mu \mathrm{~m}$ |  |  | 38 | 391 |

Sieves are selected to cover the entire range of particle sizes present in the test specimen. A nest of sieves having a $\sqrt{2}$ progression of the area of the sieve openings is recommended. The nest of sieves is assembled with the coarsest screen at the top and the finest at the bottom. Use micrometers or millimeters in denoting test sieve openings. [NOTEMesh numbers are provided in the table for conversion purposes only.] Test sieves are made from stainless steel or, less preferably, from brass or other suitable nonreactive wire.

Calibration and recalibration of test sieves is in accordance with the most current edition of ISO 3310-1. Sieves should be carefully examined for gross distortions and fractures, especially at their screen frame joints, before use. Sieves may be calibrated optically to estimate the average opening size, and opening variability, of the sieve mesh. Alternatively, for the evaluation of the effective opening of test sieves in the size range of 212 to $850 \mu \mathrm{~m}$, Standard Glass Spheres are available. Unless otherwise specified in the individual monograph, perform the sieve analysis at controlled room temperature and at ambient relative humidity.

Cleaning Test Sieves-Ideally, test sieves should be cleaned using only an air jet or a liquid stream. If some apertures remain blocked by test particles, careful gentle brushing may be used as a last resort.

Test Specimen-If the test specimen weight is not given in the monograph for a particular material, use a test specimen having a weight between 25 and 100 g , depending on the bulk density of the material, and test sieves having a $200-\mathrm{mm}$ diameter. For $76-\mathrm{mm}$ sieves, the amount of material that can be accomodated is approximately $1 / 7$ th that which can be accommodated on a $200-\mathrm{mm}$ sieve. Determine the most appropriate weight for a given material by test sieving accurately weighed specimens of different weights, such as 25,50 , and 100 g , for the same time period on a mechanical shaker. [NOTE--If the test results are similar for the $25-\mathrm{g}$ and $50-\mathrm{g}$ specimens, but the $100-\mathrm{g}$ specimen shows a lower percentage through the finest sieve, the $100-\mathrm{g}$ specimen size is too large.] Where only a specimen of 10 to 25 g is available, smaller diameter test sieves conforming to the same mesh specifications may be substituted, but the endpoint must be re-determined. The use of test samples having a smaller mass (e.g. down to 5 g ) may be needed. For materials with low apparent particle density, or for materials mainly comprising particles with a highly iso-diametrical shape, specimen weights below 5 g for a $200-\mathrm{mm}$ screen may be necessary to avoid excessive blocking of the sieve. During validation of a particular sieve analysis method, it is expected that the problem of sieve blocking will have been addressed.

If the test material is prone to picking up or losing significant amounts of water with varying humidity, the test must be carried out in an appropriately controlled environment. Similarly, if the test material is known to develop an electrostatic charge, careful observation must be made to ensure that such charging is not influencing the analysis. An antistatic agent, such as colloidal silicon dioxide and/or aluminum oxide, may be added at a 0.5 percent $(\mathrm{m} / \mathrm{m})$ level to minimize this effect. If both of the above effects cannot be eliminated, an alternative particle-sizing technique must be selected.

Agitation Methods-Several different sieve and powder agitation devices are commercially available, all of which may be used to perform sieve analyses. However, the different methods of agitation may give different results for sieve analyses and endpoint determinations because of the different types and magnitude of the forces acting on the individual particles under test. Methods using mechanical agitation or electromagnetic agitation, and that can induce either a vertical oscillation or a horizontal circular motion, or tapping or a combination of both tapping and horizontal circular motion are available. Entrainment of the particles in an air stream may also be used. The results must indicate which agitation method was used and the agitation parameters used (if they can be varied), since changes in the agitation conditions will give different results for the sieve analysis and endpoint determinations, and may be sufficiently different to give a failing result under some circumstances.

Endpoint Determination-The test sieving analysis is complete when the weight on any of the test sieves does not change by more than $5 \%$ or $0.1 \mathrm{~g}(10 \%$ in the case of $76-\mathrm{mm}$ sieves) of the previous weight on that sieve. If less than $5 \%$ of the total specimen weight is present on a given
sieve, the endpoint for that sieve is increased to a weight change of not more than $20 \%$ of the previous weight on that sieve.

If more than $50 \%$ of the total specimen weight is found on any one sieve, unless this is indicated in the monograph, the test should be repeated, but with the addition to the sieve nest of a more coarse sieve intermediate between that carrying the excessive weight and the next coarsest sieve in the original nest, i.e., addition of the ISO series sieve omitted from the nest of sieves.

## SIEVING METHODS

## Mechanical Agitation

Dry Sieving Method-Tare each test sieve to the nearest 0.1 g . Place an accurately weighed quantity of test specimen on the top (coarsest) sieve, and replace the lid. Agitate the nest of sieves for 5 minutes. Then carefully remove each from the nest without loss of material. Reweigh each sieve, and determine the weight of material on each sieve. Determine the weight of material in the collecting pan in a similar manner. Reassemble the nest of sieves, and agitate for 5 minutes. Remove and weigh each sieve as previously described. Repeat these steps until the endpoint criteria are met (see Endpoint Determination under Test Sieves). Upon completion of the analysis, reconcile the weights of material. Total losses must not exceed $5 \%$ of the weight of the original test specimen.

Repeat the analysis with a fresh specimen, but using a single sieving time equal to that of the combined times used above. Confirm that this sieving time conforms to the requirements for endpoint determination. When this endpoint has been validated for a specific material, then a single fixed
time of sieving may be used for future analyses, providing the particle size distribution falls within normal variation.

If there is evidence that the particles retained on any sieve are aggregates rather than single particles, the use of mechanical dry sieving is unlikely to give good reproducibility, a different particle size analysis method should be used.

## Air Entrainment Methods

Air Jet and Sonic Sifter Sieving—Different types of commercial equipment that use a moving air current are available for sieving. A system that uses a single sieve at a time is referred to as air jet sieving. It uses the same general sieving methodology as that described under the Dry Sieving Method, but with a standardized air jet replacing the normal agitation mechanism. It requires sequential analyses on individual sieves starting with the finest sieve to obtain a particle size distribution. Air jet sieving often includes the use of finer test sieves than used in ordinary dry sieving. This technique is more suitable where only oversize or undersize fractions are needed.

In the sonic sifting method, a nest of sieves is used, and the test specimen is carried in a vertically oscillating column of air that lifts the specimen and then carries it back against the mesh openings at a given number of pulses per minute. It may be necessary to lower the sample amount to 5 g , when sonic sifting is employed.

The air jet sieving and sonic sieving methods may be useful for powders or granules when mechanical sieving techniques are incapable of giving a meaningful analysis.
These methods are highly dependent upon proper dispersion of the powder in the air current. This requirement may be hard to achieve if the method is used at the lower end of the sieving range (i.e., below $75 \mu \mathrm{~m}$ ), when the particles tend to be more cohesive, and especially if there is any tendency for the material to develop an electrostatic charge. For the above reasons endpoint determination is particularly critical, and it is very important to confirm that the oversize material comprises single particles and is not composed of aggregates.

## INTERPRETATION

The raw data must include the weight of test specimen, the total sieving time, and the precise sieving methodology and the set values for any variable parameters, in addition to the weights retained on the individual sieves and in the pan. It may be convenient to convert the raw data into a cumulative weight distribution, and if it is desired to express the distribution in terms of a cumulative weight undersize, the range of sieves used should include a sieve through which all the material passes. If there is evidence on any of the test sieves that the material remaining on it is composed of aggregates formed during the sieving process, the analysis is invalid. $\mathbf{m S S}_{\text {(USP28) }}$

## GENERAL CHAPTERS

## General Information

## BriEFING

〈1174〉 Powder Flow，page 618 of PF 28（2）［Mar．－Apr．2002］． The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of compendial standards for this chapter．The revisions presented in this proposal represent the ADOPTION STAGE 6 draft and have been accepted by the members of the Pharmacopeial Discussion Group．Several modifi－ cations of the Stage 4 text are made．The text is modified to allow for use of density values to calculate the Compressibility Index and Hausner Ratio，where these may be available or more conveniently measured．ASTM standards are replaced with ISO standards to promote global harmonization．The Conclusions section is omit－ ted．Other minor changes and editorial changes are included．
（ETM：J．Lane）RTS－41729－1

## Add the following：

## 〈1174〉 POWDER FLOW

The widespread use of powders in the pharmaceutical in－ dustry has generated a variety of methods for characterizing powder flow．Not surprisingly，scores of references appear in the pharmaceutical literature，attempting to correlate the various measures of powder flow to manufacturing proper－ ties．The development of such a variety of test methods was inevitable；powder behavior is multifaceted and thus com－ plicates the effort to characterize powder flow．The purpose of this chapter is to review the methods for characterizing powder flow that have appeared most frequently in the phar－maceutical literature．In addition，while it is clear that no single and simple test method can adequately character－ ize the flow properties of pharmaceutical powders，this chapter proposes the standardization of test methods that may be valuable during pharmaceutical development．

Four commonly reported methods for testing powder flow are（1）angle of repose，（2）compressibility index or Hausner ratio，（3）flow rate through an orifice，and（4）shear cell．In addition，numerous variations of each of these basic meth－ ods are available．Given the number of test methods and var－ iations，standardizing the test methodology，where possible， would be advantageous．

With this goal in mind，the most frequently used methods are discussed below．Important experimental considerations are identified and recommendations are made regarding standardization of the methods．In general，any method of measuring powder flow should be practical，useful，repro－ ducible，sensitive，and yield meaningful results．It bears re－ peating that no one simple powder flow method will adequately or completely characterize the wide range of flow properties experienced in the pharmaceutical industry． An appropriate strategy may well be the use of multiple standardized test methods to characterize the various aspects of powder flow as needed by the pharmaceutical scientist．

## ANGLE OF REPOSE

The angle of repose has been used in several branches of science to characterize the flow properties of solids．Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles．Angle of re－ pose test results are reported to be very dependent upon the method used．Experimental difficulties arise as a result of segregation of material and consolidation or aeration of the powder as the cone is formed．Despite its difficulties， the method continues to be used in the pharmaceutical in－ dustry，and a number of examples demonstrating its value in predicting manufacturing problems appear in the litera－ ture．

The angle of repose is the constant, three-dimensional angle (relative to the horizontal base) assumed by a cone-like pile of material formed by any of several different methods (described briefly below).

## Basic Methods for Angle of Repose

A variety of angle of repose test methods are described in the literature. The most common methods for determining the static angle of repose can be classified on the basis of the following two important experimental variables:
(1) The height of the "funnel" through which the powder passes may be fixed relative to the base, or the height may be varied as the pile forms.
(2) The base upon which the pile forms may be of fixed diameter or the diameter of the powder cone may be allowed to vary as the pile forms.

## Variations in Angle of Repose Methods

In addition to the above methods, the following variations have been used to some extent in the pharmaceutical literature:

- Drained angle of repose is determined by allowing an excess quantity of material positioned above a fixed diameter base to "drain" from the container. Formation of a cone of powder on the fixed diameter base allows determination of the drained angle of repose.
- Dynamic angle of repose is determined by filling a cylinder (with a clear, flat cover on one end) and rotating it at a specified speed. The dynamic angle of repose is the angle (relative to the horizontal) formed by the flowing powder. The internal angle of kinetic friction is defined by the plane separating those particles sliding down the top layer of the powder and those particles that are rotating with the drum (with roughened surface).


## Angle of Repose General Scale of Flowability

Although there is some variation in the qualitative description of powder flow using the angle of repose, much of the pharmaceutical literature appears to be consistent with the classification by Carr*, which is shown in Table 1. There are examples in the literature of formulations with an angle of repose in the range of $40^{\circ}$ to $50^{\circ}$ that were manufactured satisfactorily. When the angle of repose exceeds $50^{\circ}$, the flow is rarely acceptable for manufacturing purposes.

Table 1. Flow Properties and Corresponding Angles of Repose ${ }^{*}$

| Flow Property | Angle of Repose (degrees) |
| :--- | :---: |
| Excellent | $25-30$ |
| Good | $31-35$ |
| Fair-aid not needed | $36-40$ |
| Passable-may hang up | $41-45$ |
| Poor-must agitate, vibrate | $46-55$ |
| Very poor | $56-65$ |
| Very, very poor | $>66$ |

## Experimental Considerations for Angle of Repose

Angle of repose is not an intrinsic property of the powder; i.e., it is very much dependent upon the method used to form the cone of powder. The following important considerations are raised in the existing literature:

- The peak of the cone of powder can be distorted by the impact of powder from above. By carefully building the powder cone, the distortion caused by impact can be minimized.
- The nature of the base upon which the powder cone is formed influences the angle of repose. It is recommended that the powder cone be formed on a "common

[^366]base," which can be achieved by forming the cone of powder on a layer of powder. This can be done by using a base of fixed diameter with a protruding outer edge to retain a layer of powder upon which the cone is formed.

## Recommended Procedure for Angle of Repose

Form the angle of repose on a fixed base with a retaining lip to retain a layer of powder on the base. The base should be free of vibration. Vary the height of the funnel to carefully build up a symmetrical cone of powder. Care should be taken to prevent vibration as the funnel is moved. The funnel height should be maintained approximately $2-4 \mathrm{~cm}$ from the top of the powder pile as it is being formed in order to minimize the impact of falling powder on the tip of the cone. If a symmetrical cone of powder cannot be successfully or reproducibly prepared, this method is not appropriate. Determine the angle of repose by measuring the height of the cone of powder and calculating the angle of repose, $\alpha$, from the following equation:

$$
\tan (\alpha)=\frac{\text { height }}{0.5 \text { base }}
$$

## COMPRESSIBILITY INDEX AND HAUSNER RATIO

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index. The com-
pressibility index and the Hausner ratio are determined by measuring both the bulk volume and the tapped volume of a powder.

## Basic Methods for Compressibiity Index and Hausner <br> Ratio

Although there are some variations in the method of determining the compressibility index and Hausner ratio, the basic procedure is to measure (1) the unsettled apparent volume, $V_{o}$, and (2) the final tapped volume, $V_{f}$, of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner ratio are calculated as follows:

$$
\begin{aligned}
& \text { Compressibility Index }=100 \times\left(\frac{V_{o}-V_{f}}{V_{o}}\right) \\
& \text { Hausner Ratio }=\frac{V_{o}}{V_{f}}
\end{aligned}
$$

Alternatively, the compressibility index and Hausner ratio may be calculated using measured values for bulk density ( $\rho_{\text {bukk }}$ ) and tapped density ( $\rho_{\text {tapped }}$ ) as follows:

$$
\begin{aligned}
& \text { Compressibility Index }=100 \times\left(\frac{\rho_{\text {topped }}-\rho_{\text {bulk }}}{\rho_{\text {tupped }}}\right) \\
& \text { Hausner Ratio }=\left(\frac{\rho_{\text {topped }}}{\rho_{\text {bulk }}}\right)
\end{aligned}
$$

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to, the change in volume that occurs on tapping. For the compressibility index and the Hausner ratio, the generally accepted scale of flowability is given in Table 2*.

Table 2. Scale of Flowability*

| Compressibility <br> Index (\%) | Flow Character | Hausner Ratio |
| :---: | :---: | :---: |
| $\leq 10$ | Excellent | $1.00-1.11$ |
| $11-15$ | Good | $1.12-1.18$ |
| $16-20$ | Fair | $1.19-1.25$ |
| $21-25$ | Passable | $1.26-1.34$ |
| $26-31$ | Poor | $1.35-1.45$ |
| $32-37$ | Very poor | $1.46-1.59$ |
| $>38$ | Very, very poor | $>1.60$ |

## Experimental Considerations for the Compressibility Index and Hausner Ratio

Compressibility index and Hausner ratio are not intrinsic properties of the powder; i.e., they depend on the methodology used. In the existing literature, there are discussions of the following important considerations affecting the determination of (1) the unsettled apparent volume, $V_{o}$, (2) the final tapped volume, $V_{f}$, (3) the bulk density, $\rho_{\text {bulk }}$, and (4) the tapped density, $\rho_{\text {tupped }}$ :

- The diameter of the cylinder used
- The number of times the powder is tapped to achieve the tapped density
- The mass of material used in the test
- Rotation of the sample during tapping


## Recommended Procedure for Compressibility Index and Hausner Ratio

Use a $250-\mathrm{mL}$ volumetric cylinder with a test sample weight of 100 grams. Smaller weights and volumes may be used, but variations in the method should be described with the results. An average of three determinations is recommended.

## FLOW THROUGH AN ORIFICE

The flow rate of a material depends upon many factors, some of which are particle-related and some related to the process. Monitoring the rate of flow of material through an orifice has been proposed as a better measure of powder flowability. Of particular significance is the utility of monitoring flow continuously because pulsating flow patterns have been observed even for free flowing materials. Changes in flow rate as the container empties can also be observed. Empirical equations relating flow rate to the diameter of the opening, particle size, and particle density have been determined. However, determining the flow rate through an orifice is useful only with free-flowing materials.
The flow rate through an orifice is generally measured as the mass per time flowing from any of a number of types of containers (cylinders, funnels, hoppers). Measurement of the flow rate can be in discrete increments or continuous.

## Basic Methods for Flow Through an Orifice

There are a variety of methods described in the literature.
The most common method for determining the flow rate through an orifice can be classified on the basis of three important experimental variables:
(1) The type of container used to contain the powder. Common containers are cylinders, funnels, and hoppers from production equipment.
(2) The size and shape of the orifice used. The orifice diameter and shape are critical factors in determining powder flow rate.
(3) The method of measuring powder flow rate. Flow rate can be measured continuously using an electronic balance with some sort of recording device (strip chart recorder, computer). It can also be measured in discrete samples (for example, the time it takes for 100 grams
of powder to pass through the orifice to the nearest tenth of a second or the amount of powder passing through the orifice in 10 seconds to the nearest tenth of a gram).

## Variations in Methods for Flow Through an Orifice

Either mass flow rate or volume flow rate can be determined. Mass flow rate is the easier of the methods, but it biases the results in favor of high-density materials. Because die fill is volumetric, determining volume flow rate may be preferable. A vibrator is occasionally attached to facilitate flow from the container; however, this appears to complicate interpretation of the results. A moving orifice device has been proposed to more closely simulate rotary press conditions. The minimum diameter orifice through which powder flows can also be identified.

## General Scale of Flowability for Flow Through an

 OrificeNo general scale is available because flow rate is critically dependent on the method used to measure it. Comparison between published results is difficult.

## Experimental Considerations for Flow Through an Orifice

Flow rate through an orifice is not an intrinsic property of the powder. It very much depends on the methodology used. Several important considerations affecting these methods are discussed in the existing literature:

- The diameter and shape of the orifice
- The type of container material (metal, glass, plastic)
- The diameter and height of the powder bed.


## Recommended Procedure for Flow Through an Orifice

Flow rate through an orifice can be used only for materials that have some capacity to flow. It is not useful for cohesive materials. Provided that the height of the powder bed (the "head" of the powder) is much greater than the diameter of the orifice, the flow rate is virtually independent of the powder head. Use a cylinder as the container because the cylinder material should have little effect on flow. This configuration results in flow rate being determined by the movement of powder over powder rather than powder along the wall of the container. Powder flow rate often increases when the height of the powder column is less than two times the diameter of the column. The orifice should be circular and the cylinder should be free of vibration. General guidelines for dimensions of the cylinder are as follows:

- Diameter of opening $>6$ times the diameter of the particles
- Diameter of the cylinder $>2$ times the diameter of the opening

Use of a hopper as the container may be appropriate and representative of flow in a production situation. It is not advisable to use a funnel, particularly one with a stem, because flow rate will be determined by the size and length of the stem as well as the friction between the stem and the powder. A truncated cone may be appropriate, but flow will be influenced by the powder-wall friction coefficient, making selection of an appropriate construction material an important consideration.

For the opening in the cylinder, use a flat-faced bottom plate with the option to vary orifice diameter to provide maximum flexibility and to better ensure a powder-overpowder flow pattern. Rate measurement can be either discrete or continuous. Continuous measurement using an electronic balance can more effectively detect momentary flow rate variations.

## SHEAR CELL METHODS

In an effort to put powder flow studies and hopper design on a more fundamental basis, a variety of powder shear testers and methods that permit more thorough and precisely defined assessment of powder flow properties have been developed. Shear cell methodology has been used extensively in the study of pharmaceutical materials. From these methods, a wide variety of parameters can be obtained, including the yield loci representing the shear stress-shear strain relationship, the angle of internal friction, the unconfined yield strength, the tensile strength, and a variety of derived parameters such as the flow factor and other flowability indices. Because of the ability to more precisely control experimental parameters, flow properties can also be determined as a function of consolidation load, time, and other environmental conditions. The methods have been successfully used to determine critical hopper and bin parameters.

## Basic Methods for Shear Cell

One type of shear cell is the cylindrical shear cell that is split horizontally, forming a shear plane between the lower stationary base and the upper moveable portion of the shear cell ring. After powder bed consolidation in the shear cell (using a well-defined procedure), the force necessary to shear the powder bed by moving the upper ring is determined. Annular shear cell designs offer some advantages over the cylindrical shear cell design, including the need
for less material. A disadvantage, however, is that because of its design, the powder bed is not sheared as uniformly; i.e., material on the outside of the annulus is sheared more than material in the inner region. A third type of shear cell (plate-type) consists of a thin sandwich of powder between a lower stationary rough surface and an upper rough surface that is moveable.

All of the shear cell methods have their advantages and disadvantages, but a detailed review is beyond the scope of this chapter. As with the other methods for characterizing power flow, many variations are described in the literature. A significant advantage of shear cell methodology in general is a greater degree of experimental control. The methodology is rather time-consuming and requires significant amounts of material and a well-trained operator.

## Recommendations for Shear Cell

The many existing shear cell configurations and test methods provide a wealth of data and can be used very effectively to characterize powder flow. They are also helpful in the design of equipment such as hoppers and bins. Because of the diversity of available equipment and experimental procedures, no specific recommendations regarding methodology are presented in this chapter. It is recommended that the results of powder flow characterization using shear cell methodology include a complete description of equipment and methodology used. $\mathbf{m S S}_{\text {(USP28) }}$

## PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the Staff Directory to find the contact information).

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PHARMACOPEIAL PREVIEWS ..... 2233
GENERAL CHAPTERS ..... 2235
$\langle 729\rangle$ Globule Size Distribution in Lipid Injectable Emulsions [new] ..... 2235

## GENERAL CHAPTERS

# General Tests and Assays <br> Physical Tests and Determinations 

## BRIEFING


#### Abstract

〈729〉 Globule Size Distribution in Lipid Injectable Emul－ sions．This proposed new general chapter is being previewed here to address the complex methods for analyzing globule size distri－ bution（see the Stimuli article，Examination of Selection of Light－ Scattering and Light－Obscuration Acceptance Criteria for Lipid Injectable Emulsions，in this issue of PF）．Importantly，the mean droplet size must be submicron in size，while the population of large－diameter fat globules，expressed as the percentage of fat greater than 5 micrometers（i．e．，PFAT5），must be kept at a mini－ mum to avoid obstruction of the microvasculature，particularly the capillaries of the lungs．Therefore，these two regions of the globule size distribution（mean droplet size and large－diameter tail）must be controlled within specified limits．

It is proposed that two methods be employed for testing．Method $I$ via classical（＂Mie＂）or dynamic light scattering will be designa－ ted for the mean diameter of the lipid droplets，and the range of the various droplet diameters distributed around the mean diameter， expressed as the standard deviation．Method II（light obscuration） will be designated for determining the amounts of fat globules comprising the large－diameter tail of the globule size distribution．

The publication of revised monographs for Lipid Injectable Emulsion and Egg Phospholipids（see page 401 of PF 29（2） ［Mar．－Apr．2003］）are forthcoming following the Expert Commit－ tee meeting in October 2004.


（PPI：J．Kelly）RTS－41733－1

Add the following：

〈729〉 GLOBULE SIZE
DISTRIBUTION IN LIPID
INJECTABLE EMULSIONS

## INTRODUCTION

Lipid injectable emulsions used in total parenteral nutri－ tion（TPN）therapy are sterile oil－in－water emulsions of soy－ bean oil，used to provide an ample supply of essential fatty acids，linoleic and linolenic，dispersed with the aid of an emulsifying agent in Water for Injection．Alternatively，soy－ bean oil can be mixed with other suitable oils（neutral trigly－ cerides），such as safflower oil，medium－chain triglycerides （MCT）derived from coconut or palm kernal oils，olive oil，or a marine oil，such as menhaden oil．The size of the lipid droplets is critical：because of mechanical filtration， larger－size fat globules（ $>5 \mu \mathrm{~m}$ ）can be trapped in the lungs． The essential size characteristics of a lipid injectable emul－ sion for intravenous use includes the mean diameter of the lipid droplets and the range of the various droplet diameters distributed around the mean diameter，expressed as the stan－ dard deviation．In particular，the amounts of fat globules comprising the large－diameter tail of the globule size distri－ bution are especially important with respect to infusion safe－ ty．These two regions of the globule size distribution（mean droplet size and large－diameter tail）must be controlled with－ in specified limits．

The two methods described below are used for determina－ tion of the mean lipid droplet diameter and the distribution of large－diameter globule sizes in Lipid Injectable Emulsion． These methods must be employed for testing，following the requirements specified in the limits summarized in Lipid In－ jectable Emulsion（to come）．Method I and Method II must
be validated. The methods described below to assess the quality of lipid injectable emulsions are to be performed in two stages.

## METHOD I—LIGHT-SCATTERING METHOD

For the determination of the mean droplet size of lipid injectable emulsions, either of two common light-scattering techniques may be employed: (1) dynamic light scattering (DLS), also known as photon correlation spectroscopy (PCS), or (2) classical light scattering, based on Mie scattering theory. The DLS, or PCS, technique is based on analyzing the rapid temporal fluctuations in the scattered light intensity that occur due to the random Brownian motion, or diffusion, of any particles, including lipid droplets, suspended in liquid. The intensity is measured at a given angle (usually $90^{\circ}$ ) by a suitable detector (e.g., photomultiplier tube), able to measure the rapidly fluctuating scattered light intensity produced by the suspended, diffusing droplets. These scattered intensity data are typically used to calculate the intensity autocorrelation function, which is a simple decaying exponential function in time for droplets of uniform size. A distribution of droplet sizes expresses itself by exponential functions of different decay times. The autocorrelation function generated by the scattered intensity data obtained from a given emulsion can be "inverted" by means of an appropriate deconvolution algorithm, in order to obtain the approximate distribution of intensity-weighted diffusion coefficients. From the latter, the distribution of smalldiameter droplets is calculated, using the Stokes-Einstein equation and the rules of classical (Mie) light scattering.
By contrast, classical light scattering based on Mie theory analyzes the spatial, rather than temporal, variation of the scattered light intensity, by measuring the latter as a function of the scattering angle, typically over a large range of detected angles. The temporal fluctuations in the scattering inten-
sity due to Brownian motion are averaged out in time for each angular measurement. This angular variation occurs as a consequence of the mutual interference of individual scattered waves arriving at the detector with different phases from different points within a given lipid droplet, as well as from different particles. The extent of the angular variation is significant whenever the droplet diameter is not small compared with the wavelength of the laser light (typically 635 nm ). Droplets of a given size and refractive index yield a unique curve of scattering intensity vs. angle. A distribution of droplet sizes gives rise to a final angular dependence that represents the superposition, or summation, of individual (different) intensity vs. angle curves. The measured angular dependence of the scattering intensity obtained from a given emulsion sample can be inverted by means of an appropriate deconvolution algorithm and Mie scattering theory, in order to obtain the approximate droplet size distribution.

Thus, light scattering, using either dynamic light scattering (i.e., temporal fluctuations due to droplet diffusion) or classical light scattering/Mie theory (i.e., average intensity vs. angle), can provide acceptable results for both the mean diameter and standard deviation of the droplet size distribution. For purposes of illustrating the method used in Method $I$, a dynamic light-scattering technique is described. For guidance regarding instruments employing classical Mietheory light scattering, see Light Diffraction Measurement of Particle Size $\langle 429\rangle$.

Apparatus-A suitable DLS/PCS instrument with or without the capability of automatic sample dilution is controlled by validated software and is used to perform the measurement with the scattering angle typically set at $90^{\circ}$. The intensity-weighted results (mean diameter and standard de-
viation) are reported, provided it is clearly stated which values are given and that the necessary parameter values required for all requisite calculations are also given.

Water-Pass distilled water through a filter having a 0.2 $\mu \mathrm{m}$ porosity, and degas by sonication, or use Sterile Water for Injection stored in a glass container.

Standard Preparation-To a pre-established volume of Water add an appropriate amount of concentrated suspension, containing NIST-traceable polystyrene latex standard particles or other suitable nanospheres. Gently mix the fluids to achieve a homogeneous suspension. The diluted suspension will be slightly turbid in appearance. If the DLS/ PCS instrument is equipped with an automatic dilution system, the starting concentrated sample can be analyzed by injection directly into the instrument via a syringe, with further dilution occurring automatically to optimize the droplet concentration for analysis. Alternatively, the sample would require greater manual dilution with Water (typically by at least a factor of 10 over the first dilution), and then this sample is instilled into a "drop-in" cuvette. The optimum dilution scheme that achieves the proper scattering intensity for the cuvette-based analysis will be determined by the instrument specifications. Thus, the concentration of latex in the final sample must be optimized for the DLS/PCS instrument used. This should be performed separately for three different size standards of approximately 100, 250, and 400 nm (triplicate analyses per size), and the corresponding results of intensity-weighted mean diameter and standard deviation should coincide with the expected values within acceptable errors.

Test Preparation-To a pre-established volume of Water add an appropriate volume of sample from the lipid injectable emulsion. Gently mix the fluids to achieve a homogeneous suspension. The diluted suspension will be slightly turbid in appearance. Gently mix the fluids. If the DLS/

PCS instrument is equipped with an automatic dilution system, the starting concentrated sample can be analyzed by injection directly into the instrument via a syringe. Further dilution of the sample then occurs automatically to optimize the droplet concentration for analysis, ensuring that it is not so high as to cause artifacts due to multiple scattering or interdroplet interactions. Alternatively, the sample would require greater manual dilution with water (typically by at least a factor of 10 over the first dilution), and then this sample is instilled into a "drop-in" cuvette. The optimum dilution scheme that achieves the proper scattering intensity for the cuvette-based analysis will be determined by the instrument specifications. Thus, the concentration of lipid injectable emulsion in the final sample must be optimized for the DLS/PCS instrument used.

System Suitability-Using the Standard Preparation, measure the intensity-weighted mean particle diameter and the corresponding standard deviation. The system is suitable once the sample temperature has reached equilibration and the results have stabilized and triplicate mean droplet diameter measurements are obtained within $15 \%$ of each other. The coefficient of variation (CV) should not exceed $20 \%$ of the NIST-traceable mean droplet diameter. A larger CV value indicates that the latex microspheres are not suitable as a standard because they either inherently lack uniformity or have become agglomerated to an unacceptable extent. In this case, another standard latex suspension must be selected and tested.

Procedure and Interpretation-If the DLS/PCS instrument is equipped with an automatic dilution system, use a disposable syringe to load the Standard Preparation or Test Preparation. If no automatic dilution system is used, transfer the appropriately diluted preparation to a cuvette and place the cuvette in the spectrometer. Allow the sample to equilibrate to a preset controlled temperature close to ambi-
ent (between $20^{\circ}$ and $25^{\circ}$ as per the USP definition found in the General Notices under Preservation, Packaging, Storage, and Labeling). Set the instrument scattering angle to $90^{\circ}$, and carry out the measurements. As long as the chisquared ( $\chi^{2}$ ) goodness-of-fit parameter remains acceptably low (per instrument specifications), the results for the Test Preparation are acceptable. Excessive values of chi-squared parameter suggest that the droplet distribution is not normal and may indicate an unstable emulsion. The following in-tensity-weighted, mean droplet diameter (MDD) limits for lipid injectable emulsions of various concentrations must be met:

Concentration of Dispersed Phase (\% w/v)

|  | 10 | 20 | 30 |
| :---: | :---: | :---: | :---: |
| MDD (nm) | $<300$ | $<400$ | $<500$ |

## METHOD II-LIGHT OBSCURATION OR EXTINCTION METHOD

For determination of the extent of the large-diameter droplet tail ( $>5 \mu \mathrm{~m}$ ) of lipid injectable emulsions a light obscuration (LO) or light extinction (LE) method that employs a single-particle (globule) optical sizing (SPOS) technique is used. During application of the LE/SPOS technique, passage of a droplet through a thin optical sensing zone, results in blockage of a portion of the incident light beam, causing a momentary decrease in the light intensity reaching the "extinction" detector. The magnitude of this decrease in the signal is ideally proportional to the cross-sectional area of the droplet (assumed smaller than the sensing zone thickness), i.e., to the square of the droplet diameter. As long as the fat globule concentration is below the "coincidence limit" of the sensor (determined by the flow cell and optical design), only one globule at most will pass through the sensing zone at any given time, allowing it
to be counted and accurately sized (with less than $1 \%$ coincidence events). Both the coincidence limit and the optimal flow rate must be known for the LE/SPOS sensor used. Furthermore, it is prudent to perform the large-diameter measurements at a reduced emulsion concentration, such that the measurable droplet concentration (i.e., $>1.8 \mu \mathrm{~m}$ ) is only approximately $1 / 3$ of the nominal coincidence limit for the sensor utilized. The resulting single pulse heights are converted to droplet diameters using a standard calibration curve previously constructed from NIST-traceable monosized polystyrene microspheres of known diameters. For additional guidance in the use of the light obscuration methodology, see the general chapter Particulate Matter in Injections $\langle 788\rangle$.

Apparatus-A suitable light obscuration instrument with or without the capability of automatic sample dilution and controlled by a personal computer (PC) is used for the measurement. The number- and volume-weighted particle size distribution data are reported, provided it is clearly stated which values are given and that the necessary parameter values required for all necessary calculations are also given.

Water-Pass distilled water through a filter having a 0.2 $\mu \mathrm{m}$ porosity, and degas by sonication, or use Sterile Water for Injection stored in a glass container.

Standard Preparation-To a pre-established volume of Water add an appropriate amount of concentrated suspension, containing NIST-traceable polystyrene latex standard particles or other suitable microspheres. Gently mix the fluids to achieve a homogeneous suspension. If the light obscuration instrument is equipped with an automatic dilution system, the starting concentrated sample can be analyzed by injection directly into the instrument via a syringe or Teflon ${ }^{\circledR}$ sample line. Further dilution of the sample then occurs automatically to optimize the particle concentration for analysis. Alternatively, the sample would require
greater manual dilution with water (typically by at least a factor of 10 over the first dilution). The resulting diluted sample is then instilled in an appropriate, clean container, such as a sterile Type I glass container prior to being passed through the sensor. In either case the final particle concentration is caused to lie below the coincidence limit of the sensor. The sizing and counting accuracy of the light obscuration instrument should be obtained using three different size standards of approximately $5 \mu \mathrm{~m}, 10 \mu \mathrm{~m}$, and $25 \mu \mathrm{~m}$ (triplicate analyses per size). The corresponding results for the mean diameter should coincide with the expected values, within a $10 \%$ acceptable error. In addition, the number of particle counts obtained per unit volume of diluted sample suspension should also agree, within a $10 \%$ acceptable error, of the concentration values certified in the documentation provided with each NIST-traceable size standard.

Test Preparation-To a pre-established volume of Water add an appropriate volume of sample from the lipid injectable emulsion. Gently mix the fluids to achieve a homogeneous suspension. The diluted emulsion will be slightly turbid in appearance. If the light obscuration instrument is equipped with an automatic dilution system, the starting concentrated sample can be analyzed by injection directly into the instrument via a syringe or non-reactive ${ }^{*}$ Teflon ${ }^{\circledR}$ sample line. Further dilution then occurs automatically to optimize the droplet/globule concentration for analysis. Alternatively, the sample would require greater manual dilution with water (typically by at least a factor of 10 over the first dilution). The resulting diluted sample is then instilled in an appropriate, clean container such as a sterile Type I glass container. In either case the final droplet/globule concentration is caused to lie below the coincidence limit of the sensor.

[^367]System Suitability-Using the Standard Preparation, measure the number-weighted particle diameter and the corresponding standard deviation. The system is suitable once the sample has equilibrated and the results have stabilized and triplicate mean number-weighted particle diameter measurements are obtained within $10 \%$ of each other. The measured coefficient of variation (CV) for the number-weighted particle size distribution should not deviate by more than $25 \%$ from the CV value stipulated for the NIST-traceable standard. The latter value is usually very small, assuming nearly uniform-size standard particles. Therefore, in practice the measured CV value is usually considerably larger than this ideal value, being dictated instead by the resolution of the LE/SPOS sensor. The resolution of the sensor should be sufficiently good that the measured CV value not exceed $15 \%$ of the mean diameter of the NIST-traceable standard. A larger CV value indicates that the latex microspheres are not suitable as a standard because they either inherently lack uniformity or have become agglomerated to an unacceptable extent. In this case, another standard latex suspension must be selected and tested.

Procedure and Interpretation-If the light obscuration instrument is equipped with an automatic dilution system, use a disposable syringe or Teflon ${ }^{\circledR}$ sample line to load the Standard Preparation or Test Preparation. If no automatic dilution system is used, transfer the sample to an appropriate large-volume, clean container such as a sterile Type I glass vessel containing an appropriate volume of Water. Allow the sample and Water to mix thoroughly, to achieve a homogeneous suspension. Set the instrument threshold of detection at $1.8 \mu \mathrm{~m}$, extended to an upper limit of $50 \mu \mathrm{~m}$, and employ measurement times of 120, 180, and 240 seconds for each run of each replicate of the sample ( $n=3$ runs/sample). As long as the three measurements of the vol-ume-weighted percentage of fat greater than 5 micrometers
(PFAT5) for each sample fall within $10 \%$ of each other (irrespective of run time), the results for the Test Preparation are acceptable. Values exceeding this reproducibility tolerance suggest that the sample is either unstable or the dilution has not been optimized. The volume-weighted, large-diam-
eter fat globule limits of the dispersed phase, expressed as the percentage of fat residing in globules larger than $5 \mathrm{mi}-$ crometers (PFAT5), for a given lipid injectable emulsion must be less than $0.05 \%$.

## STIMULI TO THE REVISION PROCESS

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# Examination of Selection of Light-Scattering and Light-Obscuration Acceptance Criteria for Lipid Injectable Emulsions 

David F. Driscoll, Ph.D.*


#### Abstract

The optimum methods for determining the physicochemical stability of lipid injectable emulsions have been extensively debated. USP first approached the subject as a Pharmacopeial Preview in 1991 under a proposed General Chapter $\langle 728\rangle$ Globule Size Distribution in Intravenous Emulsions. Since that time, there have been three In-Process Revisions (1994, 1995, and 1998). The newly proposed Chapter $\langle 729\rangle$ (see General Chapter $\langle 729\rangle$ Globule Size Distribution in Lipid Injectable Emulsions, which appears elsewhere in this Pharmacopeial Forum) includes two methods of analysis for assessing the stability and subsequent safety of these complex dispersions. Method I, based on either classical Mie or dynamic light scattering, will be designated for determining the mean diameter of the lipid droplets and the approximate range of the various droplet diameters distributed around the mean diameter, expressed as the standard deviation. Method II, based on light obscuration, will be designated for counting and sizing the over-sized fat globules comprising the large-diameter tail in the upper portion of the droplet/globule size distribution. This article will review the history and use of lipid injectable emulsions, the proposed methods of characterization, and the rationale for their selection.


## INTRODUCTION

Lipid injectable emulsions have been used to varying degrees in patients for approximately 80 years. In the United States, largely through research conducted under the direction of Drs. Fredrick Stare and Robert Geyer at the Harvard School of Public Health (HSPH) in the 1950s, a number of clinical trials were undertaken using both phosphatide- and nonphosphatide-containing lipid injectable emulsions (1). Ultimately, a commercial product was introduced during that time under the brand name of Lipomul I.V., which underwent extensive clinical testing. It was a $15 \% \mathrm{w} / \mathrm{v}$ cottonseed oil-based emulsion stabilized by a mixture of natural (soybean lecithin) and synthetic (Pluronic F-68) emulsifying agents. Despite numerous attempts to make a safe product and after several clinical trials, studies were stopped in the early 1960s due to a high incidence of significant adverse effects referred to as "fat overload syndrome." This syndrome was characterized by fever, diffuse abdominal pain, liver damage, lipemic serum, fat accumulation in vital organs, and blood dyscrasias. Around that time, Dr. Arvid Wretlind, a guest researcher with Stare and Geyer in Boston (2) returned to Stockholm, Sweden, where he and coworkers developed a soybean oil-based lipid injectable emulsion using egg lecithin as a surfactant. During this time, they also realized that the dosing of lipid injectable emulsion, which proved safe in dogs but not humans, was flawed because it did not account for the differences in energy expenditure, which for dogs is approximately three times as high as for humans (3). Thus, the lipid doses first tested in dogs without

[^368]problems were similar to those eventually used in humans (3 $\mathrm{g} / \mathrm{kg} /$ day of body weight) and likely explained the differences in toxicity. Once equivalent doses were given to dogs $(9 \mathrm{~g} / \mathrm{kg} /$ day of body weight), the severe and sometimes fatal adverse reactions seen in humans were reproduced in the animal model. Hence, a "dog tolerance test" for lipid injectable emulsions could be used to screen acceptable vs. unacceptable formulations of lipid injectable emulsions and subsequently led to the development of the first safe formulation under the trade name of Intralipid. The safety differences seen between the emulsions tested then and even up to the time of Dr. Wretlind's publication reviewing the development of lipid injectable emulsions (1981) resulted in his observation: ". . it is not correct to speak of fat emulsions in general terms. The name of the product and its exact composition must always be stated."
Today, a number of lipid injectable emulsion dosage forms exist, and they are much safer and commonly prescribed as caloric supplements to patients who are temporarily or even permanently incapable of assimilating nutrients via the gastrointestinal tract. For example, in addition to soybean oil, other sources of triglycerides are also used, including, for example, safflower oil, olive oil, coconut oil, palm kernel oil, and menhaden oil, and they are available in concentrations of $10 \%, 20 \%$, and $30 \% \mathrm{w} / \mathrm{v}$ formulations. In nearly every case, however, soybean oil is included in combination with one or more of these oils in order to provide sufficient amounts of the essential fatty acids linoleic acid and linolenic acid. Intravenous nutrition is reserved for a selected group of patients, and lipid injectable emulsion has been one of the key nutrients routinely provided in the clinical setting for approximately the past 30 years. The $20 \% \mathrm{w} / \mathrm{v}$ parenteral emulsion is most common, and can be administered as a separate infusion in either its man-
ufacturer's container (e.g., $200-\mathrm{mL}$ sterile glass bottle for adults) or via an alternative infusion device (e.g., a sterile syringe for neonates). Lipid injectable emulsion can also be administered as an ingredient or additive in a total parenteral nutrition (TPN) admixture containing crystalline amino acids, dextrose, electrolytes, vitamins, and minerals. These latter formulations are widely known as all-in-one or total nutrient admixtures (TNA). When lipid injectable emulsions are used to compound TNAs, differences in stability have been observed. However, in most circumstances these differences are currently considered to be related to the physicochemical properties of the oil (4) rather than due to factors associated with the formulation of lipid injectable emulsion dosage forms.

At present, the major toxicity issues associated with the administration of lipid injectable emulsions can be classified into four categories. First, the composition of the commercial product may affect the tolerance and safety of the formulation. Specifically, the concentration of the emulsifier, in relation to the amounts of long-chain triglycerides, may be excessive. Historically, $12 \mathrm{~g} / \mathrm{L}$ of egg lecithin has been a standard amount used whether the final concentration of lipid is 10 or $20 \% \mathrm{w} / \mathrm{v}$. Clearly, the phospholipids-to-triglyceride ratio is much higher in the $10 \%$ formulation and, as such, the excess phospholipids form high amounts of lipo-some-like particles. In turn, these liposomal particles interfere with lipid and lipoprotein metabolism, which has been shown to cause delayed plasma clearance of triglycerides. Consequently, $10 \%$ lipid injectable emulsions containing $12 \mathrm{~g} / \mathrm{L}$ of egg lecithin are not recommended for use in susceptible patients, and this is particularly true in preterm infants receiving parenteral nutrition (5).

Second, the pH of the formulation should be at optimal levels that maintain stability. At present, the lipid injectable emulsion monograph states a pH range of $6.0-9.0$, which reflects the established range historically used by manufacturers. In this range, the negative charge imparted by phospholipids present in egg lecithin at the droplet surface is optimized for establishing electrostatic repulsion between droplets and therefore stability of the emulsion system. Lipid injectable emulsions formulated at a pH range below 6.0 (e.g., 4.5-6.4), have shown evidence of emulsion destabilization (i.e., coalescence) before their manufacturerassigned expiration dates ( 6 ) and have been found to be associated with cerebral fat embolism in animals (7).

Third, when lipid injectable emulsions are added to parenteral nutrition admixtures containing various amounts of crystalline amino acids, dextrose, electrolytes, vitamins, and minerals forming total nutrient admixtures (TNAs), some extemporaneous formulations have become very unstable (8). Although most TNAs are stable and the practice is widely applied, certain formulation additives or conditions (e.g., iron dextran, low-osmolality admixtures, etc.) can produce admixtures in which the growth of submicron droplets into very-large-diameter fat globules is greatly accelerated. When this occurs, evidence of fat embolization in the lungs (9) and livers (10) of laboratory animals has been reported, accompanied by evidence of oxidative stress in these or-
gans. So, clearly, large-diameter globule size limits must be assigned to distinguish between stable and unstable lipid injectable emulsions.
Finally, toxicities also have occurred as a result of excessively high infusion rates, particularly with long-chain triglycerides (LCT) that are rich in omega-6 fatty acids such as soybean oil, which may adversely accentuate prostaglan-din-induced changes in blood flow. This is especially significant in patients with Adult Respiratory Distress Syndrome (ARDS) $(11,12)$. In general, such LCT infusion rates in humans should not exceed $0.11 \mathrm{~g} / \mathrm{kg} / \mathrm{hour}$ in order to avoid clinical problems (13), which is an important consideration when lipid injectable emulsions are given as an intermittent infusion (i.e., during 12 hours or less).

## PHYSICOHEMICAL CHARACTERISTICS OF LIPID INJECTABLE EMULSIONS

Lipid injectable emulsions are colloidal dispersions. In general, a colloidal dispersion of an otherwise inhomogeneous system, for example, oil-in-water used for intravenous administration, has a population of droplet sizes (upon successful homogenization) that is generally smaller than one micrometer $(\mu \mathrm{m})$ in diameter $(d)$. Within this definition, such dispersions generally fall into one of two common emulsion classifications, namely (1) micro-emulsions (mean $d<0.1 \mu \mathrm{~m}$ ), or (2) mini-emulsions (mean $d<1.0$ $\mu \mathrm{m})$. Micro-emulsions are transparent, form spontaneously, and are thermodynamically stable. In contrast, mini-emulsions are turbid, require energy to be formed, and are thermodynamically unstable. Lipid injectable emulsions are sterile oil-in-water dispersions designed for intravenous administration and have mean droplet diameters between 200 and $500 \mathrm{~nm}(0.2-0.5 \mu \mathrm{~m})$. Consequently, they can be characterized as mini-emulsions and have a limited shelf life of between 18 and 24 months.

Lipid injectable emulsions are oil-in-water mixtures consisting of internal (oil) and external (water) phases; they are made miscible by an amphoteric surfactant. The oil phase consists of various triacylglycerols or triglycerides containing fatty acids ranging in length from 8 to 22 carbons ( $\mathrm{C}_{8}-$ $\mathrm{C}_{22}$ ). These include medium-chain triglycerides (MCTs) derived from coconut or palm kernel oils ( $\mathrm{C}_{8}$ and $\mathrm{C}_{10}$ ) and various long-chain triglycerides (LCTs) also derived from plant sources such as soybean, safflower, and/or olive oils ( $\mathrm{C}_{16}$ and $\mathrm{C}_{18}$ ) or from marine sources such as menhaden oil ( $\mathrm{C}_{20}$ and $\mathrm{C}_{22}$ ). The emulsions may consist of a single oil, such as soybean oil (most common), or a mixture of two or more oils such as soybean + safflower oil, soybean + olive oil, soybean + MCT oil, soybean + MCT + fish oil, etc. The surfactant or emulsifier for parenteral emulsions is egg lecithin that contains a mixture of phospholipids. The surfactant confers emulsion stability by coating the finely homogenized droplets with a tightly packed molecular film containing various electrically charged phospholipids present in egg lecithin, which include, for example, the glycerophospholipids phosphatidyl choline and phosphatidyl ethanolamine, as shown in Figure 1. Phospholipids are sim-
ilar to triacylglycerols ( $\mathrm{R}_{1}$ and $\mathrm{R}_{2}$ ) except in the third position $\left(R_{3}\right)$, where the hydroxyl group is esterified to phosphoric acid, now phosphatidic acid, which, in turn, is esterified to an alcohol such as choline or ethanolamine. At or near physiologic pH , the polar phosphate head group is negatively charged. Consequently, because each phospholipidcoated droplet has a negatively charged surface, electrostatic repulsion between droplets occurs, preventing their aggregation by Van der Waals attractive forces and subsequent coalescence. Hence, a "safe" distance is now maintained between neighboring droplets by the presence of an interdroplet electrostatic potential energy barrier. Finally, the aqueous phase made from sterile water for injection comprises up to $90 \%$ of the emulsion volume, incrementally added during the manufacturing process to bring the formulation to its final intended volume. The major specification of the aqueous phase involves the maintenance of a sterile and pyrogen-free supply throughout the manufacturing process and subsequent shelf life of the product.

(Phosphatidate)

Commercial lipid injectable emulsions are currently available in the concentration range $10-30 \% \mathrm{w} / \mathrm{v}$ as oil-inwater dispersions, but the $30 \% \mathrm{w} / \mathrm{v}$ formulation is reserved for compounding-only (TNAs) purposes and is not intended for direct intravenous administration. All formulations are highly concentrated emulsions, considering their mean droplet sizes. For example, assuming a $20 \% \mathrm{w} / \mathrm{v}$ emulsion with a perfectly monodisperse population of droplets equaling $300 \mathrm{~nm}(0.3 \mu \mathrm{~m})$, there would be approximately $1.5 \times$ $10^{13}$ droplets per mL . In reality, assuming a normal or Gaussian distribution of droplets following homogenization, a range of sizes exists from $0.01 \mu \mathrm{~m}$, or even smaller, to 20 $\mu \mathrm{m}$ or larger (Figure 2). Obviously, stable lipid injectable emulsions must have infinitesimally small amounts of these very large fat globules in the upper portion of the globule size distribution population (i.e., large-diameter fat globules $>5 \mu \mathrm{~m}$ ), because this region is most pertinent with respect to stability and safety. These extreme outlier fat globules are generally located 3 to 5 standard deviations above the mean droplet diameter, but they nevertheless provide crucial information regarding the current quality and stability of the dispersed system. This point assumes critical importance with respect to the efficacy of the proposed methods for assessing the stability and safety of lipid injectable emulsions.

Fig. 1. General structure of glycerophospholipids.


Diameter (um)
Fig. 2. Normal probability curve and relevant droplet/globule populations for lipid injectable emulsions.

## STABILITY OF LIPID INJECTABLE EMULSIONS

For lipid injectable emulsions, the height of the potential energy barrier guarding against lipid droplet coalescence is optimized in the pH range of $6.0-9.0$. At lower pH values, the effectiveness of the barrier is compromised as the charge is reduced, becoming less negative and ultimately reaching zero at the isoelectric point of the charged phospholipids, i.e., $\mathrm{pH} \sim 3.2$ (14). As the pH falls, so too does the efficacy of the energy barrier, thereby fostering aggregation and coalescence of neighboring lipid droplets. The addition of other cations ( $\mathrm{Na}, \mathrm{K}, \mathrm{Ca}, \mathrm{Mg}, \mathrm{Fe}$, etc.) and the elevation of temperature are also consequential for the stability of lipid injectable emulsions, but these factors are mainly of significance when these formulations are used to compound a TNA. Disruption of this energy barrier by physical means (e.g., increasing temperature $>30^{\circ} \mathrm{C}$ ) or chemical means (e.g., decreasing $\mathrm{pH}<6.0$ ) can promote aggregation of lipid droplets, ultimately leading to their coalescence into very large fat globules. During the normal shelf life of a lipid injectable emulsion, the thermodynamically unstable dispersion will slowly begin to destabilize over time. The purpose of the proposed chapter and related monographs is to place acceptably safe limits on the allowable extent of these chemical and physical changes that can result in emulsion destabilization. The rate of destabilization is usually very slow and therefore barely noticeable during the shelf life of the normal product. Chemical changes resulting in measurable droplet/globule size increases over time include a decrease in pH in association with increased hydrolytic degradation of triglycerides and phospholipids (15) and the formation of free fatty acids and corresponding hydrogen ions. Current chemical specifications in the proposed lipid injectable emulsion monograph include a pH range of $6.0-9.0$ and a free fatty acid limit of 0.07 mEq per gram of oil present.

Physical evidence of emulsion instability over time must include measurable changes in the globule size distribution (GSD) indicative of coalescence. Two key regions in the distribution of oil droplet and/or globule sizes associated with the GSD have been identified in proposed chapter $\langle 729\rangle$, namely the mean droplet size and the concentration of over-size globules comprising the large-diameter tail. Current physical specifications for the mean droplet diameter limits depend on the final concentration of the oil phase of the emulsion (i.e., $\leq 0.3 \mu \mathrm{~m}$ for $10 \% ; \leq 0.4 \mu \mathrm{~m}$ for $20 \% ; \leq 0.5 \mu \mathrm{~m}$ for $30 \%$ ). Large-diameter tail limits, expressed as the volume-weighted percentage of fat residing in globules larger than 5 micrometers $\left(\mathrm{PFAT}_{5}\right)$, cannot exceed $0.05 \%$ of the total lipid present, irrespective of the final concentration of the emulsion. Importantly, measurable growth of the large-diameter fat globules is a significant and early warning of the onset of instability, whereas a measurable increase in the mean droplet size is indicative of obvious (i.e., late) global destruction of the entire emulsion system. Thus, the preselected $5-\mu \mathrm{m}$ threshold (i.e., $\mathrm{PFAT}_{5}<0.05 \%$ ) is an
important pharmaceutical limit representing a region of the particle or globule size distribution that has uniquely significant implications for stability and safety.

The $5-\mu \mathrm{m}$ threshold also has physiological importance. Intravenous infusion of a lipid injectable emulsion into the systemic circulation exposes it to the microvasculature, such as the capillary bed. This fact is potentially important because the diameter of the pulmonary capillaries is between 4 and $9 \mu \mathrm{~m}$, which means that the $5-\mu \mathrm{m}$ size threshold represents a dimension where occlusion by large fat globules may produce an embolic syndrome. The adverse consequences of occluding the microvasculature may have grave effects, especially for critically ill patients with major organ dysfunction (e.g., acute pulmonary failure requiring mechanical ventilation).

## PHYSICAL ANALYSIS OF LIPID INJECTABLE EMULSIONS

The newest In-Process Revision of Chapter $\langle 729\rangle$ Globule Size Distribution in Lipid Injectable Emulsions (published elsewhere in this issue of Pharmacopeial Forum) proposes a two-stage procedure analyzing: (1) the mean droplet diameter, and (2) the range of the various droplet diameters distributed in the extreme (outlier) population of large-diameter fat globules comprising the tail of the distribution.

## I. CHAPTER $\langle 728\rangle /\langle 729\rangle$ : PREVIOUS METHODS

USP has produced four previous versions of Chapter $\langle 729\rangle$ (formerly $\langle 728\rangle$ ) in 1991, 1994, 1995, and 1998. During this time, four droplet- or globule-sizing methods were suggested, including classical or dynamic light scattering, laser (Fraunhofer) diffraction, electrical zone sensing (EZS or Coulter Counter), and light obscuration or extinction. Light scattering (by either method) for meeting mean droplet size limits and light obscuration, or extinction, for meeting large-diameter fat globule $\left(\mathrm{PFAT}_{5}\right)$ limits have been selected as the reference methods in the most recent version of $\langle 729\rangle$. The EZS method is the electrical equivalent of light extinction because it counts particles or droplets as they pass individually through a small sensing zone. However, this method requires a supporting electrolyte solution to obtain the signal from which the particle or globule volume is obtained. The requirement for a supporting electrolyte, i.e., NaCl , to conduct EZS measurements may induce disruption of the stabilizing phospholipid emulsifier. The electrical field produced by the negative charges imparted upon the lipid droplet surfaces is screened by the added electrolyte ions, thereby permitting Van der Waals attractive forces between neighboring droplets to gain influence, promoting aggregation and eventual coalescence. This significant shortcoming, together with a susceptibility to frequent clogging and other disadvantages, has caused the EZS method to be dropped from the proposed chapter.

Laser diffraction methods for assessment of large-diameter fat globules, based on Fraunhofer diffraction (used alone or in conjunction with multi-angle classical Mie scattering) have also been eliminated from the proposed chapter. Significant problems have been demonstrated when laser diffraction (LD) instruments have been used to measure the adverse changes in the large-diameter population of fat globules found in lipid injectable emulsions. This became especially evident after a comparison study in which different LD instruments were challenged by known concentrations of $5-\mu \mathrm{m}$ latex spheres added to lipid injectable emulsions (16). Figure 3 shows the results of increasing latex concentrations plotted as the measured volume $\%$ vs. expected volume $\%$ obtained from the responses of three different LD instruments versus one light obscuration (LO) instrument. Clearly, the quantitative responses obtained from all three LD instruments were substantially inaccurate and highly nonlinear with respect to the known volume $\%$ amounts of added $5-\mu \mathrm{m}$ latex particles. For two of the LD instruments the reported volume $\%$ results significantly overstated the known values over most of the dynamic range investigated. The third LD instrument failed
to detect or quantify substantial concentrations of latex particles in the presence of the fat globule tails. This finding was not entirely surprising because ISO document 13320 specifies that the Fraunhofer approximation is valid only for relatively large particles with diameters at least 40 times the wavelength of the light source (17). At the typical laser wavelength used for LD measurements (e.g., $\sim 635 \mathrm{~nm}$ ), the minimum particle diameter measured should therefore be not smaller than $25 \mu \mathrm{~m}$, which misses the key large-diameter population of greatest interest (i.e., tail $>5 \mu \mathrm{~m}$ ) in the proposed Chapter $\langle 729\rangle$. In addition, there is the fundamental problem of limited sensitivity and resolution common to Fraunhoffer measurement. Because this is an ensemble technique, it requires the raw data obtained from particles/droplets of all sizes to be inverted by an appropriate algorithm. This process is known to be inherently ill conditioned (18) and therefore entirely unsuited to detection (quantitative or otherwise) of subtle changes in the oversize outlier tail of the globule size distribution. In contrast, the LO instrument yielded a linear response in every case because it constructed the distribution one particle or droplet at a time, requiring no inversion of the raw data.


Fig. 3. Laser diffraction (LD) vs. light obscuration (LO) in stable intravenous lipid emulsion spiked with increasing concentrations of latex spheres. Measured vs. theoretical regression plot.

## II. APPLICATION OF $\langle 729\rangle$ : CURRENT METHODS

## Method I. Light-Scattering Techniques

The use of light-scattering techniques for determination of submicron particle or droplet size distributions is widely acknowledged in a number of applications (19). Classical Mie, or "static" light scattering is based on the angular dependence of the average scattering intensity. Dynamic light scattering (DLS), also known as photon-correlation spectroscopy (PCS), is based on the temporal fluctuations due to particle/droplet Brownian motion or diffusion. These methods typically provide comparable results in determining the mean droplet size of lipid injectable emulsions. Light-scattering techniques are widely used in a variety of industries for determining mean particle or droplet diameters, and they are very useful for evaluating homogenization procedures in
achieving a desired end-point, i.e., average droplet size. As specified in the most recently proposed $\langle 729\rangle$, a not-to-exceed limit is assigned according to the final concentration of each lipid injectable emulsion dosage form. Table 1 shows the mean droplet sizes (MDS) of 16 different commercial lipid injectable emulsions. Techniques for the assessment of submicron populations of droplets typical of lipid injectable emulsions are well established, but as discussed in proposed Chapter $\langle 729\rangle$ these methods should be assessed beforehand using standard polystyrene calibrator spheres of uniform size to ensure that the peaks in the measured par-ticle-size distributions appear at the appropriate sizes. This assessment, of course, is only semiquantitative and therefore is designed to verify the proper functioning of the instrument in determining an accurate mean droplet size.

Table 1. Physical characteristics of commercially available lipid injectable emulsions ${ }^{\text {a }}$

| Product | Lot No. | $\begin{aligned} & { }^{\text {b}} \text { Mos. } \\ & \text { to } \mathrm{ED} \end{aligned}$ | ${ }^{\text {c }}$ PN $>1.8$ | PN $>5$ | $\begin{aligned} & P N \\ & > \\ & > \end{aligned}$ | ${ }^{\mathrm{d}}$ PFAT ${ }_{1.8}$ | $\mathrm{PFAT}_{5}$ | PFAT $_{10}$ | ${ }^{\text {e }}$ MDS |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Soybean Oil <br> Intralipid $10 \%$ | 12202-51 | 9 | 1224718 | 75148 | 774 | 0.024\% | 0.009\% | 0.0010\% | 286 |
| Intralipid $20 \%$ | 10776-71 | 6 | 2983655 | 8645 | 135 | 0.017\% | 0.005\% | 0.0008\% | 340 |
| Intralipid 30\% | 16115-51 | 17 | 2017816 | 12504 | 608 | 0.048\% | 0.007\% | 0.0020\% | 420 |
| $\begin{gathered} \text { Liposyn III } \\ 10 \% \end{gathered}$ | 45-351-DE | 18 | 482797 | 75456 | 5312 | 0.022\% | 0.013\% | 0.0040\% | 263 |
| $\begin{gathered} \text { Liposyn III } \\ 20 \% \end{gathered}$ | 43-440-DE | 12 | 674098 | 73822 | 2320 | 0.010\% | 0.005\% | 0.0007\% | 307 |
| $\begin{gathered} \text { Liposyn III } \\ 30 \% \end{gathered}$ | 41-395-DE | 10 | 2184390 | 340158 | 40984 | 0.040\% | 0.029\% | 0.0160\% | 301 |
| $\begin{aligned} & \text { Lipofun- } \\ & \text { din-N } \\ & 10 \% \end{aligned}$ | 8085A83 | 15 | 321923 | 3856 | 175 | 0.011\% | 0.001\% | 0.0005\% | 272 |
| $\begin{aligned} & \text { Lipofun- } \\ & \text { din-N } \\ & 20 \% \end{aligned}$ | 8082A84 | 15 | 2525720 | 67508 | 3978 | 0.016\% | 0.005\% | 0.0020\% | 332 |
| Soybean Oil Mixtures |  |  |  |  |  |  |  |  |  |
| $\begin{gathered} \text { Liposyn II } \\ 20 \% \end{gathered}$ | 47-412-DE | 16 | 744869 | 45637 | 1893 | 0.009\% | 0.004\% | 0.0010\% | 278 |
| $\begin{gathered} \text { ClinOleic } \\ 20 \% \end{gathered}$ | 9801376 | 16 | 701530 | 11598 | 785 | 0.004\% | 0.001\% | 0.0005\% | 276 |
| Structoli- <br> pid <br> 20\% | 18417-51 | 5 | 1222491 | 123661 | 4773 | 0.018\% | 0.009\% | 0.0020\% | 276 |
| $\begin{gathered} \text { Lipoplus } \\ 20 \% \end{gathered}$ | 9235A32 | 15 | 1816737 | 83642 | 5927 | 0.019\% | 0.008\% | 0.0040\% | 263 |
| $\begin{aligned} & \text { Lipofundin } \\ & \text { MCT } \\ & 10 \% \\ & \hline \end{aligned}$ | 8042A81 | 13 | 438757 | 44930 | 2731 | 0.014\% | 0.008\% | 0.0030\% | 266 |

Table 1. Physical characteristics of commercially available lipid injectable emulsions ${ }^{\text {a }}$ (Continued)

| Product | Lot No. | ${ }^{\mathrm{b}}$ Mos. <br> to $E D$ | ${ }^{\text {c }}$ PN $>1.8$ | PN $>5$ | $\begin{aligned} & P N \\ & >10 \end{aligned}$ | ${ }^{\text {d PFAT }}{ }_{18}$ | $\mathrm{PFAT}_{5}$ | PFAT $_{10}$ | ${ }^{\text {e }}$ MDS |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Lipofundin MCT | 8075A81 | 15 | 1230490 | 114299 | 5708 | 0.016\% | 0.009\% | 0.0030\% | 287 |
| 20\% |  |  |  |  |  |  |  |  |  |
| Lipovenous MCT | KK1569 | 20 | 530475 | 15483 | 109 | 0.004\% | 0.001\% | 0.0005\% | 275 |
| 20\% |  |  |  |  |  |  |  |  |  |
| $\begin{array}{r} \text { Critilip } \\ 20 \% \end{array}$ | KV1249B | 17 | 9548816 | 205183 | 3723 | 0.051\% | 0.012\% | 0.0020\% | 330 |

${ }^{\text {a }}$ Adapted and expanded from data in reference 16
${ }^{\mathrm{b}}$ Months to ED = months to expiration date at time of test
${ }^{c} \mathrm{PN}=$ Particle (or globule) number per mL
${ }^{\mathrm{d}}$ PFAT $=$ Percentage (volume-weighted) of fat determined by LE/SPOS
${ }^{\mathrm{e}}$ MDS $=$ Mean droplet size in nanometers determined by DLS

Although the mean droplet diameter is an imperative pharmacopeial limit, it is important to appreciate that en-semble-type methods such as classical Mie or dynamic light scattering, when used for determining the stability of lipid injectable emulsions, are in fact quantitatively insensitive to the consequential, and often subtle, changes in droplet size that occur in the large-diameter tail of the globule size distribution. The insensitivity of light-scattering methods for determining the instability of lipid injectable emulsions has been demonstrated previously $(8,20)$; thus arises the requirement for a second-stage analysis that forms the basis for Method II.

## Method II. Light Extinction with a Single-Particle Optical Sensing (LE/SPOS) Technique

Light obscuration or extinction is the reference method for detection of extraneous particles (e.g., dirt, fibers, glass, etc.) introduced during the production process for aqueousbased injectables; see Chapter $\langle 788\rangle$, where tolerance limits are set for particulate matter larger than 10 and $25 \mu \mathrm{~m}$ (21). Therefore, it is similarly reasonable to set limits for the concentration of large-diameter fat globules, which are the result of ongoing destabilization. Although such over-size fat globules are expected to coexist with normally distributed droplets following homogenization, their numbers should be very limited in a stable system. For emulsion-based injectables, a $5-\mu \mathrm{m}$ limit has been suggested not only for pathophysiological reasons (i.e., because this size approximates the internal diameter of capillaries where occlusion may occur) but also as an appropriate indicator of the stability of the emulsion system. It is also a size at which most currently available lipid injectable emulsions have small but measurable amounts of fat expressed as a percentage of the volume-weighted fat globules in a specified range, e.g., $d>5$ $\mu \mathrm{m}$, or $\mathrm{PFAT}_{5}$. For example, when measured by light ob-
scuration or extinction using a single-particle optical sensing (SPOS) technique, data can be reported as the number of particle counts as a function of the geometric mean diameter over a series of narrow channel widths (e.g., $<0.5 \mu \mathrm{~m}$ each) spanning the desired size range (e.g., $2-50 \mu \mathrm{~m}$ ). The $\mathrm{PFAT}_{5}$ data can be extracted by summing the volume-weighted channelized data in the large-diameter tail, $\Sigma(\# / \mathrm{mL} /$ channel $)\left(\pi d^{3} / 6\right)$ to test compliance within pharmacopeial limits. It has been shown that the $\mathrm{PFAT}_{5}$ for lipid injectable emulsions ranging in concentration from 10 to $30 \% \mathrm{w} / \mathrm{v}$ is universally less than $0.05 \%\left(\mathrm{PFAT}_{5}<0.05 \%\right)$. Table 1 also depicts the large-diameter globule concentrations (counts $/ \mathrm{mL}$ ) found in stable lipid injectable emulsions and the corresponding volume-weighted PFAT values for three different size thresholds. Thus, the $\mathrm{PFAT}_{5}$ level is an index or size threshold that reflects the state of the stability of the emulsion at any given time. Increases in $\mathrm{PFAT}_{5}$ above $0.05 \%$ indicate the onset of active or ongoing coalescence, demonstrating that the stability of the emulsion has clearly diminished.

Of equal importance, the $5-\mu \mathrm{m}$ limit has ramifications for the counting and sizing accuracy of light-obscuration or light-extinction methods. As with any analytical method, the use of optical-sizing methods to count and size largediameter fat globules in the tail of the distribution of droplets in lipid injectable emulsions has limits with respect to its accuracy and precision. Counting particles or droplets can be evaluated by using NIST-traceable calibrator number standards. This has been described previously with the LE/SPOS method, and the number of particles per mL was found to be within $10 \%$ of the expected concentration values based on the documentation provided with each standard, e.g., nominal sizes of 2, 5, 10, and $25 \mu \mathrm{~m}$ (16). These results are shown in Table 2.

Table 2. Results of numerical validation of the LE/SPOS instrument using NIST standard reference materials

| Nominal Size | Replicates | Theoretical | Measured | \% Error |
| :---: | :---: | :---: | :---: | :---: |
| $2 \mu \mathrm{~m}$ | 6 | $2.5 \times 10^{7}$ | $2.37 \pm 0.026 \times 10^{7}$ | $5.1 \pm 1.1$ |
| $5 \mu \mathrm{~m}$ | 6 | $1.0 \times 10^{7}$ | $1.09 \pm 0.001 \times 10^{7}$ | $9.4 \pm 0.1$ |
| $10 \mu \mathrm{~m}$ | 6 | $1.0 \times 10^{6}$ | $1.03 \pm 0.013 \times 10^{6}$ | $3.5 \pm 1.3$ |
| $25 \mu \mathrm{~m}$ | 6 | $3.0 \times 10^{5}$ | $3.00 \pm 0.023 \times 10^{5}$ | $0.5 \pm 0.5$ |

Sizing of particles or droplets can pose potentially serious problems related to the optical properties of the various materials. With LE/SPOS, the light-extinction data are influenced by two important physical variables: (1) the size of the individual particles or droplets being measured, and (2) the contrast of the calibrator spheres. The latter refers to the degree of mismatch between the refractive index of the particles or droplets and that of the surrounding liquid. These variables influence whether the signal produced by the optical extinction detector (i.e., the height of the pulse representing the momentary reduction in light intensity by a sized particle or globule) is appropriately quantified. In this regard, the robustness of the LE/SPOS method can be evaluated by examining the extent to which the difference between the refractive index of mono-sized, NIST-traceable polystyrene microspheres used to calibrate the instrument and the index of the fat droplets/globules affects the lightextinction signal-i.e., the decrease in light intensity caused by the passage of similarly sized lipid droplets through the sensing zone. A key question is, where in the droplet or globule size distribution does the difference in refractive index become significant? Alternatively, above what size is the difference no longer of significance? This can be addressed by investigating the extinction efficiency. The LE/ SPOS technique is based on the partial blockage, or extinction, of a monochromatic light beam traversing a flow cell when a particle or globule passes through a defined optical sensing zone or view volume. The efficiency or extent of completeness of the obscuration process is crucial to the final result. Errors potentially can occur when the light flux incident on the particle is incompletely blocked-i.e., when this fraction is less than that predicted ideally by twice the cross-sectional area of the particle ( $\pi d^{2} / 4$ for spheres). Consequently, the light that is refracted or scattered by particles of a given size is influenced by the refractive index of the material being investigated as well as that of the suspending fluid (typically water). This raises further the issues of the difference between the refractive index of the calibrator polystyrene spheres $(n=1.59)$ and that of the various oils used in injectable emulsions, e.g., soybean oil ( $\mathrm{n}=1.473$ ), safflower oil ( $n=1.462$ ), olive oil ( $n=1.468$ ), coconut oil ( $n=1.449$ ), or menhaden oil ( $n=1.465$ ) (22). The extinction efficiency, $Q$, and consequently, the light-obscuration or light-extinction results reported for lipid injectable emulsions are affected by this difference in refractive index.

The extinction efficiency provides a measure of the robustness of the LE/SPOS technique, because it addresses the error in the measured light-obscuration signal caused by differences in refractive index of the calibrating particles (typically polystyrene latex spheres) and that of the dispersed oil droplets (i.e., soybean oil, safflower oil, MCT oil, etc.). This effect is described by the extinction efficiency formula:

$$
Q(\mathrm{Ext})=2-(4 / \rho) \operatorname{SIN} \rho+\left(4 / \rho^{2}\right)(1-\operatorname{COS} \rho)
$$

$$
Q=C / G
$$

where:
$C=$ extinction cross section of particle ( $\propto$ extinction pulse height)
$G=$ physical (geometric) cross-sectional area of particle $=$ $\pi d^{2} / 4$
$C=Q^{*} G$; Limit of very large particles: $Q=2$ and therefore $C=2 * G$
$m_{l}=$ refractive index of particle; $m_{2}=$ refractive index of fluid; $m=m_{1} / m_{2}$;

$$
x=\pi d m_{2} / \lambda ; \rho=2 x\left(m_{1}\right)
$$

Figure 4 shows the results of the extinction efficiency formula outlined above as a function of particle size from 1.5 to $20 \mu \mathrm{~m}$ for polystyrene particles in water (Q-PSW), lipid droplets (soybean oil) in water (Q-LIPW), and their ratio (Q-LIPW/Q-PSW). Clearly, the dependence of light extinction on the contrast of the particles greatly diminishes above $5 \mu \mathrm{~m}$, so the extinction of light for the two different materials is nearly equivalent as the Q-ratio approaches unity, as shown in the figure. Thus, although differences in the refractive index between reference (calibrator) particles and sample droplets or globules are potentially important for particles or droplets smaller than $5 \mu \mathrm{~m}$, lipid droplets obscure light in a manner that is quantitatively similar to that of latex particles above this size. Consequently, the $5-\mu \mathrm{m}$ threshold used to meet pharmacopeial limits happens to be large enough that the differences in the refractive indices of the calibrating particles and the droplets/globules of interest do not seriously affect the results of the size-distribution measurement.


| $\circ$ | Q-PSW |
| :--- | :--- |
| - | Q-LIPW |
| $\triangle$ | Q-LIPW/Q-PSW |

Fig. 4. Extinction efficiency calculations and theoretical plot.

## CONCLUSIONS

Lipid injectable emulsions are complex dosage forms. Proposed Chapter $\langle 729\rangle$ identifies two methods that must be applied in order to validate the quality, stability, and safety of these formulations. For manufacturing purposes, Method I uses light scattering in one form or another to address the semiquantitative endpoints of the homogenization process by setting limits for the mean droplet size of the emulsion, in accordance with the final concentration of the dispersed oil phase. For the clinically important large-diameter tail of the distribution of lipid injectable emulsions, a universal limit is proposed. This is based on previous work using light obscuration, or extinction, employing a singleparticle optical sensing (SPOS) technique. Application of this method provides important qualitative and quantitative information concerning the state of stability of the dispersion because growth in this region of the globule size distribution reflects coalescence, ultimately leading to phase separation and destruction of the emulsion system. The parameter indicated in Method II of this version of Chapter $\langle 729\rangle$ is reasonable and can be easily quantified using light obscuration or extinction technology.

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# The FDA Process Analytical Technology (PAT) Initiative-An Alternative Pharmaceutical Manufacturing Practice (aPMP) 

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#### Abstract

This Stimuli article gives an overview of FDA's Process Analytical Technology (PAT) initiative and presents the perspectives of industry and the U.S. Pharmacopeia. The authors outline the scope of PAT as a scientific, risk mitigationbased approach for process-centered quality control techniques within an alternative Pharmaceutical Manufacturing Practice (aPMP) environment. The authors discuss the various elements of the PAT initiative, explore USP's initial role in PAT, and highlight the key PAT concepts. Finally, this article presents a proposed list of terms that have been identified as members of a glossary for PAT analysis.


## INTRODUCTION

FDA defines Process Analytical Technology (PAT) as a system for designing, analyzing, and controlling manufacturing by means of timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality (1). At its most basic level, PAT can be thought of as timely knowledge of critical measurements. The knowledge or information from these measurements can be used to understand and control processes. This concept can be further elaborated to include optimal applications of process analytical chemistry tools, feed-back/feed-forward process control strategies, information management tools, and product/process optimization strategies for the manufacture of pharmaceuticals. Several examples of the application of PAT techniques to pharmaceutical processes have been cited in the literature and range from the control of polymorphism, particle size and shape during API crystallization, moisture control in fluid-bed drying, to ID and assay during tableting (2-6).

A key document to understand PAT is FDA's Guidance for Industry, PAT-A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, which creates a new framework for regulating drug manufacturing (7). The guidance suggests a shift from finished-product testing to in-process testing as a means to evaluate final product quality. FDA has focused on the assessment of drug product quality by shifting to a science-based risk-mitigation strategy. FDA suggests that the industry accomplish this shift by introducing innovative technologies and techniques as alternatives to current pharmaceutical manufacturing process controls in order to try to obtain mechanistic un-

[^369]derstanding and enhanced control of pharmaceutical processes. Implementation of PAT, it is postulated, may allow reduced production cycle times and improve pharmaceutical manufacturing efficiency.
Quality systems currently are rooted in current Good Manufacturing Practices (cGMP). Current GMPs seek to continually improve product quality by requiring manufacturers to follow written validated procedures (8). This approach ensures quality by testing the manufacturing process components from beginning to end with previously agreed-upon validated specifications. Although this approach has been proven to be valid, it is suggested that PAT principles in conjunction with cGMPs may improve final product quality. The testing-to-document-quality approach (cGMP) has its origin in the Federal Register of 14 February 1963, when the first regulations to establish criteria for cGMPs in the processing, packing, and holding of drugs were published (9).
The PAT initiative attempts to augment or enhance cGMPs by introducing additional scientific, engineering, chemical, and risk mitigation-based strategies to evaluate final product quality by real-time or near real-time control of pharmaceutical manufacturing via timely measurements during processing.

## BACKGROUND

PAT's beginnings extend as far back as 1993 to a symposium sponsored by AOAC International (10). In November 2001 Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research (CDER), FDA, outlined the agency's PAT Initiative. It was promoted as an innovation in manufacturing process research and development that would achieve drug quality improvements in the U.S. pharmaceutical industry. The PAT subcommittee of the Advisory Committee for Pharmaceutical Science was established and
chaired by Ajaz Hussain, Ph.D., Deputy Director, CDER, Office of Pharmaceutical Sciences. This initiative was designed to address manufacturing-related productivity problems within the industry by encouraging process innovation in a regulatory risk-adverse industry.

On 3 September 2003, FDA published the (Draft) Guidance for Industry, PAT-A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance. Simply put, the PAT guidance is an invitation to drug manufacturers to voluntarily adopt scientific, risk-based strategies for employing alternative manufacturing strategies to increase process understanding in order to minimize process and product variability, which should result in an improvement in product quality.

Rather than relying on an empirical approach to learn and then optimize the manufacturing process, the manufacturer may chose to adopt design strategies for optimizing the
process from very early stages of conception through implementation via a design of experiment (DoE) approach. What follows from process design should logically result in a stable product with very low variability and high quality. This quality by design (QbD) (11) strategy has, as its central strategy, risk assessment tools at all levels of the design stages and especially during the placement, outfitting, and final implementation of process sensors for process fault detection (performance qualification). Risk assessment, used in conjunction with appropriate cGMPs, now can be used to determine probabilities and outcomes of manufacturing campaigns that should result in more efficient, productive, and compliant operations, along with predictable product performance attributes. These are the approaches suggested in the PAT draft guidance for effectively improving pharmaceutical manufacturing productivity. Figure 1 is a process map of a scientific, risk-based PAT approach.


Abbreviations: RTQC - Real Time Quality Control, RTQA - Real Time Quality Assurance, RTL - Real Time License Courtesy Robert S. Chisholm

Fig. 1. PAT process map

The scientific basis of PAT essentially resides in the pharmaceutical sciences, process chemistry, process engineering, process analytics (chemometrics and statistics), and process control. A central issue for pharmaceutical scientists is controlling critical product attributes that may be predictive of product performance. Identifying the right tests, whether in-process or post-production controls, for determining meaningful performance attributes, is the goal. Hussain (12) has pointed out that manufacturers currently rely on over-discriminating tests to determine if a particular process step results in a particular performance attribute. Such tests may be meaningless if the net variability in that particular process step is less than the potential range of results plus the error that could result from that particular test. PAT approaches attempt to relate meaningful measurement results based on the appropriately identified process critical control parameter(s) (PCCP) to meaningful product performance attribute(s).

## PAT AND THE GUIDANCE

FDA's Office of Pharmaceutical Sciences is exploring the qualitative and quantitative aspects of risk management (13) for integrated use in PAT programs (14). The office's Chemistry, Manufacturing, and Controls (CMC) Risk-Based Review Proposal states:

This proposal aims to carve out a list of drugs with little or low risk to focus more time on complex drugs that can have problems with product quality. The objective is to come up with a list of quality attributes and acceptance criteria for little or no risk drugs. This will result in guidance to industry with reduced information being submitted for review. An ANDA can be considered a CMC supplement where everything from manufacturing, suppliers, to manufacturing sites is changed. If a drug meets the list then the original NDA could be considered a truncated ANDA with information just like the annual report of the existing approved NDA.

This statement is significant because it reflects the agency's comments in the draft guidance with respect to implementing PAT. The draft guidance states:

Section 116 of the 1997 Food and Drug Administration Modernization Act amended the Food, Drug, and Cosmetic Act by adding section 506A (21 USC 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. We recommend that manufacturers continue to consider all relevant FDA guidance documents for recommendations on the information that should be submitted to support a given change. PAT implementation plans should be risk based. We [FDA] are proposing the following possible implementation options:

- PAT can be implemented under the facility's quality system; cGMP inspections by the Agency follow.
- PAT can be implemented following cGMP inspection by the PAT Team. The PAT Team can assist manufacturers with preoperational review of the PAT manufacturing facility and process (FDA Field Management Directive 135. http://www.fda. gov/ora/inspect_ref/fmd135a.html).

The recommendations in the inspection report can serve as a summary basis of final approval of the process and can be filed in the relevant application, when needed, and in facility databases within FDA.

- A supplement (CBE, CBE-30, or PAS) can be submitted to FDA prior to implementation and, if necessary, an inspection can be performed by a PAT Team or PAT-certified investigator before implementation.
- A comparability protocol can be submitted to the agency outlining PAT research, validation, and implementation strategies and timelines. (FDA issued a draft guidance for industry, Comparability ProtocolsChemistry, Manufacturing, and Controls Information. Once finalized, it will represent the agency's current thinking on this topic.)
- Following approval of this comparability protocol by the agency, one or a combination of these regulatory pathways can be adopted for implementation.

It should be noted that when certain PAT implementation plans neither affect the current process nor require a change in specifications, several options can be considered. Manufacturers should evaluate and discuss the most appropriate option for their situation.
Given FDA's intent to refocus its and industry's attention on emphasizing in-process testing for controlling product quality rather than post-manufacturing testing, a firm should consider a number of questions before embarking on a PAT implementation scheme:

1. What systems are suitable for PAT?
2. Process analysis and control is a shift from Quality Control of the finished product. How does one switch from the current Quality Control regulatory scheme of post-production testing to an analysis and control operation, which results in a true quality-built-in product?
3. What is meant by the phrase "timely measurement?" The pharmaceutical industry is predominantly a batch process industry - in this context what are appropriate timely measurements during processing?
4. Can batch processing be converted to continuousstream processes? Do they need to be?
5. How are critical process parameters determined and controlled?
6. How do current quality control measurements, which are designed to test the performance attributes of raw and in-process materials, predict the quality of the final product performance attributes?
7. Does in-process testing for critical quality parameters yield data that predict the final product performance attributes?
8. How are in-process performance attributes determined and measured?
9. What metrics will be used to demonstrate that a controlled process ensures acceptable final product quality?
10. What metrics will be used to assess that process perfor-mance-based specifications have been met?

These are just a few of the questions addressing the shift from a product-centered to a process-centered industry. However, the challenge to the agency and to industry will be to determine how industry will switch from a Quality Control orientation that emphasizes documented product quality via testing to a new perspective that centers on analysis and control, quality by design, and an on-going, feed-backward or feed-forward evaluation of critical process parameters and established performance-based specifications.

The agency's definition of PAT identifies the ideal or desired state of control. However, the guidance cannot supply, support, or even sanction specific approaches to PAT implementation because there is no "one shoe fits all" approach. And the agency does not want to interfere with industry innovation and thus does not want to be restrictive in its guidance. However, there are some in industry who desire more of an explanation to better understand the initiative. One way to appreciate just what the agency is asking from industry is to look at PAT from a more pragmatic perspective, one more fundamentally aligned with the agency's and the industry's primary responsibility to provide safe drugs to the public.

From this perspective, PAT is a quality system approach to setting up a regulatory strategy, more information about which can be found in CDER's Pharmaceutical cGMPs for the 21st Century-A Risk-Based Approach: Second Progress Report and Implementation Plan (15) and Final Report (16). PAT is only one element of a multicomponent major initiative concerning the regulation of drug product quality. Quality by design (QbD) is the central tenet of the Pharmaceutical cGMPs for the 21st Century, and PAT is how it can be realized. The key to thinking about PAT, then, is that quality becomes the means, not the end, to an enforcement strategy. PAT is the means to final product quality through improved process understanding.

## PAT AND QUALITY

In their book, What Is Total Quality Control?: The Japanese Way, Kaoru Ishikawa et al. (17), generally regarded as Japan's foremost authorities on the subject, define quality according to the Japanese Industrial Standard (JIS). They say:

Quality is a system of productive methods that economically produces quality goods or services meeting the requirements of consumers. Modern quality control utilizes statistical methods and is often called statistical quality control.

Ishikawa gives his own definition of quality:
To practice quality control is to develop, design, produce, and service a quality product that is most economical, most useful, and always satisfactory to the consumer.

To paraphrase Ishikawa, together these definitions for quality mean quality of a product. This can come about only when one realizes that everything done with respect to the final product is done with quality in mind from the very beginning. It is the difference between asking, "How can I make a tablet," versus "How can I make a quality tablet?" PAT offers the ability to achieve quality because it allows production to become a performance-based, quality-by-design endeavor with the ability to control quality rather than to hope for quality.

How all of this relates to improving enforcement strategy should become evident. Strategies for ensuring safety, purity, and efficacy by verifying product quality after processing have become costly and burdensome to the industry as well as to the agency. PAT introduces the ability to apply generally well-known principles from process chemistry, engineering, analysis and control, and pharmaceutical science within the six pharmaceutical business units: Manufacturing Controls, Sterile Product Controls, Packaging/Labeling Controls, Laboratory Controls, Active Pharmaceutical Ingredients (APIs), and Medical Devices Controls.
To explore the operational aspects of PAT, it is necessary to develop a functional definition for PAT. The Guidance definition is essentially a descriptive definition of PAT, and it attempts to describe the desired state of a fully engaged and optimized manufacturing process. It is appropriate, then, to ask the following questions about these descriptors:

1. What are appropriate design elements to be brought to bear on 21st century pharmaceutical manufacturing systems?
2. What systems of analysis are appropriate for determining the quality attributes of processed materials in a timely manner during processing?
3. Having selected and implemented the design, analysis, and control elements for a 21 st century pharmaceutical manufacturing system, how can one measure process analysis attributes and process control attributes in order to achieve optimal product performance?

The key elements of a functional definition of PAT include a clear description of the elements necessary for design, analysis, and control of an optimized pharmaceutical manufacturing system. A modern definition of process analytics is given by Kemeny (18):
... to maintain the desired state of product consistency by way of keeping the process composition steady at around the optimum physical and chemical conditions.

This, too, is a descriptive definition of the desired state resulting from optimized PAT, but with one important difference: The definition identifies process composition as an integral part of any pharmaceutical manufacturing process that must be considered in the choice of design specifications for placement, installation, and integration of processing equipment, analysis (of solids, liquids, sols, gels, slurries, gasses, etc.), and control (by proportional integral derivative [PID], statistical process control [SPC], digital control [DC], etc.).

Now it is possible to ask, what functional descriptors define the operations that are necessary to "... keeping the process composition steady at around the optimum physical and chemical conditions?" This question is essentially one of chemical engineering.

Lauffenburger (19) refers to the Four Ms of systems biology: measurement, mining, modeling, and manipulation: "Manipulation and measurement are on the experimental side. Mining and modeling are on the computational side." Lauffenburger borrowed the chemical engineering concept of Four Ms to help explain researching the mechanism of living systems. However, because the term evolved from chemical engineering principles, it may be a suitable functional descriptor for defining the operation of aPMP.

Lauffenburger states, "These Four Ms are part of an iterative process, beginning with manipulating the system. Once a system is perturbed, it is measured using a high-throughput, multivariate technology. The data are then mined to elucidate hypotheses that, when cast in terms of formal computational models, form the basis for a new manipulation of the system" (19). Data mining is a combination of pattern recognition coupled with statistical and database management tools to uncover hidden relationships in data. System manipulation refers to process analytical control tools that can be deployed to control a process by adjusting signals and impulses arising from the process. This explanation of the process used for biological processes really describes PAT in action and explains how to get to the desired state in the FDA definition of PAT.

Having identified the functional descriptors of PAT, it is now possible to fashion a working functional definition of PAT that places its operational components in context within the new pharmaceutical cGMPs for the 21st century. PAT can be functionally defined as the use of calibrated and automated systems for optimized processes for maintaining the desired state of product consistency by keeping the process composition steady at approximately the optimum physical and chemical conditions by data measurement and mining, modeling, and system manipulation.

Now that the PAT functional definition is established and we have a more basic understanding of PAT and its impact on the pharmaceutical process, it is important to realize that the same set of questions that was asked of the (Draft) PAT Guidance definition can also be asked of the functional definition. Clearly, the functional definition provides a specific tangible mechanism to achieve implementation. And based on the functional approach, one can actually identify when an optimal PAT manufacturing system is realized, and that is when the variability of the process critical control parameter (PCCP) can be identified as a predictor of both the process composition and the final product quality. One way of demonstrating the achievement of a causal link between a PCCP and a product attribute is to be able to express in mathematical terms the functions that relate process variability to a specific product.
The PAT Guidance attempts to achieve a mechanistic (or a mathematical) understanding of the impact of the manufacturing process on the process composition. For example, the guidance directs the user to: "develop mathematical relationships between product quality attributes and measurements of critical material and process attributes." A further development of the concept can be gleaned from an observation made by Luke V. Schneider when he describes systems biology narrowly as "mathematical modeling of biological systems" (19). In dealing with PAT systems for pharmaceutical manufacturing, we, too, are trying to develop appropriate mathematical models to describe how the process composition behaves and what effect it has on the outcome of the final product quality attribute we are interested in achieving. These efforts to understand the relationships between process and product attributes are vital because they lend insight and credibility to the mathematical concepts that must be developed for a full understanding of the correct implementation of a PAT-controlled process.
One of the unanswered questions for PAT is just how integration of PCCP with performance attributes of raw and in-process materials (process composition) will be achieved in order to obtain consistent final product quality. From the previous discussion, it appears that an approach should be to maintain the optimal physical and chemical state of the process composition so that a previously identified PCCP that has a causal link to a desired attribute will remain invariant or at least can be controlled over the range of the specified critical physical or chemical manufacturing steps that will be used to process the material. This does imply that integration will be best achieved by a multivariate approach using straightforward algebraic mathematics to compute

PCCP set points. The calibrated, automated approach turns out to be some iteration of well-known multivariate statistical process control (MSPC) tools that have a long history of acceptance in other manufacturing realms. However, it should not be interpreted to mean that the guidance or this article implies that all PAT applications will be complex or even multivariate. Defining the desired state for a particular product means one will have to identify what is known to have impact on product attributes, what is unknown, and what will come to be as recognized as unknowable in order to achieve control and understanding over a process. These initial steps may not need to rely on real-time control techniques or utilize complex multivariate mining or modeling techniques. But once enough information has been gathered from a process and its intended product, real process control, chemistry, engineering, and analysis can begin. Having achieved this level of understanding, one can began to think about implementing sophisticated multivariate statistical process control (MSPC) techniques to determine where and how to integrate these systems throughout the product life cycle.

MSPC will be applied to analytical tools that will most likely be used in PAT processes. These include but are not limited to: NIR, Raman, FTIR, UV/VIS, HPLC, GC, LC/ MS, titration, etc. Finally, a test method using one or more of the analytical tools in PAT will have to be qualified, and the qualification process most likely will involve instrument qualification, method development, method calibration, and method validation.

One possible way to think about the PAT approach with respect to all of its components in a practical way is illustrated in Figures $2 a$ and $2 b$. Figure $2 a$ relates all of the significant and practical pieces for implementing PAT previously explored in the guideline. Figure $2 b$ shows how one can integrate QbD , risk, Six Sigma, and the later calibration and validation method requirements into one holistic scheme utilizing the salient features from each and relating them together to accomplish a viable and workable PAT approach to a pharmaceutical manufacturing process.


Gary Ritchie, United States Pharmacopeia
Fig. 2a. PAT mind map

| Calibration and <br> Validation | Risk | QbD | Six Sigma |
| :---: | :---: | :---: | :---: |
| I | What do I want to measure? <br> Why do I want to measure it? <br> Where will I measure it? <br> When will I measure it? <br> How will I measure it? | DoE | Define opportunities |
| II | Relate PCCP <br> to <br> Meas <br> Meast Result <br> to <br> Product Quality Attribute | Verify sensor <br> and analyzer <br> ability by MSPC | Measure <br> performance |
| III | What is it I want to control? <br> Why do I want to control it? <br> Where will I control it? <br> When will I control it? <br> How will I control it? | Experiment, <br> test, or <br> measuring <br> procedure | Analyze opportunity |
| IV | Achieve consistent and <br> predictable product quality <br> attribute | Reiterate back <br> to step S I, II, or <br> III | Improve <br> performance <br> Control performance |

Gary Ritchie, United States Pharmacopeia
Fig. 2b. PAT Interrelationships

## PHARMACOPEIAL ROLE IN PAT: USP PERSPECTIVE

It is incumbent upon USP to participate in the evolution of PAT and to remain engaged with the pharmaceutical industry. Some have suggested that USP is more relevant to the generic industry than to innovators, primarily because most $U S P-N F$ monographs involve off-patent dosage forms. Addressing PAT would make USP as important to innovators as to generic drug manufacturers. By defining the role of PAT in the pharmaceutical industry, USP could help create a legal and readily acceptable standard for assessing and verifying PAT methods suitability under actual conditions of use. As stated in the USP Mission and Preface of $U S P-N F$ : "Authoritative standards are recognized as representing 'scientific truth' at the time they are established and can be relied upon by their users. As science and technology evolve, so do USP and NF, which undergo continuous revision."

USP proposes to facilitate and complement the FDA framework for improving product quality in pharmaceutical manufacturing. USP will accomplish this by exploring, through its various Expert Committees and Project Teams, breakthrough technologies as they evolve in order to strengthen the scientific underpinnings of the risk-based de-cision-making strategies that FDA seeks to employ within the pharmaceutical industry.

Specifically, USP proposes to implement PAT standardssetting strategies by means of Project Team 18-Process Analytical Technologies (PAT) and to recommend solutions to relevant Expert Committees. For instance, proposed General Chapter $\langle 1073\rangle$ Effusivity [see PF 30(4)] was recommended to the Pharmaceutical Dosage Forms Committee, and proposed General Chapter $\langle 1120\rangle$ Raman Spectropho-
tometry was recommended to the PA6 Committee. Other proposed chapters or PAT project team activity underway and their respective Project Team 18 Work Groups include:

1. Working Group $1-\langle 1119\rangle$ Near-Infrared Spectrophotometry (In-Process Revision) USP 27-NF 22 Second Supplement
2. Working Group 2-Multivariate Analysis/Chemometrics
3. Working Group 3-Acoustics
4. Working Group 4-Study existing USP chapters for possible revision
5. Working Group 5-Terminology/Glossary
6. Working Group 6-Rapid Microbiological Methods Applications and Technologies
Industry has voiced some concerns about USP's approach to dealing with PAT issues. Following are some responses to these concerns.

## General Notices

It has been suggested that General Notices are a perceived barrier to the PAT initiative and require further clarification. However, the General Notices of the current USP allow the use of PAT approaches as an alternative for verifying product quality: "Compliance may be determined also by the use of alternative methods chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances." On this basis some manufacturing firms have accepted FDA's invitation to voluntarily adopt scientific, risk-based strategies for employing alternative manufacturing strategies to increase process understanding. In doing so, these firms are attempting to minimize process and product variability, which should result in an improvement in product quality. Less cited is the final sentence of
the paragraph of the General Notices'statement from which the quotation above is taken: "However, Pharmacopeial standards and procedures are interrelated; therefore, when a difference appears or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive."

## PAT Chapter

USP has been asked several times to revise or clarify the General Notices regarding PAT or to create a high-level ( $>1000$ ) PAT Chapter. Given the scope and depth of the subject, we do not recommend that such a chapter be written, at least at this time. However, we do recommend making certain revisions to USP regarding aPMP. One such issue involves General Chapter $\langle 905\rangle$ Uniformity of Dosage Units. The specification, targeted to a singlet determination, is not useful for providing the appropriate criteria for a PAT method based on multiple measurements. Another urgent issue is providing appropriate analytical performance characteristics for PAT methods. Although the current General Chapter $\langle 1225\rangle$ Validation of Compendial Methods provides appropriate analytical performance characteristics, a statement or a separate general chapter would need to discuss the appropriate approaches to validate PAT methods. These are just a few of the important and relevant issues that USP should begin to address.

## PAT Technology Chapters

USP is in the process of developing chapters on modern analytical techniques. These techniques are currently implemented broadly in the industry or are under consideration by a significant proportion of manufacturers. For techniques that have broad acceptance, USP is simply working with industry to record the existing industry standards for these techniques. For techniques that show great promise for broad implementation, USP is developing chapters that are broad-based and informative without being prescriptive, thereby creating a tool kit for implementation by industry and ultimately easing the way to acceptance of the principles of PAT and, more importantly, increasing product quality.

## Chemometrics General Chapter

Chemometrics represents the extension of statistics to multivariate and very complex data sets. These mathematical techniques are critical to the successful application of many modern techniques both in the lab and in the PAT sense. This chapter will present a general overview of many of the better-understood and widely implemented techniques in use by industry. These techniques are used extensively in near-IR spectroscopy and have generated the following discussion points:

Although NIR is somewhat different from conventional analytical techniques so that validation is generally achieved by the assessment of specialized chemometric parameters,
these parameters can still be related to the fundamental validation characteristics required for any analytical method.
Data pretreatment often is a vital step in the chemometric analysis of NIR spectral data. It can be defined as the mathematical transformation of the NIR spectral data to enhance spectral features and/or remove or reduce unwanted sources of variation prior to the development of the calibration model. Calibration is the process of constructing a mathematical model to relate the response from an analytical instrument to the properties of samples. Many suitable chemometric algorithms for data pretreatment and calibration exist; the selection should be based on suitability for the intended use. Analysts can use any available data transform or algorithm that can be clearly defined in an exact mathematical expression and that gives suitable results.
The model for an NIR method is developed, stored, and applied in electronic form as part of an appropriate instrument/software package. When a model is transferred to another instrument, procedures and criteria must be applied to demonstrate that the model remains valid on the second instrument. In general, electronic model transfer is recommended only for another instrument of the same type and configuration. Several model transfer procedures exist and can be applied as appropriate. Procedures involve the use of various chemometric (mathematical and statistical) approaches with appropriate validation.

## PAT Equipment Calibration and Validation

Instrument calibration and validation represent the ongoing assurance that the measurements obtained from an instrument accurately and precisely represent the sample being analyzed. Calibration is independent of the analytical procedure and simply ensures that a signal obtained from a known standard is repeatable with time. The frequency and extent are typically not the responsibilities of USP but rather of the user. Validation is procedure and sample specific. Validation is the demonstration of the causal link between a measured value and a characteristic of the analyte. The extent of validation is variable and must be appropriate to the specific use. Therefore, USP typically has developed very broad descriptions of often-used evaluations. PAT is no different in terms of the need for validation, but it may differ in extent and frequency. A USP chapter should represent the standard evaluations that can be used in such a way that the industry can define which will be used and how they will be interpreted. Therefore, USP serves a valuable purpose by reconciling these standard approaches. Please note that USP is a living document that will be updated as necessary to ensure the applicability of the chapter and the standard.

## CONCLUSION

This Stimuli article has given an overview of FDA's PAT initiative and has reviewed several key documents associated with it, notably the Guidance for Industry, PAT-A Framework for Innovative Pharmaceutical Development,

Manufacturing, and Quality Assurance. As we have seen, the origins of PAT actually can be traced back through cGMP regulations. FDA's Office of Pharmaceutical Sciences has said that PAT implementation should be scientific and risk-based, and to these ends this article has reviewed 10 key questions that a firm should consider before embarking on a PAT implementation scheme. The ultimate goal of pharmaceutical manufacturing, and thus of PAT, is to ensure quality, so we have extensively reviewed the quality aspects of PAT implementation. This led to a discussion of the various roles that USP has played and will continue to play in the development of PAT. As a stan-dards-setting organization, USP already has demonstrated leadership by developing important chapters in key areas of concern to PAT. No less important, however, is the continuing thought leadership and innovation that USP's volunteer community will continue to contribute through the work of its project teams and expert committees.

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## PAT KEY TERMS

Terminology for Process Analytical Technology
Objective of draft: to provide a list of terms for use in general chapters related to PAT.

A priori, adj -
Accepting Criteria, $\mathrm{n}-$.
Active, n -.
Active Pharmaceutical Ingredient (API), $n-$.
Alternating Least Squares, $\mathrm{n}-$.
Analyte, n -.
Analyze, v-.
At-Line, adj - .
Automated, adj -.
Automated Measurement, $\mathrm{n}-$.
Automated Systems, $\mathrm{n}-$.
Average Change Chart, $\mathrm{n}-$.
Batch, n -.
Batch-to-Batch, adj -.
Batch Processing, $\mathrm{n}-$.
Batch Run, n -.
Batchwise, adv -.
Best Practices, $\mathrm{n}-$.
Bilinear Model, n -.
Black Box Model, n -.
Calibration, n -.
Causal Relationship, $\mathrm{n}-$.
Channel, n -.
CGMPs, n -.
Computerized System, $\mathrm{n}-$.
Correlation, $\mathrm{n}-$.
Contamination, $\mathrm{n}-$.
Continuous Processing, $n-$.
Control, n -.
Correlation, $\mathrm{n}-$.
Critical, adj -
Critical Process Parameter, $\mathrm{n}-$.
Critical Quality Attribute, n-.
Critical Quality Parameter, $\mathrm{n}-$
Cross-contamination, $\mathrm{n}-$.
Curve Resolution, n -.
Data Mining, n -.
Decompose, v -.
Deconvolution, $\mathrm{n}-$.

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Devices, n -
Design of Experiments (DoE), $\mathrm{n}-$.
Desired State, $\mathrm{n}-$.
Derivatives, $\mathrm{n}-$.
Deviation, $\mathrm{n}-$.
Diagonal, adj - .
Direct, adj .
Drug Product, n -.
Efficacy, n - .
Empirically, adv -.
End Point Detection, $\mathrm{n}-$.
End Product Quality, n-.
Estimates, n -.
Full Scale, n -.
Gray or Grey Model, n -.
Inferential, adj -.
In-Line, adj -.
In-Process Control, $\mathrm{n}-$.
In-Process Material, $n-$.
In-Process Testing, $\mathrm{n}-$.
In-Process Tests, $\mathrm{n}-$
Instrument Qualification, $\mathrm{n}-$.
Intermediate, $\mathrm{n}-$.
Invariant, adj - .
Laboratory Controls, $\mathrm{n}-$.
Laboratory Scale, $n-$.
Linear, adj - .
Linear Regression, $\mathrm{n}-$.
Loading, ger -.
Manipulation, n -.
Manufacture, $\mathrm{n}-$.
Manufacturer, n -.
Manufacturing Control, $\mathrm{n}-$.
Manufacturing Processes, $\mathrm{n}-$.
Material, n -.
Matrices, n -.
Matrix, n -.
Measurement, n -.
Measuring, ger -.
Medical Devices, n -.
Method Calibration, $\mathrm{n}-$.
Method Development, $\mathrm{n}-$.
Method Transfer, n -.
Method Validation, $\mathrm{n}-$.
Mining, ger - .
Modeling, ger - .
Monitoring, ger -.
Moving Average, $\mathrm{n}-$.
Multivariate, adj -.
Multivariate Analysis, n -.
Multivariate Statistical Process Control (MVSPC) Tools, $\mathrm{n}-$.
Multiple Linear Regression (MLR), $\mathrm{n}-$.
Non-Linear, adj -
Off-Line, adj -.
On-Line, adj -.
Operational Characteristics, $\mathrm{n}-$.
Optimization, $\mathrm{n}-$.
Orthogonal, adj -.

Output Signal, $\mathrm{n}-$.
Packaging/Labeling, $\mathrm{n}-$.
Packaging Material, $\mathrm{n}-$.
Parametric Release, n -.
Partial Least Squares (PLS), $\mathrm{n}-$.
Partial Least Squares Regression (PLSR), $\mathrm{n}-$.
Performance Attributes, $\mathrm{n}-$.
Pharmaceutical Processes, $\mathrm{n}-$.
Pilot, n -.
Prediction, $\mathrm{n}-$.
Procedure, n -.
Principal Component Analysis (PCA), $n-$.
Principal Component Regression (PCR), n-.
Process Analytical Chemistry, $\mathrm{n}-$.
Process Analytical Technology (PAT), n-.
Process Attributes, $\mathrm{n}-$.
Process Control, $\mathrm{n}-$.
Process Critical Parameters, $\mathrm{n}-$.
Process Critical Control Parameter (PCCP), $\mathrm{n}-$.
Process Parameter, $\mathrm{n}-$.
Process Quality Control, $\mathrm{n}-$.
Process Understanding, $\mathrm{n}-$.
Process Signature, $\mathrm{n}-$.
Product Performance, $\mathrm{n}-$.
Production, n -
Projection to Latent Structures, $\mathrm{n}-$.
Purity, n -.
Qualification, $\mathrm{n}-$.
Quality, n -.
Quality Assurance, n -.
Quality Control, $\mathrm{n}-$.
Quality Unit, $\mathrm{n}-$.
Quarantine, n -.
Range Chart, $\mathrm{n}-$.
Raw Material, n -.
Reference Standard, Primary, n-.
Reference Standard, Secondary, $\mathrm{n}-$.
Reprocessing of an API, $\mathrm{n}-$.
Retest Date, $\mathrm{n}-$.
Residual, adj - .
Restrictions, n -.
Reworking, ger -
Risk, n -.
Risk Analysis, n -.
Risk Assessment, n -.
Risk-Based, adj -.
Risk Evaluation, n -.
Risk Mitigation, $\mathrm{n}-$.
Run, n -.
Safety, n -.
Sample, $n-$.
Sampling, ger -.
Scale, n -.
Scale Up, n-.
Scalar, adj -.
Scores, n -.
Selectivity, n -.
Specification, $\mathrm{n}-$.

Specificity, n -.
Starting Material, n -.
Statistical Process Control, $\mathrm{n}-$.
Statistical Monitoring, $\mathrm{n}-$.
Sterile Product Control, $\mathrm{n}-$.
Systems, n -.
Time Resolved, $\mathrm{n}-$.
Temporal, adj -
Testing, ger -
Trend, n -.
Unit Batch Processing, $\mathrm{n}-$.
Univariate, adj -.

Vector, n -.
Validation, n -.
Validation Protocol, $\mathrm{n}-$.
Variation, n -.
Variant, adj -.
Wavelength, $\mathrm{n}-$.
Wavenumber, n -.
White Models, $\mathrm{n}-$.
Window, n -

# The Impact of Multiple-Unit Desiccating Containers for Prescription Packaging 

Peter Sagona, ${ }^{*}$ Jon Freedman, William Spano, and Robert Pangborn, Ph.D.


#### Abstract

Granular drying agents, referred to as desiccants, are often packaged with pharmaceuticals that are moisture sensitive. Many of these moisture-sensitive drugs are packaged in bulk quantities with desiccant and are delivered to pharmacies or prescription fulfillment groups. These drugs are then repackaged into smaller containers by pharmaciesoftentimes in a container without a desiccant. In 2003, CSP Technologies collaborated with USP's Packaging, Storage, and Distribution Expert Committee to study desiccant effects in commercially available multiple-unit pharmacy containers. Both well-closed and tightly closed containers were used in the study, as were desiccating containers. The objectives of this study were to determine the amount of moisture that entered each container and to compare the relative humidity maintained in desiccating and nondesiccating containers during a 90 -day prescription use life.


## INTRODUCTION

During the past several years, USP has been studying pharmacy containers and container-closure systems to maintain the stability of moisture-sensitive drugs throughout the prescription use life. It is understood that one important factor in maintaining the stability of moisture-sensitive drugs is to control the environment (i.e., the relative humidity) inside the container. Relative humidity ( RH ) is a measure of the moisture content in air. RH is described as a saturation percentage at a specified temperature- $100 \%$ RH is the point at which air is completely saturated.

Multiple-unit pharmacy containers are characterized as "tight" or "well-closed" by USP General Chapter $\langle 671\rangle$ Containers-Permeation guidelines based on the moisture leakage rate into the container. However, even a tightly closed container cannot remove moisture that has entered the container, particularly after an open/close cycle. Without a means for absorbing this moisture, the moisture content in the container rises, and the drug product becomes subjected to increased moisture. An ability to absorb the incoming moisture during the open/close cycle is needed to prevent the drug product from absorbing moisture.

Granular drying agents, referred to as desiccants, are often packaged with pharmaceutical drugs that are moisture sensitive. Many of these moisture-sensitive drugs are packaged in bulk quantities with desiccant and are delivered to pharmacies or prescription fulfillment groups. These drugs are then repackaged into smaller containers by pharma-cies-oftentimes in a container without a desiccant. A mul-tiple-unit pharmacy container may contain 100 or more unit doses and have a prescription use life of 90 days.

[^370]In 2003, CSP Technologies collaborated with USP's Packaging, Storage, and Distribution Expert Committee to study the effects of a desiccant in multiple-unit pharmacy containers. The study was conducted with commercially available pharmacy containers. Both well-closed and tightly closed containers were used in the study. Desiccating containers also were used. The objectives of this study were to determine the amount of moisture that entered each container and to compare the RH maintained in desiccating and nondesiccating containers during a 90 -day prescription use life.

## Test Protocol

Five different container types were used for the study:

1. Owens Illinois L-8 Container with SL-26 Screw-Loc closure-USP $\langle 671\rangle$ tightly closed.
2. Owens Illinois L-8 Container with CS-30 Snap Cap closure-USP $\langle 671\rangle$ well-closed.
3. Owens Illinois L-8 Container with SL-26 Screw-Loc closure, with a total of 6.0 grams of molecular sieve desiccant.
4. Owens Illinois L-8 Container with CS-30 Snap Cap closure, with a total of 6.0 grams of molecular sieve desiccant.
5. CSP Technologies M-3006-47 Activ-Vial with 8.0 grams of desiccant incorporated into the container inside wall.
All containers had a volume of approximately 31 cc .
A data logger was placed into each container and was used to record the temperature and RH inside each container during the test. The ambient conditions were $22^{\circ} \mathrm{C}$ and $10-$ $15 \%$ RH. One data logger suitable for use is a data logger manufactured by Hanwell Ltd., Hertford, UK, that monitors and records temperature and relative humidity (Figure 1). The RH logger is wireless and is specially designed to measure the RH inside small containers.


Fig. 1. Hanwell Hornet data logger

For each set of containers the RH was recorded for both the steady-state condition (referred to as the prescription-life condition) and the open/close condition (referred to as the use-life condition).

## Prescription-Life Condition

A set of containers was placed in an environmental chamber and was maintained at $30^{\circ} \mathrm{C}$ and $80 \% \mathrm{RH}$. The RH was recorded at regular intervals over a 90 -day period in each container type (the steady-state condition). A total of 30 containers of each type was used for a total of 150 containers.

## Use-Life Condition

A separate set of containers was set up to measure the amount of moisture that enters the container during use life. These containers were also placed in an environmental chamber maintained at $30^{\circ} \mathrm{C}$ and $80 \%$ RH. The RH was measured during a 90 -day use life during which the container was opened 3 times a day with a 1-minute opening interval. This occurred 5 days per week over the 90 -day testing period. A total of 30 containers of each type was used for a total of 150 containers.

At the completion of testing, the temperature and RH data from each logger were downloaded to a personal computer and evaluated using Hanwell's Z567 graphical software.

## Findings-Nondesiccating Containers

As can be seen in Figure 2, for containers without desiccant the RH inside the container increases rapidly from the initial condition of $10-15 \%$ RH. The results are similar in both the well-closed and tightly closed containers. The RH inside the container continued to increase over the prescription life and eventually equilibrated with the outside environment. The study found that the rise in RH was larger over the first 10 days. The containers reached a RH of $60 \%$ after 10 days in environmental conditions of $30^{\circ} \mathrm{C} / 80 \% \mathrm{RH}$ and a RH of $\sim 70 \%$ after 30 days. The RH continued to increase slowly until the RH inside the container reached $80 \%$. Based on the rapid increase in RH, the duration of the test was shortened to 30 days.
During open/close cycle testing, containers without desiccant immediately took on the relative humidity (RH) of the outside environment after the first opening. The RH remained at the $80 \%$ RH level over the entire use-life test.


Fig. 2. Temperature and relative humidity behavior of nondesiccating container (SL26-ND) in relation to time in days.

## Findings-Desiccating Containers

With respect to the prescription life condition, the RH in the containers was recorded over the testing period, initially defined as 90 days. The results indicate that all container
types with 6 grams of molecular sieve desiccant maintained a RH of $<5 \%$ over the period. The results are shown in Figure 3 and illustrate the effect of a desiccant on the RH inside the container.


Fig. 3. Temperature and percent RH observed in a container with desiccant (CSP-2D).

With respect to the use-life condition, the data loggers recorded the change in RH during the opening and closing of the containers. The containers with desiccant reestablished a low RH after each open/close cycle. On average, the RH in
the desiccated containers returned to $<5 \%$ within 20 minutes after the open/close cycle. Figure 4 illustrates the changes in RH during the open/close cycle.


Fig. 4. Percent RH maintained in desiccated pharmacy container (SL26-1D) during use-life conditions.

## Total Moisture into the Container

Again with reference to the prescription-life condition, the amount of moisture entering a container is based on:

1. the quality of the closure seal,
2. permeation rate of moisture through the container materials, and
3. the driving force within the container that has the potential to absorb moisture.
Containers used in the study were tested for moisture ingress (permeation) based on the USP $\langle 671\rangle$ test method. This method uses a calcium chloride desiccant inside the container as the driving force to maintain a moisture gradient with the ambient environment.

Based on the USP $\langle 671\rangle$ test, the moisture ingress rate for the well-closed container is $20 \mathrm{mg} /$ day, and the moisture ingress rate for the tightly closed container is $2 \mathrm{mg} /$ day.
Using nondesiccating containers, the incoming moisture is absorbed by the drug product. In desiccating containers, the desiccant absorbs the incoming moisture and not the product. Figure 5 compares the potential amount of moisture seen by the product over a 90 -day shelf life in containers with desiccant and without desiccant.

With reference to the use-life condition, over the 90-day period, the container was opened 3 times a day for 1-minute intervals. During each opening cycle the volume of air inside the container was exchanged with the ambient air. At the environmental conditions of $30^{\circ} \mathrm{C} / 80 \% \mathrm{RH}$, the amount of incoming moisture per opening (for a 31 -cc volume) is 7.2 mg .


Fig. 5. Moisture seen by product after 90 days (USP $\langle 671\rangle$ protocol).

Figure 6 compares the potential amount of moisture seen by the product over a 90 -day use life in containers with
desiccant and without desiccant.


Fig. 6. Moisture seen by product in nondesiccated and desiccated containers after 90 days under use-life conditions (USP $\langle 671\rangle$ protocol) .

The desiccating container directs moisture away from the product. Desiccants have a greater attraction for the incoming moisture and absorb the moisture before it reaches the pharmaceutical. Desiccants have the potential to dramatically reduce the amount of moisture seen by the drug.

## Desiccating Container Considerations

Desiccants are widely used in the primary packaging of pharmaceuticals. Desiccants are sold in single-unit sachets or canisters containing 1-3 grams of either silica gel or molecular sieve desiccant. Alternatively, desiccants are some-
times placed into a reservoir in the container lid. The container and the desiccating lid are 2 separate parts. All desiccants have a certain moisture capacity per unit mass of desiccant. Care must be taken to minimize the exposure of the desiccant to environmental moisture prior to packaging. For this reason desiccants are normally stored in a moisturetight package (e.g., a foil bag) prior to use. Often, a low-RH environment in the packaging area is used to ensure that the desiccant does not absorb moisture before packaging.
Desiccating containers are now commercially available with the desiccant incorporated into the inner walls of the container. The desiccant is blended into a plastic insert so that the granular desiccant is bound in the plastic and there is no separate desiccant component to manage. The con-
tainer may also incorporate a flip-top lid that protects the desiccant from absorbing environmental moisture prior to filling.

The amount of desiccant needed in the container is calculated based on:

1. the moisture leak rate into the container,
2. the storage- and use-life requirements, and
3. environmental conditions (temperature and RH ) during storage life and use life.
The manufacturers of pharmacy containers would be responsible for determining the amount of desiccant required in the container. The manufacturers will certify that the container meets the 90 -day desiccating requirements using an approved analytical method.

Nondesiccating pharmacy containers cost in the range of $\$ 0.08-0.12$ per unit depending on the container size. A desiccating container costs an additional $\$ 0.02-0.04$ per container, based on the amount (mass) of desiccant. The increased cost to use a desiccating container is relatively small compared to the protection offered to the prescription packaged.

The use of a desiccating container for a prescription is based primarily on the moisture sensitivity of the pharmaceutical; clearly, not all drugs require a desiccating con-
tainer. The pharmacist or prescription fulfillment center will decide whether to package a drug in a desiccating container based on the packaging requirements of the pharmaceutical product. Changes in pharmaceutical labeling may be necessary to instruct pharmacists in selecting the proper container for each pharmaceutical product.

## CONCLUSION

Desiccating containers provide a cost-effective means of protecting moisture-sensitive pharmaceuticals during the prescription use life. The key benefit of a desiccating container is the ability to absorb moisture that enters the container during an open/close cycle before the moisture is absorbed by the drug product. A desiccant may be included in the container using traditional methods (i.e., canister or sachets). Alternatively, currently available containers have the desiccant blended into the inner wall of the container. Suppliers of desiccating containers should provide certification that the container supports the USP container requirements for desiccating containers. Changes to the labeling requirements of pharmaceuticals may be necessary to identify which products require a desiccating container.

# Inductively Coupled Plasma-Optical Emission Spectroscopy as an Alternative to the Heavy Metals Test 

Martha Schenkenberger* and Nancy Lewen


#### Abstract

There has been growing concern regarding the use of the United States Pharmacopoeia (USP) test for Heavy Metals, Method II $\langle 231\rangle$. A recent publication (3) describes the use of inductively coupled plasma-mass spectrometry (ICPMS) as an alternative to the compendial heavy metals test. USP recognizes that the current method utilizes dated technology and has proposed that modern spectroscopic techniques be used to perform the heavy metals testing of pharmaceutical ingredients. A general chapter on plasma spectrochemistry was proposed in Pharmacopeial Forum (4).

This article describes the use of another spectroscopic technique, inductively coupled plasma-optical emission spectroscopy (ICP-OES), as an alternative to the compendial heavy metals test. ICP-OES offers many advantages over the compendial method. It is a rapid, multielement technique that can be used to assay for the following elements: antimony ( Sb ), arsenic (As), bismuth (Bi), cadmium (Cd), indium ( In ), lead ( Pb ), mercury ( Hg ), molybdenum (Mo), palladium ( Pd ), platinum ( Pt ), ruthenium $(\mathrm{Ru})$, selenium $(\mathrm{Se})$, silver $(\mathrm{Ag})$, and tin $(\mathrm{Sn})$. Other advantages to the use of this technique include the fact that only a small quantity of sample is required, and it provides element-specific results.


## INTRODUCTION

Recent publications $(1,2,3)$ have proposed the use of inductively coupled plasma-mass spectrometry (ICP-MS) as an alternative to the USP test for Heavy Metals, Method II $\langle 231\rangle$. Additionally, a general chapter on plasma spectrochemistry was proposed in Pharmacopeial Forum (4). As a result, the authors propose an inductively coupled plas-ma-optical emission spectroscopy (ICP-OES) method as a possible alternative to the compendial method in chapter $\langle 231\rangle$ for heavy metals. This method would provide ele-ment-specific quantitative results for the following elements: arsenic (As), cadmium (Cd), indium (In), tin (Sn), antimony $(\mathrm{Sb})$, lead $(\mathrm{Pb})$, bismuth $(\mathrm{Bi})$, silver $(\mathrm{Ag})$, mercury $(\mathrm{Hg})$, ruthenium $(\mathrm{Ru})$, and molybdenum (Mo). Platinum $(\mathrm{Pt})$, palladium $(\mathrm{Pd})$, and selenium $(\mathrm{Se})$ may also be determined because these elements either are frequently used as catalysts or are sufficiently toxic to warrant examination.

## EXPERIMENTAL PROCEDURE

Accurately prepare a $1 \%$ solution of sample dissolved in a suitable solvent in an acid-washed volumetric flask. (A suitable solvent is one that is capable of completely dissolving the solid sample and does not provide any analytical interferences when introduced into the ICP-OES instrument. Additionally, a suitable solvent should be relatively nonvolatile, such as deionized water, dilute nitric acid, dilute hydrochloric acid, or a solution of butoxyethanol and water [25:75].) If necessary, add an appropriate internal standard according to the guidelines detailed in the proposed general
chapter on plasma spectrochemistry in $P F$ (4). Prepare working standard solutions that contain 0.5 and $1.0 \mu \mathrm{~g} /$ mL each of $\mathrm{As}, \mathrm{Cd}, \mathrm{In}, \mathrm{Sb}, \mathrm{Pb}, \mathrm{Bi}, \mathrm{Hg}, \mathrm{Ru}, \mathrm{Mo}, \mathrm{Pt}, \mathrm{Pd}$, and, if necessary, an appropriate internal standard according to the guidelines detailed in the proposed general chapter on plasma spectrochemistry (4). Dilute to volume with the same solvent used to dissolve and dilute the sample. Prepare a second set of working standard solutions that contain 0.5 and $1.0 \mu \mathrm{~g} / \mathrm{mL}$ each of Se and Ag and, if necessary, an appropriate internal standard according to the guidelines detailed in the proposed general chapter on plasma spectrochemistry (4). Dilute to volume with the same solvent used to dissolve and dilute the sample.
Using either an axial or lateral ICP-OES instrument, select at least three wavelengths per analyte element. Follow the guidelines detailed in the proposed general chapter on plasma spectrochemistry in $P F$ (4) for calibration and analysis.

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[^371]
# Particulate Contaminants of Intravenous Medication and the Limits Set by USP General Chapter $\langle 788$ 〉 

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#### Abstract

The presence of foreign particulates in drug products is a function of the manufacturing process, and the limits on particulates are described in USP General Chapter $\langle 788\rangle$ Particulate Matter in Injections. Contamination of parenteral drugs with particulate matter, especially regarding intravenous or intrathecal injections, is potentially dangerous to the patient's health. Risks associated with the injection of particulates intravenously have been well documented.

Exhibit batch records for 406 lots in 295 drug applications for various injectable drugs from 1998 to 2002 were reviewed. Particulate counts for each lot were noted and analyzed statistically.

The mean counts for particles $\geq 25 \mu \mathrm{~m}$ were $15 \pm 43$ (mean $\pm 1 \mathrm{SD}$ ). The corresponding counts for $\geq 10 \mu \mathrm{~m}$ particles were $219 \pm 415$. Statistically significant differences in particulate contamination were observed between aseptically processed and terminally sterilized products and different types of containers (ampules, glass and plastic vials, and syringes) used to fill the drug products.

USP $\langle 788\rangle$ allows up to 6000 and 600 particles per container for $10 \mu \mathrm{~m}$ and $25 \mu \mathrm{~m}$ particulates, respectively. Based on our data it appears that the current limits are lenient and that the USP $\langle 788\rangle$ acceptance limits could be lowered.


## INTRODUCTION

It is well recognized that contaminating particles, viable or nonviable, are undesirable in sterile products intended for parenteral administration, especially those for intravenous or intrathecal injection. Harmful effects of particulate contamination are well documented both clinically and experimentally (1-11). Reducing and eliminating particulate contamination remains a goal for all sterile drug products; however, in practice, low levels of contamination with nonviable particulate remains inevitable. Improvements in manufacturing technologies have allowed better control in limiting these contaminants.

In order to control contaminants in drug products it is necessary to understand the source and the nature of these contaminants. It is well known that the type and nature of contamination depends on the manufacturing process. Various contaminants have been identified as rubber (from stoppers), glass (from vials), fiber (from uniforms), rust and metal (from machinery), silicon (from siliconization of stoppers), dust, and crystals. Other materials, such as plastic (from the molding process), also could contaminate the drug products (2, 12-16).

The methods of detection and the limits for nonviable particulate contamination in parenteral drugs are described in USP General Chapter $\langle 788\rangle$ Particulate Matter in Injections, and these limits serve as the de facto standards. USP

[^372]$\langle 788\rangle$ was first proposed in 1983, and it became official in USP XXI in 1986. According to a report by the Committee on Particulate Matter (17), particulate limits were based on data provided by FDA for 19 drug products, including small-volume parenteral (SVP) and large-volume parenteral (LVP) drug products, in which the combined mean particulate counts for $10-\mu \mathrm{m}$ particulates were reported to 59 ( $\pm 89$ ) particles per mL and the corresponding values for $25-\mu \mathrm{m}$ particulates were $13( \pm 27)$ per mL . Historical perspectives on particulate contamination limits incorporated in USP $\langle 788\rangle$ are described in commentaries (18, 19). We present data representing 110 different drugs manufactured by 51 different firms using a variety of manufacturing processes during a five-year period from 1998 to 2002. Data presented show that the limits specified in General Chapter $\langle 788\rangle$ could be significantly lowered without rejecting a large number of manufactured products. These lower limits would ensure that injectable drug products sold in the United States are of the highest quality that is reasonable.

## METHODS

In the five-year period from 1998 to 2002, the Office of Generic Drugs received and reviewed 295 Abbreviated New Drug Applications (ANDAs) for injectable drug products. The applications included drugs that were liquids, lyophilized, or sterile powder. Data for only SVPs ( $\leq 100 \mathrm{~mL} /$ container) are included in the analysis; LVPs ( $>100 \mathrm{~mL} /$ container) are excluded. It should be noted that particulates are expressed on a per-container basis in the case of SVPs and on a per-mL basis in the case of LVPs.

Exhibit batch records submitted in each of 295 ANDAs were reviewed, and the particulate counts for each lot were recorded from the Certificate of Analysis (COA) provided in the application. In most cases, the light-obscuration method was used to count particulates in the drug products; however, the specific nature of instruments used is not recorded and is not part of this analysis. If the COA did not contain numerical values for the particulate counts, then the particulate counts were obtained from the stability data. If the particulate counts were provided, they were noted and included in the analysis. The particulate data from stability studies reflected early test points only and did not represent counts at the end of the product shelf life.

In a few cases, when multiple values for the same lot were provided, e.g., when vials were tested from the beginning, middle, and end of a run, the highest value for the particulates (reflective of the worst-case scenario) were recorded and used in the analysis. In applications where data for more than one exhibition lot were provided, values for all lots were noted and analyzed. A total of 38 ANDAs were excluded either because the ANDAs were not available (13) or the particulate counts were not reported in the COA (25) or the stability data could not be included for a variety of reasons.

Overall, numerical counts for particulates were available for 228 out of 295 applications reviewed. Data for a total of 406 lots were available and entered into a Microsoft Excel spreadsheet for analysis. The analysis included calculation of the mean, standard deviation, standard error, distribution analysis, regression analysis, and $t$-Test.

## RESULTS AND DISCUSSION

## Basis of Data

Particulate data analyzed are derived from a total of 295 ANDAs received during a five-year period, 1998 to 2002, as summarized in Table 1. For generic drugs, several different firms may apply for the same drug and dosage form. Each generic drug application is required to include manufacturing batch records for a minimum of one batch representing not less than (NLT) $10 \%$ of the full production lot using the same or equivalent equipment and process as used in the manufacture of the full production lots. It should be noted that data analyzed here closely represent manufacturing conditions and reflect lots produced commercially.

Table 1 lists the number of different drugs applied for each year. The applications were submitted by 15 to 17 different applicants each year, and during a period of five years a total of 51 different applicants applied for a total of 110 different drugs. The firms included small and large companies, established as well as new firms, and included both domestic and foreign firms.

Table 1. Summary of database (1998-2002) used in the study

| Type | 1998 | 1999 | 2000 | 2001 | 2002 | Total |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: |
| Number of <br> ANDAs | 64 | 52 | 68 | 53 | 58 | 295 |
| Number of <br> Firms | 15 | 17 | 17 | 17 | 17 | $51^{*}$ |
| Number of <br> Drugs | 25 | 23 | 30 | 33 | 42 | $110^{* *}$ |
| Number of Lots by Dosage Form |  |  |  |  |  |  |
| Injection | 85 | 50 | 80 | 53 | 66 | 334 |
| For Injection | 12 | 18 | 19 | 11 | 12 | 72 |
| Number of Lots by Container Type |  |  |  |  |  |  |
| Glass vials | 77 | 63 | 92 | 54 | 68 | 354 |
| Ampules | 3 | 2 | 7 | 2 | 9 | 23 |
| Plastic Vials | 5 | 2 | 0 | 0 | 0 | 7 |
| Flexible Bags ${ }^{\dagger}$ | 0 | 1 | 0 | 3 | 3 | 7 |
| Syringe | 12 | 2 | 0 | 0 | 1 | 15 |


| Number of Lots by Sterilization Process |  |  |  |  |  |  |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: |
| Aseptic <br> Process | 64 | 53 | 72 | 48 | 57 | 294 |
| Terminal Steri- <br> lization | 33 | 15 | 27 | 16 | 21 | 112 |
| Number of Lots by Fill Volume |  |  |  |  |  |  |
| LVP Lots $^{\ddagger}$ | 0 | 0 | 10 | 4 | 4 | 18 |
| SVP Lots | 97 | 68 | 99 | 64 | 78 | 406 |

* The total represents the number of different applications during five years. The same applicant may repeat in different years. The applicant is not necessarily the manufacturer of the drug product.
** The total represents the number of different drug products during five years. The same drug may repeat in different years.
${ }^{\dagger}$ Flexible bags are almost always LVP; these are not included in the particulate analysis.
$\ddagger$ ANDAs for LVPs are not included in the present particulate analysis.
NOTE: USP General Chapter $\langle 1\rangle$ defines SVP as containers $\leq 100 \mathrm{~mL}$; for the present study we used this definition.

Particle contamination data for 406 lots of various drugs were derived from a total of 228 ANDAs, including 334 lots that were liquids and 72 lots that were either lyophilized or filled as sterile powder. All lots represented SVP dose forms ( $\leq 100 \mathrm{~mL} /$ container). Another 18 lots, representing LVP ( $>100 \mathrm{~mL} /$ container) are not included in the present data analysis.
Data for the number of lots, according to the type of container used to package the drug products, show that $87 \%$ ( 354 out of 406 ) were filled in glass vials. Data also show that $72 \%$ (294 out of 406 ) were manufactured using an aseptic process.

## Particulate Counts

The mean particulate counts over five years show consistency (Table 2). The mean counts for $\geq 25-\mu \mathrm{m}$ particulates were $11,14,16,15$, and 19 for five years from 1998 to 2002 , and the corresponding values for $\geq 10-\mu \mathrm{m}$ particulates were $214,194,274,153$, and 259 . The mean
particulate counts over the five-year period did not show statistically significant trend as indicated by their correlation coefficient ( $R^{2}$ ) values as shown in Table 7. Overall, the mean particulate counts for all 406 lots were $15 \pm 43$ (mean $\pm 1$ SD) for $\geq 25-\mu \mathrm{m}$ particles and $219 \pm 415$ for $\geq 10-\mu \mathrm{m}$ particles (Table 3).

Table 2. Particulate contamination in SVP lots 1998-2002

|  | 1998 |  | 1999 |  | 2000 |  | 2001 |  | 2002 |  |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Number of Lots | 97 |  | 68 |  | 99 |  | 64 |  | 78 |  |
| Particle Size $(\mu \mathrm{m})^{*}$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ |
| Mean* $^{*}$ | 11 | 214 | 14 | 194 | 16 | 274 | 15 | 153 | 19 | 259 |
| SD | 28 | 587 | 44 | 291 | 51 | 635 | 54 | 238 | 39 | 326 |
| Mean +3 SD | 96 | 1977 | 145 | 1067 | 170 | 2178 | 179 | 867 | 136 | 1236 |
| Maximum | 231 | 5188 | 297 | 1204 | 377 | 3856 | 418 | 1160 | 198 | 1892 |

* In SVP parenteral drugs USP $\langle 788\rangle$ allows NMT 600 particulate $(\geq 25 \mu \mathrm{~m}) /$ container and NMT 6000 particles $(\geq 10 \mu \mathrm{~m}) /$ container when using the light-obscuration method. Using the microscopic method, particulates allowed are NMT $300(\geq 25 \mu \mathrm{~m})$ and $3000(\geq 10 \mu \mathrm{~m})$ particles/container.
${ }_{* *}$ All particulate counts for SVPs reported here are based on counts per container.

It should be noted that the FDA data used by USP in 1983 to set particulate limits were based on combined data for SVP and LVP and were presented as counts per mL, although the current counts for SVP are based on counts per container; therefore, the two sets of values are not directly comparable.

## Dosage Form

A comparison of particulate contamination in drugs that are liquids (Injections) and those that are either lyophilized or filled as sterile powder (For Injection) is summarized in Table 3. The mean counts for $\geq 25-\mu \mathrm{m}$ particulate were $13 \pm$ 38 and $24 \pm 44$ among Injections and For Injections, respectively. The difference is statistically significant; i.e., the probability that the observation was by chance alone is $<0.05 \%$ ( $p<0.05$ ). Similarly, a significant difference ( $p<0.01$ ) is also observed for $\geq 10-\mu \mathrm{m}$ particulate contamination. In a Canadian study significantly higher particulate counts in powder-fill products were reported (14); however, lower particulate counts were reported in another study of 11 lots of cephalosporin filled as dry powder (20).

Table 3. Particulate contamination by dosage form

|  | All Lots | Injections | For Injection |  |  |  |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: |
| Number <br> of Lots | 406 |  | 334 |  | 72 |  |
| Particle <br> $\quad$ Size $(\mu \mathrm{m})$ |  | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ | $\geq 25$ |
| Mean | 15 | 219 | 13 | 181 | 24 | $\geq 10$ |
| SD | 43 | 415 | 38 | 384 | 44 | 401 |
| Mean <br> $\quad 3$ SD | 145 | 1465 | 128 | 1333 | 157 | 1579 |

The reason for these differences between dosage forms is not known, but it is possible that the excess particulates observed in For Injection drugs represent insoluble aggregates of undissolved product ingredients. However, the higher particulate counts could also be process-associated contamination resulting from the lyophilization process.

## Manufacturing Process

Contaminating particulates in the products manufactured using a terminal sterilization process were significantly lower $(p<0.01)$ than in products that were produced using an aseptic process, as shown in Table 4. It could be argued that at least one of the reasons for the higher particulate counts in aseptically produced drugs is that the filtration process contributes to the particulates in the filtrate. However, we know that many terminally sterilized products also include a filtration step in addition to the terminal sterilization process. Therefore, filtration is probably not a full explanation of the observation.

Table 4. Particulate contamination by sterilization process

|  | All Lots | Aseptic <br> Process | Terminal <br> Sterilization |  |  |  |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: |
| Number <br> $\quad$ of Lots | 406 |  | 294 |  | 112 |  |
| Particle <br> $\quad$ Size $(\mu \mathrm{m})$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ |
| Mean | 15 | 219 | 17 | 245 | 10 | 154 |
| SD | 43 | 415 | 45 | 438 | 24 | 289 |
| Mean <br> $\quad 3$ SD | 145 | 1465 | 153 | 1560 | 82 | 1021 |

## Container Types

A comparison of particulate contamination in drugs filled in glass vials and those filled in glass ampules shows that significantly lower ( $p<0.01$ ) counts of $\geq 25-\mu \mathrm{m}$ particulates were observed in ampules compared to glass vials; however, the difference for $\geq 10-\mu \mathrm{m}$ particulates was not statistically
significant (Table 5). A similar comparison between glass vials and plastic vials showed significantly lower contamination in plastic vials. The presence of a relatively low level of particulates in plastic compared to glass ampules has been reported previously $(21,22)$.

Table 5. Particulate contamination by container type

|  | Glass Vials |  | Ampules |  | Plastic Vials |  | Glass Syringes |  |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Number of Lots | 354 |  |  | 23 |  |  | 7 |  |
| Particle Size $(\mu \mathrm{m})$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ |
| Mean | 16 | 226 | 6 | 185 | 5 | 59 | 5 | 111 |
| SD | 45 | 426 | 7 | 232 | 4 | 50 | 3 | 207 |
| Mean $\pm 3$ SD | 151 | 1504 | 27 | 881 | 17 | 209 | 14 | 732 |

The mean levels of particulates in 15 lots of glass syringes were 5 and 111 for $\geq 25-\mu \mathrm{m}$ and $\geq 10-\mu \mathrm{m}$ particulates, respectively. The level of contamination in syringes relative to glass vials was significantly lower; similarly lower particulate counts in sterile filled syringes have been previously reported (23).

## Particulate Distribution

Statistical analysis of particulate distribution among 406 lots is shown in Table 6. Data show that very large propor-
tions of lots are clustered toward the lowest range, $\leq 100$ particles per container; in fact, the largest number of lots reported zero counts. In the case of $\geq 10-\mu \mathrm{m}$ particulates, some tailing in distribution is observed, and it is more pronounced in applications submitted in 1999 and 2002. A histogram showing the relationship between the numbers of lots studied and the level for $\geq 10-\mu \mathrm{m}$ particulates is shown in Figure 1 and for $\geq 25-\mu \mathrm{m}$ particulates in Figure 2.

Table 6. Distribution of contaminating particles, all lots combined: 1998-2002

| Number of Particulates ( $\mu \mathrm{m}$ ) | 1998 |  | 1999 |  | 2000 |  | 2001 |  | 2002 |  | Cumulative |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ | $\geq 25$ | $\geq 10$ |
| $\leq 100$ | $96^{*}$ | 61 | 65 | 42 | 94 | 53 | 63 | 44 | 73 | 33 | 391 | 233 |
| 200 | 0 | 12 | 2 | 8 | 3 | 23 | 0 | 6 | 5 | 12 | 10 | 61 |
| 300 | 1 | 6 | 1 | 4 | 1 | 5 | 0 | 2 | 0 | 11 | 3** | 28 |
| 400 | 0 | 7 | 0 | 3 | 1 | 5 | 0 | 2 | 0 | 9 | 1 | 26 |
| 500 | 0 | 2 | 0 | 2 | 0 | 5 | 1 | 2 | 0 | 3 | 1 | 14 |
| 600 | 0 | 2 | 0 | 2 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 7 |
| 700 | 0 | 4 | 0 | 1 | 0 | 1 | 0 | 4 | 0 | 1 | 0 | 11 |
| 800 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 3 |
| 900 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 4 |
| 1000 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 3 |
| 1100 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 2 |
| 1200 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 5 |
| 1300 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 1400 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1500 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| 1600 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1700 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1800 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1900 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| $\geq 2000$ | 0 | 2 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 6 |

* Numbers indicate lots with particulate counts $\leq 100$ per container.
${ }^{* *}$ Horizontal lines represent mean +3 SD cutoff.


Number of Particulates
Fig. 1. Counts for $\geq 10-\mu \mathrm{m}$ particulates in all lots combined
$\geq 25-\mu \mathrm{m}$ Particulates, All Lots


Number of Particulates
Fig. 2. Counts for $\geq 25-\mu \mathrm{m}$ particulates in all lots combined

Table 7 summarizes mean particulate counts for each dosage form by the year of application. Analysis of the data for trends in particulate counts during the five-year period shows correlation coefficient ( $R^{2}$ ) values ranging from 0.00 to 0.85 for various categories; however, none is considered
statistically significant. The mean particulate counts for $\geq$ $25-\mu \mathrm{m}$ and $\geq 10-\mu \mathrm{m}$ particulates during the five-year study period for each of the dosage forms are shown graphically in Figures 3 and 4.

Table 7. Mean particulate counts by the year of application

|  | $\geq 25-\mu \mathrm{m}$ Particulates |  |  |  | $\geq 10-\mu \mathrm{m}$ Particulates |  |  |  |  |  |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Combined | Inj.* | FIJ | Asep. | Term. | Combined | Inj. | FIJ | Asep. | Term. |
| 1998 | 11 | 12 | 7 | 8 | 17 | 214 | 216 | 203 | 283 | 80 |
| 1999 | 14 | 8 | 33 | 17 | 6 | 194 | 131 | 370 | 217 | 114 |
| 2000 | 16 | 12 | 37 | 18 | 11 | 274 | 206 | 563 | 277 | 265 |
| 2001 | 15 | 16 | 13 | 17 | 8 | 153 | 135 | 240 | 149 | 167 |
| 2002 | 19 | 18 | 30 | 24 | 8 | 259 | 215 | 499 | 301 | 146 |
| All Years | 15 | 13 | 24 | 17 | 10 | 219 | 181 | 375 | 245 | 154 |
| $R^{2}$ for $1998-2002$ | 0.850 | 0.658 | 0.097 | 0.783 | 0.359 | 0.025 | 0.0 | 0.217 | 0.007 | 0.174 |

* Inj. = Injection (liquids), FIJ = For Injection (lyophilized or powder), Asep. $=$ Aseptically Processed, Term. $=$ Terminally Sterilized.


Fig. 3. Counts for $\geq 25-\mu \mathrm{m}$ particulates by year and dosage form


Fig. 4. Counts for $10-\mu \mathrm{m}$ particulates by year and dosage form

For analysis and to identify lots with high counts, we assumed a cut-off based on a mean +3 SD, representing $99.7 \%$ of the population and that the occurrences of particulate contaminations were random. On the basis of these criteria, we identified eight lots that had counts of either $300 \geq 25$ $\mu \mathrm{m}$ or $1500 \geq 10-\mu \mathrm{m}$ particulates as shown in Table 8. These eight lots have little in common to suggest the cause of the observed high counts. Five different firms manufactured the lots. The lots included liquid as well as For Injection dosage
forms; most were filled in glass vials, but one lot was filled in glass ampules. Among the eight lots both aseptically filled and terminally sterilized lots are represented. Although most of the lots showed high counts for $\geq 10$ $\mu \mathrm{m}$ particulates, only one lot (\#5) showed relatively high counts for both $\geq 25-\mu \mathrm{m}$ and $\geq 10-\mu \mathrm{m}$ particulates. The lot (\#7) with the highest $\geq 25-\mu \mathrm{m}$ particle counts had relatively modest counts for $\geq 10-\mu \mathrm{m}$ particulates.

Table 8. High-count lots based on mean $\pm \mathbf{3}$ SD criterion (counts $>\mathbf{1 5 0 0}$ for $\geq \mathbf{1 0}-\mu \mathrm{m}$ particles or $>\mathbf{3 0 0}$ for $\geq \mathbf{2 5}-\mu \mathrm{m}$ particles)

| Lot \# | Firms* | Year | Dosage Form | $\begin{gathered} \text { Container } \\ \text { Type } \\ \hline \end{gathered}$ | Manufacturing Process | Particulate Counts** |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |  | $25-\mu \mathrm{m}$ | 10- $\mu \mathrm{m}$ |
| 1 | A | 1998 | Injection | Glass Vial | Aseptic | 28 (0.3) | 5188 (11.9) |
| 2 | A | 1998 | Injection | Glass Vial | Aseptic | 39 (0.6) | 2292 (5.0) |
| 3 | B | 2000 | For Injection | Glass Vial | Aseptic | 265 (5.8) | 3741 (8.5) |
| 4 | B | 2000 | For Injection | Glass Vial | Aseptic | 80 (1.5) | 2330 (5.0) |
| 5 | C | 2000 | Injection | Glass Vial | Aseptic | 377 (8.4) | 2385 (5.2) |
| 6 | D | 2000 | Injection | Glass Vial | Terminal | 14 (0) | 3856 (8.7) |
| 7 | D | 2001 | Injection | Glass Vial | Aseptic | 418 (9.4) | 602 (0.9) |
| 8 | E | 2002 | Injection | Ampule | Aseptic | 56 (1.0) | 1892 (4.0) |

${ }^{*}$ Individual firms, represented by letter code.
** Values in parentheses represent numbers of SD from the particulates mean for all lots.

Our study provides a clear view of the actual capabilities of the current technologies. It should be noted that data presented in the study represent exhibit lots for nearly all ANDAs for injectable drugs presented to FDA during the five-year period; therefore, statistical values reported here represent true values for the exhibit lots without bias. In the case of sterile drug products, it is reasonable to assume that the processes used in the manufacture of the exhibit lots were essentially the same as used in the manufacture of fullscale production lots; therefore, the level of particulates in exhibit lots may be a reasonable reflection of particulate contamination in the full-scale production lots.

Data summarized in Table 8 show that if particulate contamination limits were based on mean +3 SD one would have identified eight lots as the outliers, including five in which particulate counts were greater than mean +6 SD . The manufacturers would have been prompted to identify the source of particulate contamination and improve the quality of their product by lowering contamination. It should be pointed out that the injury caused by the presence of nonviable particulate contamination in the injections is well documented in the scientific literature (1-11) and must be considered when limits for particulate contamination are determined. It should be recognized that the presence of any
foreign particulate matter in an injectable drug form is undesirable; however, a certain level of contamination is allowed, as represented by limits set in USP $\langle 788\rangle$, due to practical limitations of the manufacturing technologies.

## CONCLUSION

Data provided show that low particulate counts in the parenteral drugs currently produced are the norm across the manufacturing processes representing a variety of technologies and container types. To the best of our knowledge, this is the first publication analyzing data representing a broad spectrum of manufacturing processes.

Our study shows that the contaminating particulates in injectable drug products are significantly lower than currently allowed by USP General Chapter $\langle 788\rangle$ Particulate Matter in Injections. The lower particulate counts reported here indicate that the current manufacturing technologies are performing well. However, our data show that there is a wide gap between the actual particulate contamination present in the injectable drug products and the amount of contaminants allowed under the current limits in USP $\langle 788\rangle$. The mean counts for all lots combined were 15 (SD 43) and 219 (SD 415) for $25-\mu \mathrm{m}$ and $10-\mu \mathrm{m}$ size particulates, respectively. The difference between the mean counts and the USP limits represent more than 13 SD. In statistical terms, mean +3 SD represents $99.7 \%$ of the samples in a normal distribution; current limits could be lowered without significantly increasing lot rejection due to particulate contamination.

We hope that this Stimuli article will help generate discussion about the need and usefulness of tighter limits based on recent data, such as presented here, and perhaps additional studies could be performed to establish safe limits for particulate contamination without placing excessive burden on the industry.

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# A Rapid and Simple Stability-Indicating HPLC Method for the Analysis of Valproic Acid in Divalproex Sodium Formulations 

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#### Abstract

A simple, selective, and rapid high-performance liquid chromatographic method for the analysis of valproic acid in divalproex sodium formulations was developed and validated. Sample preparation was in methanol and $0.5 \%$ sodium dodecyl sulfate ( $1: 9 \mathrm{v} / \mathrm{v}$ ) and resolved on a C8 column with UV detection at 215 nm . The mobile phase consisted of acetonitrile and 25 mM sodium dihydrogen phosphate buffer, $\mathrm{pH} 3.5(1: 1 \mathrm{v} / \mathrm{v})$ at a flow rate of $1.0 \mathrm{~mL} / \mathrm{min}$. Calibration curves were linear ( $r>0.9999$ ) over the concentration range of $5.01 \mu \mathrm{~g} / \mathrm{mL}-1002 \mu \mathrm{~g} / \mathrm{mL}$. The coefficients of variation (CVs) were $<2 \%$ for valproic acid recoveries at three concentration levels ( $70 \%, 100 \%$, and $130 \%$ ) of the finished product assay, and the intraday and interday precision CVs were $<2 \%$. Valproic acid retention times were generally about 5 min.

The quantitation limit for valproic acid related compound A was about 62 ng on the column. Mean recoveries of valproic acid related compound A spiked in drug substance and in drug product at about $0.5 \%$ of valproic acid assay concentrations were $82.1 \%$ and $107.7 \%$ in drug substance and drug product, respectively, with CVs $<15 \%$. The developed method gave good resolution between valproic acid and valproic acid related Compound A. Stability-indicating studies were performed on an HPLC system equipped with a photodiode-array detector. The drug was stable under acid, base, thermal, and UV conditions; however, additional peaks were observed with the sample treated under oxidative conditions. The method was specific and stability indicating and therefore could be employed as a more convenient and efficient option for the analysis of valproic acid and its related compounds in drug substance and formulations.


## BACKGROUND AND INTRODUCTION

Divalproex sodium, sodium hydrogen bis(2-propylpentanoate), is chemically composed of valproic acid and valproic acid sodium salt in a 1:1 molar ratio (Figure 1). Valproic acid is used as an anticonvulsant and mood stabilizer in the treatment of several seizures because of its wide spectrum of activity ( $1-3$ ). Several methods for the analysis of valproic acid in biological samples have been reported based on derivatization followed by HPLC analysis with fluorimetric detection (1-2, 4-6). Other reported methods involved LC-MS (7) and GC with electron-capture detection (8).


Fig. 1. Chemical structure of divalproex sodium
Application of compendial GC methods (9-10) for the analysis of valproic acid in drug substance and in finished formulations did not provide fast and high throughput.

[^373]Our analysis of valproic acid in finished formulation gave results of intraday and interday precision that showed coefficient of variations $>3 \%$ and $6 \%$, respectively, and sample preparations involving liquid-liquid extraction were lengthy and time consuming.

This article describes a simple HPLC method with UV detection for the quantification of valproic acid in drug substance, drug products, and dissolution samples, as well as application to related compounds. The developed method was validated under such parameters as linearity, recovery/accuracy, precision, ruggedness, robustness, specificity and selectivity, detection, and quantitation limits. The method is conveniently employed for the analysis of valproic acid in divalproex sodium delayed-release and extended-release formulations and in their respective dissolution samples, as well as monitoring related compounds in stability samples.

## EXPERIMENTAL

## Materials

USP Valproic Acid RS and USP Valproic Acid Related Compound A RS were purchased from the US Pharmacopeia (Rockville, MD, USA). Divalproex sodium API was obtained commercially from a reputable supplier (confidential information). AnalaR-grade sodium phosphate monobasic monohydrate, HPLC-grade acetonitrile, methanol, and 2-propanol (EM Science, Merck KGaA, Darmstadt, Germany) were purchased from VWR Canada. HPLC-grade
water, $o$-phosphoric acid, and sodium dodecyl sulfate (SDS) were purchased from Fischer Scientific Canada. Divalproex sodium finished drug products were formulated at our facilities, and reference products were acquired commercially.

## Instrumentation

The HPLC systems used were a Waters 2695 Separations Module equipped with a Waters 2487 dual wavelength absorbance detector for assay. A Waters solvent delivery pump (Model 600), a Waters 600E System controller, an auto injector (model 715), and a Waters 996 photodiode array detector (Waters Corporation, Milford MA, USA) were used for stress studies, along with an ERC model $3415 \alpha$ Solvent degasser. A $4.6 \times 150 \mathrm{~mm}$ Agilent Eclipse XDB Cg, $5-\mu \mathrm{m}$ column (Agilent Technologies, Palo Alto, CA, USA) was used with a mobile phase consisting of acetonitrile and 25 $\mathrm{mM} \mathrm{NaH} 2_{2} \mathrm{PO}_{4} \mathrm{pH} 3.5$ with $\mathrm{H}_{3} \mathrm{PO}_{4}(1: 1 \mathrm{v} / \mathrm{v})$ at a flow rate of $1.0 \mathrm{~mL} / \mathrm{min}$. The detector wavelength was set at 215 nm . Injection volume was $50 \mu \mathrm{~L}$ per injection, and the HPLC system equilibrated for about 30 min before the commencement of runs.

## Method

## Mobile phase

Dissolve 3.5 g of sodium phosphate monobasic monohydrate in 1000 mL of DI water. Mix well, and adjust with $o$-phosphoric acid to a pH of 3.5 . Transfer 500 mL of this solution into a 1-L volumetric flask, add 500 mL of acetonitrile, and mix well. Pass the solution through a $0.45-\mu \mathrm{m}$ nylon membrane filter, and degas before use.

## Standard Solutions

Standard Solution A-Accurately weigh about 50 mg of USP Valproic Acid RS into a $50-\mathrm{mL}$ volumetric flask. Add about 10 mL of methanol to dissolve; make up to volume with $0.5 \%$ SDS solution and mix well. Concentration of valproic acid is about $1 \mathrm{mg} / \mathrm{mL}$.

Standard Solution B-Weigh quantitatively USP Valproic Acid Related Compound A RS into a known volume of 2propanol so that the final concentration of related compound A is about $50 \mathrm{mg} / \mathrm{mL}$.

Working Standard (Resolution) Solution- Pipet 25.0 mL of Standard Solution $A$ into a $50-\mathrm{mL}$ volumetric flask. Using a Hamilton syringe, add $50 \mu \mathrm{~L}$ of Standard Solution B. Dilute with Mobile Phase to volume and mix well. Pass a portion of this solution through $0.45-\mu \mathrm{m}$ PVDF syringe filter (NOTE: a $0.45-\mu \mathrm{m}$ nylon filter failed the filter selection), discarding the first $1-2 \mathrm{~mL}$; collect the filtrate into an HPLC vial for analysis. The concentrations of valproic acid related compound A and valproic acid in the Working Standard (Resolution) Solution are about $50 \mu \mathrm{~g} / \mathrm{mL}$ and $500 \mu \mathrm{~g} / \mathrm{mL}$, respectively. Standard and Test Solutions are stable for at least 3 days at room temperature and at $4^{\circ} \mathrm{C}$. Valproic acid Standard Solution $B$ is stable for at least 2 weeks at $4{ }^{\circ} \mathrm{C}$.

## Test Solution

Weigh not fewer than twenty divalproex sodium 500 mg (valproic acid) tablets and grind into a fine powder. Place an amount equivalent to one tablet weight into each of three 1L volumetric flasks. Add 100 mL of methanol, and sonicate for about 5 min . Add about 800 mL of $0.5 \%$ SDS solution and sonicate for about 3 min . Dilute with more $0.5 \%$ SDS solution to volume and mix well. Pass a portion of this solution through a $0.45-\mu \mathrm{m}$ PVDF syringe filter, discard the first $1-2 \mathrm{~mL}$, and then collect into HPLC vial for analysis. The concentration of valproic acid in the Test preparation is about $0.5 \mathrm{mg} / \mathrm{mL}$.

## VALIDATION PROCEDURES

## System Suitability

The Resolution Solution was run at any one time for system suitability before sample analysis. Six consecutive injections of the Resolution Solution were performed and evaluated for repeatability, peak symmetry, plate count, and resolution. Typical system suitability results are summarized in Table 1.

Table 1. Summary of system suitability results for valproic acid

|  | Retention <br> Time of | Peak Area of <br> Valproic Acid <br> (AU) | USP Tailing |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Injection | Falproic <br> Acid (min.) | 880695 | 1.14 |  |  |
| Number | 5.15 | 881295 | 1.13 | USP Tangent | USP |
| 1 | 5.14 | 881303 | 1.13 | 8781 | 6807 |
| 2 | 5.17 | 880383 | 1.14 | 8804 | 6.93 |
| 3 | 5.17 | 881191 | 1.14 | 8838 | 6.96 |
| 4 | 5.17 | 881424 | 1.13 | 6894 | 6.89 |
| 5 | 5.16 | 881049 | 1.14 | 8799 | 6.93 |
| 6 | 5.16 | 0.0 | 0.5 | 8821 | 6.93 |
| Mean | 0.2 |  |  | 0.5 | 0.3 |
| \%CV |  |  |  |  |  |

## Linearity

The linearity of response for the method was determined by analyzing standard solutions of valproic acid Std 1-Std 10 in the concentration range of $2.506-1002.45 \mu \mathrm{~g} / \mathrm{mL}$ ( $\mathrm{Ta}-$ ble 2). The results show that the peak area responses are linear within the concentration range of the analysis. The correlation coefficient was $>0.9999$. Figure 2 is a linear curve of valproic acid.

Table 2. Linearity and range of valproic acid

| Standard Number | Concentration <br> $(\mu \mathrm{g} / \mathrm{mL})$ | Peak Area (AU) |
| :---: | ---: | :---: |
| 1 | 2.506 | 2293 |
| 2 | 5.012 | 7719 |
| 3 | 10.025 | 15790 |
| 4 | 25.061 | 40671 |
| 5 | 50.123 | 82031 |
| 6 | 100.245 | 163718 |
| 7 | 250.613 | 414260 |
| 8 | 501.225 | 830705 |
| 9 | 751.837 | 1249108 |
| 10 | 1002.45 | 1660370 |
| Correlation coeffi- | 1.0000 |  |
| cient, $r^{2}$ |  |  |
| Slope | 1659.4441 |  |
| Intercept | -1233.5412 |  |

Valproic acid Linear Curve


Fig. 2. Linear curve of valproic acid: concentration $2.506-1002.45 \mu \mathrm{~g} / \mathrm{mL}$

## Accuracy/Recovery

Accuracy was studied by preparing samples of divalproex sodium 500 mg (valproic acid) finished product in triplicate at the $70 \%, 100 \%$, and $130 \%$ levels of the target valproic acid concentration and assaying them according to the procedure described in the Test preparation.

A typical chromatogram of Valproic acid Working Standard (Resolution) Solution is depicted in Figure 3. Figure 4 is a typical chromatogram of sample solution at the $100 \%$
level. The mean percent recovery ranged from $99.7 \%$ to $101.7 \%$ of the label claim of valproic acid at all levels of the recovery analysis, and the CV values for each level ranged from $0.4 \%$ to $0.6 \%$. The overall mean percent recovery was $100.4 \%$ of the label claim of valproic acid with an overall CV of $0.6 \%$ (Table 3).


Fig. 3. A typical chromatogram obtained from valproic acid Working Standard (Resolution) Solution


Fig. 4. A typical chromatogram obtained from assay sample solution of divalproex sodium formulation

Table 3. Summary of accuracy/recovery results for the assay of valproic acid in divalproex sodium drug product

| Level | Sample Number | Sample Amount (mg) | Valproic Acid |  |  | \% Mean Recovery (\%CV) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  | Theoretical (mg) | $\begin{gathered} \text { Measured } \\ (\mathrm{mg}) \\ \hline \end{gathered}$ | $\%$ <br> Recovery* |  |
| 70\% | 1 | 498.82 | 351.28 | 350.61 | 99.8 | 100.0 |
|  | 2 | 497.28 | 350.20 | 350.67 | 100.1 | (0.4) |
|  | 3 | 498.52 | 351.07 | 352.41 | 100.4 |  |
| 100\% | 1 | 710.58 | 500.41 | 498.88 | 99.7 | 100.0 |
|  | 2 | 711.29 | 500.91 | 501.32 | 100.1 | (0.5) |
|  | 3 | 711.81 | 501.27 | 502.85 | 100.3 |  |
| 130\% | 1 | 925.20 | 651.55 | 654.33 | 100.4 | 101.1 |
|  | 2 | 924.58 | 651.11 | 658.96 | 101.2 | (0.6) |
|  | 3 | 924.75 | 651.23 | 662.10 | 101.7 |  |
| Mean |  |  |  |  |  | 100.4 |
| \%CV |  |  |  |  |  | 0.6 |

* Results based on mean of three injections


## System Precision

System precision was evaluated by making six consecutive injections of the system suitability (Resolution) solution. The CVs of the retention times and of the peak areas of valproic acid from the six consecutive injections of the system suitability solution injected were $0.2 \%$ and $0.0 \%$, respectively (Table 1).

## Method Precision

A method precision study was performed to determine the reproducibility of the method. Six samples were prepared at the $100 \%$ level and assayed according to the procedure described in the Test preparation. The results of the precision study are summarized in Table 4. The mean valproic acid recovery was $100.3 \%$ of the label claim for valproic acid with a CV of $0.4 \%$.

Table 4. Summary results for valproic acid method precision

|  | Sample <br> Sample <br> Number | mmount <br> $(\mathrm{mg})$ | Theoretical <br> $(\mathrm{mg})$ | Measured <br> $(\mathrm{mg})$ |
| :---: | :---: | :---: | :---: | :---: |

[^374]
## Ruggedness

Ruggedness was performed by a second analyst on six sample solutions by following the same procedure for method precision on a separate day and using a different HPLC
system. The mean valproic acid recovery was $101.8 \%$ of the label claim for valproic acid with a CV of $0.2 \%$ (Table 5).

Table 5. Summary results for valproic acid ruggedness test

| Sample <br> Number | $\begin{aligned} & \text { Sample Amount } \\ & (\mathrm{mg}) \end{aligned}$ | Valproic Acid |  | Recovery* (\%LC) |
| :---: | :---: | :---: | :---: | :---: |
|  |  | Theoretical (mg) | Measured (mg) |  |
| 1 | 717.04 | 504.96 | 516.02 | 102.2 |
| 2 | 711.22 | 500.86 | 511.10 | 102.0 |
| 3 | 712.15 | 501.51 | 510.42 | 101.8 |
| 4 | 715.19 | 503.65 | 510.01 | 101.3 |
| 5 | 711.13 | 500.80 | 509.18 | 101.7 |
| 6 | 715.05 | 503.56 | 513.99 | 102.1 |
| Mean |  |  |  | 101.8 |
| \%CV |  |  |  | 0.2 |

* Results based on mean of three injections


## Robustness

Robustness studies were performed on method precision sample \#1 by making slight variations in flow rate, amount of acetonitrile, and buffer pH changes one at a time. Acceptable robustness results were defined as falling in the $98-102 \%$ range of the target conditions result. The results of the robustness study are summarized in Table 6.

Table 6. Summary results for valproic acid robustness

| test |  |  |  |
| :--- | :---: | :---: | :---: |
| Parameter |  | $\%$ <br> Recovery* $^{*}$ | Percent <br> of Target |
| Target Conditions |  | 99.7 | 100.0 |
| Flow Rate | $0.9 \mathrm{~mL} / \mathrm{min}$ | 102.7 | 103.0 |
|  | $1.1 \mathrm{~mL} / \mathrm{min}$ | 100.9 | 101.2 |
| Buffer pH | 3.0 | 100.8 | 101.1 |
|  | 4.0 | 101.8 | 102.1 |
| Acetonitrile | $48 \%$ | 101.1 | 101.4 |
| Variation | $52 \%$ | 100.4 | 101.7 |

* Results based on mean of three injections


## Specificity and Selectivity

The specificity of the method was determined by running a blank solution followed by a placebo sample solution of
divalproex sodium formulation on an HPLC column for analysis. A typical chromatogram obtained from the placebo sample solution is shown in Figure 5.


Figure 5. A typical chromatogram obtained from divalproex sodium placebo sample solution

Selectivity was determined by performing forced degradation studies on divalproex sodium finished product and evaluating the peak purity of valproic acid from any resulting impurities from the stress treatment. Analysis of the peak purity was performed using PDA purity plots in which a purity angle, $P A$, of the valproic acid peak was generated against a threshold, TH, value. The peak is considered pure if the value is equal to or less than the threshold, $T H$, value. Table 7 is a summary of the purity angle and threshold values from the various stress condition studies performed on the finished formulation. Valproic acid peak separations and PDA spectral scans of the various forced degradation studies are shown in Figures 6-11.

Table 7. Summary results for valproic acid method forced degradation studies

| Parameter | Purity Measurement |  |
| :---: | :---: | :---: |
|  | Purity Angle, $P A$ | Threshold, TH |
| Controlled | 0.046 | 0.236 |
| Sample |  |  |
| Acid Hydrolysis | 0.045 | 0.231 |
| Base Hydrolysis | 0.054 | 0.244 |
| Oxidative Degradation | 0.020 | 0.253 |
| Thermal Degradation | 0.040 | 0.234 |
| Photo (UV) Degradation | 0.042 | 0.234 |




Fig. 6. A typical chromatogram including purity scan obtained from divalproex EC forced degradation-controlled sample solution



Fig. 7. A typical chromatogram including purity scan obtained from divalproex EC forced degradation-thermal degradation sample solution

_ Channel 996: Processed Channel: PDA 215.0 nm: Result Id: 8517: Processing Method:
Divalproex Degra M th


Fig. 8. A typical chromatogram including purity scan obtained from divalproex EC forced degradation-oxidative sample solution


- Channel 996: Processed Channel: PDA 215.0 nm: Result Id: 8515: Processing Method: Divalproex Degra M th


Fig. 9. Typical chromatogram including purity scan obtained from divalproex EC forced degradation-base hydrolysis sample solution


- Channel 996: Processed Channel: PDA 215.0 nm: Result Id: 8513: Processing Method: Divalproex Degra M th


Fig. 10. A typical chromatogram including purity scan obtained from divalproex EC forced degradation-acid hydrolysis sample solution

-_Channel 996: Processed Channel: PDA 215.0 nm: Result Id: 8574: Processing Method: Divalproex Degra M th


PA: 0.042 TH: 0.234
— Peak: Valproic Acid

- Purity

Fig. 11. A typical chromatogram including PDA purity scan obtained from divalproex EC forced degradation-photolysis sample solution

## Limit of Detection and Limit of Quantitation

Limit of detection (LOD) and limit of quantitation (LOQ) were evaluated based on valproic acid related compound A in which the peak responses were three times and ten times the baseline noise, respectively. These were estimated at 31 ng and 62 ng on the column, respectively. Valproic acid related compound A standard solutions were prepared and analyzed for linearity from the quantitation limit. The results show that the peak area responses are linear within the concentration range of $1.235-24.69 \mu \mathrm{~g} / \mathrm{mL}$ (Table 8). A linear curve for related compound A is depicted in Figure 12.

Table 8. Linearity, LOD, and LOQ of valproic acid related compound $A$

| Standard Number | Concentration, <br> $\mu \mathrm{g} / \mathrm{mL}$ | Peak Area, AU |
| :---: | :---: | :---: |
| 1 | 1.235 | 1661 |
| 2 | 2.469 | 4888 |
| 3 | 4.938 | 10926 |
| 4 | 12.345 | 29895 |
| 5 | 24.690 | 60854 |
| Slope |  | 2524.25 |
| Intercept |  | -1415.05 |
| $r / 2$ | 1.0000 |  |
| LOD |  | 0.618 |
| LOQ |  | 1.235 |



Fig. 12. Linear curve of valproic acid related compound A (concentration, $1.235-24.69 \mu \mathrm{~g} / \mathrm{mL}$ )

Valproic Acid Related Compound A Recovery in Drug Substance

Valproic acid related compound A was spiked at about the $0.5 \%$ level of the working concentration and analyzed at the $80-120 \%$ level of drug substance. The mean percent recov-
ery ranged from $80.7 \%$ to $84.8 \%$ of the spiked valproic acid related compound A level with an overall mean of $82.1 \%$ and CV of $3.4 \%$ (Table 9).

Table 9. Related compound A recovery in divalproex sodium drug substance

| Level | Sample <br> Number | Amount Spiked, $\mu \mathrm{g} /$ <br> mL | Amount Measured, <br> $\mu \mathrm{g} / \mathrm{mL}$ | Recovery, <br> $\%$ | $\%$ Mean <br> $(\% \mathrm{CV})$ |
| :--- | :---: | :---: | :---: | :---: | :---: |
| $80 \%$ | 1 | 2.469 | 2.070 | 83.8 | 80.9 |
|  | 2 | 2.469 | 1.994 | 80.8 | $(3.6)$ |
|  | 3 | 2.469 | 1.927 | 78.0 | 84.8 |
| $100 \%$ | 1 | 2.469 | 2.077 | 84.1 | $(2.4)$ |
|  | 2 | 2.469 | 2.152 | 87.2 | 80.7 |
| $120 \%$ | 3 | 2.469 | 1.054 | 83.2 | $(1.9)$ |
|  | 1 | 2.975 | 2.037 | 82.0 | 82.1 |
|  | 2 | 2.469 |  |  | 79.7 |
| Overall Mean |  |  |  |  | 3.4 |

[^375]Valproic Acid Related Compound A Recovery in Drug Product

Valproic acid related compound A was similarly spiked at about the $0.5 \%$ level of the working concentration and analyzed in drug product at the $70-130 \%$ level. Mean recov-
eries in the $70-130 \%$ level of drug product were $94.2-$ $120.6 \%$ of the spiked valproic acid related compound A level with an overall mean of $107.7 \%$ and an overall CV of 12.2\% (Table 10).

Table 10. Related compound A recovery in divalproex sodium drug product

| Level | Sample <br> Number | Amount Spiked, <br> $\mu \mathrm{g} / \mathrm{mL}$ | Amount Measured, <br> $\mu \mathrm{g} / \mathrm{mL}$ | ${ }^{*}$ Recovery, $\%$ | $\%$ Mean <br> $(\% \mathrm{CV})$ |
| :---: | :---: | :---: | :---: | :---: | :---: |
| $70 \%$ | 1 | 2.469 | 2.477 | 100.3 | 108.2 |
|  | 2 | 2.469 | 2.954 | 119.6 | $(9.3)$ |
| $100 \%$ | 3 | 2.469 | 2.586 | 104.7 |  |
|  | 1 | 2.469 | 2.981 | 120.7 | 120.6 |
|  | 2 | 2.469 | 3.103 | 125.7 | $(4.3)$ |
| $130 \%$ | 1 | 2.469 | 2.845 | 15.2 | 91.4 |
|  | 2 | 2.469 | 2.256 | 102.2 | 94.2 |
|  | 3 | 2.469 | 2.477 | 89.1 | $(7.5)$ |
| Overall |  |  |  |  | 107.7 |
| Mean, $\%$ |  |  |  |  | 12.2 |
| \%CV |  |  |  |  |  |

${ }^{*}$ Results based on mean of two injections

## Calculations

$$
\begin{aligned}
& D F= \\
& Q=
\end{aligned}
$$

dilution factor (mL) content of valproic acid (mg) in Test preparation.

## Valproic Acid Content in Test Solution

Content (mg) of valproic acid $=C_{s} \times\left(r_{u} / r_{s}\right) \times D F \times P$, where:

| $C_{s}=$ | concentration $(\mathrm{mg} / \mathrm{mL})$ of valproic acid <br> Working Standard Solution <br> average peak response of valproic acid <br> from replicate injections of Working Stan- <br> dard Solution |
| :--- | :--- |
| $r_{s}=$ | peak response of valproic acid obtained <br> from run of Test preparation |
| $r_{u}=$ | dilution factor $(\mathrm{mL})$ <br> factor $(P=288.43 / 310.41)$, when appli- <br> cable, for converting standard divalproex <br> sodium to valproic acid. |

## Valproic Acid Related Compound A Percent Content in

 Test SolutionValproic acid related compound A percent present in each sample $=\left(r_{i} \times C_{s}\right) / r_{s} \times D F / Q \times 100 \%$, where:

$$
\begin{array}{cl}
C_{s}= & \begin{array}{l}
\text { concentration }(\mathrm{mg} / \mathrm{mL}) \text { of related com- } \\
\text { pound A in the Resolution Solution }
\end{array} \\
r_{s}=\quad \begin{array}{l}
\text { average related compound A peak re- } \\
\text { sponse from replicate injections of the }
\end{array} \\
r_{i}=\quad \begin{array}{l}
\text { Resolution Solution } \\
\text { peak response of related compound A } \\
\text { from run of Test preparation }
\end{array}
\end{array}
$$

## Any Individual Unknown Impurity Percent Content in Test Solution

Any individual unknown impurity percent present in each sample $=\left(r_{i} / r_{t}\right) \times 100 \%$, where:

| $r_{i}=$ | peak response of any individual unknown im- <br> purity, except solvent peak, from run of Test |
| :--- | :--- |
| $r_{t}=$ | preparation <br> sum of responses of all peaks in the chroma- <br> togram, excluding the solvent peak. |

## RESULTS AND DISCUSSION

The $\% \mathrm{CV}$ of the peak areas of valproic acid from the six consecutive injections of the system suitability solution injected was $0.0 \%$. The mean theoretical plate count based on USP tangent calculations for valproic acid peak from the six consecutive injections of the system suitability solution was 8821, and the resolution between valproic acid related compound A and valproic acid was 6.9 (Table 1).
Linearity was demonstrated between the peak response and concentration in the range from the quantitation limit of $2.506-1002.45 \mu \mathrm{~g} / \mathrm{mL}$, giving a correlation coefficient, $r^{2}$, of 1.0000 . This linear relationship with $r^{2}=1.0000$ was again demonstrated where the standard calibration curve ( $n=5$ ) ranged from $100.245 \mu \mathrm{~g} / \mathrm{mL}$ to $1002.45 \mu \mathrm{~g} /$
mL to include the assay concentration of about $500 \mathrm{ug} / \mathrm{mL}$. A linear calibration curve of valproic acid was constructed using the GC method (9) over the concentration range from
$34.2 \mu \mathrm{~g} / \mathrm{mL}$ to $546.4 \mu \mathrm{~g} / \mathrm{mL}$ and gave a correlation coefficient of $r^{2}=0.9968$. The linear curve of valproic acid by GC analysis is depicted in Figure 13.


Fig. 13. GC linear curve of valproic acid: concentration $34.2-546.4 \mu \mathrm{~g} / \mathrm{mL}$

Recovery of valproic acid from finished product was well within the acceptable range of $90.0-110.0 \%$ (9) with CV $<1.0 \%$ at all three concentration levels. The mean percent recovery ranged from $100.0 \%$, CV of $0.4 \%$ at the $70 \%$ level, to $101.1 \%$, CV of $0.6 \%$ at the $130 \%$ level. These recoveries and low CVs (Table 3) indicate the method's high degree of
accuracy. Assay run time was set at ten minutes because no extraneous peaks were observed beyond the retention time of valproic acid (Figure 4).

Recoveries of valproic acid using the pharmacopeial method (9) gave mean recovery of $100.8 \%$ with CV of $3.3 \%$ (Table 11). The intraday and interday precision CVs were in the range of about $3 \%-6 \%$ compared to the HPLC procedure of less than $1.0 \%$.

Table 11. Summary results for valproic acid GC recovery

|  |  | Valproic Acid |  | Recovery |
| :---: | :---: | :---: | :---: | :---: |
| Analysis Number | Sample Amount <br> $(\mathrm{mg})$ | Theoretical (mg) | Valproic Acid <br> Measured $(\mathrm{mg})$ |  |
| 1 | 88.45 | 54.81 | 56.63 | \%LC |
| 2 | 88.45 | 54.81 | 56.73 | 103.3 |
| 3 | 89.39 | 55.39 | 56.42 | 103.5 |
| 4 | 89.39 | 55.39 | 56.32 | 101.9 |
| 5 | 89.12 | 55.22 | 53.25 | 101.7 |
| 6 | 89.12 | 55.22 | 53.94 | 96.4 |
| Mean |  |  |  | 97.7 |
| \%CV |  |  | 100.8 |  |

The system precision expressed as CV was $0.2 \%$ for retention time and $0.0 \%$ for peak area (Table 1). Method precision CV based on label claim was $0.4 \%$ with a mean recovery of $100.3 \%$, indicating the accuracy of the method (Table 4).

Ruggedness evaluated by a second analyst using different equipment on a different day gave a mean valproic acid recovery of $101.8 \%$ and a CV of $0.2 \%$ (Table 5). Robustness parameters involving changes in pH of buffer solution and in the composition of organic content in the mobile phase gave results that were within the acceptable range of $\pm 2 \%$
of the target condition recovery. The flow rate at $1.1 \mathrm{~mL} / \mathrm{min}$ also met the acceptable range for target conditions; however, the $0.9 \mathrm{~mL} / \mathrm{min}$ flow rate failed this specification.

Selectivity was based on forced degradation of diva1proex sodium finished product and on evaluation of the peak purity of valproic acid from any resulting degradants from the stress treatment. Analysis of valproic acid peak purity was performed using Millennium32 software and evaluating the purity from PDA spectral scan. Valproic acid peaks from all stress studies had purity angles lower than their respec-
tive threshold values, indicating that the valproic acid peak was well resolved from any impurity resulting from the forced degradation studies.

Recoveries of valproic acid related compound A spike at twice the quantitation limit ( $0.5 \%$ of assay concentration) in the $80-120 \%$ level of drug substance gave an overall mean of $82.1 \%$ and CV of $3.4 \%$ (Table 9). Mean recoveries in the $70-130 \%$ level of drug product gave an overall mean of $107.7 \%$ and a CV of $12.2 \%$ (Table 10). The CV values are an indication of the accuracy in the recoveries of spiked valproic acid related compound $A$ when present in either drug substance or drug products.

There are no interfering peaks appearing on the chromatograms for both blank and placebo at the retention time of valproic acid; therefore, this method meets the acceptance criteria for specificity. Selectivity was demonstrated via forced degradation studies, indicating that the valproic acid peak was well resolved from any impurity resulting from the stress studies and thus establishing the stability-indicating capability of the method.

## CONCLUSION

This report summarizes the results of the method development and validation for the determination of valproic acid in divalproex sodium finished products by HPLC. Performance validation criteria for system suitability, linearity, specificity/selectivity, recovery/accuracy, precision, ruggedness, and robustness were all met. The limit of detection (LOD) and limit of quantitation (LOQ) for valproic acid related compound A as well as its recovery in drug substance and drug product were well established. This potential im-
purity was not found in divalproex sodium raw material; however, it was employed in system suitability studies and could be used in its quantitation or for any other unknown impurity that may result from any stress condition.

This simple, rapid, and specific validated HPLC method is sensitive, accurate, and reproducible; it offers a rapid alternative for the analysis of valproic acid in drug substance, drug products, and dissolution samples.

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# Veterinary Application of In Vitro Dissolution Data and the Biopharmaceutics Classification System 

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#### Abstract

The Biopharmaceutics Classification System (BCS) has been developed for human pharmaceutical compounds to predict oral drug absorption. A similar approach for evaluating in vitro data regarding dissolution, solubility, and permeability of veterinary oral dosage formulations has not been applied to predict oral absorption in animals. However, if reliable data can be generated, it may be possible to apply these principles to veterinary drugs. Before this can happen, obstacles must be overcome. Because of differences in anatomy and physiology between animals and people, extrapolations to veterinary drug formulations may not be applicable. Veterinary drug formulations also may differ in their size, excipient content, and use compared to human drug formulations. There is a clear need to examine the application of in vitro data regarding dissolution and permeability for product evaluation and regulatory decisions. This article and future scientific presentations will explore the potential for this application.

Upon resolution of these questions and following appropriate adjustments to testing methods for permeability, solubility, and dissolution assessments, we will be able to apply, with confidence, BCS principles to oral formulations intended for use in dogs. We believe that the extrapolation of BCS principles to oral formulations for use in canines will prove to be an extremely valuable contribution to veterinary medicine.

This Stimuli article on the potential applications of BCS to veterinary drugs was endorsed by the USP Veterinary Drugs Expert Committee. Reader comments about the suggested applications of in vitro solubility, permeability, dissolution data, and the BCS are invited. These comments should be directed to Ian F. DeVeau, Ph.D., at the Department of Standards Development, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790, telephone: 301.816.8178; fax: 301.816.8373; e-mail: ifd@usp.org.


## INTRODUCTION

The USP Veterinary Drugs Expert Committee (EC) formed an ad hoc committee to examine and make recommendations about in vitro dissolution and oral absorption of veterinary pharmaceutical compounds. The basis for this initiative has been the development of the Biopharmaceutics Classification System (BCS) for human pharmaceutical compounds. The BCS is one of the most significant tools recently developed to facilitate product development and regulatory decisions (1). By understanding a compound's solubility and permeability characteristics, pharmaceutical scientists can develop a mechanistic approach to predict the influence of variables such as food, formulation, dosing regimen, and disease on drug absorption from the gastrointestinal (GI) tract. By understanding the relationship between a drug's in vivo absorption profile and the in vitro solubility and dissolution characteristics, one can identify conditions under which the in vitro data could serve as a surrogate for in vivo bioequivalence testing. The correlation between in vitro data and in vivo absorption is abbreviated as IVIVC.

Pharmaceutical compounds can be grouped into one of the following categories:

[^376]CLASS I: High Solubility, High Permeability: generally very well absorbed compounds.
CLASS II: Low Solubility, High Permeability: exhibit dissolution rate-limited absorption.
CLASS III: High Solubility, Low Permeability: exhibit permeability-limited absorption.
CLASS IV: Low Solubility, Low Permeability: very poor oral bioavailability.
The rate of product dissolution may influence the resulting plasma concentration/time profile if the drug is Class II. However, for Class I or III drugs, other factors may influence drug absorption. For example, for Class I compounds (highly soluble, highly permeable) the rate of gastric emptying rather than product performance is the rate-limiting step in determining the bioavailability characteristics. For these formulations, marked difference in in vitro dissolution profiles may occur without any resulting differences detected in product bioavailability (2, 3, 4). Similarly, highly soluble, poorly permeable compounds (Class III) dissolve rapidly. However, in these cases, it is not the rate of drug dissolution that is usually rate-limiting but rather diffusion across biological membranes. Therefore, we can again assume that for Class III compounds, if dissolution is faster than the rate of gastric emptying then differences in product dissolution will not affect product bioavailability. For Class III compounds, as long as absorption occurs via linear processes, the absolute amount of drug absorbed can be increased with a higher dose (5).

On the other hand, for high-permeability, low-solubility compounds (Class II), the rate and extent of product dissolution will have a significant role in defining the resulting blood concentration/time profile (6). This may be attributable to problems associated with either particle size (termed dissolution-limited absorption) or drug solubility (termed solubility-limited absorption). When absorption is limited by solubility, particle size exerts minimal effect on the fraction of drug absorbed. In this situation, fraction of drug absorbed can be improved only by enhancing drug solubility. For example, solubility can be improved by including in the product formulation a surfactant or other excipient that may improve solubility. Conversely, for some compounds particle size also exerts a significant effect on absorption. In these cases, solubility is not a limiting factor, and improvement in the fraction of drug absorbed can be achieved by decreasing particle size, which increases surface area.

## FDA CURRENT USE OF BCS CONCEPTS

FDA's Center for Drug Evaluation and Research (CDER) has incorporated BCS concepts into several guidance documents, including several pertaining to scale-up and post-approval changes, as well as a guidance for the waiver of in vivo bioequivalence study requirements for high-solubil-ity/high-permeability drug products (Class I) based on in vitro dissolution data (7). To be granted a waiver of in vivo bioequivalence study requirements, CDER recommends that in vitro dissolution tests be conducted under the following conditions:

- The test apparatus should be USP Apparatus 1 at 100 rpm or Apparatus 2 at 50 rpm (8). Testing should be conducted in 900 mL of each of the following dissolution media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.
- For each formulation, a minimum of 12 dosage units should be evaluated and a dissolution profile generated. Two dissolution profiles are considered similar when the $f_{2}$ value is $\geq 50$.
- To allow the use of mean data, the coefficient of variation should not exceed $20 \%$ at the earlier time points (e.g., 10 minutes) or $10 \%$ at all other time points. If, under all dissolution conditions, both the test and reference products dissolve $85 \%$ or more within 15 minutes, profile comparisons are not necessary.


## Controlled-Release Dosage Forms

The absorption of controlled-release dosage forms is, by definition, dissolution rate-limited. Because drug permeability characteristics must be sufficiently high to ensure the presence of sink conditions within the GI tract, the appropriate candidates for these products are Class I or II compounds (9). Moreover, to develop an IVIVC for these
products, test procedures must account for the changing environments to which the oral dosage form will be exposed as it traverses the GI tract. These include:

- The impact of changes in fluid volume, surfactants, and motility patterns on product dissolution and drug solubility
- Regional anatomic differences in intestinal permeability and surface area
- Regional physiologic differences in intestinal metabolism and secretion.


## WHY CONSIDER VETERINARY APPLICATION OF BCS PRINCIPLES?

The scientific basis for drug classification in humans has been thoroughly tested, and the criteria for drug classification and biowaivers were shown to accurately predict product in vivo performance. Recently, Kassim et al. (10) developed BCS classifications for 325 medicines contained in the World Health Organization (WHO) Essential Drug List. Permeability was classified based on correlations of human intestinal permeability of 29 reference drugs with the estimated logarithm of the partition coefficient (Log P) or CLogP lipophilicity values. Metoprolol was chosen as the reference compound for permeability and $\log \mathrm{P}$ or Clog P . $\log \mathrm{P}$ and CLogP were linearly correlated ( $r^{2}=0.78$ ) for 104 drugs. A total of 53 (43.1\%) and 62 (50.4\%) drugs on the WHO list exhibited Log P and CLogP estimates, respectively, that were greater than or equal to the corresponding metoprolol value and were classified as high-permeability drugs.

Considering the economic constraints under which veterinary product development, regulation, and practice must function, the incorporation of BCS principles would be extremely beneficial to veterinary medicine. The cost of development of veterinary pharmaceutical formulations is very expensive compared to the financial return in a market that is comparatively smaller than the human market. The benefits of applying BCS principles to veterinary drug formulations would be felt by the drug sponsor with lower costs of development, and veterinarians and animal owners would benefit from greater availability of medications. Unfortunately, the extrapolation of these criteria to veterinary species is not straightforward. There remain numerous interspecies differences in GI physiology that may influence clear-cut interpretation of permeability classifications. In addition, unlike the situation for human medicine, body size (among breeds of dogs, for example) determines the dosage strength used in veterinary species. Tablet sizes in veterinary medicine tend to span a large range so that the drugs can be safely and conveniently administered. Thus, the use of a set volume of fluid and dosage strength for defining drug solubility may not be appropriate in veterinary medicine. Lastly, the current criteria used for defining a rapidly dissolving product may not be appropriate in animal species for which the GI transit rate can be markedly greater than that observed in humans.

The potential importance of these variables needs to be considered prior to using BCS concepts as a predictive tool in veterinary species. Nevertheless, there can be enormous value in having such a system available for classifying veterinary compounds. Upon considering the many veterinary species for which medications may be prescribed, the USP ad hoc committee agreed that the greatest benefit would derive from developing this tool for use in dogs, rather than considering all other species at this time.

## Limit the Analysis to Formulations for Dogs

From a regulatory perspective, addressing this question first in dogs will have the largest impact on the development and regulation of veterinary pharmaceuticals. Most oral veterinary solid drugs are developed for dogs. In addition, dogs are often included as one of the preclinical species in which drugs are tested prior to use in humans. Consequently, there is a wealth of information already generated in dogs due to their ease of handling and because they are one of the species traditionally used for preclinical drug development/toxicological evaluation. There are fewer oral drugs for cats. Many oral drugs for horses tend to be in a paste or granule formulation. Cattle medications are most often given by injection or are orally mixed in water or feed. Therefore, the practical approach is to initially limit our study to oral formulations for dogs.

It is our hope that by examining those aspects of solubility, permeability, and in vitro dissolution test criteria that may be different in dogs versus humans we can better understand how interspecies differences may influence drug classification. The aim of the ad hoc USP committee is to develop guidelines that may be used for dogs, and these guidelines may eventually be developed into a new USP General Chapter on evaluation of veterinary oral pharmaceutical formulations. As a follow-up to this process, we will ultimately strive to extend our findings to support drug classification in other animal species.

## BENEFITS DERIVED FROM ESTABLISHING THE BCS FOR DOGS

Numerous potential benefits could be derived by establishing BCS principles for facilitating the development and regulation of drugs and oral drug products for use in dogs. These include:

- Use in initial drug candidate selection
- Use in the development of product formulations
- Improvement of our understanding of drug products for which bioavailability may be different from that observed in humans (extralabel use) and those drugs that may have significant bioavailability problems when obtained from compounding pharmacies
- Regulatory applications:
- Waiver of Class I (and possibly Class III) compounds
- Help establish in vitro dissolution methods and specifications that have in vivo relevance and can
be used to determine conditions under which additional in vivo bioavailability study data may not be necessary (the development of in vivo/in vitro cor-relations-IVIVC).


## OBJECTIVES OF THIS USP INITIATIVE

The Veterinary Drug EC established this ad hoc USP committee with the mission to review the pertinent literature, examine original research, collect data on oral absorption of compounds in dogs, obtain public input, and possibly direct new research initiatives with the following goals in mind:

- To delineate ways in which in vivo dissolution and drug permeability can differ between humans and dogs.
- To develop a list of points to consider when developing in vitro dissolution methods intended to reflect potential formulation effects on product bioavailability in dogs.
- To explore the possibility of developing canine IVIVC and consider whether or not the criteria used to support waivers in human subjects is appropriate for supporting waivers of in vivo bioequivalence study requirements in dogs (particularly with regard to Class I and III compounds).
- Because of the recent interest in nonsteroidal anti-inflammatory drugs (NSAIDs) in canine veterinary practice, the criteria for these drugs should be examined even though they are considered Class II according to BCS review.
- To develop a list of excipients that can affect drug absorption in dogs. There may be excipients that can affect product bioavailability in a manner that may not be identified under in vitro test conditions. This list would be used to compare with a list of corresponding excipient effects recognized to occur in humans.
One of the first initiatives of the USP ad hoc committee will be to prepare a list of drugs for which data are available in dogs and classify them based on the model developed for compounds included on the WHO Essential Drug List (10). In this classification scheme, the following criteria will be considered:
- Is a related drug used under clinical practice conditions in dogs?
- Are there adequate data available to evaluate oral absorption in dogs?
- Is the drug approved within the U.S. for oral administration to dogs?
- Which of these human drug products may be subject to extralabel use in dogs?
- Are there differences in the dosage forms of these compounds when administered to humans versus dogs?
- Are there drugs that are frequently compounded from the human formulation for animal use by compounding pharmacies?


## PROBLEMS WITH INTERSPECIES EXTRAPOLATIONS

One of the obstacles to overcome in applying the BCS to formulations of compounds used in dogs is interspecies extrapolation. Drugs administered to people may cause different absorption profiles in dogs because of a variety of factors. Some comparisons of oral absorption of drugs in humans versus dogs have been reviewed (11, 12, 13). The differences in oral absorption between dogs and humans can be partially explained by differences in anatomy and physiology (11, 14, 15). Interspecies differences in drug bioavailability are most often the consequence of variables such as GI transit time, in vivo dissolution, presystemic metabolism, physicochemical interactions with gut contents, bacterial digestion, and site-specific differences in absorptive surface area. The diversity in GI anatomy and function reflects differences in dietary habits of the animals (16). For example, carnivores, such as dogs, possess a relatively simple colon but well-developed small intestine (long villi), which is consistent with a diet that is low in fiber but high in fat and protein. As a generalization, gastric emptying time influences the systemic appearance of rapidly dissolved, well-absorbed drugs.

## Differences in Gastric and Intestinal pH between Dogs and People

Dogs have lower basal acid secretion than do people (14, 11). The effect of food on gastric pH also differs across species. Generally, the gastric pH of fasted dogs is highly variable, ranging between 3 and 8 (17). In addition, a higher pH in the intestine of dogs by comparison with humans may result in better absorption of drugs that are weak bases, but this can be influenced by feeding. Following a meal, gastric acid secretion rates in dogs exceed those of humans and are slower to return to baseline. The postprandial gut pH in humans tends to exceed that observed in dogs due to the strong buffering action of the diet, returning to baseline values within approximately one hour (14).

A radiotelemetric technique (Heidelberg capsule) for monitoring canine GI function provided continuous pH profiles for baseline (fasted) and postprandial states (18). During a 6 -hour test period in 4 Beagles, the baseline (fasting) gastric pH ranged between 0.9 and 2.5 (first 30 minutes of testing). The postprandial gastric pH values varied between 0.5 and 3.5 (first 30 minutes of testing). Baseline duodenal pH values during the initial 5 minutes after gastric emptying varied from 4.5 to 7.5 . They varied between 4.5 to greater than 8.0 (during the initial 60 minutes following gastric emptying). The intestinal pH tended to increase linearly over the initial 60 -minute postprandial period. The mean gastric residence time of the capsule was 74 minutes in the fasted state (range 0 to 240 minutes), and postprandially the capsule remained in the stomach for the duration of the

6-hour observation period. This study highlights the variability in pH and gastric motility that can occur even within a single breed of dog.

In some cases, interspecies differences in product bioavailability are a result of dissimilarity in GI pH. Because dogs have higher basal intestinal pH and lower basal acid secretion in the stomach than do people, these differences appeared to be responsible for dissimilarities in the bioavailability of indomethacin (19), metronidazole (20), and cinnarizine (21). In other situations, pH dependence appears to be related to product formulation rather than the active compound, as was the case when the relative bioavailability of two formulations of L-735,524, an HIV protease inhibitor, was different when tested in rats versus dogs (22). Two extended-release formulations of theophylline developed for humans did not show an extended-release profile for dogs (23). The elimination half-life of theophylline in dogs was only slightly longer for extended-release oral formulations compared with the IV formulation, which would not be considered sufficient for extended release. Theophylline from these capsules and tablets was rapidly and completely absorbed and had to be administered every 12 hours in dogs to maintain therapeutic plasma concentrations. These studies were performed in unfed dogs, in which intestinal pH is higher than humans. It is possible that different findings would occur if there had been comparisons with fed dogs.

## Differences between Dogs and People in Gastric Emptying

Particle dispersion is important for optimizing in vivo dissolution characteristics of low-solubility or slowly dissolving dosage forms. In humans, particle density has been demonstrated to significantly impact gastric emptying time, with heavier particles (e.g., $2.8 \mathrm{~g} / \mathrm{cm}^{3}$ ) being retained longer than less-dense particles (e.g., $1.5 \mathrm{~g} / \mathrm{cm}^{3}$ ) (24).

As is the case for humans, particle size affects gastric emptying time in veterinary species. In dogs, very small particles (e.g., $1 \mathrm{~g} / \mathrm{cm}^{3}, 1.6 \mathrm{~mm}$ diameter) empty more rapidly than do particles whose diameter exceeded 2.4 mm (25). Particles greater than 7 mm were not emptied from the canine stomach until 6-8 hours after food intake during a late phase of digestion (26). When one compares the gastric emptying of fasted humans, dogs, and minipigs, the order in rate of gastric emptying is dogs $>$ humans $>$ minipigs (27). These differences are observed both with tablets (enteric coated aspirin, diameter $5.8 \mathrm{~mm}, 1.24 \mathrm{~g} / \mathrm{cm}^{3}$ and barium sulfate tablets, 6.0 mm diameter, $1.52 \mathrm{~g} / \mathrm{cm}^{3}$ ) and granules (diameters $=0.1 \mathrm{~mm}$, density $=1.17$ and 1.34 $\mathrm{g} / \mathrm{cm}^{3}$ respectively). Tablets empty more rapidly than do granules in dogs, but they are cleared at a similar rate in humans. For example, in dogs, the absorption of drug from granules continued to occur even after 10 hrs postdose. In contrast, peak concentrations in humans occurred within about 5 hours after administration.

Despite the faster gastric emptying observed for dogs versus humans in the fasted state, food appeared to result in a substantially greater delay in the emptying of large particles
(tablets) and pellets in dogs as compared to humans (28). These effects of particle size were demonstrated with aspirin tablets. When human-labeled enteric coated aspirin tablets were administered to dogs (29) the tablets were poorly digested and retained in the stomach. These tablets (diameter 13 mm ) were coated with phthalate, which prevented digestion of the tablets. If animals were fed, the enteric coated tablets were more likely to be retained in the stomach, which was demonstrated by comparing once-daily feeding to thrice-daily feeding. However, neither particle size nor prandial state affects the rate of intestinal transit (30, 24).

Density influences gastric emptying, and particles with densities closest to that of the gastric contents are emptied the fastest. Very light or very heavy particles emptied with greater difficulty. In part, the slower emptying of large particles may be due to retropulsion induced by gastric contraction. Similarly, viscosity affects the rate of gastric emptying, and time to emptying and the volume of gastric contents increase in accordance with the viscosity of the ingesta (31).

Although much attention has been given to the impact of particle size, luminal fluid volume is also a critical variable in determining the time for gastric emptying. Studying gastric emptying in dogs, Gupta and Robinson (32) demonstrated that fluid volume markedly affects the gastric emptying of particles, regardless of particle density. Greater fluid volumes tended to increase the initial rate of gastric transit, although the time for $100 \%$ emptying of particles was completed more rapidly at smaller fluid volumes. Thus, viscosity, fluid volume, and particle size are all critical variables for ensuring that particle dispersion will occur within the GI tract (32).

## Differences between Dogs and People Regarding Intestinal Drug Absorption

The majority of orally administered drugs are absorbed via passive transcellular transport (33). Transcellular transport generally occurs when the compound is un-ionized, although there are examples of ionized molecules that are absorbed via transcellular processes $(34,35)$. Molecular movement across biological membranes is complicated by differences in membrane polarity, hydrophobicity, and density along the gastrointestinal tract (30). Most drugs are absorbed in the small intestine, and little absorption occurs in the colon. In addition to cellular membrane barriers to drug diffusion, significant impedance is also affected by the components of the gastric and intestinal mucous layer such as phosphatidyl choline, cholesterol, and linoleic acid, which retard the diffusion of small lipophilic molecules such as propranolol and hydrocortisone (37). Small hydrophilic molecules such as mannitol appear to freely diffuse through this lipoid barrier. Mucous gel-forming components, such as mucin and DNA, exert far less negative effects on the diffusion of lipophilic molecules. However, they may serve to block the diffusion of peptides and proteins.

For passive diffusion mechanisms, whether a drug is absorbed via paracellular or transcellular mechanisms is determined by both physicochemical and physiological factors.

Although the primary determinant is usually related to the drug's properties, the physiological characteristics of the animal, such as membrane diffusion surface, diffusion distance, and membrane permeability also can play a key role. Lennernas (38) noted that changing certain physiological characteristics such as the effective permeability of the membrane ( $P_{e f f}$ ) or the time available for drug absorption (intestinal residence time) can alter the fraction of drug absorbed.
In addition to passive mechanisms, active transport is important to the absorption of several compounds. Beta-lactam antibiotics, such as amoxicillin, as well as other amino $\beta$ lactams, are absorbed in the proximal small intestine via a carrier-mediated system that can be saturated (39). The car-rier-mediated absorption system for aminopenicillins is most likely the dipeptide carrier system (40). Both active and passive transport mechanisms may occur simultaneously for the same molecule. A determination of which mechanism(s) has the dominant role tends to be compound specific and may not be well predicted by in vitro systems (33). Nevertheless, it must be remembered that even active transport mechanisms require that the drug penetrate the intestinal cells via the transcellular route.
Different intestinal length and transit can influence comparative interspecies drug absorption. Intestinal transit time influences the absorption of drugs with limited mucosal permeability, carrier-mediated uptake, drugs subject to intestinal degradation, or products whose dissolution is the rate-limiting step for systemic absorption (41, 42). Dogs have a shorter absolute intestine length and shorter intestinal length to body length ratio compared to people. Corresponding to a shorter intestinal length in dogs is a shorter gastrointestinal transit time compared to that of people (2 hours vs. 4 hours, respectively). The impact of interspecies differences in GI transit time was underscored by the failure of Beagle dogs to adequately model the human bioavailability of acetaminophen sustained-release tablets (42), griseofulvin tablets (43), valproic acid (44), and ampicillin (45).

Intestinal transit time can be a critical determinant of product bioavailability for dissolution rate-limited formulations. In this regard, marked interspecies differences are again observed. For example, when fluid or particulate markers are administered via intragastric administration, the percent of dose excreted in the feces from hrs 0 to 24 in dogs and mature swine are $55 \%$ and $7 \%$ for the fluid markers, respectively, and $40 \%$ and $2 \%$ for particulate markers, respectively (46). Some of this difference can be accounted for by differences in intestinal length between pigs and dogs. The ratio of body length to intestine length is $1: 14$ and $1: 6$ in pigs and dogs, respectively (46). (Ratios for humans are similar to those of pigs.) Sustained-release preparations (eroding matrix) of the lipophilic compound propylthiouracil demonstrate very poor bioavailability in dogs because of the very short GI transit time. Generally, the product will reach the canine colon ( $2-3$ hours) before having had an opportunity to dissolve (47). Accordingly, we can expect that a low-solubility compound or a product for-
mulated to provide slow dissolution characteristics will tend to exhibit a poorer bioavailability in the canine compared to the swine.

For Class III drugs, intestinal permeability rather than in vitro dissolution is the rate-limiting step in drug absorption. For compounds exhibiting permeability-limited absorption, dissolution rate is generally less important than the rate of intestinal transit. Therefore, some formulations of Class III and IV compounds can have markedly different dissolution rates without affecting the blood concentration/time profile $(48,49)$.

Dogs can compensate for the shorter intestinal length with longer intestinal villi, which provide more surface area for absorption. Because they possess greater surface area for diffusion compared to people, dogs actually absorb many drugs orally much better than do humans (12). The bioavailability of small hydrophilic compounds tends to be greater in species such as dogs where both pore diameter and surface area tend to exceed that in humans (11).

The crypts, villi, and microvillae are critical for increasing the GI surface area. Highly permeable drugs generally are absorbed upon contact with the intestinal membrane, and the majority of absorption occurs at the villus tip (50). Because the radial surface area does not markedly differ across species, we would expect there to be minimal (if any) differences in the absorption of highly permeable compounds across animal species. Therefore, there is an assumption that the basic composition of intestinal epithelial cells is relatively similar across species, and intestinal membrane permeability will be comparable across target animal species (51). However, significant interspecies differences in intestinal absorptive surfaces can result from differences in the size, number of pores, and shape of the intestinal villi $(14,50)$. In addition, dogs have higher bile salt secretion, which increases the solubility of some poorly water-soluble drugs.

Paracellular absorption (between cells) also can be important, and interspecies differences in this pathway should not be discounted. Paracellular diffusion involves both diffusion and a convective volume flow through water-filled intercellular channels whose diameter is approximately $3-10 \AA$ in humans (38). Accordingly, the size and number of paracellular spaces influence the intestinal absorption of most hydrophilic compounds. This, in turn, is affected by the mucosal surface area and by cellular density (52). In humans, the small intestinal surface area for paracellular absorption is approximately $0.01 \%$ of the total membrane surface area. For this reason, unless the molecule is extremely small (e.g., <200 Da), paracellular transport will have a minor role in drug absorption (33).

Greater paracellular transport observed in dogs may be attributable to either interspecies differences in pore diameter or a difference in the number of pores on the intestinal villi, the latter reflecting differences in the effective surface area across regions of the small intestine (53). This difference in surface area for paracellular absorption may
impact the relative bioavailability of small hydrophilic (low-permeability, high-solubility) compounds such as furosemide (54). There was also greater bioavailability of large molecular weight polyethylene glycol (PEG) in dogs compared to rats, which has been ascribed to the presence of larger and more frequent pores in the canine intestine (55).
Permeability is not necessarily constant throughout the GI tract. Although for some compounds drug absorption appears to be site independent (56), for others it is site dependent (57). When drug absorption is site dependent, the availability of dissolved drug at the absorption site can be a limiting factor in product bioavailability. Across species, the location in the intestinal tract where the free drug is presented can markedly influence product absorption. In people, amoxicillin (and possibly other $\beta$-lactam antibiotics) is preferentially absorbed in the duodenum and jejunum but poorly absorbed from the more distal regions of the small intestine (ileum), and no absorption occurs distal to the ileum from the various segments of the large intestine (57). Differences in site-specific drug metabolism are known to occur across animal species (58). This may be a reason why dicloxacillin, although not an aminopenicillin, demonstrates only poor oral availability in dogs ( $23 \%$ ) (59) but much higher oral availability in people ( $50-85 \%$ ).

## FACTORS THAT AFFECT THE BCS CLASSIFICATION

Although differences in canine versus human GI characteristics, as described in this article, will clearly influence interspecies differences in drug and drug product bioavailability, the question remains whether these differences will also influence the BCS classification of a compound. Current guidelines for in vitro dissolution of oral dosage forms used in humans specify a specific volume into which the drug is dissolved. This volume is meant to simulate the volume of the stomach (for example, 900 mL ). This volume needs to be rescaled for dogs. However, dog breeds obviously cover a wide range of sizes from small toy breeds to the giant breeds. Because the administered dosage strength for dogs is related to body weight, this leads to questions of whether or not gastric volume scales in proportion to body size. To date, there are no data available upon which to resolve this question.

## Defining the Test Conditions

Because there may be a need to use a smaller volume for in vitro dissolution testing of oral products for dogs, the solubility of the product may not be extrapolated directly from human data. This uncertainty leads to the potential need to reconsider the BCS definition of solubility when applied to oral products for dogs. Based on the USP definition, solubility is defined as the extent to which molecules from a solid are removed from its surface by a solvent (60):

Very soluble
Freely soluble
Soluble
Sparingly soluble
Slightly soluble
Very slightly soluble
Practically insoluble

Less than 1 part solvent needed to dissolve 1 part solute From 1 to 10 parts solvent needed to dissolve 1 part solute From 10 to 30 parts solvent needed to dissolve 1 part solute From 30 to 100 parts solvent needed to dissolve 1 part solute From 100 to 1,000 parts solvent needed to dissolve 1 part solute From 1,000 to 10,000 parts solvent needed to dissolve 1 part solute More than 10,000 parts solvent needed to dissolve 1 part solute

FDA's Center for Drug Evaluation and Research (CDER) uses somewhat different definitions of solubility (7). One of the questions to resolve for developing BCS concepts for formulations in dogs is whether a USP-like definition of solubility is more appropriate than the definition currently used by CDER. For example, which definition (above) corresponds to "highly soluble?"

Similarly, the question of the pH of the medium must be addressed. Currently, a highly soluble drug is expected to dissolve under all pH conditions. However, we recognize that there are species-specific differences in gastric and intestinal pH that may not only affect drug solubility but also the conditions under which in vitro testing should occur. As discussed previously in this article, pH conditions in the stomach and intestine vary tremendously in dogs and cannot be extrapolated from humans.

## OBJECTIVES OF THE USP COMMITTEE

The USP Veterinary Drugs Expert Committee formed the ad hoc committee to organize and facilitate gathering data and information that will address many of the questions presented above. This committee intends to hold a scientific meeting that will bring together experts from veterinary academia, the pharmaceutical industry, and FDA to share information. The goals of the meeting are multifold. First, we would like to obtain public comment on the value of this initiative to veterinary medicine. If there is agreement that this initiative will have a positive impact on the practice and development of pharmaceuticals intended for use in dogs, we will explore answers to the questions that need to be addressed, define potential research initiatives, and determine strategies for moving this initiative forward.

## SPECIFIC QUESTIONS TO ADDRESS

During this time for public comment, we will explore the following questions that must be resolved before BCS principles can be extrapolated to facilitating pharmaceutical decisions in dogs:

## Solubility

Currently CDER defines a highly soluble drug as one in which the highest dosage strength completely dissolves in 250 mL or less of aqueous buffer, $\mathrm{pH} 1-7.5$. This volume reflects the gastric fluid volume of a fasted human after consuming an oral dose with 8 oz of liquid.

- In veterinary species, is 250 mL an appropriate volume for evaluating solubility? This question is critical because it is impractical to expect animal owners to encourage their pets to drink a cup of water after swallowing an oral medication.
- What is the volume of the canine stomach ( $\mathrm{mL} / \mathrm{kg}$ ) , and does canine gastric volume vary linearly with body weight?
- Is the dissolution pH range specified for humans appropriate for the canine situation?


## Permeability

Can we simply extrapolate permeability classification across animal species, or are there sufficient data available to consider interspecies differences in both transcellular and paracellular pathways?

- Are there canine-specific in vitro systems available?
- In the CDER guidance, in some cases highly permeable drugs can be defined by a systemic availability $(F)$ of $>90 \%$. In dogs, however, there is a greater tendency for high first-pass drug loss by comparison with that observed in humans. Highly permeable drugs may still have poor systemic availability due to first-pass metabolism. Therefore, how can we readily assess highly permeable drugs under these circumstances?
- When tests are properly validated (7), animal in situ intestinal perfusion data can be used to support human permeability classifications for passively absorbed compounds. (Caution is expressed with regard to potential misclassification when efflux transporters are present.) Is it feasible to have similar systems validated for developing permeability classifications for dogs?


## Dissolution

Are the currently available in vitro dissolution specifications appropriate for pharmaceutical formulations administered to dogs?

- Consider the differences in gastric emptying time: Dogs tend to have more rapid gastric emptying than humans. The magnitude of this difference is a function of particle size. In contrast, in some cases food appears to have a more profound effect on inhibiting gastric emptying compared to humans. Therefore, what is an appropriate time frame for defining a rapidly dissolving compound in dogs? Currently, CDER guidance on biowaivers (7) states that dissolution must be $\geq 85 \%$ for both products to be considered rapidly dissolving. For slower dissolu-
tion, the $f_{2}$ criterion must be applied. Will this criterion adequately cover the dog?
- What is the potential impact of differences in ionic composition of GI fluids?
- What is the appropriate pH range? Canine fasted gastric pH is reported to range from 3 to 8 . In most human subjects, fasted gastric pH values range from 1 to 3 .
- What is the appropriate agitation speed of the apparatus?


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## NOMENCLATURE

This section includes supplements to the latest edition of the USP Dictionary of USAN and International Drug Names that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

## USP Dictionary of USAN and International Drug Names 2004 USP DICTIONARY SUPPLEMENT 4

IMPORTANT-Save this Supplement. This and all supplements appearing in $P F$ are needed to keep the 2004 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2004) edition will be included in the next complete edition of the Dictionary.

## New United States Adopted Names (USAN)

The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of $P F$ for other new USAN to supplement the Dictionary main volume.

Abatacept [2004] (ab a ta' sept). $\left(\mathrm{C}_{1965} \mathrm{H}_{3080} \mathrm{~N}_{479} \mathrm{O}_{695} \mathrm{~S}_{16}\right)$. 1-25Oncostatin $M$ (human precursor) fusion protein with CTLA-4 (antigen) (human) fusion protein with immunoglobulin G1 (human heavy chain fragment). Molecular weight is approximately 92,000 daltons ( 46,000 daltons per chain). CAS-332348-12-6. INN. Treatment of autoimmune diseases such as rheumatoid arthritis (selective co-stimulation modulator; binds to the $B 7$ family of molecules expressed on antigen-presenting cells $(A P C)$ ). (Bristol-Myers Squibb) $\diamond B M S-188667$ MGVLLTQRTL LSLVLALLFP SMASMAMHVA QPAVVLASSR GIASFVCEYA SPGKATEVRV TVLRQADSQV TEVCAATYMM GNELTFLDDS ICTGTSSGNQ VNLTIQGLRA MDTGLYICKV ELMYPPPYYL GIGNGTQIYV IDPEPCPDSD QEPKSSDKTH TSPPSPAPEL LGGSSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PG**K*
** - C-terminus (predominant species)

*     - C-terminus (cDNA)
underline -N -glycosylation

Alglucosidase Alfa [2004] (al gloo kose' i dase).
$\mathrm{C}_{4758} \mathrm{H}_{7262} \mathrm{~N}_{1274} \mathrm{O}_{1369} \mathrm{~S}_{35}$. 105,338 . (1) Glucosidase, prepro- $\alpha-$ [199-arginine, 223-histidine] (human); (2) [199-Arginine, 223-histidine]prepro- $\alpha$-glucosidase (human). CAS-420794-05-0. INN. Treatment of Pompe's disease (enzyme replacement therapy). (Genzyme) $\diamond r h G A A$ MGVRHPPCSH RLLAVCALVS LATAALLGHI LLHDFLLVPR ELSGSSPVLE ETHPAHQQGA SRPGPRDAQA HPGRPRAVPT QCDVPPNSRF DCAPDKAITQ EQCEARGCCY IPAKQGLQGA QMGQPWCFFP PSYPSYKLEN ${ }^{*}$ LSSSEMGYTA TLTRTTPTFF PKDILTLRLD VMMETENRLH FTIKDPANRR YEVPLETPRV HSRAPSPLYS VEFSEEPFGV IVHRQLDGRV LLWTTVAPLF FADQFLQLST SLPSQYITGL AEHLSPLMLS TSWTRITLWN RDLAPTPGAN LYGSHPFYLA LEDGGSAHGV FLLNSNAMDV VLQPSPALSW RSTGGILDVY IFLGPEPKSV VQQYLDVVGY PFMPPYWGLG FHLCRWGYSS TAITRQVVEN * MTRAHFPLDV QWNDLDYMDS RRDFTFNKDG FRDFPAMVQE LHQGGRRYMM IVDPAISSSG PAGSYRPYDE GLRRGVFITN ETGQPLIGKV WPGSTAFPDF TNPTALAWWE DMVAEFHDQV PFDGMWIDMN EPSNFIRGSE DGCPNNELEN PPYVPGVVGG TLQAATICAS SHQFLSTHYN LHNLYGLTEA IASHRALVKA RGTRPFVISR STFAGHGRYA GHWTGDVWSS WEQLASSVPE ILQFNLLGVP LVGADVCGFL GNึTSEELCVR WTQLGAFYPF MRNHNSLLSL PQEPYSFSEP AQQAMRKALT LRYALLPHLY TLFHQAHVAG ETVARPLFLE FPKDSSTWTV DHQLLWGEAL LITPVLQAGK AEVTGYFPLG TWYDLQTVPI EALGSLPPPP AAPREPAIHS EGQWVTLPAP LDTINVHLRA GYIIPLQGPG LTTTTESRQQP MALAVALTKG GEARGELFWD DGESLEVLER GAYTQVIFLA RNNTIVNELV RVTSEGAGLQ LQKVTVLGVA TAPQQVLSNG VPVSN*FTYSP DTKVLDICVS LLMGEQFLVS WC

*     - glycosylation sites

Avanafil [2004] (av an' a fil). $\mathrm{C}_{23} \mathrm{H}_{26} \mathrm{ClN}_{7} \mathrm{O}_{3}$. 483.95. (1) 5-Pyrimidinecarboxamide, 4-[[(3-chloro-4-methoxyphenyl)meth-yl]amino]-2-[(2S)-2-(hydroxymethyl)-1-pyrrolidinyl]- N -(2-pyrimidinylmethyl)-; (2) 4-[(3-Chloro-4-methoxybenzyl)amino ]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]- $N$-(pyrimi-din-2-ylmethyl)pyrimidine-5-carboxamide; (3) (S)-4-(3-Chloro-4-methoxybenzylamino)-2-(2-hydroxymethylpyrroli-din-1-yl)- $N$-pyrimidin-2-ylmethyl-5-pyrimidinecarboxamide. CAS-330784-47-9. Treatment of erectile dysfunction. (Tanabe Seiyaku) $\triangleleft T A-1790$


Bemotrizinol [2004] (be moe' trye zi nol). $\mathrm{C}_{38} \mathrm{H}_{49} \mathrm{~N}_{3} \mathrm{O}_{5}$. 627.80. (1) Phenol, $2,2^{\prime}$-[6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diyl]bis[5-[(2-ethylhexyl)oxy]; (2) 2,2'-[6-(4-Methoxyphe-nyl)-1,3,5-triazine-2,4-diyl]bis[5-[(2-ethylhexyl)oxy]phe-nol].CAS-187393-00-6. UVA absorber (intended for use as a topical sunscreen). Tinosorb S (Ciba Specialty Chemicals) [Note-The International Nomenclature Cosmetic Ingredient Name (INCI) for bemotrizinol is bis-ethylhexyloxyphenol methoxyphenol triazine.] $\triangleleft B E M T$; FAT 70'884


Bisoctrizole [2004] (bis ok' trye zole). $\mathrm{C}_{41} \mathrm{H}_{50} \mathrm{~N}_{6} \mathrm{O}_{2}$. 658.90. (1) Phenol, 2, 2'-methylenebis[6-( 2 H -benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)-; (2) 2,2'-Methylenebis[6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol]. CAS-103597-45-1. UVA absorber (intended for use as a topical sunscreen). Tinosorb M (Ciba Specialty Chemicals) [NoteThe International Nomenclature Cosmetic Ingredient Name (INCI) for bisoctrizole is methylene bis-benzotriazolyl tetramethylbutylphenol.] $\diamond M B B T$; FAT 75 '634


Canfosfamide Hydrochloride [2004] (kan fos' fa mide). $\mathrm{C}_{26} \mathrm{H}_{40} \mathrm{Cl}_{4} \mathrm{~N}_{5} \mathrm{O}_{10} \mathrm{PS} . \mathrm{HCl}$ 823.93. (1) Glycine, $\mathrm{L}-\gamma$-glutamyl-3-[[2-[[bis[bis(2-chloroethyl)amino]phosphinyl]oxy]ethyl]sul-fonyl]-L-alanyl-2-phenyl-, monohydrochloride, $(2 R)-;$ (2) (2S)-2-Amino-5-[[(1R)-1-[[[2-[[bis[bis(2-chloroethyl)amino ]phosphinyl]oxy]ethyl]sulfonyl]methyl $]-2-[[(R)$-carboxy-phenylmethyl]amino]-2-oxoethyl]amino]-5-oxopentanoic acid monohydrochloride. CAS-439943-59-6. Antineoplastic (activated by glutathione S-transferase (GST P1-1)). Telcyta (Tanabe, Japan) $\diamond$ TLK286; TER286


Deferasirox [2004] (de fer' a sir ox). $\mathrm{C}_{21} \mathrm{H}_{15} \mathrm{~N}_{3} \mathrm{O}_{4}$. 373.36. (1) Benzoic acid, 4-[3,5-bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl]-; (2) 4-[3,5-Bis(2-hydroxyphenyl)-1H-1,2,4-triazol-1yl]benzoic acid. CAS-201530-41-8. INN. Treatment of iron overload (iron chelator). (Novartis Pharma AG, Switzerland) $\checkmark I C L 670 A$


Etalocib [2004] (e tal' oh kib). $\mathrm{C}_{33} \mathrm{H}_{33} \mathrm{FO}_{6}$. 544.61. (1) Benzoic acid, 2-[3-[3-[(5-ethyl-4'-fluoro-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-2-propylphenoxy]-; (2) 2-[3-[3-[(5-Ethyl-4'-fluoro-2-hydroxybiphenyl-4-yl)oxy]propoxy]-2-propylphenoxy]benzoic acid. CAS-161172-51-6. Antineoplastic (inhibits formation of 5-LO, LTB ${ }_{4}, L T C_{4}$, and thromboxane $B_{2}\left(T x B_{2}\right)$; activates PPAR $\gamma$ nuclear receptors). (Lilly) $\checkmark$ LY293111


Iboctadekin [2004] (ib ok' ta de' kin). $\mathrm{C}_{801} \mathrm{H}_{1264} \mathrm{~N}_{212} \mathrm{O}_{252} \mathrm{~S}_{10}$ 18,217.00. (1) Human interleukin-18 (recombinant, expressed in Escherichia coli); (2) Purified iboctadekin is a recombinant human cytokine, interleukin-18 (IL-18) belonging to the IL-1 family, also known as interferon- $\gamma$-inducing factor (IGIF), expressed in a nonpathenogenic strain of Escherichia coli. Iboctadekin, consisting of 157 amino acids, is formed in
vivo following the activation of proIL-18 by caspase-4 and consists of a single polypeptide chain that is not glycosylated. The protein contains four cysteine residues present as free sulfhydryl groups. CAS-479198-61-3. Treatment of disseminated solid tumors. (GlaxoSmithKline) $\diamond S B-485232$
YFGKLESKLS VIRNLNDQVL FIDQGNRPLF EDMTDSDCRD NAPRTIFIIS MYKDSQPRGM AVTISVKCEK ISTLSCENKI ISFKEMNPPD NIKDTKSDII FFQRSVPGHD NKMOFESSSY EGYFLACEKE RDLFKLILKK EDELGDRSIM FTVQNED

Pralatrexate [2004] (pral" a trex' ate). $\mathrm{C}_{23} \mathrm{H}_{23} \mathrm{~N}_{7} \mathrm{O}_{5} .477 .50$. (1) LGlutamic acid, $N$-[4-[1-[(2,4-diamino-6-pteridinyl)methyl $]$-3-butynyl]benzoyl]-; (2) (2S)-2-[[4-[(1RS)-1-[(2,4-Diaminop-teridin-6-yl)methyl]but-3-ynyl] benzoyl]amino]pentanedioic acid. CAS-146464-95-1. Treatment of malignancies. (Allos Therapeutics) $\diamond P D X$


Raxibacumab [2004] (rax" ee bak' ue mab). Immunoglobulin G1, anti-(anthrax protective antigen) (human monoclonal PA heavy chain), disulfide with human monoclonal PA $\lambda$-chain, dimer. CAS-565451-13-0. Treatment of anthrax infection. ABthrax (Human Genome Sciences)

Talactoferrin Alfa [2004] (ta lak" toe for' rin).
$\mathrm{C}_{3345} \mathrm{H}_{5215} \mathrm{~N}_{963} \mathrm{O}_{1015} \mathrm{~S}_{37}$ (protein). (1) Lactoferrin (recombinant human LF00); (2) [11-L-Threonine, 29-L-arginine]lactoferrin(human) produced by Aspergillus niger var. awamori. Molecular weight is approximately 80,000 daltons (glycosylated). CAS-308240-58-6. Recombinant human lactoferrin (rhLF), intended for use as an anti-infective (antimicrobial and antiviral); anti-inflammatory, and antineoplastic. (Agennix) $\diamond L F 00$
GRRRRSVQWC TVSQPEATKC FQWQRNMRRV RGPPVSGIKR DSPIQCIQAI AENRADAVTL DGGFIYEAGL APYKLRPVAA EVYGTERQPR THYYAVAVVK KGGSFQLNEL QGLKSCHTGL RRTAGWNVPI GTLRPFLN̈WT GPPEPIEAAV ARFFSASCVP GADKGQFPNL CRLCAGTGEN KCAFSSQEPY FSYSGAFKCL RDGAGDVAFI RESTVFEDLS DEAERDEYEL LCPDNTRKPV DKFKDCHLAR vPSHAVVARS VNGKEDAIWN LLRQAQEKFG KDKSPKFQLF GSPSGQKDLL FKDSAIGFSR VPPRIDSGLY LGSGYFTAIQ NLRKSEEEVA ARRARVVWCA vGEQELRKCN QWSGLSEGSV TCSSASTTED CIALVLKGEA DAMSLDGGYV YTAGKCGLVP VLAENYKSQQ SSDPDPNCVD RPVEGYLAVA VVRRSDTSLT WNSVKGKKSC HTAVDRTAGW NIPMGLLFNQ TGSCKFDEYF SQSCAPGSDP RSNLCALCIG DEQGENKCVP NSNERYYGYT GAFRCLAENA GDVAFVKDVT VLQNTDGNNN EAWAKDLKLA DFALLCLDGK RKPVTEARSC HLAMAPNHAV VSRMDKVERL KQVLLHQQAK FGRNGSDCPD KFCLFQSETK NLLFNDNTEC LARLHGKTTY EKYLGPQYVA GITNLKKCST SPLLEACEFL RK

Temsirolimus [2004] (tem" sir oh' li mus). $\mathrm{C}_{56} \mathrm{H}_{87} \mathrm{NO}_{16}$. 1030.30. (1) Rapamycin, 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]; (2) $(3 S, 6 R, 7 E R, 10 R, 12 R, 14 S, 15 E, 17 E$, $19 E, 21 S, 23 S, 26 R, 27 R, 34 a S)-9,10,12,13,14,21,22,23,24,25$, 26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methyl-ethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone 4'-[2,2-bis(hydroxymethyl)propionate]; (3) Rapamycin 42-[2,2-bis-(hydroxymethyl)propionate]. CAS-162635-04-3. Antineoplastic ( $m$ TOR inhibitor). (Wyeth) $\diamond C C I-779$


Tetraxetan [2004] (te trax' e tan). $\mathrm{C}_{16} \mathrm{H}_{28} \mathrm{~N}_{4} \mathrm{O}_{8}$. 404.42. (1)
1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid; (2) $2,2^{\prime}, 2^{\prime \prime}, 2^{\prime \prime \prime}-(1,4,7,10$-Tetraazacyclododecane-1,4,7,10-tetryl)tetraacetic acid. CAS-60239-18-1. Radical designation for a chelating agent. (Immunomedics) [Note-Tetraxetan has been used in conjunction with yttrium Y 90 epratuzumab tetraxetan (N04/58) and yttrium Y 90 labetuzumab tetraxetan (N04/59).] $\diamond D O T A$


Torapsel [2004] (tore ap' sel). $\mathrm{C}_{2726} \mathrm{H}_{4186} \mathrm{~N}_{710} \mathrm{O}_{846} \mathrm{~S}_{20}$ (peptidic part). 61,083 (peptidic part). 42-89-Glycoprotein (human clone PMT21:PL85 P-selectin glycoprotein ligand 1) fusion protein with immunoglobulin (human constant region). CAS-204658-47-9. INN. P-selectin antagonist. (Wyeth) $\langle W A Y 164339$
QatEYEYLDY DFLPETEPPE MLRNSTDTTP LTGPGTPEST TVEPAARPHT CPPCPAPEAL GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPVPIEKT ISKAKGQPRE PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK

Yttrium Y 90 Epratuzumab Tetraxetan [2004] (it' ree um epra too' zoo mab te trax' e tan). (1) Immunoglobulin G1, anti-(human CD22 (antigen)) (human-mouse monoclonal hLL2 $\gamma$ chain), disulfide with human-mouse monoclonal hLL2 $\kappa$ chain, dimer, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid conjugate, yttrium-90Y chelate; (2) Immunoglobulin G1 (human-mouse monoclonal hLL2 $\gamma$-chain anti-human antigen CD22), disulfide with human-mouse monoclonal
hLL2 $\kappa$-chain, dimmer, $2,2^{\prime}, 2^{\prime \prime}, 2^{\prime \prime \prime}$-(1,4,7,10-tetraazacyclodo-decane-1,4,7,10-tetryl)tetraacetic acid conjugate, yttrium90 Y . Molecular weight is approximately 150,000 daltons. CAS-501423-25-2. Radioimmunotherapy (RAIT) for nonHodgkin's B-cell lymphoma (monoclonal antibody). (Immunomedics) $\diamond^{90} \mathrm{Y}$-DOTA-hLL2

Yttrium Y 90 Labetuzumab Tetraxetan [2004] (it' ree um la be too zoo' mab te trax' e tan). (1) Immunoglobulin G1, anti-(human carcinoembryonic antigen) (human-mouse monoclonal hMN-14 $\gamma$-chain), disulfide with human-mouse monoclonal hMN-14 $\kappa$-chain, dimer, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid conjugate, yttrium-90Y chelate; (2) Immunoglobulin G1 (human-mouse monoclonal hMN-14 $\gamma$ chain anti-human carcinoembryonic antigen), disulfide with
human-mouse monoclonal hMN-14 $\kappa$-chain, dimer, $2,2^{\prime}, 2^{\prime \prime}, 2^{\prime \prime \prime}$-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetryl)tetraacetic acid conjugate, yttrium-90Y chelate. Molecular weight is approximately 150,000 daltons. CAS-501423-309. Radioimmunotherapy (RAIT) for CEA-expressing tumors in colorectal, pancreatic, lung, breast, ovarian, and medullary thyroid cancer. (Immunomedics) $\stackrel{夕}{ }^{90} Y-D O T A-h M N 14$

Yttrium Y 90 Tacatuzumab [2004] (tak a tue' zoo mab). Immunoglobulin G1, anti-(human $\alpha$-fetoprotein) (human-mouse monoclonal hAFP-31 $\gamma 1$-chain), disulfide with human-mouse monoclonal hAFP-31 $\beta$-chain dimer, yttrium-90Y chelate. CAS-500784-58-7. Tumor eradication. AFP-Cide (Immunomedics) $\diamond h A F P-31$

## Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

Aplindore Fumarate [2004] (ap lin dor). $\mathrm{C}_{18} \mathrm{H}_{18} \mathrm{~N}_{2} \mathrm{O}_{3} \cdot \mathrm{C}_{4} \mathrm{H}_{4} \mathrm{O}_{4}$. 426.42. [Palindore is INN.] (1) 8 H -1,4-Dioxino[2,3-e]indol-8-one, 2,3,7,9-tetrahydro-2-[[(phenylmethyl)amino]methyl]-, 2(S)-, (2E)-2-butenediotate (1:1); (2) (2S)-2-[(Benzylamino)-methyl]-2,3,7,9-tetrahydro-8H-1,4-dioxino[2,3-e]indol-8-one (E)- butenedioate (1:1). CAS-189681-71-8; CAS-189681-707 [palindore]. Antischizoprenic (low intrinsic activity modulator of human dopamine $D_{2} / D_{3}$ receptors). (Wyeth) [Name previously used: Palindore Fumarate.] $\checkmark D A B-452$


Enoxaparin Sodium [1995] (ee nox a pa' rin). (1) Enoxaparin sodium; (2) Sodium salt of a low-molecular weight heparin obtained by alkaline depolymerization of the benzyl ester of heparin from porcine mucosa. CAS-679809-58-6. INN; BAN; MI. Antithrombotic intended for use in the treatment of deep vein thrombosis; prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, and treatment of acute deep vein thrombosis. Clexane (Aventis); Lovenox (Aventis) $\triangleleft R P$ 54563; PK 10169

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## Proposed and Recommended International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Helath Organization (WHO).

Under its charter, the WHO is empowered simply to recommend specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as proposals ("Proposed International Nonproprietary Names"). A period of four months from the date of publication in WHO Drug Information is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested par-
ties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as recommendations ("Recommended International Nonproprietary Names"), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

## Proposed International Nonproprietary Names

The following 50 names have been selected by the World Health Organization (WHO) as Proposed International Nonproprietary Names. This list, with chemical names or descriptions and the molecular formulae, appears in WHO Drug Information, Vol 18, No. 1, 2004.

Any comments or formal objections to the proposed names should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Proposed INN | Therapeutic Indication | Proposed INN | Therapeutic Indication |
| :---: | :---: | :---: | :---: |
| Adecatumumab | Immunomodulator | Omigapil | Neuroprotective agent |
| Arfomoterol | Bronchodilator | Paclitaxel Poliglumex | Antineoplastic |
| Banoxatrone | Antineoplastic | Parathyroid Hormone | Hormone |
| Batabulin | Antineoplastic | Pasireotide | Inhibition of growth hormone |
| Becampanel | AMPA receptor antagonist |  | release |
| Beminafil | Vasodilator | Pelitrexol | Antineoplastic |
| Binodenoson | Adenosine receptor A agonist | Pruvanserin | Serotonin receptor antagonist |
| Cetrolizumab Pegol | Immипитodulator | Ramelteon | Selective melatonin receptor |
| Ciluprevir | Antiviral (HCV) |  | agonist |
| Clazosentan | Endothelin receptor antagonist | Ranibizumab | Immипотodulator |
| Clofarabine | Antineoplastic | Razaxaban | Anticoagulant |
| Daglutril | Antihypertensive (neutral en- | Resequinil | Psychostimulant |
| Dextofisopam | dopeptidase inhibitor) Anxiolytic | Rivaroxaban | Blood-coagulation factor Xa inhibitor |
| Doranidazole | Radiosensitizing agent | Sabarubicin | Antineoplastic, antibiotic |
| Ecopladib | Cytosolic phospholipase $A_{2}$ inhibitor | Solabegron Tadekinig Alfa | Beta $_{3}$-adrenoreceptor agonist Anti-inflammatory |
| Emapunil | Mitochondrial benzodiazepine receptor agonist) | Tanaproget | Nonsteroidal progesterone receptor agonist |
| Enzastaurin | Antineoplastic | Taneptacogin Alfa | Anticoagulant |
| Eslicarbazepine | Anticonvulsant | Taprizosin | Alpha $1_{1}$-adrenoreceptor antago- |
| Esoxybutynin | Antispasmodic |  | nist |
| Imidafenacin | Muscarin receptor antagonist | Teduglutide | Gastrointestinal functions nor- |
| Lumiliximab | Immunomodulator |  | malizing agent |
| Maropitant | Neurokinin $N K_{1}$ receptor antagonist | Tocilizumab Uliprisnil | Immunomodulator <br> Progesterone receptor modula- |
| Mubritinib | Antineoplastic |  | tor |
| Muraglitazar | Antidiabetic | Urtoxazumab | Immunomodulator |
| Nebentan | Endothelin receptor antagonist | Valtorcitabine | Antiviral |
| Netupitant | Neurokinin $N K_{1}$ receptor antagonist | Vildagliptin Zanolimumab | Antidiabetic agent Immunomodulator |

## Recommended International Nonproprietary Names

The following 58 nonproprietary names have been selected by the World Health Organization (WHO) as Recommended International Nonproprietary Names. This list, with chemical names or
descriptions and the molecular formulae, appears in WHO Drug Information, Vol 18, No. 1, 2004.

| Recommended INN | Recommended INN | Recommended INN | Recommended INN |
| :--- | :--- | :--- | :--- |
| Adargileukin Alfa | Edotecarin | Icofungipen | Pritumumab |
| Alamifovir | Edratide | Icrocaptide | Ralfinamide |
| Aprinocarsen | Elsilimomab | Iferanserin | Rebimastat |
| Belimumab | Elvucitabine | Istradefylline | Segesterone |
| Cantuzumab Mertansine | Epitumomab Cituxetan | Ixabepilone | Semapimod |
| Cimicoxib | Eptotermin Alfa | Ladostigil | Sufugolix |
| Dabuzalgron | Exatecan Alideximer | Lapatinib | Tacapenem |
| Dacinostat | Exenatide | Lomeguatrib | Tafluprost |
| Dalbavancin | Firocoxib | Odiparcil | Talizumab |
| Deligoparin Sodium | Fispemifene | Omiganan | Technetium (99mTc) Nitrido- |
|  |  | Pactimibe | Tesofensine |
| Desvenlafaxine | Fluorescein Lisicol | Patupilone | Tifenazoxide |
| Dibotermin Alfa | Freselestat | Pertuzumab | Tisocalcitate |
| Diquafosol | Galiximab | Ulifloxacin |  |
| Disermolide | Hemoglobin Raffimer |  | Varenicline |
| Edifolgide |  |  |  |

## Suggested United States Adopted Names

The United States Adopted Names (USAN) program is the specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs while the drugs are still in the investigational stages. The American Medical Association (AMA), the American Pharmaceutical Association (APhA), and the United States Pharmacopeial Convention (USPC) jointly sponsor the USAN program with representation from the FDA.

Each U.S. Adopted Name is chosen with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official United States Pharmacopeia or National Formulary. A measure of the prestige and recognition of the value of the USAN program can be found in the following regulations published by the Commissioner of Food and Drugs and the Secretary of Health and Human Services in the Federal Register of February 1988.

All who are concerned with the prescription, dispensing, use, sale or manufacture of drugs may, in the absence of the designation of an official name by the FDA, rely on the current compendial name or the U.S. Adopted Name (USAN) listed in this volume as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act.
A formal procedure ${ }^{1}$ is followed by the USAN Council in selecting an established name for a drug. The USAN Council Secretary is also an ex officio member of the International Nonproprietary Names (INN) Committee. USAN Guiding Principles are concordant with World Health Organization (WHO) principles, and all USANs for substances also named by the INN Committee are sys-
tematically processed through the INN Committee. This ensures that, with very rare exceptions, USANs are identical to INNs and available for world-wide use.

A suggestion for a USAN originates usually from a firm or an individual who has developed a substance of potential therapeutic utility to the point where there is a distinct possibility of its being marketed in the United States of America. Occasionally, the initiative is taken by the USAN Council in the form of a request to parties interested in a substance for which a nonproprietary name appears to be lacking.

Submissions to the USAN Council are expected to conform to the established Guiding Principles ${ }^{2}$ and to be reasonably free from conflict with other names, including both trademarks and nonproprietary names. An effort is made to discourage the occasional, undesirable practice of incorporating in trademarks the syllables used in an established nonproprietary name, or syllables recommended for USAN. Such trademarks may act as a bar to the subsequent adoption of appropriate nonproprietary names for closely related drugs.

The suggested nonproprietary names for the drugs described in the following list are under consideration by the USAN Council. The name(s) being considered for each drug substance, and the applicable category, are separated by double spacing from the name(s) and category for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.
Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Suggested USAN | Category |
| :--- | :--- |
| Ancripentoc | Antiviral; treatment of autoim- |
| Ancriviroc | mune conditions (CCR5 antag- |
| Broxicicra | onist) |
| Metirafiv |  |
| Queviracir |  |
| Queviracrent |  |
| Quevircirant |  |
| Quicrentevir |  |
| Quintacirin |  |
| Racirfivant |  |
| Ranticicra |  |
| Ranticicrant |  |
| Ranticirpant |  |
| Rantirafiv |  |
| Viracirin |  |
| Zeptacirin | Treatment of cancer |
| Aneoganib |  |
| Axisanib |  |
| Trexisanib | Anxiolytic; anticonvulsant; |
| Aramatinib | antispastic; antimigraine; |
| Dasatinib |  |
| Dasmaintinib stabilizer; analgesic |  |
| Sabexitinib |  |
| Sarbextinib |  |

[^377]| Suggested USAN | Category |
| :--- | :--- |
| Agipartrant | Reduction of thrombotic events <br> in patients with acute coronary <br> Torapiparant <br> syndrome and patients with a <br> history of recent myocardial in- <br> farction (MI), thrombotic <br> stroke, or established peripher- <br> al arterial disease |
|  | Anti-inflammatory and antimi- <br> crobial (nanocrystalline silver) |
| Agvexital | Treatment of Maroteaux-Lamy <br> Silvexital |
| syndrome (Mucopolysacchari- |  |
| dosis [MPS]) |  |
| Alsufatase |  |
| Galsulfase <br> Sultaminase <br> Sultamitase | Treatment of schizophrenia |
| Ampaglufuran |  |
| Ampaxazole |  |


| Suggested USAN | Category |
| :---: | :---: |
| Arcadenoson Filadenoson Miladenoson Paladenoson | An adjunct to nuclear myocardial perfusion imaging in patients unable to exercise adequately |
| Astematide <br> Metapotide <br> Metavitide | Treatment of metastatic hormone refractory prostate cancer (HRPC) |
| Beclabucol Camobucol Cetabucol Glibucolide Glidobucol Glybucolide | Anti-inflammatory; treatmemt of rheumatoid arthritis |
| Brevafermin Tegafermin Velafermin | Treatment and/or prevention of mucositis |
| Cemtulimarev-Alfa Cemtulirev-Alfa | Treatment of pancreatic cancer; treatment of CEA-bearing cancers |
| Cemtulimarev-Beta Cemtulirev-Beta | Treatment of pancreatic cancer; treatment of CEA-bearing cancers |
| Centinavir Epsinavir Zavitanavir | Treatment of resistant HIV/ AIDS (HIV-I protease inhibitor) |
| Cimerban <br> Liopixen <br> Melopixen <br> Mentaberel <br> Peliberel <br> Pelopixen <br> Penapixen <br> Pixaberan <br> Pixemebor | Treatment of rheumatoid arthritis |
| Cintredekin Besudotox Dekincept Sudotox Litredekincept Sudotox Trekincept Sudotox Trezdekincept Sudotox Trezikincept Sudotox Trezileukin 38Q-Sudotox | Antineoplastic |
| Closafupermin <br> Karyopermin <br> Megapermin <br> Rocafupermin <br> Rocapoetin <br> Romiplostim <br> Tegafupermin <br> Tegaluplermin <br> Tegapoetin <br> Temiplostim | Treatment of immune thrombocytopenic purpura (ITP) |


| Suggested USAN | Category |
| :--- | :--- |
| Cribavirin | Antiviral; prodrug of ribavirin |
| Locarabine |  |
| Patarabine |  |
| Paribavirin |  |
| Pribavirin |  |
| Vabavirin |  |
| Viramidine |  |
|  |  |
| Dalbavancin |  |
|  |  |
| Antibiotic |  |


| Suggested USAN | Category |  | Suggested USAN |
| :--- | :--- | :--- | :--- |

## Suggested International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO). INNs for substances originating within the United States are applied for through the USAN Council. INN and USAN Guiding Principles are concordant, which assures that, with very few exceptions, INNs and USANs are identical.

Under its charter, the WHO is empowered simply to recommend specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as proposals ("Proposed International Nonproprietary Names"). A period of four months from the date of publication in WHO Drug Information is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event
that no objection is received, the WHO proceeds with listing and publishing the names so devised as recommendations ("Recommended International Nonproprietary Names"), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

The names for the drugs that are categorized in the following list are under consideration for the selection of new Proposed International Nonproprietary Names. The name(s) being considered for each drug substance, and the applicable category, are separated by double spacing from the name(s) and category for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

| Suggested INN | Category |
| :--- | :--- |
| Cedratide | Treatment for systemic lupus <br> Edratide <br> Leptidematosus |
| Sletide | Treatment of malignant glioma, <br> including glioblastoma multi- <br> forme and anaplastic astrocy- <br> toma |
| Cintredekin Besudotox | Antibiotic |
| Dalbavancin | Treatment of rheumatoid ar- <br> thritis and psoriasis, cutaneous |
| T-cell lymphoma |  |


| Suggested INN | Category |
| :--- | :--- |
| Iloprost | Treatment of pulmonary arter- <br> ial hypertension |
| Itrapide | Management of obesity in dogs |
| Mertriapide |  |
| Mitrapide |  |
| Mitratapide | Triapide |
| Lipofuridine |  |
| Orafluridine |  |
| Orudine |  |


| Suggested INN | Category |
| :--- | :--- |
| Olmesartan | Treatment of glaucoma; ocular <br> hypertension therapeutic agent <br> (angiotensin II receptor antag- <br> onist) |
| Pentadol | Analgesic |
| Tapentadol | Reversal agent for neuromus- <br> cular blocking agents |
| Procarogammadex <br> Pronagammadex <br> Sugammadex | Antiviral, prodrug of ribavirin |
| Vabavirin |  |

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| 1012772 | Dehydrated Alcohol ( 1.2 mL /ampule; 5 ampules) | F0D031 | \$156 |
| 1012699 | Alcohol Determination-Acetonitrile ( $5 \mathrm{~mL} /$ ampule; 5 ampules) | F0C419 | \$156 |
| 1012688 | Alcohol Determination-Alcohol ( $5 \mathrm{~mL} /$ ampule; 5 ampules) | F0C399 | \$156 |
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| 1076206 | Powdered Black Cohosh Extract (1.5 g) | F0D086 | \$520 |
| 1076341 | Boric Acid (1 g) (AS) | F0D036 | \$200 |
| 1082708 | Butylated Hydroxytoluene ( 500 mg ) (AS) | F0D122 | \$156 |
| 1086334 | Calcium Acetate (1 g) (AS) | F0D156 | \$156 |
| 1086403 | Calcium Carbonate (1 g) (AS) | F0D099 | \$156 |
| 1086436 | Calcium Chloride (1 g) (AS) | F0D153 | \$156 |
| 1086855 | Calcium Hydroxide (1 g) (AS) | F0D168 | \$156 |
| 1087406 | Calcium Sulfate (1 g) (AS) | F0D236 | \$156 |
| 1087701 | Candelilla Wax (250 mg) | F0D123 | \$156 |
| 1091505 | $\begin{array}{\|l} \hline \begin{array}{l} \text { Caprylocaproyl Polyoxylglycerides } \\ (200 \mathrm{mg}) \end{array} \\ \hline \end{array}$ | F0C312 | \$175 |
| 1098118 | Cefpiramide ( 300 mg ) | F0C203 | \$156 |
| 1098027 | Cefpodoxime Proxetil ( 350 mg ) | F0C192 | \$156 |
| 1098322 | Cellaburate ( 350 mg ) (Cellulose Acetate Butyrate) | F0D220 | \$156 |
| 1105009 | Powdered Chaste Tree Extract (1.5 g) | F0C406 | \$520 |
| 1111307 | Chlorhexidine Related Compounds $(50 \mathrm{mg})$ | F0D017 | \$487 |
| 1115545 | Chlorogenic Acid ( 50 mg ) | F0C420 | \$156 |
| 1140393 | Clonidine ( 200 mg ) | F0C401 | \$156 |
| 1140418 | Clonidine Related Compound A $(25 \mathrm{mg})$ | F0C373 | \$487 |
| 1140429 | Clonidine Related Compound B ( 25 mg ) | F0C403 | \$487 |
| 1148806 | Corn Oil (1 g) (AS) | F0D181 | \$156 |
| 1150207 | Cottonseed Oil (1 g) (AS) | F0D173 | \$156 |
| 1152701 | Cyclandelate ( 200 mg ) | F0C384 | \$156 |
| 1187080 | Dibutyl Phthalate (200 mg) | F0D125 | \$156 |
| 1231728 | Powdered Echinacea Purpurea Extract (1 g) | F0D018 | \$520 |
| 1231706 | Powdered Echinacea Angustifolia <br> Extract (1 g) | F0D019 | \$520 |
| 1269414 | Fenbendazole Related Compound A ( 30 mg ) | F0D009 | \$487 |
| 1269425 | Fenbendazole Related Compound B ( 30 mg ) | F0D008 | \$487 |
| 1270355 | Ferrous Sulfate (1.5 g) (AS) | F0D196 | \$156 |
| 1272204 | Fludarabine Phosphate ( 300 mg ) | F0C374 | \$156 |


| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1288463 | Gemcitabine Hydrochloride ( 200 mg ) | F0D037 | \$156 |
| 1305507 | 2E, 4E-Hexadienoic Acid Isobutylamide $(25 \mathrm{mg})$ | F0C353 | \$540 |
| 1311306 | Homopolymer Polypropylene (3 Strips) | F0C096 | \$156 |
| 1349014 | Isoflurane Related Compound A (0.1 mL ) | F0C232 | \$487 |
| 1349025 | Isoflurane Related Compound B (0.1 mL ) | F0C233 | \$487 |
| 1356698 | Lactase (200 mg) | F0D032 | \$156 |
| 1356847 | Lamivudine Resolution Mixture A $(10 \mathrm{mg})$ | F0D024 | \$487 |
| 1356950 | Lauroyl Polyoxylglycerides ( 500 mg ) (AS) | F0D020 | \$156 |
| 1358503 | Leuprolide Acetate (200 mg) | F0C430 | \$1,525 |
| 1367708 | Linoleoyl Polyoxylglycerides (100 mg) | F0C283 | \$156 |
| 1370270 | Loratadine ( 200 mg ) | F0C414 | \$260 |
| 1370280 | Loratadine Related Compound A ( 15 mg ) | F0D229 | \$487 |
| 1370291 | Loratadine Related Compound B ( 15 mg ) | F0D230 | \$487 |
| 1374248 | Magnesium Chloride (1 g) (AS) | F0D157 | \$156 |
| 1374260 | Magnesium Hydroxide (1 g) (AS) | F0D158 | \$156 |
| 1374361 | Magnesium Sulfate (1 g) (AS) | F0D160 | \$156 |
| 1375127 | Manganese Chloride (1 g) (AS) | F0D150 | \$156 |
| 1375149 | Manganese Sulfate (1 g) (AS) | F0D151 | \$156 |
| 1378012 | Medroxyprogesterone Acetate Related Compound A ( 25 mg ) | F0C427 | \$500 |
| 1434011 | Methylphenidate Hydrochloride Erythro Isomer Solution ClI ( 0.5 mL ) | F0C368 | \$560 |
| 1441243 | Metoprolol Related Compound B ( 50 mg ) | F0C377 | \$520 |
| 1441254 | Metoprolol Related Compound C ( 20 mg ) | F0C344 | \$520 |
| 1441265 | Metoprolol Related Compound D ( 50 mg ) | F0C378 | \$520 |
| 1441298 | Metoprolol Succinate ( 200 mg ) | F0C415 | \$156 |
| 1444279 | Mirtazapine ( 350 mg ) | F0D155 | \$800 |
| 1445211 | Mitoxantrone System Suitability Mixture ( 0.3 mg ) | F0D010 | \$500 |
| 1449530 | Nabumetone Related Compound A $(15 \mathrm{mg})$ | F0D165 | \$487 |
| 1457469 | Naratriptan Hydrochloride (125 mg) | F0C360 | \$208 |
| 1460703 | Nevirapine Anhydrous ( 100 mg ) | F0D159 | \$156 |
| 1460714 | Nevirapine Hemihydrate ( 100 mg ) | F0D034 | \$156 |
| 1460725 | Nevirapine Related Compound A $(15 \mathrm{mg})$ | F0D035 | \$487 |
| 1460736 | Nevirapine Related Compound B $(15 \mathrm{mg})$ | F0D033 | \$487 |
| 1478152 | Oleoyl Polyoxylglycerides (100 mg) | F0C313 | \$156 |
| 1478630 | Ondansetron Resolution Mixture ( 50 mg ) | F0D242 | \$487 |
| 1485125 | Oxybutynin Related Compound B ( 20 mg ) | F0D061 | \$487 |
| 1485136 | ```Oxybutynin Related Compound C (20 mg)``` | F0D062 | \$487 |
| 1492040 | Palm Oil (1 g) (AS) | F0D179 | \$156 |
| 1500262 | Paroxetine Related Compound E Mixture ( 25 mg ) | F0D225 | \$487 |
| 1500273 | Paroxetine Related Compound F $(10 \mathrm{mg})$ | F0D237 | \$487 |
| 1500284 | Paroxetine Related Compound G ( 10 mg ) | F0D110 | \$487 |

New Items at a Glance (Continued)

| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1525707 | Phenothiazine ( 500 mg ) (AS) | F0D231 | \$156 |
| 1547925 | Polysorbate $20(2 \mathrm{~g})$ (AS) | F0D130 | \$156 |
| 1547936 | Polysorbate 40 (2 g) (AS) | F0D204 | \$156 |
| 1547947 | Polysorbate $60(2 \mathrm{~g})$ (AS) | F0D131 | \$156 |
| 1547969 | Polysorbate $80(2 \mathrm{~g})$ (AS) | F0D132 | \$156 |
| 1548101 | Potassium Benzoate (1 g) (AS) | F0D161 | \$156 |
| 1548134 | Potassium Bicarbonate (1 g) (AS) | F0D074 | \$156 |
| 1548167 | Potassium Carbonate (1 g) (AS) | F0D075 | \$156 |
| 1548190 | Potassium Chloride (1 g) (AS) | F0D127 | \$156 |
| 1548280 | Potassium Iodide (1 g) (AS) | F0D078 | \$156 |
| 1572208 | Propionic Acid ( $1.5 \mathrm{~mL} /$ ampule; 3 ampules) (AS) | F0D029 | \$156 |
| 1601102 | Residual Solvents Mixture - Class 1 ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C407 | \$156 |
| 1601146 | Residual Solvent Class 1 - Benzene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C408 | \$156 |
| 1601168 | Residual Solvent Class 1 - Carbon Tetrachloride ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C409 | \$156 |
| 1601180 | Residual Solvent Class 1-1,2Dichloroethane ( $1.2 \mathrm{~mL} / \mathrm{ampule}$; 3 ampules) | F0C412 | \$156 |
| 1601204 | Residual Solvent Class 1-1,1Dichloroethene ( $1.2 \mathrm{~mL} / \mathrm{ampule}$; 3 ampules) | F0C411 | \$156 |
| 1601226 | Residual Solvent Class 1-1,1,1Trichloroethane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0C410 | \$156 |
| 1601281 | Residual Solvents Class 2 - Mixture A ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D051 | \$156 |
| 1601306 | Residual Solvent Class 2 - Mixture C ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D182 | \$156 |
| 1601340 | Residual Solvent Class 2 - Acetonitrile ( $1.2 \mathrm{~mL} / \mathrm{ampule} ; 3$ ampules) | F0D049 | \$156 |
| 1601361 | Residual Solvent Class 2 Chlorobenzene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D048 | \$156 |
| 1601383 | Residual Solvent Class 2 - Chloroform ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D186 | \$156 |
| 1601408 | Residual Solvent Class 2 - Cyclohexane ( $1.2 \mathrm{~mL} / \mathrm{ampule} ; 3$ ampules) | F0D047 | \$156 |
| 1601420 | Residual Solvent Class 2-1,2Dichloroethene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D040 | \$156 |
| 1601463 | Residual Solvent Class 2-1,2- <br> Dimethoxyethane ( $1.2 \mathrm{~mL} / \mathrm{ampule}$; 3 ampules) | F0D185 | \$156 |
| 1601485 | Residual Solvent Class 2 - $\mathrm{N}, \mathrm{N}$ Dimethylacetamide ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D169 | \$156 |
| 1601500 | Residual Solvent Class 2 - N,N- <br> Dimethylformamide ( $1.2 \mathrm{~mL} /$ ampule; <br> 3 ampules) | F0D189 | \$156 |
| 1601521 | Residual Solvent Class 2-1,4-Dioxane ( $1.2 \mathrm{~mL} / \mathrm{ampule} ; 3$ ampules) | F0D050 | \$156 |


| Cat. No. | Description | Curr. Lot | Price |
| :---: | :---: | :---: | :---: |
| 1601543 | Residual Solvent Class 2-2Ethoxyethanol ( $1.2 \mathrm{~mL} / \mathrm{ampule}$; 3 ampules) | F0D195 | \$156 |
| 1601565 | Residual Solvent Class 2 - Ethylene Glycol ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D191 | \$156 |
| 1601587 | Residual Solvent Class 2 - Formamide ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D188 | \$156 |
| 1601623 | Residual Solvent Class 2 - Methanol ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D045 | \$156 |
| 1601645 | Residual Solvent Class 2-2Methoxyethanol ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D194 | \$156 |
| 1601667 | Residual Solvent Class 2 - <br> Methylbutylketone ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D202 | \$156 |
| 1601689 | Residual Solvent Class 2 - <br> Methylcyclohexane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D044 | \$156 |
| 1601441 | Residual Solvent Class 2 - Methylene Chloride ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D046 | \$156 |
| 1601703 | Residual Solvent Class 2 - NMethylpyrrolidone ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D183 | \$156 |
| 1601725 | Residual Solvent Class 2 - Nitromethane ( $1.2 \mathrm{~mL} / \mathrm{ampule} ; 3$ ampules) | F0D210 | \$156 |
| 1601747 | Residual Solvent Class 2 - Pyridine ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D215 | \$156 |
| 1601769 | Residual Solvent Class 2 - Sulfolane ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D187 | \$156 |
| 1601770 | Residual Solvent Class 2 Tetrahydrofuran ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D043 | \$156 |
| 1601780 | Residual Solvent Class 2 - Tetralin ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D228 | \$156 |
| 1601805 | Residual Solvent Class 2 - Toluene ( $1.2 \mathrm{~mL} /$ ampule; 3 ampules) | F0D042 | \$156 |
| 1601827 | Residual Solvent Class 2 - <br> Trichloroethylene ( $1.2 \mathrm{~mL} / \mathrm{ampule}$; 3 ampules) | F0D221 | \$156 |
| 1601849 | Residual Solvent Class 2 - Xylenes ( $1.2 \mathrm{~mL} / \mathrm{ampule} ; 3$ ampules) | F0D041 | \$156 |
| 1613407 | Sodium Acetate (1 g) (AS) | F0D083 | \$156 |
| 1613757 | Sodium Carbonate Anhydrous (1 g) (AS) | F0D100 | \$156 |
| 1613859 | Sodium Citrate (1 g) (AS) | F0D172 | \$156 |
| 1614396 | Sodium Metabisulfite (1 g) (AS) | F0D111 | \$156 |
| 1614454 | Sodium Nitrite (1 g) (AS) | F0D117 | \$156 |
| 1614807 | Sodium Sulfate Anhydrous (1 g) (AS) | F0D112 | \$156 |
| 1615107 | Sodium Thiosulfate (1 g) (AS) | F0D178 | \$156 |
| 1667585 | Titanium Dioxide (1 g) (AS) | F0D079 | \$156 |
| 1708762 | Valsartan ( 350 mg ) | F0C147 | \$156 |
| 1711155 | Vecuronium Bromide ( 50 mg ) | F0C367 | \$156 |
| 1724747 | Zinc Oxide (2 g) (AS) | F0D170 | \$156 |
| 1724769 | Zinc Sulfate (1 g) (AS) | F0D133 | \$156 |

## ORDERING DIRECT FROM THE US PHARMACOPEIA

## Sending Your Order

## STEP \#1: PREPARE YOUR ORDER USING YOUR COMPANY'S PURCHASE ORDER, A USP ORDER FORM, OR A FORMAL USP PRICE QUOTE FROM CUSTOMER SERVICE,

- In all correspondence, refer to your Purchase Order number, your USP Customer Number, and/or USP Price Quote number.
- Purchase Order numbers are required for all credit term orders.


## STEP \#2: GIVE USP THE DELIVERY CONTACT NAME AND TELEPHONE NUMBER

- Having a specific recipient on your order will increase delivery speed.
- A contact name is required for all publications and subscriptions orders.
- Although not required, providing a contact email address will expedite communication of problems or issues with your order, especially internationally.


## STEP \#3: USE THE MOST EFFICIENT PAYMENT METHOD YOU CAN

1. Valid Visa, Master Card, or American Express
2. Credit terms with USP USP will extend an automatic credit limit of US\$2000 for all customers in USA and Canada. All others can apply for credit terms by sending an e-mail to our Accounting Department at em@usp.org or calling 301-881-0666 x 8177.
3. Check drawn on a USA Bank
(USP Rating: q q )
4. Wire transfer
(USP Rating: q )

Use only if necessary. If you must, please include your USP Quote number and/or customer number on the wire transmission information. Please fax a copy of your wire receipt and order to USP once the wire has been sent so we know to expect it.
Customers are responsible for paying all bank fees for wire transfers.
STEP \#4: SEND USP YOUR ORDER QUICKLY AND SECURELY

1. USP Store at http://store.usp.org. (USP Rating: q q q q q)

As soon as you click the "confirm and submit order" button, we have it, and you will get an immediate confirmation by email.
2. Telephone at 301-881-0666 or 800-227-8772. (USP Rating: q q q q ) Customer Service Rep will take your order M-F from 8:30 AM - 5:00 PM EST.
3. Fax to 301-816-8148. (USP Rating: q q q ) USP will confirm your order within one business day by return fax.
4. Mail to 12601 Twinbrook Pkwy, Rockville, MD 20852. (USP Rating: $q$ ) USP does not recommend ordering by mail when you require fast processing.

## USP Ordering and Return Policies

- USP Reference Standards may not be returned for refund or exchange.
- USP publications and subscription are returnable within 30 days from the date of invoicing. USP Electronic Subscriptions can be cancelled within 30 days of activation for a full refund minus shipping charges.
- Prices and package sizes are subject to change without notice. USP will honor all USP Price Quotes through the expiration date on the quote.
- Customers are financially responsible for duplicate orders in the following cases:
- Confirming orders not clearly marked as confirming that are sent to USP.
- Submitting the same order multiple times (i.e., via phone, fax, email, USP Store, mail, or any combination thereof.)
- Orders that are put on credit hold by USP due to either poor credit record with USP or exceeding the credit limit established by USP must be cleared by customers within 14 days. Otherwise, these orders are automatically cancelled and you must reorder.


## USP Backorder Fulfillment Policy

- USP will automatically ship any backorder that becomes available within 30 days of the order date.
- After 30 days, customers will get a Notice of Availability (NOA). Customers then have 45 days to respond to the notice or the order will be automatically cancelled.


## Problems, Concerns, or Technical Support

USP has a well trained staff for order and product support.

| Order Issues, Concerns, or Suggestions | Reference Standards Technical Service |
| :--- | :--- |
| USP Customer Service | Kellie L. Campbell, Technical Services Scientist |
| Phone: 301-881-0666 or 1-800-227-8772 | Phone: 301-816-8129 |
| Fax: 301-816-8148 | Fax: 301-998-6807 |
| Email: custsvc@usp.org | Email: rstech@usp.org |
| General Issues, Concerns or Suggestions | Electronic Product and USP Store Support |
| Vicki Phillos, Customer Service Manager | Errol McDonald, Technical Support Analyst |
| Phone: 301-816-8114 | Phone: 301-816-8168 |
| Fax: 301-998-6819 | Fax: 301-816-8280 |
| Email: vp@usp.org | Email: support@usp.org |
|  |  |
| International Controlled Substances | Monograph and General Chapter Support |
| USP Foreign Controls Group | Department of Standards Development |
| Phone: 301-881-0666 x8164 | Phone: 301-816-8344 |
| Fax: 301-998-6819 | Fax: 301-816-8299 |
| Email: foreigncontrols@usp.org | Email: cl@usp.org |

## Shipping

- USP does not ship any products to post office boxes. Please include a street address or your order will be returned to you.
- International customers are responsible for paying all customs duties, taxes, or tariffs levied for importation of USP products.
- Customers can request shipment on cold packs for an additional $\$ 25.00$ charge
- Customers can request special, guaranteed, same-day shipping for an additional $\$ 75.00$ charge.


## Shipping Carriers

USP uses DHL as the default shipping carrier because we have negotiated favorable shipping rates with DHL, which we pass on to our customers. However, we use alternative carriers for locations to which there is no DHL service, as listed below. Customers can choose their own carrier by giving USP their DHL, UPS, or FedEx account number when ordering.

| Location | Shipper | Products |
| :--- | :--- | :--- |
| Algeria | Commercial Carrier Door to Airport | All Products |
| Puerto Rico | FedEx | Reference Standards |
| Puerto Rico | UPS (Blue or Red Label) | Publications |

## Preferred carriers for dangerous goods

Reference Standards that have been classified as dangerous goods have specific requirements for shipping. Please consult the table below to find the preferred carrier for any order that contains a Reference Standard that has been classified as a dangerous good by the United Nations.

| DHL | FedEx International | UPS <br> (Blue or Red Label) | Commercial Carrier Door to Airport |
| :---: | :---: | :---: | :---: |
| Australia, Austria, Belgium, Bulgaria, China, Czech Republic, Denmark, Estonia, Ethiopia, Finland, France, Germany, Great Britain, Greece, Hong Kong, Hungary, Iceland, India, Iraq, Ireland, Italy, Japan, South Korea, Latvia, Libya, Lithuania, Luxembourg, Malaysia, Morocco, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Singapore, Solvakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, United States | United Arab Emirates, Armenia, Argentina, American Samoa, Bosnia \& Herzegovina, Barbados, Bangladesh, Benin, Bolivia, Canada, Costa Rica, Cyprus, Dominican Republic, Ecuador, Guam, Guyana, Honduras, Indonesia, Israel, Jamaica, Kenya, Kuwait, Sri Lanka, Moldova, Macedonia, Macau, Malta, Namibia, Oman, Panama, Pakistan, Palestinian Territory, Paraguay, Qatar, Saudi Arabia, Senegal, El Salvador, Trinidad \& Tobago, Ukraine, Uganda, Uruguay, Venezuela, Virgin Island (U.S.), Yemen, Yugoslavia, South Africa, Zimbabwe | Puerto Rico | Algeria, Brazil, Chile, Croatia, Colombia, Fiji, Guatemala, Egypt, Jordan, Lebanon, Mexico, Peru, Romania, Russia, |

## Special Instructions for International Customers

- Ordering direct from USP or an authorized distributor is the fastest method to get results: Using product resellers, such as book or chemical supply houses, can add up to eight weeks to your order fulfillment time. Typically, USP processes orders for all our customers in less than two business days. USP cannot control how long a reseller keeps your order before giving it to USP for processing or how long they hold the product before passing it along to you.
- Apply for credit terms with USP: Many international customers must prepay, because they have not applied for payment terms with USP. Having payment terms allows you to place orders using your company purchase order and pay once you get USP's invoice.
- If you must prepay, please use a valid credit card: Credit cards are the easiest payment method. Avoid checks or wire transfers, if possible.
- If you must prepay, get an Official USP Price Quote before ordering: Having an Official USP Price Quote allows you to arrange payment with the security of knowing the price will not change for 45 days. Also please reference the USP Quote number on all checks, wires, and/or credit card orders. This will improve accuracy and shorten order processing time.
- Customs Clearance: USP does not offer customs clearance services. We suggest that you arrange for a customs broker to facilitate clearance or allow DHL to clear customs for you. Customs clearance is often the longest part of your product delivery time. Customers are responsible for paying all customs duties, taxes, or tariffs levied for bringing USP products into your country.
- Language: USP has a diverse workforce. If you are having trouble communicating in English, please ask your customer service representative to find a USP employee who can translate. USP Customer Service has English and Spanish language capabilities on staff.
- Problems or Issues: USP has regional account managers who can support your product inquiries, technical questions, or needs for general information in addition to those listed above.

Dennis Hall - Senior International Account Manager - Europe
Phone: 301-816-8558
Fax: 301-816-8236
Email: dh@usp.org
Chris Ayer - Senior International Account Manager - Asia
Phone: 301-816-8235
Fax: 301-816-8236
Email: ca@usp.org
Kevin Correa - International Account Manager - Latin America
Phone: 301-816-8238
Fax: 301-816-8236
Email: kcl@usp.org
Robert Tyler - Senior National Account Manager - Canada
Phone: 301-816-8233
Fax: 301-816-8236
Email: rt@usp.org
Jane Webster - International Sales and Marketing Director - All Other Areas
Phone: 301-816-8528
Fax: 301-816-8236
Email: jzw@usp.org

## CONTROLLED SUBSTANCE ORDERS - ITEMS REGULATED BY THE U.S. DRUG ENFORCEMENT ADMINISTRATION (DEA)

## DEA REQUIREMENTS FOR ORDERS SHIPPED WITHIN UNITED STATES

List Chemicals: Below is a list of Reference Standards categorized by the DEA as List Chemicals

| Catalog \# | Product Description |
| :--- | :--- |
| 1202005 | Dihydroergotamine Mesylate $(250 \mathrm{mg})$ |
| 1236007 | Ephedrine Sulfate $(200 \mathrm{mg})$ |
| 1240004 | Ergonovine Maleate $(100 \mathrm{mg})$ |
| 1241506 | Ergotamine Tartrate $(150 \mathrm{mg})$ |
| 1241550 | Ergotaminine $(100 \mathrm{mg})$ |
| 1430000 | Methylergonovine Maleate $(50 \mathrm{mg})$ |
| 1533909 | Phenylpropanolamine Bitartrate $(100 \mathrm{mg})$ |
| 1534005 | Phenylpropanolamine Hydrochloride $(250 \mathrm{mg})$ |
| 1581005 | Pseudoephedrine Hydrochloride $(125 \mathrm{mg})$ |
| 1581504 | Pseudoephedrine Sulfate $(200 \mathrm{mg})$ |

- The DEA requires that USP have on file one of the following to fulfill List Chemical Orders:
- Copy of Customers' current DEA Registration
- Letter on company letterhead stating the intended use of the list chemical for each order placed

DEA Schedule I and II: A list of all DEA Controlled Substances is found at the end of the USP Reference Standards product listing.

- The DEA requires the following for Schedule I and II orders:
- Orders in writing.
- Copy of Customers' current DEA Registration on file with USP
- DEA form 222-C, properly completed.

DEA Schedule III, IV, and V: A list of all DEA Controlled Substances is found at the end of the USP Reference Standards product listing.

- The DEA requires the following for Schedule III, IV, and V orders:
- Copy of Customers' current DEA Registration on file with USP


## DEA REQUIREMENTS FOR ORDERS SHIPPED OUTSIDE UNITED STATES

To facilitate efficient and correct ordering, please contact Julie Smith at (301) 816-8164 or Liz Eslinger at (301) 816-8626 or email foreigncontrols@usp.org.

## FEES AND ORDERING

1. Add $\$ 25.00$ to all unit prices for all DEA Controlled Substances and List Chemicals shipped outside the Untied States.
2. The shipping charge for all DEA Controlled Substances shipped outside the United States is $\$ 220.00$ per order.
3. Order for controlled substances to be shipped outside the United States must include the following:
a. Full payment (See Step \#3: Payment Methods above) or Purchase Order for customers with approved credit terms from USP.
b. An import permit (in English or with an English translation attached) valid for six months from the date of its receipt by USP Customer Service.
c. A statement of non-reexport and use for medical or scientific purposes (in English or with an English Translation attached).

USP cannot ship controlled substances outside the United States without an export permit. While it typically takes 6-10 weeks to get the permit from the DEA, USP has no control over the time in which permits are issued.

Upon receiving the Export Permit from the DEA, USP completes the order process and ships the order in 1-3 days via our controlled substance freight forwarder (Door-to-Airport).

## Special Instructions for Mexican Customers

In addition to the DEA processing period:

1. Add one week for USP to obtain a certificate from the Mexican Embassy authorizing the shipment to enter Mexico.
2. Customers must pay an additional $\$ 114$ to cover the cost of the fee charged by the Mexican Embassy for this certificate.

## CHROMATOGRAPHIC REAGENTS

## Chromatographic Reagents Used in USP-NF and <br> Pharmacopeial Forum

November-December 2004

|  | AMIFOSTINE |  |  | DSD Mgh \#2600 |
| :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(6) | L1 | Ultrasphere ODS | Assay \& Chrom. purity. | $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}, 5 \mu \mathrm{~m}$, manufacturer Beckman Instruments. |
|  | AMIFOSTINE FOR INJECTION |  |  | DSD Mgh \#2603 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(6) | L1 | Ultrasphere ODS | Assay \& Chrom. purity. . . . | $4.6 \mathrm{~mm} \times 25 \mathrm{~cm}, 5 \mu \mathrm{~m}$, manufacturer Beckman Instruments. |
|  | CLORAZEPATE DIPOTASSIUM |  |  | DSD Mgh \#18720 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(6) | L1 | MicroBondapak C18 | Related compounds | Test I and Test II: $30 \mathrm{~cm} \times 3.9 \mathrm{~mm}$, manufacturer Waters. |
|  | ESTRADIOL AND NORETHINDRONE ACETATE TABLETS |  |  | DSD Mgh \#30615 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(6) | L1 | Waters Symmetry | Assay | $15 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 4 \mu \mathrm{~m}$, manufacturer Waters Corp. |
| 30(6 | L1 | Nova-Pak C18 | Chromatographic purity | $30 \mathrm{~cm} \times 3.9 \mathrm{~mm}, 4 \mu \mathrm{~m}$, manufacturer Waters Corp. |
|  | FAMOTIDINE FOR ORAL SUSPENSION |  |  | DSD Mgh \#32607 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(6) | L1 | Inertsil ODS-3 | Assay and Related Compounds | $25 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer GL Science. |
|  | FEXOFENADINE HYDROCHLORIDE TABLETS |  |  | DSD Mgh \#852 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(6) | L11 | Zorbax SB Phenyl | Assay and Related Compounds | $25 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer Agilent Technologies. |
| 30(6) | L1 | Spherisorb ODS | Dissolution | $10 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer Waters Corp. |
|  | FOSINOPRIL SODIUM |  |  | DSD Mgh \#34315 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(6) | L3 | Resolve Silica | Assay and Related Compounds | Test 1: $15 \mathrm{~cm} \times 3.9 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer Waters Corp. |
| 30(6) | L12 | PartiSphere SAX | Related compounds | Test 2: $12.5 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer Whatman. |
| 30(6) | L11 | Hypersil BDS Phenyl | Related compounds | Test 3: $25 \mathrm{~cm} \times 4.6 \mathrm{~m}, 5 \mu \mathrm{~m}$, manufacturer Thermo Electron. |


| $\begin{gathered} \text { PF } \\ 30(6) \end{gathered}$ | FOSINOPRIL SODIUM AND HYDROCHLOROTHIAZIDE TABLETS |  |  | DSD Mgh \#34330 |
| :---: | :---: | :---: | :---: | :---: |
|  | LGS\# | Reagent Brand | Type of Test | Comments |
|  | L10 | Zorbax SB-CN | Dissolution | $25 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer Agilent Technologies. |
| FOSINOPRIL SODIUM TABLETS |  |  |  | DSD Mgh \#34320 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(6) | L1 | Apex ODS | Dissolution | $15 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 5 \mu \mathrm{~m}$, manufacturer Jones Chrom. Inc. |
| RAMIPRIL |  |  |  | DSD Mgh \#73030 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(6) | L1 | Kromasil KR 100 | Assay | $15 \mathrm{~cm} \times 4.6 \mathrm{~mm}, 3 \mu \mathrm{~m}$, manufacturer EKA Nobel. |
| THIOGUANINE |  |  | Type of Test | DSD Mgh \#82810 |
| PF | LGS\# | Reagent Brand |  | Comments |
| 30(6) | L1 | Hypersil BDS C-18 | Assay and Limit of . | Assay and limit of guanine. $4.6 \mathrm{~mm} \times 5 \mathrm{~cm}, 5 \mu \mathrm{~m}$, manufacturer Thermo Electron. |
|  | VANCOMYCIN HYDROCHLORIDE |  |  | DSD Mgh \#87760 |
| PF | LGS\# | Reagent Brand | Type of Test | Comments |
| 30(6) | L1 | XTerra RP 18 | Limit of . | Limit of monodechlorovancomycin. $4.6 \mathrm{~mm} \times 25$ cm , manufacturer Waters Corp. |


[^0]:    * The USP-NF (USP28-NF23), the Supplement (Supp), or the Interim Revision Announcement (IRA) for which the revision proposal is

[^1]:    * If you are not immediately able to submit comments but you intend to do so, please notify USP by using the Intent to Comment form provided before the section Chromatographic Reagents Used in USP-NF and PF.

[^2]:    * HDQ Indicates USP Headquarters items.
    $\dagger$ The Expert Committee has been renamed. The old name, Excipients-Substances and Characterization (ESC) has been changed to Excipient Monograph Content (EMC).

[^3]:    * Tentative

[^4]:    All inquiries and comments regarding $U S P 27$ text and $N F 22$ text should be addressed to the Executive Secretariat, USP-NF, 12601 Twinbrook Parkway, Rockville, MD 20852.

[^5]:    * A suitable sinker is available from VanKel, www.varianinc.com, catalog number 12-3062.

[^6]:    ${ }^{1}$ Bergey's Manual of Systematic Bacteriology, Vol. 2, Sneath, P.H.A., Nair, N.S., Sharpe, M.E., Holt, J.G., Eds.; Williams \& Wilkins: Baltimore, Md., 1986.

[^7]:    ${ }^{1}$ Bergey's Manual of Systematic Bacteriology, Vol 2.; Sneath, P.H.A., Nair, N.S., Sharpe, M.E., Holt, J.G., Eds.; Williams \& Wilkins: Baltimore, Md., 1986.

[^8]:    * AS contains sodium chloride, dextrose, adenine, and other substances that support red cell survival and function. Examples of such solutions are AS-1, AS-3, and AS-5.

[^9]:    * A suitable cellulose membrane is available as Cuprophan 80M, from Membrana GmbH, Oehder Strasse 28, D-42289, Wuppertal, Germany, fax number +49 0202605715 .

[^10]:    Omeprazole Delayed-Release Capsules, page 424 of $P F$ 29(2) [Mar.-Apr. 2003]. It is proposed to have two Drug release tests, one for the reference listed drug (RLD) and the other for one of the approved generics. Also, some modifications are being made in the Assay.

[^11]:    * A suitable sonicator is Sonifier 250 (or equivalent), equipped with a $12-\mathrm{mm}$ tip, from Branson Ultrasonic Corp., Danbury, CT, in which an output control value of 3 and a cycle time of $75 \%$ generates a power ouput of 43 W .

[^12]:    ${ }^{1}$ Suitable cellulose acetate membranes for electrophoresis are available from Malta Chemetron SRL, Milano, Italy (www.maltachemetron.com); Fluka Chemical Corp., Milwaukee, WI; and DiaSys Corp., Waterbury, CT (www.diasys.com).
    ${ }^{2}$ Suitable applications are available from DiaSys Corp., Waterbury, CT (www.diasys.com); and Helena Laboratories, Beaumont, TX (www.helena.com).

[^13]:    ${ }^{1}$ Safety includes design to prevent electric shock or gas exposition and burns, where operators can wear protective clothing and gloves against burns from touching hot surfaces.
    ${ }^{2}$ Descriptions of different types of dry-heat sterilizing equipment and detailed guidelines for determining, monitoring, and controlling the operating parameters have been published by the Health Industry Manufacturers Association in Report No. 78-1.7, Operator Training for Dry Heat Sterilizing Equipment, and by the Parenteral Drug Association, Inc., in Technical Report No. 3, Validation of Dry Heat Processes Used for Sterilization and Depyrogenation.
    ${ }^{3}$ Standard for BIER/EO Gas Vessels, 1 July 1992, Association for the Advancement of Medical Instrumentation (AAMI), 3330 Washington Boulevard, Suite 440, Arlington, VA 22201-4598.
    ${ }^{4}$ Standard for BIER/Steam Vessels, 1 July 1992, AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201-4598.

[^14]:    * A suitable standard is available from the manufacturer of the instrumen fation.

[^15]:    ${ }^{1}$ Refer to ISO 7864, Sterile hypodermic needles for single use.

[^16]:    ${ }^{5}$ Available as Frel TSK HN 40F distribud Merek Co.

[^17]:    ${ }^{7}$ Available as CarboPac MA1 and distributed by Dionex Corporation.
    ${ }^{8}$ Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.
    ${ }^{9}$ Available as OmniPac PAX-500 and distributed by Dionex Corporation.
    ${ }^{10}$ Available as Chiralpak AD from Chiral Technologies, Inc., 730 Springdale Drive, P.O. Box 564, Exton, PA 19341.
    ${ }^{11}$ Available as TSK IC SW Cation from TosoHaas.
    ${ }^{12}$ Available as IonPac CS14 distributed by Dionex Corporation (www.dionex.com).
    ${ }^{13}$ Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).
    ${ }^{14}$ Available as IC-Pak C M/D from Waters Corp. (www.waters.com).
    ${ }^{15}$ Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem)
    a Available as PRP-X100 from Hamilton Company (www.hamiltoncompany.com).

[^18]:    ${ }^{\mathrm{b}}$ Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, \#125-0143), Group Headquarters, Bio-Rad Laboratories, 2000 Alfred Nobel Dr., Hercules, California 94547 (www.discover.bio-rad.com).
    ${ }^{\text {c }}$ Available as Supelcosil ABZ from Supelco. (www.sigmaaldrich.com/supelco)
    ${ }^{\text {d }}$ Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05789 and 05371, respectively). (www.tosohbiosep.com)
    ${ }^{21}$ Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem)
    ${ }^{23}$ Available as IC-Pak C M/D from Waters Corp. (www.waters.com).

[^19]:    ${ }^{16}$ A suitable grade is available commercially as "SP2100/0.1\% Carbowax 1500 " from Supelco, Inc., Supelco Park, Bellefonte, PA 16823.
    ${ }^{17}$ A suitablegrade is avilablecommercially as "Opima-Delta_3" from Machery-Nagel, Ine., 215 River Vale Read, River Vale, NJ 07675.
    ${ }^{\mathrm{e}}$ A suitable grade is available commercially as Famewax from Restek.
    ${ }^{18}$ Unless otherwise specified in the individual monograph, silanized support is intended.

[^20]:    ${ }^{19}$ Commercially available as SP1500 on Carbopack B from Supelco.

[^21]:    ${ }^{1}$ Multiple measurements (or, equivalently, the experimental errors associated with the multiple measurements) are independent from one another when they can be assumed to represent a random sample from the population. In such a sample, the magnitude of one measurement is not influenced by, nor does it influence the magnitude of, any other measurement. Lack of independence implies the measurements are correlated over time or space. Consider the example of a 96 -well microtiter plate. Suppose that whenever the unknown causes that produce experimental error lead to a low result (negative error) when a sample is placed in the first column and these same causes would also lead to a low result for a sample placed in the second column, then the two resulting measurements would not be statistically independent. One way to avoid such possibilities would be to randomize the placement of the samples on the plate.

[^22]:    ${ }^{5}$ In general, the sample size required to compare the precision of two methods will be greater than that required to compare the accuracy of the methods.

[^23]:    ${ }^{7}$ This could be calculated using a computer spreadsheet. For example, in Microsoft ${ }^{\circledR}$ Excel the formula would be: FDIST((R/A)*FINV (alpha, $n-1, n-1$ ), $n-1, n-1$ ), where $R$ is the ratio of variances at which to determine power (e.g., $\mathrm{R}=1$, which was the value chosen in the power calculations provided in the above table) and A is the maximum ratio for acceptance (e.g., $\mathrm{A}=4$ ). Alpha is the significance level, typically 0.05 .

[^24]:    ${ }^{8}$ When testing equivalence, a $5 \%$ level test corresponds to a $90 \%$ confidence interval.

[^25]:    ${ }^{1}$ Sample mean is based on the 15 data points presented in Table 1.

[^26]:    * CIP 100; available from Steris Corporation, Mentor, Ohio, 44060-1824.

[^27]:    ${ }^{1}$ For further information on sample preparation, see the following: ANSI/AAMI/ISO/CEN Standard 10993-12-1996: Biological Evaluation of Medical Devices-Part 12: Sample Preparation and Reference Materials.

[^28]:    1 For further information on sample preparation, see ANSI/ AAMI/ISO/CEN Standard 10993-12-1996: Biological Evaluation of Medical Devices-Part 12: Sample Preparation and Reference Materials

[^29]:    ${ }^{2}$ Basketter D.A. Guinea pig predictive tests for contact hypersensitivity. In Immunotoxicology and Immunopharmacology, $2^{\text {nd }}$ ed.; Dean, J.H, Luster, M.I., Munson, A.E., Kimber, I., Eds; Raven Press, Ltd: New York, 1994; pp 693-702.

[^30]:    ${ }^{1}$ The Biopharmaceutics Classification Scheme is outlined in the FDA Guidance Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification System.

[^31]:    ${ }^{2}$ See FDA Guidance Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitroland In Vivo Correlations.

[^32]:    ${ }^{3}$ See the FDA Guidance Dissolution Testing of ImmediateRelease Solid Oral Dosage Forms.

[^33]:    ${ }^{1}$ USP Dictionary of USAN and International Drug Names, Preface.

[^34]:    ${ }^{2}$ Ibid., Appendix VII.

[^35]:    * Shipping this list chemical internationally requires a 15-day waiting period, but does not require an import permit.

[^36]:    * CAS numbers are provided for informational purposes only and their listing in the USP Reference Standards Catalog does not indicate official designation of any CAS number to a salt, isomer, hydration state, or other chemical form of any specific Reference Standard or Authentic Substance.

[^37]:    *See Page 8 for Change Code Interpretation www.usp.org Note: Where the Current Lot is blank the item is not in distribution

[^38]:    *See Page 8 for Change Code Interpretation

[^39]:    *See Page 9 for Change Code Interpretation www.usp.org Note: Where the Current Lot is blank the item is not in distribution

[^40]:    *Note-Specifying date(s) when you expect to submit comments to the Executive Secretariat will not necessarily result in a deferment of the implementation of the proposal(s) referred to.

[^41]:    * The USP-NF (USP28-NF23), the Supplement (Supp), or the Interim Revision Announcement (IRA) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

[^42]:    * If you are not immediately able to submit comments but you intend to do so, please notify USP by using the Intent to Comment form provided before
    the section Chromatographic Reagents Used in USP-NF and PF.

[^43]:    * HDQ Indicates USP Headquarters items.
    $\dagger$ The Expert Committee has been renamed. The old name, Excipients-Substances and Characterization (ESC) has been changed to Excipient Monograph Content (EMC).

[^44]:    All inquiries and comments regarding USP 27 text and NF 22 text should be addressed to the Executive Secretariat, USP-NF, 12601 Twinbrook Parkway, Rockville, MD 20852.

[^45]:    USP Alteplase RS
    USP Amiloxate RS
    USP Positive Bioreaction RS
    USP Cinoxate RS
    USP Decoquinate RS
    USP Diethylstilbestrol Diphosphate RS
    USP Enalapril Related Compound B RS
    USP Enzacamene RS
    USP Fludeoxyglucose RS
    USP Ginseng Extract RS
    USP Gonadorelin Hydrochloride RS
    USP Hypericin RS
    USP Lactase RS
    USP Medroxyprogesterone Acetate Related Compound A RS
    USP Menotropins RS
    USP Methyldopa-Glucose Reaction Product RS
    USP Mibolerone RS
    USP Narasin RS
    USP Ondansetron Related Compound B RS
    USP Potassium Perchlorate RS
    USP Pyrethrum Extract RS

[^46]:    * Refer to the Calculations for section on Relative Potency for the definitions of $\mathrm{x}_{\mathrm{j}}$ and $y_{i j k}$.

[^47]:    9-Fluorenylmethyl chloroformate solution-Transfer 200 me of 9 -flurenylmethyl chloreformate to a 50 mL volt metric flask, dilute with acetonitrile to volume, and mix. Prepare fresh just prior to use. [NOTE-This solution contains about 4 mg of 9 flurrenylmethyl chloroformate per

[^48]:    ${ }^{1}$ Four tests for Graftskin are specified: Histological characterization, Gene expression profile, Barrier integrity assessment, and Metabolic activity assessment. The histological examination of the 3-dimensional organotypic structure demonstrates control of the Graftskin manufacturing process and shows a bilayered construct with a dermal matrix, differentiated epidermis, and developed stratum corneum. Reference photomicrographs, representing examples of both passing and failing Graftskin units, are specified to assist in ascertaining quality. PCR analysis of the gene expression profile of a finished Graftskin unit demonstrates that its keratinocytes and fibroblasts are producing cytokines that have been documented to influence wound healing. The test also demonstrates cell purity. Graftskin is positive for the gene expression of Interleukin-1 $\alpha$, Platelet-derived growth factor, and Transforming growth factor- $\beta 1$. Graftskin is negative for the gene expression of Interleukin-4, which is produced neither by fibroblasts nor keratinocytes. Glyceral-dehyde-3-phosphate dehydrogenase is run with this assay as a housekeeping gene, and Graftskin is positive for the expression of this gene. The Barrier integrity assessment demonstrates the presence of a stratum corneum and the functionality of the epithelium in Graftskin. The purpose of the Metabolic activity assessment is to demonstrate cellular viability of the article.

[^49]:    ${ }^{2}$ A microwave oven suitable for histological preparation can be obtained from Energy Beam Sciences, Inc., 11 Bowles Road, P.O. Box 468, Agawam, MA.
    ${ }^{3}$ A suitable paraffin for use is Accumate (im) Tissue Embedding/Infiltration Medium, which can be obtained from Sigma Diagnostics, 545 S. Ewing Ave., St. Louis, MO 63103.

[^50]:    ${ }^{4}$ A suitable paraffin for use is Paraplast ${ }^{\circledR}$ X-Tra Tissue Embedding Medium ASTM, melting point $50^{\circ}$ to $54^{\circ}$, which can be obtained from Fisher Scientific, 200 Park Ln, Pittsburgh, PA 15275.
    ${ }^{5}$ A suitable histological adhesive for use is Histoslide ${ }^{\circledR}$ Adhesive, which can be obtained from Poly Scientific R \& D Corp., 70 Cleveland Ave., Bay Shore, NY 11706-1282.

[^51]:    $\overline{{ }^{6} \text { A suitable histological xylene substitute can be obtained }}$ from Shandon, Inc., 171 Industry Drive, Pittsburgh, PA 15275.

[^52]:    ${ }^{7}$ A suitable RNA extraction solution is Trizol ${ }^{\circledR}$ reagent, which can be obtained from Invitrogen Corp., 1600 Faraday Ave., P.O. Box 6482, Carlsbad, CA 92008.
    ${ }^{8}$ A suitable buffer can be obtained from the RT-for-PCR Kit, BD Biosciences Clontech, 1020 East Meadow Circle, Palo Alto, CA 94303-4230.

[^53]:    ${ }^{9}$ Suitable DNA primer pairs can be obtained from BD Biosciences Clontech, 1020 East Meadow Circle, Palo Alto, CA 94303-4230

[^54]:    ${ }^{11}$ An agarose suitable for electrophoresis analysis of Graftskin cytokine PCR product is SeaKem ${ }^{\circledR}$ GTG agarose and can be obtained from BioWhittaker Molecular Applications, Inc., 191 Thomaston St., Rockland, ME 04841.

[^55]:    ${ }^{12}$ A suitable buffered solution of $100-b p$ DNA ladder markers can be obtained from BioWhittaker Molecular Applications, Inc., 191 Thomaston St., Rockland, ME 04841.

[^56]:    ${ }^{13}$ A suitable Percutaneous absorption apparatus, not including the Percutaneous absorption insert is a Costar ${ }^{\circledR}$ 6 -well culture cluster, flat bottom with lid and a Costar ${ }^{\circledR}$ Transwell ${ }^{\circledR}, 24 \mathrm{~mm}$ in a 6 -well cluster plate with lid and can be obtained from Corning Life Sciences, 45 Nagog Park, Acton, MA 01720.

[^57]:    ${ }^{14}$ A suitable Silicon grease is High Vacuum Silicon Lubricant for Glass and can be obtained from Dow Corning Corporation, P.O. Box 0994, Midland, MI 48686-0994.

[^58]:    (PA3: S. Salado) RTS-40845-1

[^59]:    ${ }^{1}$ A suitable $I g G$ : agarose suspension can be obtained from Sigma-Aldrich Corp., St. Louis, MO (www.sigmaaldrich.com); product number A6284.
    ${ }^{2}$ A suitable Calibrator diluent can be obtained from R\&D Systems Inc., 614 McKinley Place N.E., Minneapolis, MN (www.bioscience.org/company/r\&d.htm); part number 8953000.

[^60]:    ${ }^{3}$ A suitably sensitive ELISA test kit for the quantitation can be obtained from R\&D Systems Inc., 614 McKinley Place N.E., Minneapolis, MN (www.bioscience.org/company/ r\&d.htm); product number DFB50.

[^61]:    ${ }^{4}$ A suitable solution of 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyl tetrazolium bromide can be obtained from American Type Culture Collection, P.O. Box 1549, Manassas, VA (www.atcc.org).
    ${ }^{5}$ A suitable sodium dodecyl sulfate detergent reagent can be obtained from American Type Culture Collection, P.O. Box 1549, Manassas, VA (www.atcc.org).

[^62]:    ${ }^{6}$ A suitable buffered solution containing 10,000 USP Penicillin Units of penicillin per mL and 10 mg streptomycin per mL can be obtained from Sigma-Aldrich Corp., St. Louis, MO (www.sigmaaldrich.com).
    ${ }^{7}$ A suitable horse serum can be obtained from American Type Culture Collection, P.O. Box 1549, Manassas, VA (www.atcc.org).
    ${ }^{8}$ A suitable fetal bovine serum can be obtained from American Type Culture Collection, P.O. Box 1549, Manassas, VA (www.atcc.org).

[^63]:    $\mathbf{\Delta 1}_{1 \mathbf{\Delta U S P 2 8}}$

[^64]:    * A suitable cartridge is the Waters, Oasis MAX Vac RC cartridge, particle size $30 \mu \mathrm{~m}$, part 186000371.]

[^65]:    Adipic Acid. Because there is no existing $N F$ monograph for this excipient, a new monograph based on the Adipic Acid monographs in the European Pharmacopoeia Fourth Edition, Food Chemical Codex IV, and the $53^{\text {rd }}$ Session of the Joint FAO/WHO Expert Committee on Food Additives is proposed.
    (EMC: K. Russo) RTS-40209-1

[^66]:    * In those countries or jurisdictions where thioacetamide cannot be used, add 10 mL of freshly prepared hydrogen sulfide TS to each of the tubes, mix, allow to stand for 5 minutes, and view downward over a white surface.

[^67]:    ${ }^{-}$Commercially prepared plates may be substituted for plates prepared as
    directed herein.

[^68]:    ${ }^{2}$ Whatman No. 3MM filter paper or equivalent.

[^69]:    ${ }^{3}$ Suitable equipment is available from Regis-Chemical Company, Morton Greve, It.

[^70]:    ${ }^{5}$ Available as Fracel TSK HW 40F and distribud by Merek and
    ■YMC-Pack PVA-SIL manufactured by YMC Co., Ltd.■1S (USP27)

[^71]:    ${ }^{6}$ Available as TSKgel G4000 SWXL from TosoHaas (www.tosohaas.com).
    ${ }^{7}$ Available as CarboPac MA1 and distributed by Dionex Corporation.

[^72]:    ${ }^{8}$ Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.
    ${ }^{9}$ Available as OmniPac PAX-500 and distributed by Dionex Corporation.
    ${ }^{10}$ Available as Chiralpak AD from Chiral Technologies, Inc., 730 Springdale Drive, P.O. Box 564, Exton, PA 19341.
    ${ }^{11}$ Available as TSK IC SW Cation from TosoHaas.
    ${ }^{12}$ Available as IonPac CS14 distributed by Dionex Corporation (www.dionex.com).
    ${ }^{13}$ Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).
    ${ }^{14}$ Available as IC-Pak C M/D from Waters Corp. (www.waters.com).
    ${ }^{15}$ Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem)
    ${ }^{\text {a }}$ Available as PRP-X100 from Hamilton Company (www.hamiltoncompany.com).

[^73]:    $\overline{{ }^{16}}$ A suitable grade is available commercially as "SP2100/0.1\% Carbowax
    1500 " from Supelco, Inc., Supelco Park, Bellefonte, PA 16823.

[^74]:    ${ }^{\mathrm{e}}$ A suitable grade is available commercially as Famewax from Restek.
    ${ }^{18}$ Unless otherwise specified in the individual monograph, silanized support is intended.
    ${ }^{19}$ Commercially available as SP1500 on Carbopack B from Supelco.

[^75]:    Most suppliers test for adventitious agents according to 9 CFR 113, which was developed by the Center for Veterinary Biologics, Animal and Plant Health Inspection Service, United States Department of Agriculture. These tests may differ from those used to test products developed for human use (e.g., mycoplasma).

[^76]:    ${ }_{3}^{2}$ See Performance Testing. Often AMs are aliquoted or stored at different concentrations, in different buffers, or under conditions that are different from those stated on the label or previously validated. Data should be generated that demonstrate the stability and preservation of activity of the AM under the conditions that are specific to the manufacturing application.
    Beta lactam antibiotics should not be used as AMs due to the risk of patient hypersensitivity.

[^77]:    ${ }^{5}$ These AMs should be produced from nonmammalian, recombinant sources (i.e., microbially grown in the absence of ani-mal-derived growth medium components).
    ${ }_{7}^{6}$ See Performance Testing.
    7 Often AMs are aliquoted or stored at different concentrations, in different buffers, or under conditions that are different from those stated on the label or previously validated. Data should be generated that demonstrates the stability and preservation or activity of the AMs under the conditions that are specific to the manufacturing application.

[^78]:    ${ }_{9}^{8}$ See Performance Testing.
    ${ }^{9}$ Often AMs are aliquoted. or stored at different concentrations, in different buffers, or under conditions that are different from those stated on the label or previously validated. Data should be generated that demonstrate the stability and preservation or activity of the AM under the conditions that are specific to the manufacturing application.

[^79]:    ${ }^{1}$ USP Dictionary of USAN and International Drug Names, Preface.

[^80]:    ${ }^{2}$ Ibid., Appendix VII.

[^81]:    (C) 2004 The United States Pharmacopeial Convention, Inc. All Rights Reserved.

[^82]:    * Shipping this list chemical internationally requires a 15-day waiting period, but does not require an import permit.

[^83]:    * CAS numbers are provided for informational purposes only and their listing in the USP Reference Standards Catalog does not indicate official designation of any CAS number to a salt, isomer, hydration state, or other chemical form of any specific Reference Standard or Authentic Substance.

[^84]:    *See Page 9 for Change Code Interpretation
    www.usp.org Note: Where the Current Lot is blank the item is not in distribution

[^85]:    *See Page 9 for Change Code Interpretation www.usp.org Note: Where the Current Lot is blank the item is not in distribution

[^86]:    *See Page 9 for Change Code Interpretation www.usp.org Note: Where the Current Lot is blank the item is not in distribution

[^87]:    *See Page 9 for Change Code Interpretation www.usp.org Note: Where the Current Lot is blank the item is not in distribution

[^88]:    *See Page 9 for Change Code Interpretation www.usp.org Note: Where the Current Lot is blank the item is not in distribution

[^89]:    * The USP-NF (USP28-NF23), the Supplement (Supp), or the Interim Revision Announcement (IRA) for which the revision proposal is

[^90]:    * If you are not immediately able to submit comments but you intend to do so, please notify USP by using the Intent to Comment form provided before
    the section Chromatographic Reagents Used in $U S P-N F$ and $P F$.

[^91]:    * HDQ Indicates USP Headquarters items.
    $\dagger$ The Expert Committee has been renamed. The old name, Excipients-Substances and Characterization (ESC) has been changed to Excipient Monograph Content (EMC).

[^92]:    All inquiries and comments regarding USP 27 text and $N F 22$ text should be addressed to the Executive Secretariat, USP-NF, 12601 Twinbrook Parkway, Rockville, MD 20852.

[^93]:    * A suitable cellulose membrane is available as Cuprophan 80M, from Membrana GmbH, Oehder Strasse 28, D-42289, Wuppertal, Germany, fax number +4902026057 15 .

[^94]:    * A suitable grade is available from Analytical Research and Testing, Somerville, NJ; Fax: 908-725-8848.

[^95]:    in which + -is the respense of each-individual peak, exeept these of compenent $B_{1+n}$ andeompenent $B_{4 b}$, and + is the sum of the respenses of all of the peaks in the chremategram.

[^96]:    ${ }^{z}$ Note that the designations $S$ and $P$ no longer designate weight elasses but rather weight grades, that is, design limitations such as range of density of materials, surface area, sufface finish, corrosimn resistanee, and hardmess.

[^97]:    ${ }^{1}$ Copies of ASTM standard E617 may be obtained from ASTM, 100 Barr Harbor Drive, West Conshohocken, PA 19428-2959.

[^98]:    * In those countries or jurisdictions where thioacetamide cannot be used, add 10 mL of freshly prepared hydrogen sulfide TS to each of the tubes, mix, allow to stand for 5 minutes, and view downward over a white surface.

[^99]:    + Commereially prepared plates may be substituted for plates prepared as directed herein.

[^100]:    ${ }^{3}$ Whatman No . 3MM filter paper or equivalent.

[^101]:    ${ }^{3}$ Suitable equipment is available from-Regis Chemieal Company, Morten-Grove, HL .

[^102]:    - $R_{R} \cdot \square_{\text {1S }}$ (USP28)

[^103]:    ${ }^{5}$ Available as ${ }^{\text {- YMC-Pack PVA-SIL manufactured by YMC Co., }}$ Ltd.■1S (USP27) and distributed by Waters Corp. (www.waters.com). ■1S (USP28)

[^104]:    ${ }^{6}$ Available as TSKgel G4000 SWXL from ToseHas (wnore hats.eem).
    -Tosoh Biosep (www.tosohbiosep.com).■1S (USP28)
    ${ }^{7}$ Available as CarboPac MA1 and distributed by Dionex Corpera tion.
    -Corp. (www.dionex.com)..1S (USP28)
    ${ }^{8}$ Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.
    ${ }^{9}$ Available as OmniPac PAX-500 and distributed by Dionex Cor peration.
    ${ }^{\text {a }}$ Corp. (www.dionex.com).■1S (USP28)

[^105]:    ${ }^{c}$ Available as Supelcosil ABZ from Supelco (www.sigmaaldrich.com/supelco).
    ${ }^{\text {d }}$ Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05789 and 05371 , respectively). (www.tosohbiosep.com)

[^106]:    ${ }^{16}$ A suitable grade is available commercially as "SP2100/0.1\% Carbowax 1500" from Supelco, Inc., Supeleo Park, Bellefonte, PA 16823.
    (www.sigma-aldrich.com/supelco)..1S (USP28)

[^107]:    ${ }^{17}$ A suitable grade is available commereially as＂Optima Delta 3＂ frem Machery Nagel，Ine．， 215 River Vale Read，River Vale，NH 07675
    ${ }^{\mathrm{e}}$ A suitable grade is available commercially as Famewax from Restek．
    ＂（www．restekcorp．com）．■1S（USP28）
    ${ }^{18}$ Unless otherwise specified in the individual monograph，sila－ nized support is intended．
    ${ }^{19}$ Commercially available as SP1500 on Carbopack B from Su－ pelco．

[^108]:    ${ }^{1}$ In December 1996, the "Action Plan for the Provision of Useful Prescription Medicine Information" was presented to the Secretary of Health and Human Services. The plan, commonly known as the "Keystone Plan," described certain criteria for written prescription medicine information. These criteria are described in detail in the action plan, which can be found at www.fda/cder/offices/ods/keystone.pdf.

[^109]:    * Opinions from Prof. R. Laenger (Univ. Vienna, Austria); Prof. H. Lindorf (Univ. Central de Venezuela); and Prof. M. Gattuso (Univ. Nac. Rosario, Argentina) were also taken in consideration.

[^110]:    * Correspondence should be addressed to Jean Gallery, Dissolution Center, D-R4P4, Bldg. R1B, Abbott Laboratories, 1401 Sheridan Rd., North Chicago, IL 60064-6249, USA; telephone 847.938.4950; e-mail jean.gallery@ abbott.com

[^111]:    * Correspondence should be addressed to Lynn Torbeck at Torbeck Associates, 2000 Dempster Plaza, Evanston, IL 60202; e-mail lynn@torbeck.org.

[^112]:    ${ }^{2}$ Ibid., Appendix VII.

[^113]:    * Shipping this list chemical internationally requires a 15-day waiting period, but does not require an import permit.

[^114]:    * CAS numbers are provided for informational purposes only and their listing in the USP Reference Standards Catalog does not indicate official designation of any CAS number to a salt, isomer, hydration state, or other chemical form of any specific Reference Standard or Authentic Substance.

[^115]:    *See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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[^157]:    Moving?
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    Fax: (301) 816-8148.

[^158]:    * If you are not immediately able to submit comments but you intend to do so, please notify USP by using the Intent to Comment form provided before
    the section Chromatographic Reagents Used in $U S P-N F$ and $P F$.

[^159]:    * HDQ Indicates USP Headquarters items.

[^160]:    * Tentative

[^161]:    All inquiries and comments regarding USP 27 text and NF 22 text should be addressed to the Executive Secretariat, USP-NF, 12601 Twinbrook Parkway, Rockville, MD 20852.

[^162]:    ${ }^{1}$ A suitable Buffered formalin can be obtained from VWR International, 1310 Goshen Pkwy., West Chester, PA 19380.
    ${ }^{2}$ A suitable histological tissue cassette can be obtained from Sakura Finetek U.S.A., Inc., 1750 West 214th St., Torrance, CA 90501.
    ${ }^{3}$ A suitable histological tissue cassette basket can be obtained from Sakura Finetek U.S.A., Inc., 1750 West 214th St., Torrance, CA 90501.
    ${ }^{4}$ A suitable histological xylene substitute is Citrosolve ${ }^{\text {® }}$ Clearing Agent, available from Fisher Scientific, 200 Park Ln., Pittsburgh, PA 15275.
    ${ }^{5}$ A suitable paraffin for use is Tissue Prep* 2 Embedding Media, available from Fisher Scientific, 200 Park Ln., Pittsburgh, PA 15275.

[^163]:    ${ }^{6}$ A suitable histological adhesive for use is Histoslide $\circledR$ Adhesive, which can be obtained from Poly Scientific Research Corp., 70 Cleveland Ave., Bay Shore, NY 117061282.

[^164]:    ${ }^{7}$ A suitable bluing reagent can be obtained from Sigma-Aldrich Corp., P.O. Box 14508, St. Louis, MO 63178.

[^165]:    ${ }^{8}$ A suitable Diaminobenzidine solution can be obtained from Sigma-Aldrich Corp., P.O. Box 14508, St. Louis, MO 63178; catalog number D-6815.

[^166]:    ${ }^{9}$ A suitable normal rabbit serum can be obtained from Dako Corp., 6392 Via Real, Carpinteria, CA 93013.
    ${ }^{10}$ Suitable rabbit anti-human fibronectin antibodies can be obtained from Dako Corp., 6392 Via Real, Carpinteria, CA 93013.
    ${ }^{11}$ Suitable antibody diluent can be obtained from Dako Corp., 6392 Via Real, Carpinteria, CA 93013.
    ${ }^{12}$ Suitable biotinylated goat anti-rabbit antibody solution can be obtained from BioGenex, 4600 Norris Canyon Rd., San Ramon, CA 94583.
    ${ }^{13}$ A suitable streptavidin conjugated horseradish peroxidase solution can be obtained from BioGenex, 4600 Norris Canyon Rd., San Ramon, CA 94583.

[^167]:    ${ }^{14}$ A suitable fetal bovine serum can be obtained from HyClone, 925 West 1800 South, Logan, UT 84321; catalog number SH30070.03.

[^168]:    ${ }^{15}$ A suitable Proteinase $K$ solution can be obtained from Roche Diagnostics Corp., Roche Applied Sciences, P.O. Box 50414, 9115 Hague Rd., Indianapolis, IN 46250-0414.

[^169]:    ${ }^{16}$ A suitable polyglactin mesh can be obtained from Ethicon Co., Johnson \& Johnson Corp., 425 Hoes Ln., P.O. Box 6800, Piscataway, NJ 08855.

[^170]:    $\langle 601\rangle$ Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers, USP 27 page 2253 and page 1176 of PF 29(4) [July-Aug. 2003]. The previously published revisions to this chapter, targeted for adoption in USP 28-NF 23, include the proposed title change to Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers and the addition of Delivered-Dose Uniformity testing for nasal sprays. The term "target-delivered dose" was introduced and defined as the mean, about which the variance of the delivered dose was to be determined and specified. Changes were also introduced to add a new instrument, the "Next Generation Pharmaceutical Impactor". Finally, the methods for determining aerodynamic size distributions with all impactors were revised to reflect the current state-of-the-art, and these methods were harmonized between the European Pharmacopoeia and the USP wherever possible. In the present revision the Aerosols Expert Committee is responding to requests from equipment manufacturers and industrial testing consortia to clarify the specifications for some of the apparatuses defined in the chapter while simultaneously making minor editorial corrections to the previously proposed version. It is also now pro-

[^171]:    ${ }^{2}$ A suitable cascade impactor is available as Model Mk II from Graseby the., 500 Techmelegy Ceumt, Smyma, GA, 30082 . Thermo-Electron, 27 Forge Parkway, Franklin, MA 02038.■1s (USP28) The im-pac tor is used without the preseparator. The inhaler is connected to theimpac tor via the induction port, atop the entrance cone shown in Figure 4. If an equivalent impactor is employed, the induction port in Figure $4 a$ should be used, although the entrance cone (Fig. 4b) should be replaced with one to fit the impactor in question. Note that the internal surfaces of the induction port (Fig. 4a) are designed to fit flush with their counterparts in the entrance cone (Fig. 4b). This design avoids aerosol capture at the junction of the two pipes.

[^172]:    ${ }^{3}$ The cascade impactor is available as the Model 160 Marple-Miller Impactor from MSP Corporation, Minneapolis, MN. The inhaler should be connected to the impactor via the induction port, shown in Fig. 4a.

[^173]:    ${ }^{a}$ An example being ASCO product number 8030G13 (Automatic Switch Company, 60 Hanover Road, Florham Park, NJ 07932) or equivalent. See also Footnote $h$ in Table 1.
    ${ }^{\mathrm{b}}$ Gast product type 1023, 1423, or 2565 (Gast Manufacturing Inc., PO Box 97, Benton Harbor, MI 49022) or equivalent.
    ${ }^{c}$ An example being Eaton Product number 45610-400 (Eaton Corporation, Automotive Products Division, 901 South 12th Street, Watertown, WI 53094) or equivalent.
    ${ }^{\text {d }}$ Parker Hannifin type 8FV12LNSS, or equivalent (Parker Hannifin plc, Riverside Road, Barnstable, Devon EX31 1NP, UK). See also Footnote $h$ in Table 1.

[^174]:    ${ }^{1}$ See Fig. 8.
    ${ }^{2}$ Measurements in mm unless otherwise stated.

[^175]:    ${ }^{1}$ Measurements in mm with tolerances according to ISO 2768-m, unless otherwise stated.
    ${ }_{2}^{2}$ See Fig. 8 a.
    ${ }^{3}$ Including gasket.
    ${ }^{4}$ Relative centerline of stage compartment. n.a.: not applicable.

[^176]:    The five-stage impinger is available from Copley Instruments, plc, Not tingham, UK. The inhaler should be connected to the impactor via the induction port, shown in Fig. 4 and Fig. $4 a$

[^177]:    ${ }^{6}$ The cascade impactor is available as the Next Generation Pharmaceutical Impactor from MSP Corporation, Minneapolis, MN.

[^178]:    ${ }_{2}^{1}$ See Figure 9 c.
    $2{ }^{2}$ See Figure 9 b.

[^179]:    ${ }^{\text {a }}$ Stages 6 and 7 are omitted from Apparatus 3 at flow rates $>60 \mathrm{~L}$ per minute; thus, values for b and c should be omitted for Apparatus 3, where necessary.
    ${ }^{6}$ The filter stage in Apparatus 4 is Stage 5 (see Figure 8).
    ${ }^{c}[($ mass on stage $/ \Sigma \mathrm{B}) \times 100] \%+($ total $\%$ of $\Sigma \mathrm{B}$ from stages below $)$.
    ${ }^{d}$ The $50 \%$ cutoff diameter of the stage immediately above that indicated (e.g., for Stage 4, enter the cutoff diameter for Stage
    3; for Apparatus 2 or 4, calculate as $\mathrm{D}_{50, Q}$ from Eq. 1; for Apparatus 5 or 6, calculate as $\mathrm{D}_{50, Q}$ from Eq. 2 using $\boldsymbol{a}^{\mathbf{4}}$ Table
    7). $\Delta U S P 28$ Values entered in the Table are correct for Apparatus $1,2,4,5$, and 6 only when used at $28.3,60.0,60.0,60.0$, and 60.0

    L per minute, respectively.
    ${ }^{\mathrm{e}}$ The $D_{50}$ values are only valid at a flow rate of 28.3 L per minute. $\mathbf{\Delta S P 2 8}$

[^180]:    * $\mu \mathrm{S} / \mathrm{cm}($ microSiemens per centimeter $)=\mu \mathrm{mho} / \mathrm{cm}=$ reciprocal of megohm-cm.

[^181]:    ${ }^{1}$ American Public Health Association, Washington, DC 20005
    ${ }^{2}$ U.S. Environmental Protection Agency Publication EPA-600-R-94-111, Cincinnati, OH.

[^182]:    -Use within 3 days and standardize immediately before use. ■1S (USP28)

[^183]:    Dissolve about 14 g of iodine in a solution of 36 g of potassium iodide in 100 mL of water, add 3 drops of hydrochloric acid, dilute with water to 1000 mL , and standardize the solution as follows.

[^184]:    ${ }^{+}$A Ubbelehde 1 C viscosimeter is equivalent to a Cannen-Fenske 150-viceosimeter. A Ubbelehde 1 viseosimeter is equivalent to a-Cannen Fenske 100 viseosimeter.
    ² Cemmerially availableconductivity ealibration solutions for conductiv ity meter standardization, standardized by metheds traceable to the National Institute of Science and Technology (NHST), may be used. Solutions prepared acerding to instruetions given-in ASTM Standard D1125 may be used provided the enduetivity of the resultant solution is the same as that of the selution prepared frem the NIST certified materiat.

[^185]:    ${ }^{3}$ A suitable apparatus is deseribedas the-Seet Volumeter in ASTM B B-329, available-frem the American Seciety for Testing and Materials, 100 Bari Harbor Drive, West Censhoheeken, PA 19429-2959.

[^186]:    A suitable-seientifieally aceredited-souree-is the-National Institute-of Standareds and-Technology, Gaithersburg, Marylant.

[^187]:    ${ }^{1}$ AstraZeneca R\&D Mölndal, 43183 Mölndal, Sweden.
    ${ }^{2}$ IPEC Europe Harmonization Committé. To whom all correspondence should be addressed.

[^188]:    * Correspondence should be addressed to Petr Jandik, R\&D Technical Manager, Dionex Corporation, 445 Lakeside Drive, Sunnyvale, CA 94085; phone 408.481.4590; fax 408.732.2007; e-mail Petr.Jandik@Dionex.com.

[^189]:    * Correspondence should be addressed to C. Jeanne Taborsky, Senior Consultant, SciRegs Consulting, 6333 Summercrest Drive, Columbia, MD 21045.

[^190]:    ${ }^{1}$ USP Dictionary of USAN and International Drug Names, Preface.

[^191]:    ${ }^{2}$ Ibid., Appendix VII.

[^192]:    * Shipping this list chemical internationally requires a 15-day waiting period, but does not require an import permit.

[^193]:    * CAS numbers are provided for informational purposes only and their listing in the USP Reference Standards Catalog does not indicate official designation of any CAS number to a salt, isomer, hydration state, or other chemical form of any specific Reference Standard or Authentic Substance.

[^194]:    *See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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[^234]:    * The USP-NF (USP28-NF23), the Supplement (Supp), or the Interim Revision Announcement (IRA) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

[^235]:    Moving?
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    Fax: (301) 816-8148.

[^236]:    * If you are not immediately able to submit comments but you intend to do so, please notify USP by using the Intent to Comment form provided before
    the section Chromatographic Reagents Used in $U S P-N F$ and $P F$.

[^237]:    * HDQ Indicates USP Headquarters items.

[^238]:    * Tentative

[^239]:    All inquiries and comments regarding USP 27 text and NF 22 text should be addressed to the Executive Secretariat, USP-NF, 12601 Twinbrook Parkway, Rockville, MD 20852.

[^240]:    USP Alteplase RS
    USP Amiloxate RS
    USP Bupropion Hydrochloride Related Compound A RS
    USP Bupropion Hydrochloride Related Compound B RS
    USP Bupropion Hydrochloride Related Compound C RS
    USP Bupropion Hydrochloride Related Compound D RS
    USP Bupropion Hydrochloride Related Compound E RS
    USP Bupropion Hydrochloride Related Compound F RS
    USP Cinoxate RS
    USP Decoquinate RS
    USP Diethylstilbestrol Diphosphate RS
    USP Enalapril Related Compound B RS
    USP Enzacamene RS
    USP Fludeoxyglucose RS
    USP Ginseng Extract RS
    USP Gonadorelin Hydrochloride RS
    USP Hypericin RS
    USP Lactase RS
    USP Menotropins RS
    USP Methyldopa-Glucose Reaction Product RS
    USP Mibolerone RS

[^241]:    BRIEFING

    Modafinil Tablets-See briefing under Modafinil.
    (PA1: K. Russo; BPC: M. Marques; PSD: C. Okeke; NL: C. Barnstein) RTS—39507-2; 39869-2

[^242]:    8 Available as Antifoam Reagent, catalog number 2210, from Dow Corning Corporation, Midland, MI.
    ${ }^{9}$ Available Albumin Standard (8 g/d $/$ ), eataleg number A 1533 , frem SigmaChemienl-Co, St. Leuris, MQ-

    - Available as Bovine Serum Albumin, SRM 927c, Standard Reference Materials, National Institute of Standards and Technology, Gaithersburg, MD. $\quad$ 2S (USP28)

[^243]:    ${ }^{7}$ A suitable IgG: agarese suspension can be obtained frem Sigma Aldrich Corp., St. Louis, MO (ww.sigmatldrich. eem); product number A6284.
    ${ }^{2}$ A suitable-Calibrater diltuent can be obtained from-R\&D Systems Inc., 614 MeKinley Place N.E., Minneapelis, MN (www.bioscience.org/eompany/r\&d.htm); part number 8953000.

[^244]:    ${ }^{1}$ A suitably sensitive ELISA test kit for the quantitation can be obtained from R\&D Systems Inc., 614 McKinley Place N.E., Minneapolis, MN (www.bioscience.org/company/ r\&d.htm); product number DFB50.

[^245]:    ${ }^{4}$ A suitable buffered solution containing 10,000 USP Penicillin Units of penicillin per mL and 10 mg streptomycin per mL can be obtained from Sigma-Aldrich Corp., St. Louis, MO (www.sigmaaldrich.com).
    ${ }_{5}$ A suitable horse serum can be obtained from American Type Culture Collection, P.O. Box 1549, Manassas, VA (www.atcc.org).
    ${ }^{6}$ A suitable fetal bovine serum can be obtained from American Type Culture Collection, P.O. Box 1549, Manassas, VA (www.atcc.org).

[^246]:    Ointment Base
    Gaprylocaproyl Macregolglycerides
    -Caprylocaproyl Polyoxylglycerides ${ }_{\text {■ } 1 \mathrm{~S}}$ (NF23)
    Diethylene Glycol Monoethyl Ether
    ■ Lauroyl Macrogolglycerides $_{\mathbf{L I S}_{\text {(NF23) }}}$
    Lineoy/Macrogolglyeerides
    ■ineoyl Polyoxylglycerides $_{\text {■ }^{1 S}(\text { NF23 }}$

    ## Lanolin

    Ointment, Hydrophilic
    Ointment, White
    Oleoyl Macrogolgyyerides

[^247]:    Ammonio Methacrylate Copolymer, $N F 22$ page 2820. It is proposed to revise Identification test $B$ to clarify that either a polytef sheet or a glass plate could be used to perform the test.
    (EMC: D. Bempong) RTS-41548-1

    ## Change to read:

    Identification-
    A: Infrared Absorption $\langle 197 \mathrm{~K}\rangle$.
    B: Pour a few mL of the solution prepared for the Viscosity test onto a polytef sheet

    - $_{\text {Or }}$ glass plate, $\boldsymbol{m}_{2 \mathrm{~S}}$ (NF23)
    and allow the solvent to evaporate: a clear film results.

[^248]:    ${ }^{+}$Commereially prepared plates may be-substituted for plates prepared as directed herein.

[^249]:    ${ }^{2}$ Whatman No. 3MM filter paper or equivalent.

[^250]:    ${ }^{3}$ Stritable equipment is avilable from-Regis Chemieal Company, Morton Grove, It.

[^251]:    ${ }^{5}$ Available as ${ }^{\text {■ YMC-Pack PVA-SIL manufactured by YMC Co., Ltd. }}$
    $\square_{\text {and distributed by Waters Corp. (www.waters.com). }}^{\square}$ 1S (USP28)
    ■1S (USP27)

[^252]:    ${ }^{6}$ Available as TSKgel G4000 SWXL from (m).
    $\mathbf{■}^{\text {Tosoh Biosep (www.tosohbiosep.com).■1S (USP28) }}$
    ${ }^{7}$ Available as CarboPac MA1 and distributed by Dionex Cerperation.
    $\boldsymbol{\square}_{\text {Corp. (www.dionex.com). }}$ 1S (USP28)
    ${ }^{8}$ Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.
    ${ }^{9}$ Available as OmniPac PAX-500 and distributed by Dionex
    $\boldsymbol{\square}_{\text {Corp. (www.dionex.com). }}$ (1S (USP28)
    ${ }^{10}$ Available as Chiralpak AD from Chiral Technologies, Inc., 730-Spring dale Drive, P.O. Box 564, Exton, PA 19341.
    $\boldsymbol{\square}_{\text {(www.chiraltech.com).■1S (USP28) }}$

[^253]:    ${ }^{11}$ Available as TSK IC SW Cation from
    $\boldsymbol{m}_{\text {Tosoh Biosep (www.tosohbiosep.com). }}$ 1S (USP28)
    ${ }^{12}$ Available as IonPac CS14 distributed by Dionex
    $\square_{\text {Corp. }}$ 1S (USP28)
    (www.dionex.com).
    ${ }^{13}$ Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).
    ${ }^{14}$ Available as IC-Pak C M/D from Waters Corp. (www.waters.com).
    ${ }^{15}$ Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem)
    ${ }^{16}$ Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, \#125-0143), Group Headquarters, Bio-Rad Laboratories, 2000 Alfred Nobel Dr., Hercules, California 94547 (www.discover.bio-rad.com).
    ${ }^{\text {a }}$ Available as Supelcosil ABZ from Supelco (www.sigma-aldrich.com/supelco).
    ${ }^{\mathrm{b}}$ Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05789 and 05371, respectively). (www.tosohbiosep.com)

[^254]:    ${ }^{17}$ A suitable grade is available commercially as "SP2100/0.1\% Carbowax 1500" from Supelco, Inc., Supeleo Park, Bellefonte, PA 16823.

    - (www.sigma-aldrich.com/supelco).■1S (USP28)
    +8 A suitable-grade is avilable emmericially as "Optima-Delta_3" from Machery Nagel, Ine., 215 River Vale Read, River Vale, NJ 07675.
    ${ }^{c}$ A suitable grade is available commercially as Famewax from Restek.
    ■ (www.restekcorp.com).■1S (USP28)
    ${ }^{19}$ Unless otherwise specified in the individual monograph, silanized support is intended.

[^255]:    ${ }^{20}$ Commercially available as SP1500 on Carbopack B from Supelco.

[^256]:    ${ }^{2}$ Adapted from the European Pharmacopoeia, 4th Edition, 2002, p. 50.

[^257]:    ${ }^{1}$ J. A. Troller, D. T. Bernard, and V. W. Scott. Measurement of Water Activity. In: Compendium of Methods for the Microbiological Examination of Foods. American Public Health Association, Washington, DC, 1984 pp.124-134.

[^258]:    ${ }^{2}$ AOAC International Official Method 978.18. In: Official Methods of Analysis of AOAC International, 17th edition, AOAC International, Gaithersburg, Maryland.

[^259]:    ${ }^{1}$ A number of guidelines dealing particularly with the development and validation of sterilization cycles and related topics have been published. These include, of the Parenteral Drug Association, Inc. (PDA) Validation of Steam Sterilization Cycles (Technical Monograph No. 1), Validation of Aseptic Filling for Solution Drug Products (Technical Monograph No. 2) and Validation of Dry Heat Processes Used for Sterilization and Depyrogenation (Technical Monograph No. 3), and of the Pharmaceutical Manufacturers Association (PMA) Validation of Sterilization of Large-Volume Parenterals-Current Concepts (Science and Technology Publication No. 25). Other series of technical publications on these subjects of the Health Industry Manufacturers Association (HIMA) include Validation of Sterilization Systems(Report No. 78-4.1), Sterilization Cycle Development (Report No. 78-4.2), Industrial Sterility: Medical Device Standards and Guidelines (Document \#9, Vol. 1) and Operator Training . . . . for Ethylene Oxide Sterilization, for Steam Sterilization Equipment, for Dry Heat Sterilization Equipment and for Radiation Sterilization Equipment (Report Nos. 78-4.5 through 4.8). Recommended practice guidelines published by the Association for the Advancement of Medical Instrumentation (AAMI) include Guideline for Industrial Ethylene Oxide Sterilization of Medical De-vices-Process Design, Validation, Routine Sterilization(No. OPEO-12/81) and Process Control Guidelines for the Radiation Sterilization of Medical Devices (No. RS-P 10/82). These detailed publications should be consulted for more extensive treatment of the principles and procedures described in this chapter.
    ${ }^{2}$ An autoclave cycle, where specified in the compendia for media or reagents, is a period of 15 minutes at $121^{\circ}$, unless otherwise indicated.

[^260]:    ${ }^{3}$ See Ethylene Oxide, Encyclopedia of Industrial Chemical Analysis, 1971, 12, 317-340, John Wiley \& Sons, Inc., and Use of Ethylene Oxide as a Sterilant in Medical Facilities, NIOSH Special Occupational Hazard Review with Control Recommendations, August 1977, U. S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Division of Criteria Documentation and Standards Development, Priorities and Research Analysis Branch, Rockville, MD.

[^261]:    ${ }^{4}$ Detailed descriptions of these procedures have been published by the Association for the Advancement of Medical Instrumentation (AAMI) in the document entitled "Process Control Guidelines for Radiation Sterilization of Medical Devices" (No. AAMI RS-P 10/82).

[^262]:    ${ }^{5}$ Consult "Microbiological Evaluation of Filters for Sterilizing Liquids," Health Industry Manufacturers Association, Document No. 3, Vol. 4, 1982.

[^263]:    ${ }^{6}$ Awailable published standards for sueh controlled work areas inelude the following: (1) Federal-Standard No. 209B, Clean Roem and Werk Station Requirements for a Controlled Envirenment, Apr. 24, 1973. (2) NASA Standard-for Clean-Roem and-Work Stations-for Mierebially Centrelled Envirenment, publieation NHB5340.2, Aug. 1967. (3) ContaminationCen Envirof Arerospace Facilities, U.S. Air-Foree, T.O. $00-25$ 203-1 Dec. 1972 , ehange-1 1-Qet. 1974 .

    - Available published standards for such controlled work areas include the following: (1) NASA Standard for Clean Room and Work Stations for Microbially Controlled Environment, publication NHB5340.2, Aug. 1967. (2) Contamination Control of Aerospace Facilities, U.S. Air Force, T.O. 00-25-203 I Dec. 1972, change 1-1 Oct. 1974, (3). ISO 13408-1 Aseptic Processing of Health Care Products Part 1: General Requirements 1998. (4) EU Guide to Good Manufacturing Practice Revision to Annex 1, Manufacture of Sterile Medical Products, May 2003. (5) ISO 14644-1 Cleanrooms and Associated Controlled Environments, Classification of Air Cleanliness 2003

    12S (USP28)

[^264]:    ${ }^{7}$ Radioactive Pharmaceutical Products-Because of rapid radioactive decay, it is not feasible to delay the release of some radioactive pharmaceutical products in order to complete sterility tests on them. In such cases, results of sterility tests provide only retrospective confirmatory evidence for sterility assurance, which therefore depends on the primary means established in the manufacturing and validation and certification procedures.

[^265]:    * The apparatus meeting these specifications is available from laboratory supply houses such as VanKel Technology Group, 13000 Weston Parkway, Cary, NC 27513, or from Erweka Instruments, Inc., 56 Quirk Road, Milford, CT 06460.

[^266]:    ${ }^{1} F_{0}$ is defined as the calculated equivalent microbial lethality at $121.1^{\circ}$ when using a biological indicator microorganism with a $D$ value of $1.0 \mathrm{mi}-$ nute and a Z value of $10.0^{\circ}$ in the product being sterilized.

[^267]:    Fig. 2 Water for phamacentical purpeses.

[^268]:    For additional guidance encerning mierobial water testing methodelogy, eonsult Standard Methods for the Examination of Water and Wastewnter 18th Edition, Ameriean Publie Health Association, Washingten DC, 20005.

[^269]:    ${ }^{1}$ A membrane filter with an absolute rating of $0.45 \mu \mathrm{~m}$ is generally considered preferable even though the cellular width of some of the bacteria in the sample may be narrower than this. The efficiency of the filtration process still allows the retention of a very high percentage of these smaller cells and is adequate for this application. Filters with smaller porosity ratings may be used if desired, but for a variety of reasons the ability of the retained cells to develop into visible colonies may be compromised, so count accuracy must be verified by a reference approach.
    ${ }^{2}$ When colony counts are low to undetectable using the indicated minimum sample volume, it is generally recognized that a larger sample volume should be tested in order to gain better assurance that the resulting colony count is more statistically representative. The sample volume to consider testing is dependent on the user's need to know (which is related to the established alert and action levels and the water system's microbial control capabilities) and the statistical reliability of the resulting colony count. In order to test a larger sample volume, it may be necessary to change testing techniques, e.g., changing from a pour plate to a membrane filtration approach. Nevertheless, in a very low to nil count scenario, a maximum sample volume of around 250 to 300 mL is usually considered a reasonable balance of sample collecting and processing ease and increased statistical reliability. However, when sample volumes larger than about 2 mL are needed, they can only be processed using the membrane filtration method.
    ${ }^{3}$ Also known as Standard Methods Agar, Standard Methods Plate Count Agar, or TGYA, this medium contains tryptone (pancreatic digest of casein), glucose and yeast extract.

[^270]:    Organic volatile impurities, Method $I T\langle 467\rangle$ : meets the requirements._NF23

[^271]:    ${ }^{*}$ Correspondence should be addressed to John T. Geary at 5816 Buxton Drive, Chester, VA 23831-1507; e-mail gearyjt@aol.com.

[^272]:    * The article does not reflect individual opinions.
    $\dagger$ Current membership: Darrell Abernethy, M.D., Ph.D.; Judy Boehlert, Ph.D.; Edward Cohen, Ph.D.; James DeMuth, Ph.D; Marilyn Fredrickson, M.D.; Thomas Foster, Pharm.D.; Sally Seaver, Ph.D.; Alexander Shepherd, M.D., Ph.D.; Paul Schiff, Jr., Ph.D.; Salomon Stavchansky, Ph.D.; Timothy Wozniak, Ph.D.; and Roger Williams, M.D
    $\ddagger$ Judy Boehlert, Ph.D.; Edward Cohen, Ph.D.; Ashok V. Katdare, Ph.D.; Sharon Northup, Ph.D.; Lynn Yeoman, Ph.D.; Timothy Wozniak, Ph.D.
    ${ }^{\S}$ John Fowler; Eric Sheinin, Ph.D.; Joseph Valentino, J.D.

[^273]:    ${ }^{1}$ FDA's regulations in $21 C F R 314.70$ diminish this approach to some extent by requiring manufacturers to supplement their applications when USP deletes a test or relaxes a standard.

[^274]:    ${ }^{2}$ The numerical division of General Chapters is somewhat artificial: Some below 1000 have little bearing or impact, and some that are above 1000 , if they are referenced in a monograph or adopted in legislation, can be enforceable.

[^275]:    ${ }^{3}$ Medicare authorizes payment for drugs and biologicals that cannot be self-administered and are furnished by a provider in the provider's office. Drugs and biologicals are defined as those included or approved for inclusion in USP-NF, the U.S. Homeopathic Pharmacopeia, or in New Drugs or Accepted Dental Remedies, or those approved by the hospital's pharmacy and drug therapeutics committee

[^276]:    ${ }^{4}$ The general topic was addressed at a satellite symposium during the 2003 annual meeting of the American Association of Pharmaceutical Scientists in Salt Lake City.
    ${ }^{5}$ Articles include excipients, drug substances, and dosage forms/products.
    ${ }^{6}$ The general approach was presented to the Council of Experts Executive Committee in December 2002. In response, the Executive Committee formed an ad hoc committee to consider the issue. The ad hoc committee met on two occasions, endorsed the general approach, and presented their conclusions to the Executive Committee in the July 2003 meeting. The ad hoc committee is listed in the authorship of this article.

[^277]:    ${ }^{7}$ T. Layloff et al., The FDA Regulatory Methods Validation Program and New and Abbreviated New Drug Applications, Pharm. Technol., 24(1) 2000, 30-42.
    ${ }^{8}$ Under Section 802 of the U.S. Food, Drug, \& Cosmetic Act, manufacturers are allowed to export drugs not approved in the U.S. to certain countries as long as the drugs are appropriately labeled and in compliance with that country's laws. These countries include Australia, Canada, Israel, Japan, New Zealand, Switzerland, Norway, South Africa, and European Union countries. USP could rely on decisions by these authorities to set certain acceptance criteria.

[^278]:    * Correspondence should be addressed to David Porter, Ph.D., Associate Director, Department of Standards Development, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790, telephone 301.816.8225, e-mail dap@usp.org.

[^279]:    * Correspondence should be addressed to: Patrick N. Shaklee, BioCascade Incorporated, 107 Skyline Drive, P.O. Box 98, Arlington, WI 53911 USA.

[^280]:    * invalid estimate (nonparallelism)

[^281]:    * invalid estimate (nonparallelism)

[^282]:    * $N T=$ not tested

[^283]:    * Correspondence should be addressed to Theodore H. Meltzer, Ph.D., Capitola Consulting Co., 8103 Hampden Lane, Bethesda, MD 20814-1124; telephone 301.986.8640; fax 301.986.9085.

[^284]:    * Correspondence should be addressed to Ian DeVeau, Senior Scientist, Department of Drug Standards, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852-1790; telephone 301.816.8178; fax 301.816.8373; e-mail ifd@usp.org

[^285]:    ${ }^{2}$ Ibid., Appendix VII.

[^286]:    * Shipping this list chemical internationally requires a 15-day waiting period, but does not require an import permit.

[^287]:    * CAS numbers are provided for informational purposes only and their listing in the USP Reference Standards Catalog does not indicate official designation of any CAS number to a salt, isomer, hydration state, or other chemical form of any specific Reference Standard or Authentic Substance.

[^288]:    *See Page 9 for Change Code Interpretation http://store.usp.org Note: Where the Current Lot is blank the item is not in distribution

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[^335]:    * The USP-NF (USP28-NF23), the Supplement (Supp), or the Interim Revision Announcement (IRA) for which the revision proposal is

[^336]:    Moving?
    Our subscribers' records and publication labels are computergenerated. Please send your new address, and your latest label, or an exact copy of it, to: USPC, PF Customer Service Dept., 12601 Twinbrook Parkway, Rockville, MD 20852.
    Fax: (301) 816-8148.

[^337]:    * If you are not immediately able to submit comments but you intend to do so, please notify USP by using the Intent to Comment form provided before
    the section Chromatographic Reagents Used in USP-NF and PF.

[^338]:    * HDQ Indicates USP Headquarters items.

[^339]:    All inquiries and comments regarding USP 27 text and NF 22 text should be addressed to the Executive Secretariat, USP-NF, 12601 Twinbrook Parkway, Rockville, MD 20852.

[^340]:    ${ }^{1}$ 3-[2-(diaminomethyleneamino)-1,3-thiazol-4-ylmethyl-sulfinyl]- $N$-sulfamoyl-propanamidine
    ${ }^{2}$ 3-[2-(diaminomethyleneamino)-1,3-thiazol-4-yl-methylthio]-propanoic acid
    ${ }^{3}$ 3-[2-(diaminomethyleneamino)-1,3-thiazol-4-yl-methylthio]- $N$-sulfamoyl-propanamide
    ${ }^{4}$ 3-[2-(diaminomethyleneamino)-1,3-thiazol-4-yl-methylthio]- propanamide

[^341]:    * A Whatman Partisphere RTF C18 brand of L1 column has been shown to be an appropriate column.

[^342]:    ${ }^{1}$ A suitable mixer mill can be obtained from Retsch Inc., 74 Walker Lane, Newtown, PA 18940 (www.retsch-us.com; 267-757-0351), product number MM 301.

[^343]:    ${ }_{2}^{1}$ Ranitidine related compound A
    ${ }_{3}^{2}$ Ranitidine related compound C
    ${ }^{3}$ Ranitidine related compound B

[^344]:    ${ }^{1}$ Suitable cellulose acetate membranes for electrophoresis are available from Malta Chemetron SRL, Milan, Italy (www.maltachemetron.com); Fluka Chemical Corp., Milwaukee, WI; and DiaSys Corp., Waterbury, CT (www.diasys.com).
    ${ }^{2}$ Suitable applications are available from DiaSys Corp., Waterbury, CT (www.diasys.com); and Helena Laboratories, Beaumont, TX (www.helena.com).

[^345]:    ${ }^{+}$Commereially prepared plates may be-substituted for plates prepared as direct herein.

[^346]:    ${ }^{2}$ Whatman No. 3MM filter paper or equivalent.

[^347]:    ${ }^{3}$ Suitable equipment is available-from-Regis-Chemieal Company, Merten
    Grove, H.

[^348]:    ${ }^{5}$ Available as $\boldsymbol{m}_{\text {YMC-Pack PVA-SIL manufactured by YMC Co., Ltd. }}$
    $\mathbf{m}_{\text {and distributed by Waters Corp. (www.waters.com). } \quad 1 \text { (USP28) }}$
    ■1S (USP27)

[^349]:    ${ }^{6}$ Available as TSKgel G4000 SWXL from (em).
    Tosoh Biosep (www.tosohbiosep.com).■1S (USP28)
    ${ }^{7}$ Available as CarboPac MA1 and distributed by Dionex
    ${ }^{\square}$ Corp. (www.dionex.com).■1S (USP28)

[^350]:    ${ }^{8}$ Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.
    ${ }^{9}$ Available as OmniPac PAX-500 and distributed by Dionex ■Corp. (www.dionex.com).■1S (USP28)
    ${ }^{10}$ Available as Chiralpak AD from Chiral Technologies, Inc., 730 -Sprine dale Drive, P.O. Box 564, Exton, PA 19341.
    (WWW.chiraltech.com).■1S (USP28)
    ${ }^{11}$ Available as TSK IC SW Cation from
    ■Tosoh Biosep (www.tosohbiosep.com).■1S (USP28)
    ${ }^{12}$ Available as IonPac CS14 distributed by Dionex
    ■Corp.■1S (USP28)
    (www.dionex.com).
    ${ }^{13}$ Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).
    ${ }^{14}$ Available as IC-Pak C M/D from Waters Corp. (www.waters.com).
    ${ }^{15}$ Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem)
    ${ }^{16}$ Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, \#125-0143), Group Headquarters, Bio-Rad Laboratories, 2000 Alfred Nobel Dr., Hercules, California 94547 (www.discover.bio-rad.com).
    ${ }^{\text {a }}$ Available as Supelcosil ABZ from Supelco (www.sigma-aldrich.com/supelco).

[^351]:    ${ }^{\mathrm{b}}$ Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05789 and 05371, respectively). (www.tosohbiosep.com)

[^352]:    ${ }^{17}$ A suitable grade is available commercially as "SP2100/0.1\% Carbowax 1500 " from Supelco, Inc., Supeleo Park, Bellefonte, PA 16823.
    ■(www.sigma-aldrich.com/supelco).■1S (USP28)
    +8 A suitable-grade-is available-emmmereially as "Optima-Delta-3", frem Maehery Nagel, Ine., 215 River Vale Read, River Vale, NH 07675.
    ${ }^{c}$ A suitable grade is available commercially as Famewax from Restek.
    -(www.restekcorp.com).■1S (USP28)
    ${ }^{19}$ Unless otherwise specified in the individual monograph, silanized support is intended.

[^353]:    ${ }^{20}$ Commercially available as SP1500 on Carbopack B from Supelco.

[^354]:    ${ }^{1}$ Ascenzi, J.M., Ed. Handbook of Disinfectants and Antiseptics, $5^{\text {th }}$ ed.; Marcel Dekker: New York, 1995; Block, S.S., Ed. Disinfection, Sterilization, and Preservation, $5^{\text {th }}$ ed.; Lippincott Williams \& Wilkins Publishers: Philadelphia, 2000. Russell, A.D.; Hugo, W.B.; Ayliffe, G.A.J., Eds. Principles and Practices of Disinfection, Preservation and Sterilization, $3^{\text {rd }}$ ed.; Blackwell Science Inc.: London, 1999.

[^355]:    ${ }^{2}$ Denny, V.F.; Marsik, F.J. Current Practices in the Use of Disinfectants within the Pharmaceutical Industry. PDA J. of Pharmaceutical Sci. and Tech., 1997, 51, (6), 227-228.

[^356]:    ${ }^{3}$ Guniff, P.A., Ed. Official Metheds of Analysis of AOAG International, $15^{\text {th }}$-d., Association of Official Analytieal Chemists: Arlington, VA, 1999 AOAC International Official Methods of Analysis, 15, 16, and $17^{\text {th }}$ editions. Arlington, VA.

[^357]:    ${ }^{1}$ See International Conference on Harmonization EWG Q1 A\&B; see also FDA Guidance for Industry: Stability Testing of Drug Substances and Drug Products (www.fda.gov).

[^358]:    ${ }^{1}$ One method of deaeration is as follows: Heat the medium, while stirring gently, to about $41^{\circ}$, immediately filter under vacuum using a filter having a porosity of $0.45 \mu \mathrm{~m}$ or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other deaeration techniques for removal of dissolved gases may be used.

[^359]:    ${ }^{1}$ ASTM E1840-96(2002) Standard Guide for Raman Shift Standards for Spectrometer Calibration, ASTM International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA, USA, 19428-2959.

[^360]:    ${ }^{2}$ NIST-traceable tungsten white light source statement: While the calibration of the Raman frequency (or Raman shift, $\mathrm{cm}^{-1}$ ) axis using pure materials and an existing ASTM standard is well accepted, techniques for calibration of the Raman intensity axis are not. Intensity calibrations of Raman spectra can be accomplished with certified white light sources.
    ${ }^{3}$ NIST SRM 2241: Ray, K. G.; McCreery, R L. Raman intensity correction standard for systems operating with 785nm excitation. Appl. Spectrosc. 1997 51, 108-116.

[^361]:    ${ }^{4}$ Chalmers, J., Griffiths, P., Eds. Handbook of Vibrational Spectroscopy; John Wiley \& Sons, Ltd: New York, 2002.

[^362]:    * International Organization for Standardization (ISO) International Standards 14644-1, $-2,-3$, and -7

[^363]:    ■1S (USP28)

[^364]:    Optical miereseopy for particlecharacterization can generally be applied to particles in the size range be 0.5 and $100 \mu \mathrm{~mm}$ ．The lower limit is impesed by the resolving power of the mieroseope． The characterization of smaller particles canoften be acemplished by means of electron optieal imaging techniques such as those de seribed under Scanning Electron Microscopy $\langle 1481$ 〉 where practi－ eal image resolution approaches $0.01 \mu \mathrm{~m}$ ．The upper limit is less definite and is determined by the increased difficulty associated with the eharacterization of larger particles．Particle－size distribu tion by use of analytieal sieving（see Patiele Size Distribution Es timation by Analytied Sieving（786））may be performed where the majority of the particles are larger than about $75 \mathrm{\mu m}$ ，although it ean be used for some powders having smaller particle sizes where the methed can be validated．Often stereo mieroseopy can be ause ful aid with larger partieles，yet it is not as definitive．Optienl mi

[^365]:    ${ }^{+}$ISO-3310-1:2000(E) analytieal sievespecifieatiens are identieal to these of the appropriate neminal apertare-in ASTM-E11-01-US Standard-Sieve Series.

[^366]:    Carr, R.L. Evaluating Flow Properties of Solids. Chem. Eng. 1965, 72, 163-168.

[^367]:    Polyvinyl chloride (PVC) with diethylhexylphthalate (DEHP) has been shown to induce breakdown of lipid injectable emulsions (Drug Product Problem Reporting System. USP File Access No. 11173, May 15, 1991).

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    $\dagger$ The views presented in this article do not necessarily reflect those of FDA. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

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[^374]:    * Results based on mean of three injections

[^375]:    * Results based on mean of two injections

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[^377]:    ${ }^{2}$ Ibid., Appendix VII.

